Injectable local anaesthetic agents for dental anaesthesia

Review information

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What's new

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History

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Abstract

Background

Pain during dental treatment, which is a common fear of patients, can be controlled successfully by local anaesthetic. Several different local anaesthetic formulations and techniques are available to dentists.

Objectives

Our primary objectives were to compare the success of anaesthesia, the speed of onset and duration of anaesthesia, and systemic and local adverse effects amongst different local anaesthetic formulations for dental anaesthesia. We define success of anaesthesia as absence of pain during a dental procedure, or a negative response to electric pulp testing or other simulated scenario tests. We define dental anaesthesia as anaesthesia given at the time of any dental intervention.

Our secondary objective was to report on patients' experience of the procedures carried out.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library; 2018, Issue 1),

MEDLINE (OVID SP), Embase, CINAHL PLUS, WEB OF SCIENCE, and other resources up to 31 January 2018. Other resources included trial registries, handsearched journals, conference proceedings, bibliographies/reference lists, and unpublished research.

Selection criteria

We included randomized controlled trials (RCTs) testing different formulations of local anaesthetic used for clinical procedures or simulated scenarios. Studies could apply a parallel or cross-over design.

Data collection and analysis

We used standard Cochrane methodological approaches for data collection and analysis.

Main results

We included 123 studies (19,223 participants) in the review. We pooled data from 68 studies (6615 participants) for meta-analysis, yielding 23 comparisons of local anaesthetic and 57 outcomes with 14 different formulations. Only 10 outcomes from eight comparisons involved clinical testing.

We assessed the included studies as having low risk of bias in most domains. Seventy-three studies had at least one domain with unclear risk of bias. Fifteen studies had at least one domain with high risk of bias due to inadequate sequence generation, allocation concealment, masking of local anaesthetic cartridges for administrators or outcome assessors, or participant dropout or exclusion.

We reported results for the eight most important comparisons.

Success of anaesthesia

When the success of anaesthesia in posterior teeth with irreversible pulpitis requiring root canal treatment is tested, 4% articaine, 1:100,000 epinephrine, may be superior to 2% lidocaine, 1:100,000 epinephrine (31% with 2% lidocaine vs 49% with 4% articaine; risk ratio (RR) 1.60, 95% confidence interval (CI) 1.10 to 2.32; 4 parallel studies; 203 participants; low-quality evidence).

When the success of anaesthesia for teeth/dental tissues requiring surgical procedures and surgical procedures/periodontal treatment, respectively, was tested, 3% prilocaine, 0.03 IU felypressin (66% with 3% prilocaine vs 76% with 2% lidocaine; RR 0.86, 95% CI 0.79 to 0.95; 2 parallel studies; 907 participants; moderate-quality evidence), and 4% prilocaine plain (71% with 4% prilocaine vs 83% with 2% lidocaine; RR 0.86, 95% CI 0.75 to 0.99; 2 parallel studies; 228 participants; low-quality evidence) were inferior to 2% lidocaine, 1:100,000 epinephrine.

Comparative effects of 4% articaine, 1:100,000 epinephrine and 4% articaine, 1:200,000 epinephrine on success of anaesthesia for teeth/dental tissues requiring surgical procedures are uncertain (RR 0.85, 95% CI 0.71 to 1.02; 3 parallel studies; 930 participants; very low-quality evidence).

Comparative effects of 0.5% bupivacaine, 1:200,000 epinephrine and both 4% articaine, 1:200,000 epinephrine (odds ratio (OR) 0.87, 95% CI 0.27 to 2.83; 2 cross-over studies; 37 participants; low-quality evidence) and 2% lidocaine, 1:100,000 epinephrine (OR 0.58, 95% CI 0.07 to 5.12; 2 cross-over studies; 31 participants; low-quality evidence) on success of anaesthesia for teeth requiring extraction are uncertain.

Comparative effects of 2% mepivacaine, 1:100,000 epinephrine and both 4% articaine, 1:100,000 epinephrine (OR 3.82, 95% CI 0.61 to 23.82; 1 parallel and 1 cross-over study; 110 participants; low-quality evidence) and 2% lidocaine, 1:100,000 epinephrine (RR 1.16, 95% CI 0.25 to 5.45; 2 parallel studies; 68 participants; low-quality evidence) on success of anaesthesia for teeth requiring extraction and teeth with irreversible pulpitis requiring endodontic access and instrumentation, respectively, are uncertain.

For remaining outcomes, assessing success of dental local anaesthesia via meta-analyses was not possible.

Onset and duration of anaesthesia

For comparisons assessing onset and duration, no clinical studies met our outcome definitions.

Adverse effects (continuous pain measured on 170-mm Heft-Parker visual analogue scale (VAS))

Differences in post-injection pain between 4% articaine, 1:100,000 epinephrine and 2% lidocaine, 1:100,000 epinephrine are small, as measured on a VAS (mean difference (MD) 4.74 mm, 95% CI -1.98 to 11.46 mm; 3 cross-over studies; 314 interventions; moderate-quality evidence). Lidocaine probably resulted in slightly less post-injection pain than articaine (MD 6.41 mm, 95% CI 1.01 to 11.80 mm; 3 cross-over studies; 309 interventions; moderate-quality evidence) on the same VAS.

For remaining comparisons assessing local and systemic adverse effects, meta-analyses were not possible. Other adverse effects were rare and minor.

Patients' experience

Patients' experience of procedures was not assessed owing to lack of data.

Authors' conclusions

For success (absence of pain), low-quality evidence suggests that 4% articaine, 1:100,000 epinephrine was superior to 2% lidocaine, 1:100,000 epinephrine for root treating of posterior teeth with irreversible pulpitis, and 2% lidocaine, 1:100,000 epinephrine was superior to 4% prilocaine plain when surgical procedures/periodontal treatment was provided. Moderate-quality evidence shows that 2% lidocaine, 1:100,000 epinephrine was superior to 3% prilocaine, 0.03 IU felypressin when

surgical procedures were performed.

Adverse events were rare. Moderate-quality evidence shows no difference in pain on injection when 4% articaine, 1:100,000 epinephrine and 2% lidocaine, 1:100,000 epinephrine were compared, although lidocaine resulted in slightly less pain following injection.

Many outcomes tested our primary objectives in simulated scenarios, although clinical alternatives may not be possible.

Further studies are needed to increase the strength of the evidence. These studies should be clearly reported, have low risk of bias with adequate sample size, and provide data in a format that will allow meta-analysis. Once assessed, results of the 34 ‘Studies awaiting classification (full text unavailable)’ may alter the conclusions of the review.

Plain language summary

Injectable local anaesthetic agents for preventing pain in participants requiring dental treatment

Review question

This review assessed the evidence for providing successful local anaesthesia that prevents pain during a dental procedure. Included studies compared injections of local anaesthetic to help people requiring dental treatment and to prevent painful sensations tested in an experimental way (such as using cold, a sharp probe, or an electric stimulus).

Background

An injection of local anaesthetic prevents a person from feeling pain. It is given in one specific area rather than in the whole body. Although pain during dental treatment can be successfully managed, it is a common fear of patients.

Several different local anaesthetics are available to dentists, as well as a variety of ways to deliver them, to prevent pain. Factors that appear to influence success include increased difficulty in anaesthetizing teeth in the presence of inflammation, variable susceptibility of different teeth to local anaesthesia, different operative procedures performed on the tooth (for example, it appears easier to achieve successful anaesthesia for dental extractions than for root canal treatment), and various techniques and solutions used to give the local anaesthetic.

We investigated whether injection of one local anaesthetic solution was more effective than another for preventing pain during dental treatment or during an experimental study, and whether this effect occurred quickly or lasted a sufficient length of time, if any unwanted effects occurred, and people’s experience of the dental procedures. Local adverse events might include pain during or after injection, or long-lasting anaesthesia. Systemic effects due to the local anaesthetic solution can include allergic reactions and changes in heart rate and blood pressure.

Study characteristics

Two reviewers searched the literature to identify studies that compared different local anaesthetic solutions injected into people undergoing dental treatment or volunteers who had the same outcomes measured in experimental ways. Within every trial, each person was randomly assigned to receive one of the local anaesthetics under study. The search was up-to-date as of 31 January 2018.

We found 123 trials with 19,223 male and female participants. These trials investigated pain experienced during dental treatment including surgery, extraction, periodontal (gum) treatment, tooth preparation, root canal treatment, anaesthesia of nerves within teeth (pulps) tested using an electric pulp tester or cold stimulant, and anaesthesia of soft tissues measured following pricking of gums or self-reported by the participant. We pooled data from 68 studies (6615 participants). This resulted in eight outcomes when seven different local anaesthetic solutions were tested during dental treatment, two outcomes assessing pain during and after injection of local anaesthetic, and 47 outcomes tested with a pulp tester or by pricking of gums or self-reported by participants.

Key results

The review suggests that of the 14 types of local anaesthetic tested, evidence to support the use of one over another is limited to the outcome of success (absence of pain), from three comparisons of local anaesthetic. Findings show that 4% articaine, 1:100,000 epinephrine was superior to 2% lidocaine, 1:100,000 epinephrine in posterior teeth with inflamed pulps requiring root canal treatment. No difference between these solutions was seen when pain on injection was assessed, and although lidocaine resulted in less post-injection pain, the difference was minimal. Researchers found that 2% lidocaine, 1:100,000 epinephrine was superior to 3% prilocaine, 0.03 IU felypressin and 4% prilocaine plain for surgical procedures and surgical procedures/periodontal treatment, respectively. Speeds of onset were within clinically acceptable times, and durations were variable, making them suitable for different applications. Both of these latter outcomes were tested in experimental ways that may not reflect clinical findings. Unwanted effects were rare. Patients' experience of the procedures was not assessed owing to lack of data.

Quality of the evidence

From comparisons of local anaesthetics in this review, all appeared effective and safe with little difference between them. Available evidence ranged from moderate to very low in quality. Some studies fell short, in terms of quality, owing to small numbers of participants, unclear reporting of study methods, and reporting of data in a format that was not easy to combine with other data. Further research is required to clarify the effectiveness and safety of one local anaesthetic over another.

Background

Description of the condition

Local anaesthesia is the most common form of pain control in dentistry. Several different formulations and various techniques are used to attain local anaesthesia in the mouth. Some of these methods, such as periodontal ligament and intrapulpal anaesthesia, are unique to dentistry. Pain can occur during a variety of dental interventions, which commonly involve some form of surgery or stimulation of the dental pulp by cutting dentine. Common dental treatments causing pain, which can be prevented by using local anaesthetic, include the placement of restorations, endodontic treatment in teeth with irreversible pulpitis, and extraction of teeth. During these treatments, pain is always felt, and completion may be impossible without local anaesthetic. Even with local anaesthetic delivered by infiltration or block anaesthesia, certain treatments such as endodontic treatment in teeth with irreversible pulpitis may still be painful, with the success rate of local anaesthesia as low as 23% (Claffey 2004).

As well as producing the desired local effect of pain control, dental local anaesthetic solutions may produce unwanted localized and systemic effects.

Description of the intervention

Although local anaesthesia is perceived to be a technique associated with a high success rate, failure of local anaesthetic injections is a feature of dental practice (Kaufman 1984). A search of the literature reveals that the efficacy of dental local anaesthesia varies. For example, the success rate reported for anaesthesia of mandibular permanent central incisor teeth ranges from 0% - in Meechan 2002 - to 100% - in Rood 1977.

How the intervention might work

Although no systematic review has examined the topic of failure of all dental local anaesthetic solutions, a number of factors appear to influence success. Teeth are more difficult to anaesthetize in the presence of inflammation. It has been reported that patients with irreversible pulpitis are eight times more likely than controls to suffer failure of local dental anaesthesia (Hargreaves 2001). Different teeth vary in their susceptibility to local anaesthesia. Mandibular incisor teeth are more difficult to anaesthetize than posterior teeth after inferior alveolar nerve block injection (IANB) (Clark 1999). The success of intraligamentary injections has been reported to be poorer with mandibular incisors than with maxillary teeth (White 1998). The success of dental anaesthesia varies with the operative procedure performed on the tooth, for example, it appears easier to achieve successful anaesthesia for dental extractions than for endodontic therapy (Malamed 1982). The method of dental local anaesthesia used affects success. It has been reported that mandibular central incisor teeth are more likely to be anaesthetized by an infiltration injection than by a periodontal ligament anaesthesia (Meechan 2002). The local anaesthetic solution chosen has been shown to influence efficacy. The effectiveness of periodontal ligament anaesthesia has been reported to be much greater when a vasoconstrictor is included in the formulation (Gray 1987). The concentration and choice of local anaesthetic agent also appear to be important (Rood 1976). The efficacy of infiltration techniques in the mandible seems to be influenced by the choice of solution (Meechan 2010).

Unwanted effects of dental local anaesthesia may be localized or systemic. Local adverse events include trismus; long-lasting anaesthesia or paraesthesia (Garisto 2010; Haas 1995; Hillerup 2006); paralysis of motor nerves; and interference with special senses such as vision (Rood 1972). Systemic effects may be due to the local anaesthetic or an added vasoconstrictor. Allergy is rare. Systemic effects that may occur include toxicity from the local anaesthetic that may manifest as altered cardiovascular or central nervous system effects. Systemic effects of the vasoconstrictor principally affect the cardiovascular system and are seen as changes in heart rate and blood pressure (Meechan 2001). Drug interactions with concurrent medication may also occur (Meechan 1997).

Why it is important to do this review

We are conducting this systematic review to determine which local anaesthetic solution is most successful for dental interventions owing to the current popularity of some formulations, such as those of articaine, for which growing evidence suggests that they provide more successful anaesthesia than other formulations. A rigorous systematic review of the success rate of local anaesthesia is needed to inform evidence-based practice. This review will consider only injectable agents used for dental blocks or infiltration, while excluding supplemental injections.

Objectives

Our primary objectives were to compare the success of anaesthesia, the speed of onset and duration of anaesthesia, and systemic and local adverse effects amongst different local anaesthetic formulations for dental anaesthesia. We define success of anaesthesia as absence of pain during a dental procedure, or a negative response to electric pulp testing or other simulated scenario tests. We define dental anaesthesia as anaesthesia given at the time of any dental intervention.

Our secondary objective was to report on patients' experience of the procedures carried out.

Methods

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that tested different formulations of local anaesthetic. These RCTs looked at either clinical procedures carried out under local anaesthesia or simulated scenario studies that made objective measurements of the success of local anaesthetic.

Clinical and simulated scenario studies were of a parallel or cross-over design to compare solutions. When suitable data

were available from cross-over trials and it was appropriate to include them in a meta-analysis, we adopted the approach recommended by Elbourne 2002. When possible, we included the data showing results from paired analyses (i.e. when estimates of within-patient treatment effects and standard errors were available, or could be obtained from authors, or could be computed). If this was not possible, we combined data from the first period only as if they were derived through a parallel study design. We also used this approach if the study used a cross-over design but the cross-over design was in fact inappropriate (e.g. when the duration of carry-over effect exceeded the wash-out period). When paired data, or data from the first period, were not available, we treated the data from cross-over studies as if derived from a parallel study, then performed sensitivity analysis with cross-over data removed.

We also used RCTs to assess participants' experience and to look at local and systemic adverse effects.

Types of participants

We included participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested.

We define adults as over 16 years of age.

We excluded any participants taking regular medications that may alter their pain perception.

Types of interventions

Interventions in participants undergoing clinical procedures or participating in simulated scenario trials included:

- all commercial preparations of dental local anaesthetic versus all other commercial preparations of dental local anaesthetic;
- one dosage of local anaesthetic versus a different dose of local anaesthetic administered by the same injection technique (the higher dosage may be delivered in one injection or more); and
- one concentration of local anaesthetic versus a similar volume but higher concentration of local anaesthetic given by the same injection technique.

Examples of commercial local anaesthetic solutions considered for inclusion in the review include:

- 2% lidocaine (with no epinephrine, 1:50,000 epinephrine, 1:80,000 epinephrine, 1:100,000 epinephrine, or 1:200,000 epinephrine);
- 4% articaine hydrochloride (HCl) (with no epinephrine, 1:100,000 epinephrine, 1:100,000 epinephrine, or 1:400,000 epinephrine);
- 3% prilocaine HCl (with 0.03 international units/mL (IU/mL) octapressin);
- 4% prilocaine HCl (with no epinephrine, or 1:200,000 epinephrine);
- 2% mepivacaine (with 1:20,000 levonordefrin or 1:100,000 epinephrine);
- 3% mepivacaine (with no epinephrine); and
- 0.5% bupivacaine (with 1:200,000 epinephrine).

We considered only primary infiltration and block anaesthesia and did not consider supplemental anaesthesia.

Types of outcome measures

Primary outcomes

Our primary outcome measure was the degree of anaesthesia.

- Success of local anaesthesia, measured by the absence of pain during a procedure via a visual analogue scale (VAS) or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia by an electric pulp tester or cold stimulus.
- Speed of onset (from time of injection to complete anaesthesia) and duration (time from onset until anaesthesia disappeared) of anaesthesia, measured by the absence of pain during a procedure seen on a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia by an electric pulp tester or cold stimulus.
- Adverse effects: local and systemic, when the cause of the harmful effect is attributed to the local anaesthetic formulation, including:
  - pain on injection (solution deposition), measured on a VAS;
  - pain following injection, measured by VAS;
  - paraesthesia following injection; and
  - allergy to local anaesthetic.

Outcomes were classified separately by the oral tissues tested or the testing method used, which included the following.

- Clinical testing of:
  - healthy pulps - hard and soft tissues;
  - healthy pulps;
  - diseased pulps with irreversible pulpitis;
  - different tissues, pooled; and
  - tissues, when tissues tested were unclear.
- Simulated scenario testing of:
  - healthy pulps;
  - diseased pulps with irreversible pulpitis; and

- soft tissues.

Secondary outcomes

Our secondary outcome measure was the experience of participants:

- including but not limited to preference and overall experience.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library; 2018, Issue 1), which contains the Cochrane Oral Health and Anaesthesia, Critical and Emergency Care Groups' Trials Registers (see Appendix 1 for the detailed search strategy); MEDLINE (Ovid SP, 1946 to January 2018; see Appendix 2); Embase (Ovid SP, 1980 to January 2018; see Appendix 3); the Cumulative Index to Nursing and Allied Health Literature (CINAHL) PLUS (EBSCOhost, 1937 to January 2018; see Appendix 4); and the Institute for Scientific Information (ISI) Web of Science (1956 to January 2018; Appendix 5). We ran all searches on 31 January 2018.

Our search strategy combined the subject search with the Cochrane Highly Sensitive Search Strategy for identifying Randomized Controlled Trials (RCTs) (as published in the *Cochrane Handbook for Systematic Reviews of Interventions;* Higgins 2011a). The subject search used a combination of controlled and free-text terms.

Other electronic sources

We searched other available databases including the following.

- IndMED (1985 to January 2018).
- KoreaMED (1958 to January 2018).
- Panteleimon (1998 to January 2018).
- Australian New Zealand Clinical Trials Registry (ANZCTR) (2005 to January 2018).
- Ingenta Connect (1973 to January 2018).

We ran all searches on 31 January 2018.

We also searched bibliographies, reference lists, and websites related to local anaesthetic use.

We did not impose a language restriction. We included publications published in all languages following translation.

Searching other resources

Handsearching

We handsearched the following journals when they had not already been searched as part of the Cochrane handsearching programme.

- *Anesthesia Progress* (March 1966 to January 2018).
- *Journal of Endodontics* (January 1975 to January 2018).
- *International Endodontic Journal* (April 1967 to January 2018).
- *International Journal of Oral Surgery* (1972 to December 1985), continued as *International Journal of Oral and Maxillofacial Surgery* (February 1986 to January 2018).
- *Oral Surgery, Oral Medicine, Oral Pathology* (January 1948 to December 1994), continued as *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* (January 1995 to December 2011), then as *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* (January 2012 to January 2018).
- *Journal of the American Dental Association* (January 1948 to January 2018).
- *Pediatric Dentistry* (March 1979 to January 2018).
- *British Dental Journal* (January 1948 to January 2018).
- *Journal of Dental Research* (February 1948 to January 2018).
- *General Dentistry* (January 1976 to January 2018).
- *Journal of the Canadian Dental Association* (February 1948 to January 2018).

We carried out all searches on 31 January 2018.

We checked the bibliographies of papers and review articles to find any studies not revealed by other search methods.

Unpublished trials

We searched OpenSIGLE (System for Information on Grey Literature in Europe) (1996 to 31 January 2018) for any relevant unpublished dissertations. We searched for additional relevant trials in:

- National Research Register Archive (2000 to 2007) (database has now been archived);
- UK Clinical Research Network (UKCRN) Study Portfolio (January 2008 to 31 January 2018); and
- metaRegister of Controlled Trials (2000 to 31 January 2018).

We attempted to identify unpublished studies and ongoing trials by contacting:

- editors of relevant journals;
- authors of RCTs already identified;
- local anaesthetic manufacturers; and

- researchers known to the review authors.

Evidence on adverse effects

We gathered information on adverse effects from RCTs and from national adverse drug effect databases (searched up to 31 January 2018).

- Medicines and Healthcare Products Regulatory Agency.
- http://www.hpra.ie/.
- European Database of Suspected Adverse Drug Reaction Reports (European Medicines Agency).

Conference proceedings

We considered conference proceedings if, during our search, full-text articles had been published or data from trial authors were made available. These included conference proceedings from:

- Annual Session of the American Association of Endodontists (1985 to 31 January 2018).

Data collection and analysis

Selection of studies

Two review authors (GST and AM) independently read all titles and abstracts of publications retrieved through our search. We obtained any papers considered suitable for the review (which met our inclusion criteria) in their full version, including those for which a decision could not be made from just the title and abstract. When we were initially unable to make a decision, we (GST and AM) independently assessed the papers to see whether inclusion criteria for the review were met. We resolved disagreements initially by mutual discussion; when we could not resolve a difference of opinion, we involved a third review author - John Meechan (JM). We assessed the degree of agreement by using the kappa statistic.

Our inclusion and exclusion criteria for the main study of effects were as follows.

Inclusion criteria

- Randomized controlled trials (RCTs) evaluating the efficacy of a commercially available dental local anaesthetic agent

Exclusion criteria

- Trials investigating postoperative pain control

Data extraction and management

Two review authors carried out the data abstraction independently (GST and AM).

Two review authors (GST and AM) used a data extraction form to record data from individual studies. We used five studies previously chosen as fulfilling the review selection criteria to pilot the form to ensure that data obtained were adequate for the review's purposes. We obtained or clarified missing or unclear data by contacting study authors.

We obtained data as follows.

Study characteristics

- Study authors
- Year of trial
- Country where study was performed
- Source of funding
- Study design
- Method of randomization
- Method of allocation
- Study population inclusion and exclusion criteria
- Age
- Blinding of participants, operator, and assessor
- Intervention description
- Number of participants recruited and number completing the trial
- Reasons for withdrawal
- Overall sample size
- Methods used to estimate sample size (statistical power)
- Statistical methods used
- Unit of analysis
- Use of intention-to-treat (ITT) analysis

Outcomes and/or confounders

- Presence or absence of pain during a procedure measured by VAS or other appropriate method
- Measurement of pulpal anaesthesia by an electric pulp tester
- Speed of onset of anaesthesia
- Duration of anaesthesia
- Measurement of area of soft tissue anaesthesia
- Patient experiences - these include but are not limited to preferences and overall experience

- Adverse events

After extracting data, we performed double data entry and screened the database for inconsistencies as a quality assurance measure.

Assessment of risk of bias in included studies

Two review authors (GST and AM) independently assessed the quality of the chosen RCTs. We assessed those trials selected in four areas that have been shown to affect the size of treatment effect, including:

- method of randomization;
- concealed allocation of treatment;
- blinding of participants, therapists, and outcome assessors; and
- information on reasons for withdrawal by trial group (ITT analysis).

We resolved disagreements by discussion between authors.

We based the quality components on those derived from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), defined as follows.

Randomization

We graded this as:

- adequate if the randomization sequence was generated by a random number table (computer-generated or not), a tossed coin, shuffled cards, or picking randomly mixed, masked cartridges of local anaesthetic from a container;
- unclear if the randomization method used was not explained well or no method was reported; or
- inadequate if randomization methods included alternate assignment, hospital number, and odd/even birth date.

Concealment of allocation

Adequate allocation concealment methods included:

- central concealment of allocation such as by telephone to pharmacy or trial office;
- pharmacy use of sequentially numbered or coded containers; or
- use of sequentially numbered, opaque envelopes.

Allocation concealment was unclear if the study referred to allocation concealment but did not adequately explain the method, or if the study reported no method of allocation concealment.

Concealment was inadequate in studies for which randomization methods could not be concealed, such as alternate assignment, hospital number, and odd or even birth date.

Blinding

An assessment was made of the adequacy of blinding of participants, caregivers, and examiners. Blinding was assessed as:

- adequate;
- inadequate; or
- unclear.

Participants entering studies were assessed to ensure that any who failed to complete their trials were accounted for. Studies utilizing an intention-to-treat (ITT) analysis were included.

When data were unclear or missing, we contacted the authors of studies to clarify the data. In circumstances for which clarification was not possible, we assessed the effect of inclusion of studies by performing sensitivity analysis.

Measures of treatment effect

For binary data, we expressed pooled outcomes as pooled odds ratios (ORs), risk ratios (RRs), and associated 95% confidence intervals (CIs). For continuous data, we expressed pooled outcomes as pooled mean differences (MDs) and associated 95% CIs.

When a data and analysis had only one included study (orphan study), it was not entered into a data and analysis table. Instead, the outcome was placed in the appropriate additional table (Table 1; Table 2; Table 3; Table 4; Table 5). When an orphan study was the sole study entered into a subgroup, its data were still analysed if data were available from other studies included in other subgroups in the data and analysis table.

Unit of analysis issues

The studies identified were a combination of parallel and cross-over studies. Therefore, to pool data for both types of studies, we performed the meta-analysis in several stages.

- We performed a meta-analysis on parallel-group studies only, using the ‘inverse variance’ method to generate odds ratios. We used a fixed-effect analysis or random-effects analysis model depending on whether there were signs of statistical heterogeneity from the I^2 and P value. From these values, we generated logs of the OR and standard errors (SEs).
- We used Microsoft Excel to generate the log of the OR and associated SEs for cross-over studies from the studies' paired data, if available.
- We completed the meta-analysis using Review Manager (RevMan 2014) by entering the generic inverse variance data of logs of the OR and associated SEs from both types of studies using the 'inverse variance' method. We used a fixed-effect

or random-effects analysis model depending on whether there were signs of statistical heterogeneity from the I^2 and P value ($P \leq 0.05$, $I^2 \geq 50\%$ (substantial heterogeneity)).

When paired data were not available, we used data from cross-over studies in the analysis as if they were derived from parallel studies to estimate the overall effect of interest in the meta-analysis. The confidence intervals were wider when we used this approach; therefore we performed a sensitivity analysis while removing the data from cross-over studies from the meta-analysis, when present.

We assessed statistical heterogeneity by calculating the 'Q' statistic and I^2 (Higgins 2011a).

Dealing with missing data

When data were unclear or missing, we contacted study authors to clarify the data. In circumstances for which clarification was not possible, we assessed the effect of including these studies by performing sensitivity analysis.

Assessment of heterogeneity

We planned to assess sources of heterogeneity between studies by performing sensitivity analyses and meta-analysis regression (STATA 13) while exploring, quantifying, and controlling for this factor whenever it was possible to do so. Our planned analyses for heterogeneity are outlined below.

Participant characteristics

- Participants undergoing treatment or volunteers

Treatment characteristics

- Clinical procedure carried out
- Type of local anaesthetic administered
- Dosage of local anaesthetic given
- Concentration of local anaesthetic used
- Number of similar injections given
- Number of injection techniques applied
- Types of injection techniques used

Study design characteristics

- Randomization
- Allocation concealment
- Blinding
- Completeness of follow-up
- Simulated scenario studies using a cross-over design and evaluating carry-over effects
- Length of study
- Source of funding

We considered the following subgroups for analysis.

- Tooth type
- Presence of inflammation (pulpitis)
- Tissue type anaesthetized
- Treatment type
- Type of injection
- Age of participant
- Type of study (treatment vs simulated scenario)
- Pharmaceutical company sponsorship

When we identified other important sources of heterogeneity during the course of the review, we explored and identified these as post hoc analyses.

Assessment of reporting biases

We planned to assess the possibility of publication bias and other possible biases related to the size of trials via graphical methods, the Begg and Mazumdar adjusted rank correlation test (Begg 1994), and the regression asymmetry test (Egger 1997).

Data synthesis

We collated data into evidence tables, grouped according to local anaesthetic. We formulated a descriptive summary to determine the quality of data, checking further for study variations in terms of study characteristics, quality, and results. This assisted us in confirming the suitability of further synthesis methods, including possible meta-analysis.

We used fixed-effect or random-effects meta-analyses as appropriate, based on the 'Q' statistic ($P < 0.10$) to combine quantitative data. For continuous data, we expressed pooled outcomes as pooled MDs with their associated 95% CIs. For binary data, these were predominantly pooled ORs or RRs and associated 95% CIs.

Subgroup analysis and investigation of heterogeneity

We grouped outcomes according to which dental tissues required anaesthesia.

- Studies testing healthy pulps and hard and soft tissues (e.g. extractions).
- Studies testing healthy pulps (e.g. cavity preparations).
- Studies testing diseased pulps with irreversible pulpitis.
- Studies testing different individual dental tissues, when their results were pooled.
- Studies in which it was unclear exactly which dental tissues required anaesthesia (e.g. endodontic treatment when necrotic or inflamed pulps may have been treated).
- Studies in which healthy pulps were tested in simulated scenarios.
- Studies in which diseased pulps with irreversible pulpitis were tested in simulated scenarios.
- Studies in which soft tissues were tested in simulated scenarios.

In addition, we conducted a subgroup analysis of those studies chosen for meta-analysis to see if it was appropriate to combine studies concerned with anaesthesia in the maxilla, the mandible, or both jaws pooled/when the jaw tested was not clear.

We combined the results of trials only if levels of clinical heterogeneity were low to ensure that effects measured were meaningful. We assessed statistical heterogeneity by calculating the 'Q' statistic and I^2 (Higgins 2011a). We performed analysis using Review Manager (RevMan 2014).

Sensitivity analysis

We performed sensitivity analyses to investigate the robustness of results of our primary outcomes. We did this to explore the influence of study quality in terms of those factors influencing bias: generation and concealment of the randomisation sequence, blinding, attrition bias, reporting bias, or other bias. We also explored the influence of cross-over studies, for which paired data were not available, on the same outcome.

'Summary of findings' tables and GRADE

We used the GRADE approach to assess the quality of evidence related to each of the outcomes. We used the GRADE profiler (GRADEpro GDT) to import data from RevMan 2014 and to create 'Summary of findings' tables for the eight major comparisons in this review.

- 4% articaine, 1:100,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 1).
- 3% prilocaine, 0.03 IU felypressin versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 2).
- 4% articaine, 1:200,000 epinephrine versus 4% articaine, 1:100,000 epinephrine (Summary of findings table 3).
- 4% prilocaine plain versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 4).
- 4% articaine, 1:200,000 epinephrine versus 0.5% bupivacaine, 1:200,000 epinephrine (Summary of findings table 5).
- 0.5% bupivacaine, 1:200,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 6).
- 4% articaine, 1:100,000 epinephrine versus 2% mepivacaine, 1:100,000 epinephrine (Summary of findings table 7).
- 2% mepivacaine, 1:100,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 8).

When assessing the quality of evidence for each outcome including pooled data from RCTs, we downgraded evidence from 'high quality' by one level for serious (or by two levels for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

Two review authors (GST and AM) independently assessed the quality of evidence for each outcome. When we were unable to come to an agreement on assessment of quality, we (GST and AM) resolved disagreements initially by mutual discussion. When a difference of opinion could not be resolved, we involved a third review author - John Meechan (JM).

We included in the 'Summary of findings' tables the following outcomes for a variety of local anaesthetic comparisons.

- Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method, or by measuring pulpal anaesthesia via an electric pulp tester or cold stimulus.
- Speed of onset and duration of anaesthesia.
- Adverse effects: local and systemic.

Results

Description of studies

Results of the search

Our search identified 1601 citations from MEDLINE, 2791 from Embase, 1351 from CENTRAL, 2544 from CINAHL PLUS, 595 from Web of Science, and 2566 from other electronic sources, yielding a total of 11,448 citations. We performed searches in other Internet databases and identified 2566 citations (Australian New Zealand Clinical Trials Registry (ANZCTR); IndMED;Ingenta Connect; KoreaMED; Panteleimon). From all these databases, we found 3148 citations to be duplicates and 7903 to be irrelevant studies or studies that were not RCTs.

Other sources revealed 255 citations from bibliographies/reference lists; 56 from conference proceedings, of which 16 were available only as an abstract; and 63 from handsearched journals. From these, we found 39 to be duplicate citations and 73 to be irrelevant studies or studies that were not RCTs.

Searching for unpublished dissertations on Internet databases (OpenSIGLE) and other resources (metaRegister of Controlled Trials; National Research Register Archive; UK Clinical Research Network (UKCRN) Study Portfolio) revealed two additional studies (searched in December 2013). These were found on the National Research Register Archive. After communication, we excluded one because it was not completed (the study author is an author of this review - JM) and we

excluded the second (author - Simpson E) because it included participants treated under sedation. Since the time this database was archived, the original references have no longer been available for referencing.

We repeated the searches at regular intervals up to 31 January 2018.

Removal of irrelevant or non-randomized controlled trials and duplicates and screening by their titles resulted in 659 articles. We screened all of these using their abstracts, which led to exclusion of 317 and further screening of 342 full-text articles. This relatively large number comprised relevant studies, older articles with vague titles and no abstract, a large number of non-English titles, and articles that initially appeared to be testing different outcomes but may have been testing our primary objectives.

We located 56 conference proceedings, of which 39 abstracts were published as full-text articles at a later date; one had been published in full in the conference proceeding. We had identified these through our database searches and handsearches. Of 16 unpublished abstracts, we deemed three to be relevant. We located one recently and placed it in the category of 'Ongoing studies' (see Characteristics of ongoing studies) (Sheikh 2014), we emailed one study author to request data (Caicedo 1996), and we found that another study author was deceased (Iqbal 2009).

We entered 34 studies under Characteristics of studies awaiting classification. These studies require translation or further information from study authors.

We attempted to contact authors by email for clarification of study methods and to obtain data. We emailed the authors of 103 studies to request further information and found that 20 provided no means of contact. The authors of 73 studies replied to our queries, and the authors of 30 studies did not reply. For 18 studies, we made initial contact with study authors but received no replies to further emails. We found that the authors of four studies were deceased (Albertson 1963; Chilton 1971; Fertig 1968; Nespeca 1976).

We described the included studies under Characteristics of included studies.

We used 123 articles (19,223 participants) for qualitative analysis and determined that 68 of these (6615 participants) were suitable for quantitative analysis. Many studies compared more than two formulations of local anaesthetic and reported numerous outcomes including success and onset and duration of local anaesthesia in different tissues. This meant that we found more comparisons and outcomes than individual studies. Only 68 studies were suitable for meta-analysis because 57 were classified as orphan studies and 80 provided data that were not usable in meta-analysis for certain comparisons and outcomes. We summarized in Table 1; Table 2; Table 3; Table 4; Table 5; and Table 6 data for primary outcomes that were not included in meta-analysis. Adverse effects were rare and were difficult to compare; we summarized in Table 7 data that were not suitable for meta-analysis.

The flow diagram for studies from start to finish is shown in Figure 1.

Included studies

We considered only commercially available formulations used for dental anaesthesia, leading to inclusion of studies comparing outcomes for different formulations of lidocaine, articaine, mepivacaine, prilocaine, and bupivacaine. We identified a total of 123 RCTs (19,223 participants) that met our inclusion criteria and were published in peer-reviewed journals.

Types of interventions

We investigated the success of dental anaesthesia among participants in studies that used clinical or simulated scenario testing.

For clinical studies, we classified outcomes by the dental tissues that were anaesthetized and tested (pulp, hard and soft tissues combined, healthy pulps, pulps with signs and symptoms of irreversible pulpitis; as well as individual tissues that underwent different dental interventions followed by pooling of results and tissues for which testing was unclear). These studies looked at pain associated with a variety of dental interventions including:

- extraction/surgical treatment (30 studies);
- endodontic treatment of teeth with irreversible pulpitis (20 studies);
- surgical and non-surgical root canal treatment (Moore 1983);
- surgical periodontal treatment (Moore 2007);
- restorative procedures including cavity preparation and crown preparation in vital teeth (8 studies);
- various treatments for which results were pooled (9 studies); and
- treatment for which the exact clinical procedure was not specified (Albertson 1963).

Simulated scenario testing of success involved testing one or more dental tissues per study, although clinical testing of local anaesthetic success may also have been performed.

The tissues tested were:

- healthy pulps, using a cold stimulus (Porto 2007; Sancho-Puchades 2012);
- healthy pulps, using an electric pulp tester (38 studies);
- diseased pulps with irreversible pulpitis, using a cold stimulus (Atasoy Ulusoy 2014; Cohen 1993; Sherman 2008);
- diseased pulps with irreversible pulpitis, using an electric pulp tester (Allegretti 2016; Kanaa 2012; Sampaio 2012; Sood 2014; Tortamano 2009; Visconti 2016);
- soft tissues, using an appropriate method (33 studies); and
- soft tissues, using an electric pulp tester (Haas 1990; Haas 1991).

Eleven studies did not assess local anaesthetic success (Costa 2005; Donaldson 1987; Fertig 1968; Kalia 2011; Lasemi 2015; Linden 1986; Martinez-Rodriguez 2012; Nespeca 1976; Oliveira 2004; Tofoli 2003; Tortamano 2013).

The speed of onset of anaesthesia was measured in various ways.

- Healthy pulps, using a cold stimulus (Sancho-Puchades 2012).
- Healthy pulps, using an electric pulp tester (35 studies).
- Soft tissues, using an appropriate method (46 studies).
- Various dental tissues, using a clinical procedure (Kramer 1958; Mumford 1961; Nespeca 1976).
- Method of testing was not clear (Nespeca 1976), but it was assumed to be onset of soft tissue anaesthesia (Bradley 1969; Gangarosa 1967; Silva 2012; Thakare 2014), or it was not a conventional technique (Gazal 2017).

Duration of anaesthesia was measured in several ways.

- Healthy pulps, using an electric pulp tester (17 studies).
- Soft tissues, using an appropriate method (45 studies).
- Various dental tissues, using a clinical procedure (Mumford 1961; Weil 1961).
- Method of testing was not clear (Khoury 1991; Thakare 2014).

Types of injections

Types of injection used in each study included:

- inferior alveolar nerve blocks (27 studies);
- inferior alveolar nerve blocks and buccal infiltrations using the same local anaesthetic formulation for both injections (23 studies);
- inferior alveolar nerve blocks and a different local anaesthetic formulation for the infiltrations (Aggarwal 2009; Haase 2008);
- maxillary infiltrations (29 studies);
- mandibular infiltrations (9 studies);
- a mixture of mandibular and maxillary infiltrations (Haas 1990; Haas 1991; Kramer 1958); and
- a mixture of separate dental blocks and infiltration anaesthesia (24 studies).

We found one study found that used each of the following techniques: a mental block (Batista da Silva 2010), an infraorbital block (Berberich 2009), a palatal-anterior superior alveolar nerve block (Burns 2004), and a high-tuberosity maxillary second nerve block (Forloine 2010).

Two studies did not specify the type of injection technique used (Albertson 1963; Pässler 1996).

The volume of solution used for each injection ranged from 0.18 mL in Bortoluzzi 2009 to over 4.5 mL in Silva 2012, although this volume could have been greater in studies that used variable amounts of local anaesthetic.

Locations of studies

The 123 studies were conducted in 19 countries, which included USA (43 studies); Brazil (18 studies); India (16 studies); Germany and Spain (six studies each); Turkey (five); UK, Australia, Canada, and Iran (four studies each); Sweden (three studies); Lebanon and Saudi Arabia (two studies each); and Finland, Israel, Moldova, Thailand, Pakistan, and Republic of Korea (one study each). All were single-centre studies, apart from Karm 2017 and two multi-centre trials (Malamed 2000a; Malamed 2000b), although these were possibly documenting the same study. However, attempts to contact the first study author to confirm this were unsuccessful.

All studies were conducted in a university or hospital setting, apart from two studies that were conducted in private practice (Chilton 1971; Fertig 1968), one study that took place in a specialist endodontic practice (Cohen 1993), one study that was undertaken in both hospital and private practice (Gangarosa 1967), and one study that was conducted at a military base (Nespeca 1976).

Types of study design

We identified 54 RCTs that used a parallel design. Of these, 10 looked at purely clinical outcomes (Bradley 1969; Hosseini 2016; Kolli 2017; Lima 2009; Malamed 2000a; Malamed 2000b; Nabeel 2014; Pässler 1996; Srinivasan 2009; Yadav 2015), four looked at purely simulated scenario outcomes (Fertig 1968; Hersh 1995; Martinez-Rodriguez 2012; Srisurang 2011), and 40 looked at both clinical and simulated scenario outcomes.

We identified 68 RCTs that applied a cross-over design. Of these, two looked at purely clinical outcomes (Moore 2007; Thakare 2014), 48 looked at purely simulated scenario outcomes, and 18 looked at both clinical and simulated scenario outcomes.

One study compared local anaesthesia success in participants having teeth extracted but it was not clear whether the study used a parallel or cross-over design (Keskitalo 1975). Attempts to contact the first study author to clarify this were unsuccessful.

Types of participants

A total of 19,223 participants were recruited to the 123 studies. Numbers in each study ranged from 10 in Ruprecht 1991 to 3703 in Kramer 1958. The ages of participants ranged from four years in Malamed 2000a and Malamed 2000b to 81 years in Nordenram 1990. One hundred eleven studies stated an average age, a range of ages, or both. However, 12 studies gave no indication of the age of participants (Albertson 1963; Cohen 1993; Fertig 1968; Gangarosa 1967; Hosseini

2016; Kalia 2011; Kramer 1958; Martinez-Rodriguez 2012; Sadove 1962; Sherman 2008; Stibbs 1964; Weil 1961), although when we communicated with the study author, we discovered that one of these - Cohen 1993 - involved mainly adults. Ninety-five studies had a varying mixture of male and female participants, six had only male participants (Gazal 2015; Gazal 2017; Kammerer 2014; Knoll-Kohler 1992a; Knoll-Kohler 1992b; Ruprecht 1991), and 22 gave no indication of the male-to-female ratio.

When studies defined their measurement of anaesthetic success differently than we did or presented findings in a unit other than percentage or number of successful outcomes, we recalculated these values when possible (Table 8). Alternatively, we sought data that would allow us to do these calculations, if they were not available. This also applied to other aspects of the paper that needed clarification.

Excluded studies

We excluded eight clinical studies that initially appeared to be suitable for inclusion in the review because studies were non-randomized (Cowan 1964; Cowan 1968; Hassan 2011; Raab 1990; Shruthi 2013), the solutions tested were not commercially available (Adler 1969), or solutions were compared against a placebo - as in Kanaa 2009 - or against sedation that was used in the study - as in Caruso 1989. We described these reasons for exclusion in the Characteristics of excluded studies.

Ongoing studies

We identified three ongoing studies as abstracts when handsearching journals (Caicedo 1996; Iqbal 2009; Sheikh 2014), although they have not yet been published. We will attempt to contact these study authors (attempts so far have been unsuccessful). We described these studies under Characteristics of ongoing studies.

Studies awaiting classification

We found 34 studies that are still awaiting classification. These were published in Japanese (Manabe 2005; Oka 1990; Ouchi 2008; Shimada 2002), Korean (Im 2010; Lee 2004), or Chinese journals (27 studies), or we obtained full-text articles too late to include these studies in the review (da Silva-Junior 2017). The Chinese studies were identified in four systematic reviews (Su 2014a; Su 2014b; Su 2016; Xiao 2010), but we have not been able to obtain them. We will make a further attempt and will translate these papers, if obtained, along with the Japanese and Korean studies, before we decide to include or exclude them from this review. When possible, we described these studies under Characteristics of studies awaiting classification.

Risk of bias in included studies

Most of the included studies had risk of bias that was low or unclear. Most had unclear risk of bias because journal articles presented information that was unclear, and because contact could not be made with study authors. When contact with study authors was made, most studies were confirmed as having low risk of bias. A few instances of high risk of bias were noted; these were related to random sequence generation and allocation concealment (Maruthingal 2015; Trieger 1979; Trullenque-Eriksson 2011), blinding of participants and personnel administering local anaesthetic (Trullenque-Eriksson 2011), blinding of outcome assessment (Maruthingal 2015; Naik 2017; Trieger 1979), and incomplete outcome data (Albertson 1963; Arrow 2012; Chilton 1971; Epstein 1965; Epstein 1969; Kammerer 2014; Knoll-Kohler 1992a; Moore 2006; Sadove 1962; Stibbs 1964; Trullenque-Eriksson 2011; Weil 1961).

We have shown the proportion of studies with low, high, and unclear risk of bias in Figure 2. We have displayed the risk of bias summary in Figure 3. The Characteristics of included studies table details the risk of bias of each study.

We have provided below a summary of the risk of bias of included studies.

Allocation (selection bias)

For random sequence generation, we graded 66 studies as having low risk of bias, 54 as having unclear risk of bias, and three as having high risk of bias (Maruthingal 2015; Trieger 1979; Trullenque-Eriksson 2011). Most studies used a computer programme to generate the randomization sequence, but others used random number tables, an online random number generator, tossing a coin, and randomly picking a card, envelope, or masked local anaesthetic cartridge. Those with high risk of bias had a predetermined order for local anaesthetic allocation (Maruthingal 2015), used the alphabet based on the family name of each participant (Trieger 1979), or allowed clinicians to have some choice of the local anaesthetic used (Trullenque-Eriksson 2011).

For allocation concealment, we graded 70 studies as having low risk of bias, 50 as having unclear risk of bias, and three as having high risk of bias (Maruthingal 2015; Trieger 1979; Trullenque-Eriksson 2011).

Blinding (performance bias and detection bias)

We graded most of the included studies as having low or unclear risk of bias for blinding of participants and personnel (performance bias) and for blinding of outcome assessment (detection bias). We graded 99 studies as having an adequate risk of bias for blinding of participants and personnel, 23 as having unclear risk, and one as having high risk (Trullenque-Eriksson 2011).

We graded 99 studies as having low risk of bias for blinding of outcome assessment and 30 as having unclear risk. We graded three studies as having high risk of bias for blinding of outcome assessment when no attempt was made to blind the local anaesthetic used (Maruthingal 2015; Naik 2017; Trieger 1979).

The description of the blinding technique varied between studies, with some including very detailed descriptions (Mason

2009), and others mentioning that the study was blinded only in the abstract (Sierra Rebolledo 2007). A few studies described the coding of local anaesthetic but offered no explanation of the coding system used (i.e. it could have included simple coding of two or more letters or numbers, which if used for certain local anaesthetics with obvious differences in their properties could allow determination of the identity of each of the local anaesthetics used).

Incomplete outcome data (attrition bias)

Only a few studies had any serious omissions of data. High risk of bias was judged to have occurred when there had been a high attrition rate (> 20%), especially if this was seen more in one group than in another. We graded 117 studies as having outcomes with low risk of bias and 23 as having outcomes with unclear of risk of bias.

We graded 12 studies as having outcomes with high risk of bias. One study had a very high attrition rate of 47% (Keskitalo 1975), and another study had a marked attrition rate (Khoury 1991). For Keskitalo 1975, 141 cases were not included because teeth were not suitable for the study, possibly following further radiographic examination. Groups were still balanced after their removal and reasons for removal were similar, so we graded risk of bias for this study as low. Khoury 1991 did not include data for 282 participants. Reasons for dropouts and whether dropouts were equal among groups were not clear, so we graded risk of bias as unclear.

Some studies excluded participants who had been anaesthetized with inferior alveolar nerve block if lower lip soft tissue anaesthesia had not been achieved. These participants were re-appointed and the inferior alveolar block was repeated; if successful a second time, this approach was classified as successful. If after a further injection participants still were not experiencing lower lip anaesthesia, some were excluded completely or were replaced with new participants and testing was repeated. When details of those excluded were available, we classed them as failures and also for any subsequent clinical procedure or simulated scenario test that was completed. It was not always possible to take this approach. For Forloine 2010, a cross-over study, we found that it was not possible to calculate overall failure rates, but as loss of participants was balanced across groups, we graded risk of bias as low. Although recalculation was not possible for the cross-over study Sierra Rebolledo 2007, the final numbers seemed to be greater in one group than in the other. As the reasons for this were not clear, we graded risk of bias as unclear. In the parallel study Ashraf 2013, it also was not clear from which group participants had been removed; therefore we graded risk of bias for this study as unclear.

Owing to the nature of the studies included in this review, we had to assess risk of attrition bias for several different outcomes within the same study in most cases. Therefore we added rows to the risk of bias tables under Characteristics of included studies.

We graded risk of attrition bias for the success of local anaesthesia, measured by the absence of pain during a procedure assessed on a visual analogue scale (VAS) or by other appropriate method as low in 63 studies, unclear in six studies, and high in one study (Trullenque-Eriksson 2011). Clinical success was not assessed in 53 studies. We graded risk of attrition bias as unclear for a variety of reasons including the numbers of participants entering the trials (Albertson 1963; Gangarosa 1967), numbers completing the trial (Sierra Rebolledo 2007), clear numbers, number of participants tested with each local anaesthetic not stated (Ashraf 2013; Kramer 1958), and a high dropout rate occurred resulting in groups of similar size when it was not clear if the groups were equal in size at the start of the trial (Khoury 1991). In the only study with high risk of bias (Trullenque-Eriksson 2011), 46% of participants from each group were excluded for a variety of reasons.

We graded risk of attrition bias for the success of pulpal anaesthesia, measured by an electric pulp tester or a cold stimulus, as low in 49 studies, unclear in zero studies, and high in zero studies. Pulpal anaesthesia, measured by an electric pulp tester or a cold stimulus, was not assessed in 74 studies.

We graded risk of attrition bias for the success of soft tissue anaesthesia, measured by the absence of pain during a procedure assessed on a VAS or by other appropriate method including using an electric pulp tester - in Haas 1990 and Haas 1991 - as low in 34 studies, unclear in one study (Ashraf 2013), and high in zero studies. Soft tissue success was not assessed in 88 studies. In the only study with unclear risk of bias (Ashraf 2013), six participants who did not report lip numbness were excluded from the study. However it was not clear from the journal article which groups these participants were excluded from, as they should have been classed as failures.

We graded risk of attrition bias for the onset of pulpal anaesthesia, measured by an electric pulp tester or a cold stimulus, as low in 32 studies, unclear in two studies, and high in three studies. Onset of pulpal anaesthesia was not assessed in 89 studies. We graded risk of attrition bias as unclear for two studies because journal articles did not state the numbers of participants assessed for each local anaesthetic solution (Jaber 2010; Maruthingal 2015). We graded studies as having high risk of bias owing to the small numbers of participants assessed and differences in group sizes in two studies (Kammerer 2014: 4/10 for 4% articaine, no vasoconstrictor vs 10/10 for other formulations; and Knoll-Kohler 1992a: 6/10 for 2% lidocaine, 1:200,000 epinephrine vs 10/10 for other formulations). These two studies each tested three local anaesthetics, so when group sizes were equal, we graded outcomes as having low risk of bias. We graded Moore 2006 as having high risk of bias owing to the relatively small number of participants and differences in group sizes between 4% articaine, no vasoconstrictor; 4% articaine, 1:100,000 epinephrine; and 4% articaine, 1:100,000 epinephrine groups. We graded outcomes for these latter two groups, when numbers of participants were better balanced, as having low risk of bias.

We graded risk of attrition bias for the onset of soft tissue anaesthesia, measured by self-assessment or following gingival probing, as low in 35 studies, unclear in eight studies, and high in two studies. Onset of soft tissue anaesthesia was not assessed in 78 studies. Gross 2007 measured onset only at 15 minutes following injection; therefore we did not

assess data. We graded risk of attrition bias as unclear for outcomes from eight studies because journal articles did not state the numbers of participants assessed for each local anaesthetic solution (Abdulwahab 2009; Bradley 1969; Gangarosa 1967; Hersh 1995; Sancho-Puchades 2012; Santos 2007; Sherman 1954) or because the number of participants completing the trial was not clear (Sierra Rebolledo 2007). In the two studies with high risk of bias, high dropout rates of up to 29% in Arrow 2012 and 46% in Trullenque-Eriksson 2011 were seen in some groups; these may underestimate the true dropout rates.

We graded risk of attrition bias for the duration of pulpal anaesthesia, measured by an electric pulp tester or a cold stimulus, as low in 15 studies, unclear in zero studies, and high in three studies. Duration of pulpal anaesthesia was not assessed in 108 studies. We graded outcomes as being at high risk of bias because of the small numbers of participants assessed and differences in group size between the two studies (Kammerer 2014: 4/10 for 4% articaine, no vasoconstrictor vs 10/10 for other formulations; and Knoll-Kohler 1992a: 6/10 for 2% lidocaine, 1:200,000 epinephrine vs 10/10 for other formulations). Each of these two studies tested three local anaesthetics, and for outcomes with equal group sizes, we graded them as having low risk of bias. We graded Moore 2006 as having high risk of bias owing to the relatively small number of participants and differences in group sizes between 4% articaine, no vasoconstrictor; 4% articaine, 1:100,000 epinephrine; and 4% articaine, 1:100,000 epinephrine groups. We graded outcomes between these latter local anaesthetics, when numbers of participants were better balanced, as having low risk of bias.

We graded the risk of attrition bias for the duration of soft tissue anaesthesia, measured by self-assessment or following gingival probing, as low in 21 studies, unclear in 16 studies, and high in eight studies. Onset of soft tissue anaesthesia was not assessed in 78 studies. We rated outcomes from studies that did not state the numbers of participants assessed as having unclear risk of attrition bias. For eight studies (Albertson 1963; Chilton 1971; Epstein 1965; Epstein 1969; Sadove 1962; Stibbs 1964; Trullenque-Eriksson 2011; Weil 1961), we graded risk of attrition bias as high because dropouts for each local anaesthetic solution were high in number and numbers were variable among the different groups included in the study. The exact reason why the expected number of participants was not assessed was unknown, although it could have been lack of compliance with reporting the time anaesthesia completely disappeared, or it could have been due to side effects. The estimated percentage dropout may be an underestimate, as soft tissue success, on which this could be calculated, often was not known and would be greater than clinical anaesthetic success, for which researchers often provided the only data available to estimate attrition bias.

We graded the risk of attrition bias for adverse events as low in 66 studies, unclear in seven studies, and high in one study. Adverse events were not assessed in 49 studies. In studies for which the numbers of participants assessed were not stated (Albertson 1963; Chapman 1988; Gangarosa 1967; Khoury 1991; Kramer 1958; Mumford 1961; Porto 2007), we graded risk of bias as unclear. In the only study with an outcome graded as having high risk of bias, a high dropout rate of up to 46% was seen in some groups, and this may underestimate the true dropout rate (Trullenque-Eriksson 2011).

We graded risk of attrition bias for the onset of anaesthesia, measured by self-assessment of pain during a clinical procedure, as low in two studies (Mumford 1961; Nespeca 1976), unclear in one study, and high in zero studies. Onset of anaesthesia was not assessed in 120 studies. We graded risk of attrition bias as unclear for one study because the journal article did not clearly state the number of participants assessed for each local anaesthetic solution (Kramer 1958).

We graded risk of attrition bias for the duration of anaesthesia, measured by self-assessment of pain during a clinical procedure, as low in one study (Mumford 1961), unclear in zero studies, and high in zero studies. We did not assess data from Weil 1961, as measurement of duration ended when the clinical procedure was completed (i.e. before pain was experienced). Duration of anaesthesia was not assessed in 122 studies.

Selective reporting (reporting bias)

We graded all included studies as having low risk of reporting bias, apart from one, which we graded as having unclear risk because researchers did not provide details of pulpal anaesthesia onset times (Sancho-Puchades 2012).

Other potential sources of bias

Eleven studies received funding or were supplied with local anaesthetic from the solution's manufacturer (Arrow 2012; Donaldson 1987; Gangarosa 1967; Karm 2017; Knoll-Kohler 1992b; Linden 1986; Moore 2006; Moore 2007; Ruprecht 1991; Stibbs 1964; Weil 1961). Three other studies may have received funding from local anaesthetic manufacturers (Malamed 2000a; Malamed 2000b; Mumford 1961). Three studies had authors who had an association with the trial's sponsors, which in each case was declared (Kammerer 2014; Moore 2006; Moore 2007).

The potential for introducing bias was unknown; therefore we graded the risk of bias as unclear (in most cases, all solutions were provided by the same manufacturer rather than a single local anaesthetic provided by one manufacturer and other product provided by a rival manufacturer).

Effects of interventions

Clinical outcomes

4% articaine, 1:100,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method

We pooled the results of four studies measuring the success of local anaesthesia of maxillary and mandibular posterior teeth with irreversible pulpitis, requiring endodontic access and instrumentation (Analysis 1.1), measured using a VAS (no pain). The four pooled, parallel studies included 203 participants (203 episodes of dental anaesthesia) in total (Allegretti 2016; Claffey 2004; Srinivasan 2009; Tortamano 2009). Data for Srinivasan 2009 were for maxillary buccal infiltrations for first premolars and first molars, while data from the mandibular studies used an inferior alveolar nerve block injection (IANB) for first molar and second molar teeth (Allegretti 2016); second premolar, first molar, second molar, and third molar teeth (Tortamano 2009); and first premolar, second premolar, first molar, and second molar teeth (Claffey 2004). Their pooling favoured articaine over lidocaine (risk ratio (RR) 1.60, 95% confidence interval (CI) 1.10 to 2.32), with little heterogeneity between studies (P = 0.33, I^2 = 13%). Pooling of just the three mandibular studies using an IANB suggested no evidence of a difference between formulations (RR 1.32, 95% CI 0.81 to 2.16), as well as no heterogeneity (P = 0.42, I^2 = 0%). The test for subgroup differences revealed evidence of moderate heterogeneity (P = 0.16, I^2 = 49%).

We downgraded the outcome from high to low quality owing to imprecision (sample size of 203 participants/episodes of anaesthesia and 70 events) and study limitations (one trial - Srinivasan 2009 - having unclear risks of selection bias). For the three mandibular studies using an IANB, we downgraded the outcome from high to moderate quality owing to imprecision (sample size of 163 participants/episodes of anaesthesia and 44 events).

Primary outcome 3: adverse effects: local and systemic

We pooled the results of three studies measuring pain on injection for local anaesthesia of maxillary and mandibular posterior teeth (Analysis 1.8), measured using a Heft-Parker VAS. The three pooled, cross-over studies included 157 participants (314 episodes of dental anaesthesia) in total (Evans 2008; Mikesell 2005; Robertson 2007). Data were included for pain during injection of an IANB in Mikesell 2005 and following maxillary and mandibular buccal infiltrations, respectively (Evans 2008; Robertson 2007). All infiltrations were adjacent to first molar teeth, and pain was measured only during the deposition of local anaesthetic. Pooling suggested no evidence of a difference between lidocaine and articaine (mean difference (MD) 4.74 mm, 95% CI -1.98 to 11.46 mm), with no heterogeneity between studies (P = 0.51, I^2 = 0%). The test for subgroup differences also revealed evidence of no heterogeneity (P = 0.51, I^2 = 0%).

We conducted a sensitivity analysis (Table 9) that excluded one study in which topical anaesthetic was not used before injection (Robertson 2007), which suggested no evidence of a difference between formulations (MD 7.46 mm, 95% CI -0.70 to 15.61 mm) with no heterogeneity between studies (P = 0.90, I^2 = 0%).

We downgraded the outcome one level from high to moderate quality owing to imprecision (95% CI includes no effect and an appreciable benefit for 2% lidocaine, 1:100,000 epinephrine/sample size of 157 participants/314 episodes of anaesthesia).

We pooled the results of three studies measuring the pain following injection for local anaesthesia of maxillary and mandibular posterior teeth (Analysis 1.9), measured using a Heft-Parker VAS. The three pooled, cross-over studies included 156 participants (309 episodes of dental anaesthesia) in total (Evans 2008; Mikesell 2005; Robertson 2007). Data were included for pain following injection of an IANB in Mikesell 2005 and following maxillary and mandibular buccal infiltrations, respectively (Evans 2008; Robertson 2007). All infiltrations were adjacent to first molar teeth, and peak pain data from the day of the injection were used. Pooling suggested that injection of lidocaine resulted in less pain than articaine (MD 6.41 mm, 95% CI 1.01 to 11.80 mm), with little heterogeneity between studies (P = 0.24, I^2 = 30%). The test for subgroup differences also revealed evidence of moderate heterogeneity (P = 0.24, I^2 = 30.3%).

We downgraded the outcome one level from high to moderate quality owing to imprecision (sample size of 156 participants/309 episodes of anaesthesia).

Other adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies. We have summarized the data for these outcomes in Table 7.

We have summarized the above outcomes in Summary of findings table 1.

3% prilocaine, 0.03 IU felypressin versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method

We pooled the results of two parallel studies (Analysis 2.1) measuring the success of local anaesthesia of teeth/dental tissues requiring surgical procedures (Khoury 1991), or those requiring extraction/apicectomy, measured by the absence of pain (Pässler 1996). The two studies included 907 participants (907 episodes of dental anaesthesia) in total. Data were pooled from the Pässler 1996 study, testing the anterior part of the mouth (injection type not stated), and from the Khoury 1991 study, using combined data for infiltration anaesthesia and IANB while testing a selection of teeth and dental tissues (not stated). Pooling favoured lidocaine over prilocaine (RR 0.86, 95% CI 0.79 to 0.95), with evidence of no heterogeneity between studies (P = 0.59, I^2 = 0%).

We downgraded the outcome one level from high to moderate quality owing to study limitations, including an unclear risk of attrition bias (Khoury 1991), and the fact that both trials reported unclear methods of randomization sequence generation and allocation concealment. We have summarized this outcome in Summary of findings table 2.

4% articaine, 1:200,000 epinephrine versus 4% articaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method

We pooled the results of three parallel studies measuring the success of local anaesthesia during surgical

procedures, including extractions and apicectomies, measured by the absence of pain (Analysis 3.1). The three pooled studies included 930 participants (930 episodes of dental anaesthesia) in total (Khoury 1991; Lima 2009; Pässler 1996). Data for Lima 2009, were for maxillary third molars using infiltration anaesthesia, data from Khoury 1991 were for various types of teeth, and Pässler 1996 tested mandibular anterior and premolar teeth, although these latter two studies used multiple injection techniques and did not state the exact methods applied. Pooling suggested no evidence of a difference between formulations of articaine (RR 0.85, 95% CI 0.71 to 1.02), with substantial heterogeneity between studies (P = 0.04; I^2 = 68%). The test for subgroup differences also revealed substantial heterogeneity (P = 0.05, I^2 = 68%).

We downgraded the outcome three levels from high to very low quality because of study limitations (unclear risk of attrition bias - Khoury 1991) and because two trials - Khoury 1991 and Pässler 1996 - had unclear risks of selection bias, imprecision (95% CI includes no effect and an appreciable benefit for 4% articaine, 1:100,000 epinephrine), and inconsistency (substantial, unexplained heterogeneity). We have summarized this outcome in Summary of findings table 3.

4% prilocaine plain versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method

We pooled the results of two parallel studies measuring the success of local anaesthesia during periodontal procedures (Chilton 1971), as well as extractions (Epstein 1965), measured by the absence of pain (Analysis 4.1). The two pooled studies included 228 participants (228 episodes of dental anaesthesia) in total. Data for both studies were for various types of teeth using maxillary infiltration anaesthesia as well as IANB, and in the case of Chilton 1971, it was not specified whether infiltrations were confined to the maxilla. Pooling favoured lidocaine over prilocaine (RR 0.86, 95% CI 0.75 to 0.99) with low heterogeneity between studies (P = 0.37; I^2 = 5%). Pooling of just IANB data suggested no evidence of a difference between formulations (RR 0.96, 95% CI 0.73 to 1.26), with moderate heterogeneity (P = 0.18, I^2 = 43%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.55, I^2 = 0%).

We downgraded the outcome two levels from high to low quality because of study limitations, including that both trials reported unclear methods of randomization sequence generation and allocation concealment and imprecision (sample size of 228 participants and 179 events). For the two mandibular studies using an IANB, we downgraded the outcome from high to low quality for the same reasons (sample size in this case was 92 participants/episodes of anaesthesia and 64 events). We have summarized these outcomes in Summary of findings table 4.

0.5% bupivacaine, 1:200,000 epinephrine versus 4% articaine, 1:200,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method

We pooled the results of two cross-over studies measuring the success of local anaesthesia during extraction of lower third molar teeth, measured by the absence of pain (Analysis 5.1). The two pooled studies included 37 participants (74 episodes of dental anaesthesia) in total (Sancho-Puchades 2012; Trullenque-Eriksson 2011). Data were included for third molar teeth using IANB and mandibular buccal infiltration. Pooling suggested no evidence of a difference between articaine and bupivacaine (odds ratio (OR) 0.87, 95% CI 0.27 to 2.83), with moderate heterogeneity between studies (P = 0.18, I^2 = 44%).

We conducted a sensitivity analysis (Table 9) that excluded the cross-over study Trullenque-Eriksson 2011 because this study had high risk of selection, performance, and attrition bias, which meant that the cross-over study Sancho-Puchades 2012 became an orphan study (OR 2.00, 95% CI 0.37 to 10.92).

We downgraded the outcome two levels from high to low quality, first because of study limitations, as the two trials had unclear - as in Sancho-Puchades 2012 - or high risk - as in Trullenque-Eriksson 2011 - of bias related to methods of randomization sequence generation and allocation concealment. In addition, Trullenque-Eriksson 2011 had high risk of bias for blinding of participants and personnel, provided incomplete outcome data (high attrition rate of 46%), and showed imprecision (sample size of 37 participants/74 episodes of anaesthesia, 95% confidence interval includes no effect and an appreciable benefit for both solutions). We have summarized this outcome in Summary of findings table 5.

0.5% bupivacaine, 1:200,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method

We pooled the results of two cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, hard and soft tissues, tested clinically by extraction of third molar teeth (Analysis 6.1). The two pooled studies included 31 participants (62 episodes of dental anaesthesia) in total (Bouloux 1999; Laskin 1977). Data were included for mandibular third molars alone using an IANB and buccal infiltration (Laskin 1977), and for mandibular and maxillary third molars using an IANB and buccal infiltration, or greater palatine nerve block and buccal infiltration, respectively (Bouloux 1999). Pooling suggested no evidence of a difference between lidocaine and bupivacaine (OR 0.58, 95% CI 0.07 to 5.12), with evidence of moderate heterogeneity between studies (P = 0.17, I^2 = 47%). The test for subgroup differences revealed evidence of moderate heterogeneity (P = 0.17, I^2 = 47%).

We conducted a sensitivity analysis (Table 9) that excluded the cross-over study Laskin 1977, for which paired data were not available, which meant that Bouloux 1999 became an orphan study (OR 0.14, 95% CI 0.01 to 2.77).

We downgraded the outcome two levels from high to low quality because of study limitations, with one trial - Laskin 1977 - reporting unclear methods of randomization sequence generation and imprecision (95% confidence interval includes no

effect and an appreciable benefit for both solutions, sample size of 31 participants/62 episodes of anaesthesia and 25 events). We have summarized this outcome in Summary of findings table 6.

4% articaine, 1:100,000 epinephrine versus 2% mepivacaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method

We pooled the results of one cross-over study - Colombini 2006 - and one parallel study - Gazal 2017 - measuring the success of local anaesthesia during extraction of lower third molar teeth and various maxillary teeth, respectively (Analysis 7.1), measured by the absence of pain. The two pooled studies included 110 participants (130 episodes of dental anaesthesia) in total. Data were included for IANB and mandibular buccal infiltration (Colombini 2006), as well as for maxillary, buccal, and palatal infiltrations (Gazal 2017). Pooling suggested no evidence of a difference between mepivacaine and articaine (OR 3.82, 95% CI 0.61 to 23.82), with no heterogeneity between studies (P = 0.86, I^2 = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.86, I^2 = 0%).

We downgraded the outcome two levels from high to low quality, first owing to study limitations (the study Colombini 2006 had unclear risks of bias related to methods of randomization sequence generation, allocation concealment, and blinding of participants, personnel, and outcome assessment). There was also imprecision (95% CI includes no effect and an appreciable benefit for 4% articaine, 1:100,000 epinephrine, with sample size of 110 participants/130 episodes of anaesthesia). We have summarized this outcome in Summary of findings table 7.

2% mepivacaine, 1:100,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method

We pooled the results of two studies measuring the success of local anaesthesia of mandibular, molar teeth with irreversible pulpitis, requiring endodontic access and instrumentation (Analysis 8.1), measured by the absence of pain. The two pooled, parallel studies included 68 participants (68 episodes of dental anaesthesia) in total (Allegretti 2016; Visconti 2016). Data from Allegretti 2016 were for IANB (3.6 mL) for mandibular first and second molars, and data from Visconti 2016 were for IANB (3.6 mL) for mandibular first molars. Pooling suggested no evidence of a difference between formulations (RR 1.16, 95% CI 0.25 to 5.45), with substantial heterogeneity between studies (P = 0.09, I^2 = 65%).

We downgraded the outcome two levels from high to low quality owing to imprecision (sample size of 68 participants/68 episodes of anaesthesia, 95% CI includes no effect and an appreciable benefit for both formulations) and inconsistency (wide variation in point estimates and substantial, unexplained heterogeneity). We have summarized this outcome in Summary of findings table 8.

Other outcomes (including simulated scenario testing)

4% articaine, 1:100,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus

We pooled the results of seven cross-over studies and one parallel study (Srisurang 2011), measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 1.2). The eight pooled studies included 309 participants (586 episodes of dental anaesthesia) in total (Abdulwahab 2009; Batista da Silva 2010; Evans 2008; Jaber 2010; Kanaa 2006; Mikesell 2005; Robertson 2007; Srisurang 2011). Data were for first premolars (Srisurang 2011), as well as for first molars (Evans 2008), using maxillary buccal infiltration, mandibular buccal infiltration (Abdulwahab 2009; Kanaa 2006; Robertson 2007), and IANB (Mikesell 2005); for second premolars using mental blocks (Batista da Silva 2010); and for central incisors using mandibular labial and lingual infiltrations (Jaber 2010). Pooling favoured articaine over lidocaine (OR 2.71, 95% CI 1.74 to 4.22), with evidence of no heterogeneity between studies (P = 0.45, I^2 = 0%). Pooling of just the two maxillary buccal infiltration studies - Evans 2008 and Srisurang 2011 - suggested no evidence of a difference between formulations (OR 1.41, 95% CI 0.54 to 3.73) and provided evidence of no heterogeneity between studies (P = 0.61, I^2 = 0%). Pooling of just the three mandibular buccal infiltration studies - Abdulwahab 2009, Kanaa 2006, and Robertson 2007 - also favoured articaine over lidocaine (OR 4.88, 95% CI 2.30 to 10.37) with evidence of no heterogeneity between studies (P = 0.60, I^2 = 0%). The test for subgroup differences also revealed evidence of little heterogeneity (P = 0.24, I^2 = 27%).

We conducted a sensitivity analysis (Table 9) that excluded four cross-over studies without paired data (Abdulwahab 2009; Evans 2008; Mikesell 2005; Robertson 2007), which favoured articaine over lidocaine (OR 3.28, 95% CI 1.23 to 8.80), with evidence of no heterogeneity between studies (P = 0.46, I^2 = 0%).

We noted study limitations (unclear methods of randomization sequence generation and allocation concealment) in one study (Srisurang 2011). We also noted indirectness (success defined as only one - in Abdulwahab 2009 - or two - in Batista da Silva 2010, Evans 2008, Kanaa 2006, and Robertson 2007 - negative responses to maximal electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum electric pulp tester values). Therefore, we downgraded the outcome two levels from high to low quality.

We pooled the results of six studies measuring the success of local anaesthesia of soft tissues, as self-reported by participants (Analysis 1.3). Two pooled, cross-over studies - Kanaa 2006 and Mikesell 2005 - and four parallel studies - Allegretti 2016, Claffey 2004, Poorni 2011, and Tortamano 2009) included 355 participants (443 episodes of dental

anaesthesia) in total. Data from these studies were for anaesthesia of the lower lip using IANB (Allegretti 2016; Claffey 2004; Mikesell 2005; Poorni 2011; Tortamano 2009), or using buccal infiltration (Kanaa 2006). Pooling suggested no evidence of a difference between formulations (RR 1.03, 95% CI 0.99 to 1.07), with little heterogeneity between studies (P = 0.30, I^2 = 17%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.33, I^2 = 0%).

We conducted a sensitivity analysis (Table 9) that excluded two cross-over studies (Kanaa 2006; Mikesell 2005), whose data were not paired. This also suggested no evidence of a difference between lidocaine and articaine (RR 1.02, 95% CI 0.98 to 1.07; P = 0.47, I^2 = 0%).

We downgraded the outcome one level from high to moderate quality owing to indirectness (soft tissue anaesthesia is a poor indicator of pulp and hard tissue anaesthesia).

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of six cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 1.4). The six pooled studies included 202 participants (402 episodes of dental anaesthesia) in total (Evans 2008; Kalia 2011; Knoll-Kohler 1992b; Robertson 2007; Ruprecht 1991; Tortamano 2013). Data were included for central incisors - in Knoll-Kohler 1992b and Ruprecht 1991 - and for first molars - in Evans 2008 - using maxillary infiltration; for first molars using mandibular buccal infiltration (Robertson 2007), for mandibular molars using IANB (Tortamano 2013), and for a variety of maxillary and mandibular teeth using various injections whose outcomes were combined (Kalia 2011). Pooling suggested no evidence of a difference between lidocaine and articaine (MD -0.63 minutes, 95% CI -1.69 to 0.42 minutes), with evidence of substantial heterogeneity between studies (P = 0.002, I^2 = 73%). Pooling of just maxillary infiltration data suggested no evidence of a difference between the two formulations (MD 0.45 minutes, 95% CI -1.10 to 2.00 minutes), with moderate heterogeneity (P = 0.2, I^2 = 38%). The test for subgroup differences revealed substantial heterogeneity (P = 0.001, I^2 = 81%).

We downgraded the outcome three levels from high to very low quality owing to study limitations (unclear risks of selection (Kalia 2011; Knoll-Kohler 1992b; Ruprecht 1991); performance and detection bias (Kalia 2011; Ruprecht 1991); imprecision (95% CI includes no effect and an appreciable benefit for articaine); inconsistency (not all confidence intervals overlap, substantial heterogeneity, and wide variation in point estimates); and indirectness (pulp testing repeated at intervals that are large compared with the onset times measured, and onset may occur at less than maximum electric pulp tester values).

We pooled the results of three cross-over studies measuring the duration of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 1.5). The three pooled studies included 52 participants (104 episodes of dental anaesthesia) in total (Knoll-Kohler 1992b; Ruprecht 1991; Tortamano 2013). Data were included for central incisors using maxillary labial infiltration (Knoll-Kohler 1992b; Ruprecht 1991); and for mandibular molars using IANB (Tortamano 2013). Pooling suggested no evidence of a difference between lidocaine and articaine (MD 21.87 minutes, 95% CI -10.96 to 54.71 minutes), with evidence of considerable heterogeneity between studies (P < 0.0008, I^2 = 86%). Pooling of just maxillary infiltration data also suggested no evidence of a difference between the two formulations (MD 5.50 minutes, 95% CI -11.33 to 22.33 minutes), with no heterogeneity (P = 1.00, I^2 = 0%). The test for subgroup differences revealed considerable heterogeneity (P = 0.0002, I^2 = 93%).

We downgraded the outcome three levels from high to very low quality owing to study limitations (two studies - Knoll-Kohler 1992b and Ruprecht 1991 - had unclear risks of bias for random sequence generation, and one study - Ruprecht 1991 - had unclear risks of bias related to methods of allocation concealment and blinding of outcome assessment, imprecision (sample size of 52 participants/104 episodes of anaesthesia and 95% CI includes no effect and an appreciable benefit for both formulations), and inconsistency (not all confidence intervals overlap, considerable unexplained heterogeneity, and wide variation in point estimates). Indirectness (clinical anaesthesia may be present at less than maximum pulp tester readings) was also present .

We pooled the results of six studies measuring the onset of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 1.6). The four pooled, cross-over studies - Kalia 2011, Kanaa 2006, Kambalimath 2013, and Silva 2012 - and two parallel studies - Bhagat 2014 and Martinez-Rodriguez 2012 - included 637 participants (818 episodes of dental anaesthesia) in total. Data were included for subjective testing of soft tissues using mandibular buccal infiltration (Kanaa 2006), IANB (Bhagat 2014), IANB supplemented with buccal infiltration (Kambalimath 2013; Martinez-Rodriguez 2012; Silva 2012), and a variety of injections whose outcomes were combined (Kalia 2011). Times for Silva 2012 were assumed to be for soft tissues (lower lip, measured subjectively) because of their speed of onset. Pooling favoured articaine over lidocaine (MD -0.23 minutes, 95% CI -0.45 to -0.01 minutes), with evidence of considerable heterogeneity (P = 0.00001, I^2 = 87%). Pooling of data for just IANB supplemented with buccal infiltration favoured articaine over lidocaine (MD -0.11 minutes, 95% CI -0.20 to -0.03 minutes), with evidence of no heterogeneity (P = 0.42, I^2 = 0%). The test for subgroup differences revealed evidence of considerable heterogeneity (P = 0.00001, I^2 = 92%).

We conducted a sensitivity analysis (Table 9) that excluded four cross-over studies whose data were not paired (Kalia 2011; Kanaa 2006; Kambalimath 2013; Silva 2012). Pooling favoured articaine over lidocaine (MD -0.18 minutes, 95% CI -0.30 to -0.07 minutes; P = 0.23, I^2 = 29%).

We downgraded the outcome three levels from high to very low quality owing to study limitations (unclear risks of selection and detection bias in Bhagat 2014, Kalia 2011, Kambalimath 2013, Martinez-Rodriguez 2012, and Silva 2012, and unclear risk of performance bias in Kambalimath 2013, Martinez-Rodriguez 2012, and Silva 2012), inconsistency (not all confidence intervals overlap and considerable heterogeneity is evident), and indirectness (soft tissue anaesthesia is a poor indicator of

onset of clinical anaesthesia).

We pooled the results of two studies measuring the duration of local anaesthesia of mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 1.7). Pooled parallel studies included 422 participants (422 episodes of dental anaesthesia) in total (Bhagat 2014; Martinez-Rodriguez 2012). Data were included for IANB supplemented with buccal infiltration (Martinez-Rodriguez 2012), and with IANB alone (Bhagat 2014). Pooling favoured articaine over lidocaine (MD 56.88 minutes, 95% CI 44.08 to 69.69 minutes), with evidence of no heterogeneity (P = 0.43, I^2 = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.43, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to study limitations (unclear risks of selection and detection bias in both studies and unclear risk of performance bias in one study - Martinez-Rodriguez 2012) and indirectness (soft tissue anaesthesia is a poor indicator of duration of clinical anaesthesia).

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

3% prilocaine, 0.03 IU felypressin versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus

No data from the included studies were available for meta-analysis.

Primary outcome 2: speed of onset and duration of anaesthesia (data for onset and duration were not included in the meta-analysis)

No data from the included studies were available for meta-analysis.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% articaine 1:200,000 epinephrine versus 4% articaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of five cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested using an electric pulp tester (Analysis 3.2). The five pooled studies included 248 participants (496 episodes of dental anaesthesia) in total (Abdulwahab 2009; Kammerer 2014; McEntire 2011; Moore 2006; Ruprecht 1991). Data were included for first molar teeth using mandibular buccal infiltration (Abdulwahab 2009; McEntire 2011); for central incisor teeth using maxillary labial infiltration (Kammerer 2014; Ruprecht 1991); for canine teeth using IANB (Moore 2006); and for first premolar teeth using maxillary buccal infiltration (Moore 2006). Pooling suggested no evidence of a difference between formulations of articaine (RR 0.97, 95% CI 0.87 to 1.08), with evidence of no heterogeneity between studies (P = 0.87, I^2 = 0%). Pooling of just the three maxillary infiltration studies also suggested no evidence of a difference between formulations (RR 0.99, 95% CI 0.92 to 1.06) and no heterogeneity between studies (P = 0.98, I^2 = 0%). Pooling of just the two mandibular buccal infiltration studies also suggested no evidence of a difference between the formulations (RR 0.88, 95% CI 0.70 to 1.10), with no heterogeneity between studies (P = 0.96, I^2 = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.43, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to study limitations (unclear risks of random sequence generation in Moore 2006 and Ruprecht 1991; and of allocation concealment and detection bias in Ruprecht 1991). Indirectness was also present (success defined as only one in Abdulwahab 2009 and Kammerer 2014, as two in McEntire 2011, or as three in Moore 2006 negative responses to the maximal electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum electric pulp tester values).

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of five cross-over studies measuring onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 3.3). The five pooled studies included 162 participants (322 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006; Ruprecht 1991; Tofoli 2003; Tortamano 2013). Data were included for central incisors (Kammerer 2014; Ruprecht 1991), as well as for first premolars (Moore 2006), using maxillary infiltration, and for canines (Moore 2006), first premolars (Tofoli 2003), and mandibular molars (Tortamano 2013), using IANB. Pooling suggested no evidence of a difference between formulations of articaine (MD 0.15 minutes, 95% CI -0.42 to 0.73 minutes), with no heterogeneity between studies (P = 0.99, I^2 = 0%). Pooling of just maxillary infiltration data suggested no evidence of a difference between the two formulations (MD 0.02 minutes, 95% CI -0.69 to 0.73 minutes), with no heterogeneity between studies (P = 0.91, I^2 = 0%). Pooling of just IANB data also suggested no evidence of a difference between the two formulations (MD 0.41 minutes, 95% CI -0.58 to 1.40 minutes), with no heterogeneity between studies (P = 0.98, I^2 = 0%). The test for subgroup differences revealed no heterogeneity between studies (P = 0.52, I^2 = 0%).

We downgraded the outcome three levels from high to very low quality owing to imprecision (95% CI includes no effect and appreciable benefit for 4% articaine, 1:100,000 epinephrine, with sample size of 162 participants/322 episodes of anaesthesia) and indirectness (pulp testing is repeated at intervals that are large compared with the onset times measured, and clinical anaesthesia may have been present at less than maximum electric pulp tester values). We also noted study limitations (unclear risks of random sequence generation in Moore 2006 and Ruprecht 1991, and allocation concealment and detection bias in Ruprecht 1991).

We pooled the results of five cross-over studies measuring the duration of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 3.4). The five pooled studies included 162 participants (322 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006; Ruprecht 1991; Tofoli 2003; Tortamano 2013). Data were included for central incisors - Kammerer 2014 and Ruprecht 1991 - and first premolars - Moore 2006 - using maxillary infiltration, and for canines (Moore 2006), first premolars (Tofoli 2003), and mandibular molars (Tortamano 2013) using IANB. Pooling favoured 4% articaine, 1:100,000 epinephrine over 4% articaine, 1:200,000 epinephrine (MD -8.98 minutes, 95% CI -15.17 to -2.79 minutes), with evidence of little heterogeneity between studies (P = 0.39, I^2 = 5%). Pooling of just the maxillary infiltration data suggested no evidence of a difference between the two formulations (MD -6.62 minutes, 95% CI -13.68 to 0.44 minutes), with little heterogeneity between studies (P = 0.21, I^2 = 35%). Pooling of just IANB data favoured 4% articaine with 1:100,000 epinephrine over 4% articaine with 1:200,000 epinephrine (MD -16.80 minutes, 95% CI -29.65 to -3.95 minutes), with no heterogeneity between studies (P = 0.86, I^2 = 0%). The test for subgroup differences revealed moderate heterogeneity (P = 0.17, I^2 = 46%).

We downgraded the outcome three levels from high to very low quality owing to imprecision (sample size of 162 participants/322 episodes of anaesthesia), study limitations (unclear risks of random sequence generation in Moore 2006 and Ruprecht 1991), allocation concealment and detection bias (Ruprecht 1991), and indirectness (clinical anaesthesia may have been present at less than maximum electric pulp tester values).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% prilocaine plain versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested using an electric pulp tester (Analysis 4.2). The two pooled studies included 60 participants (120 episodes of dental anaesthesia) in total (Katz 2010; McLean 1993). Data were included for first molars using maxillary buccal infiltration (Katz 2010), as well as IANB (McLean 1993). Pooling suggested no evidence of a difference between formulations (RR 0.93, 95% CI 0.75 to 1.17), with evidence of no heterogeneity between studies (P = 0.76, I^2 = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.77, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (sample size of 120 episodes of anaesthesia/85 events) and indirectness (success defined in one study - Katz 2010 - as only two negative responses to the maximal electric pulp tester output for 10 minutes not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 4.3). The two pooled studies included 52 participants (103 episodes of dental anaesthesia) in total (Katz 2010; McLean 1993). Data were included for first molars using maxillary infiltration (Katz 2010), as well as IANB (McLean 1993). Pooling suggested no evidence of a difference between formulations (MD -0.96 minutes, 95% CI -2.87 to 0.95 minutes), with evidence of no heterogeneity between studies (P = 0.68, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.68, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (95% CI includes no effect and an appreciable benefit for both formulations, sample size of 52 participants/103 episodes of anaesthesia) and indirectness (pulp testing is repeated at intervals that are large compared with onset times measured, and clinical anaesthesia may be present at less than maximum pulp tester readings).

We pooled the results of two studies measuring the onset of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 4.4). Pooled cross-over study - McLean 1993 - and parallel study - Chilton 1971 - data included 406 participants (436 episodes of dental anaesthesia) in total. Testing was done by using a gingival stick or subjective testing, depending on which occurred first, in McLean 1993. It was assumed that subjective anaesthesia would occur before anaesthesia using gingival sticks. Data were included for subjective testing of soft tissues using IANB and infiltration when the jaw was not stated in Chilton 1971. Pooling suggested no evidence of a difference between formulations (MD 0.02 minutes, 95% CI -0.10 to 0.14 minutes), with evidence of no heterogeneity between studies (P = 0.51, I^2 = 0%). The test for subgroup differences revealed little heterogeneity (P = 0.27, I^2 = 18%).

We conducted a sensitivity analysis (Table 9) that excluded the cross-over study McLean 1993, whose data were not paired,

which meant that Chilton 1971 became an orphan study (MD 0.02 minutes, 95% CI -0.10 to 0.14 minutes).

We downgraded the outcome two levels from high to low quality owing to study limitations (unclear methods of randomization sequence generation and allocation concealment in Chilton 1971 and indirectness; soft tissue anaesthesia is a poor indicator of onset of clinical anaesthesia).

We pooled the results of three parallel studies measuring the duration of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 4.5). The three pooled studies included 698 participants (698 episodes of dental anaesthesia) in total (Chilton 1971; Epstein 1965; Epstein 1969). Data were included for maxillary buccal infiltration (Epstein 1965; Epstein 1969), IANB (Chilton 1971; Epstein 1965; Epstein 1969), and infiltration for which the jaw was not stated (Chilton 1971). Pooling favoured lidocaine over prilocaine (MD -33.95 minutes, 95% CI -48.05 to -19.84 minutes), with evidence of substantial heterogeneity between studies (P = 0.02, I^2 = 64%). Lidocaine was also favoured over prilocaine when just maxillary infiltration data were pooled (MD -47.36 minutes, 95% CI -63.24 to -31.49 minutes), with no heterogeneity between studies (P = 0.78, I^2 = 0%). Lidocaine was also favoured over prilocaine when just IANB data were pooled (MD -21.09 minutes, 95% CI -37.23 to -4.94 minutes), with moderate heterogeneity between studies (P = 0.13, I^2 = 52%). The test for subgroup differences revealed substantial heterogeneity (P = 0.04, I^2 = 69,8%).

We downgraded the outcome three levels from high to very low quality because of study limitations (all three studies reported unclear methods of randomization sequence generation and allocation concealment and had high risk of attrition bias), indirectness (soft tissue anaesthesia is a poor indicator of duration of clinical anaesthesia), and inconsistency (with substantial unexplained heterogeneity).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

0.5% bupivacaine, 1:200,000 epinephrine versus 4% articaine, 1:200,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus

No data from the included studies were available for meta-analysis.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 5.2). Pooled studies included 69 participants (138 episodes of dental anaesthesia) in total (Gregorio 2008; Trullenque-Eriksson 2011). Data were included for subjective testing of soft tissues using IANB and additional infiltration. Pooling favoured articaine over bupivacaine (MD -0.85 minutes, 95% CI -1.26 to -0.44 minutes), with evidence of no heterogeneity between studies (P = 0.98, I^2 = 0%).

We performed a sensitivity analysis (Table 9) that excluded Trullenque-Eriksson 2011, which had high risk of selection, performance, and attrition bias; this resulted in the cross-over study Gregorio 2008 becoming an orphan study (MD -0.85 minutes, 95% CI -1.27 to -0.43 minutes).

We downgraded the outcome three levels from high to very low quality. There were study limitations, as the included trials had unclear - in Gregorio 2008 - or high risk - in Trullenque-Eriksson 2011 - of bias related to randomization sequence generation and allocation concealment. In addition, one study had high risk of bias, with blinding of participants and personnel and incomplete outcome data (high attrition rate of 46%) (Trullenque-Eriksson 2011). Imprecision (sample size of 69 participants/138 episodes of anaesthesia) and indirectness (soft tissue anaesthesia is a poor indicator of onset of clinical anaesthesia) were also present.

We pooled the results of two cross-over studies measuring duration of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 5.3). The two pooled studies included 39 participants (78 episodes of dental anaesthesia) in total (Trullenque-Eriksson 2011; Vilchez-Perez 2012). Data were included for maxillary buccal infiltration (Vilchez-Perez 2012), as well as IANB (Trullenque-Eriksson 2011). Pooling favoured bupivacaine over articaine (MD -172.61 minutes, 95% CI -239.69 to -105.53 minutes), with no heterogeneity between studies (P = 1.00, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 1.0, I^2 = 0%).

We performed a sensitivity analysis (Table 9) that excluded Trullenque-Eriksson 2011, which had high risk of selection, performance, and attrition bias; this resulted in the cross-over study Vilchez-Perez 2012, becoming an orphan study (MD -172.55 minutes, 95% CI -249.73 to -95.37 minutes).

We downgraded the outcome three levels from high to very low quality. There were study limitations, as the included trials had unclear - Vilchez-Perez 2012 - or high risk - Trullenque-Eriksson 2011 - of bias related to randomization sequence generation. In addition, one study had high risk of bias related to allocation concealment, blinding of participants and personnel, and incomplete outcome data (high attrition rate of 46%) (Trullenque-Eriksson 2011). Imprecision (sample size of 39 participants/78 episodes of anaesthesia) and indirectness (soft tissue anaesthesia is a poor indicator of

duration of clinical anaesthesia) were present.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

0.5% bupivacaine, 1:200,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of three cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 6.2). The three pooled studies included 90 participants (180 episodes of dental anaesthesia) in total (Abdulwahab 2009; Fernandez 2005; Gross 2007). Data were included for maxillary and mandibular first molars using maxillary buccal infiltration (Gross 2007), mandibular buccal infiltration (Abdulwahab 2009), and IANB (Fernandez 2005). Pooling suggested no evidence of a difference between lidocaine and bupivacaine (RR 0.80, 95% CI 0.62 to 1.05), with no heterogeneity between studies (P = 0.92, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.92, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (90 participants/180 episodes of anaesthesia and 92 events, and 95% CI includes no effect and an appreciable benefit for lidocaine) and indirectness (success defined in one study - Abdulwahab 2009 - as only one negative response and in another study - Gross 2007 - as only two negative responses to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 6.3). The two pooled studies included 63 participants (116 episodes of dental anaesthesia) in total (Fernandez 2005; Gross 2007). Data were included for first molars using maxillary buccal infiltration (Gross 2007), as well as IANB (Fernandez 2005). Pooling favoured 2% lidocaine, 1:100,000 epinephrine over 0.5% bupivacaine, 1:200,000 epinephrine (MD 3.32 minutes, 95% CI 0.27 to 6.37 minutes), with no heterogeneity between studies (P = 0.97, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.97, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (sample size of 63 participants/116 episodes of anaesthesia) and indirectness (pulp testing is repeated at intervals that are large compared with onset times measured, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

We pooled the results of three studies measuring the speed of onset of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 6.4). The pooled, parallel study Moore 1983 and the cross-over studies Fernandez 2005 and Laskin 1977 included 79 participants (126 episodes of dental anaesthesia) in total. The infiltrations used were assumed to be pooled from both jaws in the parallel study, and IANBs were used in the cross-over studies, with - Laskin 1977 - and without - Fernandez 2005 - an additional buccal infiltration. Testing was done by using subjective self-reporting of onset in all three studies. Pooling suggested no evidence of a difference between lidocaine and bupivacaine (MD 0.02 minutes, 95% CI -1.07 to 1.10 minutes), with evidence of substantial heterogeneity between studies (P = 0.06, I^2 = 64%). The test for subgroup differences revealed moderate heterogeneity (P = 0.06, I^2 = 64%).

We conducted a sensitivity analysis (Table 9) that excluded the cross-over studies without paired data (Fernandez 2005; Laskin 1977), which meant that the parallel study Moore 1983 became an orphan study (MD -0.90 minutes, 95% CI -1.96 to 0.16 minutes).

We downgraded the outcome three levels from high to very low quality because of study limitations, with one trial - Laskin 1977 - reporting unclear methods of randomization sequence generation, imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations, sample size of 79 participants/126 episodes of anaesthesia), indirectness (soft tissue anaesthesia is a poor indicator of onset of clinical anaesthesia), and inconsistency (substantial heterogeneity).

We pooled the results of six studies measuring the duration of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 6.5). The two pooled, parallel studies (Moore 1983; Nespeca 1976), along with four cross-over studies (Fernandez 2005; Gross 2007; Laskin 1977; Linden 1986), included 232 participants (332 episodes of dental anaesthesia) in total. Testing was done by using subjective self-reporting of duration in all six studies. Data were included for maxillary (Gross 2007; Moore 1983), mandibular (Laskin 1977), and buccal infiltrations, as well as for IANBs - Fernandez 2005 - and infiltrations that were assumed to be pooled from both jaws (Linden 1986; Nespeca 1976). Pooling favoured bupivacaine over lidocaine (MD 222.88 minutes, 95% CI 135.99 to 309.76 minutes), with evidence of considerable heterogeneity between studies (P < 0.00001, I^2 = 92%). Bupivacaine was also favoured over lidocaine when the combined mandibular and maxillary infiltration data were pooled (MD 224.26 minutes, 95% CI 47.01 to 401.50 minutes), with considerable heterogeneity (P = 0.01, I^2 = 84%). Pooling just the maxillary infiltration data suggested no evidence of a difference between lidocaine and bupivacaine (MD 109.52 minutes, 95% CI -39.40 to 258.44 minutes), with

substantial heterogeneity (P = 0.03, I² = 78%). The test for subgroup differences revealed evidence of considerable heterogeneity (P = 0.03, I² = 62%).

We conducted a sensitivity analysis (Table 9) that excluded the four cross-over studies without paired data (Fernandez 2005; Gross 2007; Laskin 1977; Linden 1986), which left two parallel studies (Moore 1983; Nespeca 1976). Pooling favoured bupivacaine over lidocaine (MD 261.07 minutes, 95% CI 195.96 to 326.18 minutes; P = 0.12, I² = 53%).

We downgraded the outcome three levels from high to very low quality because of study limitations, including reporting unclear methods of randomization sequence generation (Laskin 1977; Nespeca 1976), allocation concealment, and unclear methods of blinding of participants, personnel, and outcome assessors (Nespeca 1976). Imprecision (sample size of 232 participants/332 episodes of anaesthesia), indirectness (soft tissue anaesthesia is a poor indicator of duration of clinical anaesthesia), and inconsistency (not all confidence intervals overlap, substantial heterogeneity, and wide variation of point estimates) were also present.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experience: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% articaine, 1:100,000 epinephrine versus 2% mepivacaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by using self-reported patient pain or anaesthesia

We pooled the results of two studies measuring the success of local anaesthesia of soft tissues, self-reported by participants (Analysis 7.2). The pooled, cross-over study - Bortoluzzi 2009 - and the parallel study - Allegretti 2016 - included 68 participants (92 episodes of dental anaesthesia) in total. Data for these studies were for anaesthesia of the lower lip using IANB - Allegretti 2016 - or buccal infiltration - Bortoluzzi 2009. Pooling suggested no evidence of a difference between formulations (RR 1.07, 95% CI 0.73 to 1.59), with substantial heterogeneity between studies (P = 0.06, I² = 72%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.38, I² = 0%).

We conducted a sensitivity analysis (Table 9) that excluded the cross-over study Bortoluzzi 2009, whose data were not paired, which resulted in Allegretti 2016 becoming an orphan study (RR 1.00, 95% CI 0.92 to 1.09).

We downgraded the outcome three levels from high to very low quality owing to imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations, sample size of 68 participants/92 episodes of anaesthesia and 75 events), indirectness (soft tissue anaesthesia is a poor indicator of pulp and hard tissue anaesthesia), and inconsistency (substantial heterogeneity).

Primary outcome 2: speed of onset and duration of anaesthesia

No data from the included studies were available.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

2% lidocaine, 1:100,000 epinephrine versus 2% mepivacaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus

No data from the included studies were available for meta-analysis.

Primary outcome 2: speed of onset and duration of anaesthesia

No data from the included studies were available.

Primary outcome 3: adverse effects: local and systemic

No studies were used in meta-analyses. We have summarized orphan study data in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

2% lidocaine, 1:50,000 epinephrine versus 2% lidocaine, 1:80,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of mandibular teeth with healthy pulps, tested using an electric pulp tester (Analysis 9.1). The two pooled studies included 60 participants (120 episodes of dental anaesthesia) in total (Dagher 1997; Yared 1997). Data were included for first molars using

mandibular buccal infiltration (Dagher 1997), as well as IANB (Yared 1997). Pooling suggested no evidence of a difference between formulations of lidocaine (RR 0.81, 95% CI 0.65 to 1.01), with evidence of no heterogeneity between studies (P = 0.86, I² = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.88, I² = 0%).

We downgraded the outcome three levels from high to very low quality because of study limitations, including one trial (Yared 1997), which reported unclear methods of randomization sequence generation, and another trial (Dagher 1997), which reported unclear methods of blinding of outcome assessors; both described unclear methods of allocation concealment. Imprecision (95% confidence interval includes no effect and an appreciable benefit for 2% lidocaine, 1:80,000 epinephrine, sample size of 60 participants/120 episodes of anaesthesia/85 events) and indirectness (clinical anaesthesia may be present at less than maximum pulp tester readings) were also present.

Primary outcome 2: speed of onset and duration of anaesthesia

No data from the included studies were available for meta-analysis.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

2% lidocaine, 1:50,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of seven cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 10.1). The seven pooled studies included 210 participants (420 episodes of dental anaesthesia) in total (Berberich 2009; Dagher 1997; Knoll-Kohler 1992a; Mason 2009; Wali 2010; Yared 1997; Yonchak 2001). Data were included for first molars using mandibular buccal infiltration (Dagher 1997), IANB (Wali 2010; Yared 1997), and maxillary buccal infiltration (Mason 2009). Data were also included for central incisors using maxillary labial infiltration (Knoll-Kohler 1992a), lateral incisors using mandibular labial infiltration (Yonchak 2001), and canine teeth using infraorbital block (Berberich 2009). Pooling suggested no evidence of a difference between formulations of lidocaine (RR 0.99, 95% CI 0.88 to 1.12), with evidence of no heterogeneity between studies (P = 0.90, I² = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.63, I² = 0%).

Pooling of just the two maxillary buccal infiltration studies suggested no evidence of a difference between solutions (RR 0.97, 95% CI 0.88 to 1.08), with no heterogeneity between studies (P = 0.75, I² = 0%). Pooling of just the two mandibular buccal infiltration studies suggested no evidence of a difference between solutions (RR 1.00, 95% CI 0.70 to 1.43), with no heterogeneity between studies (P = 0.73, I² = 0%). Pooling of just the two IANB studies suggested no evidence of a difference between solutions (RR 0.92, 95% CI 0.69 to 1.22), with evidence of no heterogeneity (P = 0.42, I² = 0%).

We downgraded the outcome three levels from high to very low quality owing to study limitations, including two trials reporting unclear methods of randomization sequence generation (Knoll-Kohler 1992a; Yared 1997), two trials reporting unclear methods of allocation concealment (Dagher 1997; Yared 1997), and one trial having unclear risk of bias for outcome assessment (Dagher 1997). Imprecision (sample size of 210 participants/420 episodes of anaesthesia and 282 events) was present. Indirectness (success defined in two studies - Berberich 2009 and Mason 2009 - as only two negative responses, and in one study - Knoll-Kohler 1992a - as only one negative response to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings) was also present.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of four cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 10.2). The four pooled studies included 92 participants (184 episodes of dental anaesthesia) in total (Berberich 2009; Knoll-Kohler 1992a; Mason 2009; Wali 2010). Data were included for lateral incisors and first molars using maxillary buccal infiltration (Knoll-Kohler 1992a; Mason 2009), canines using infraorbital nerve block (Berberich 2009), and first molars using IANB (Wali 2010). Pooling suggested no evidence of a difference between formulations (MD -0.44 minutes, 95% CI -1.66 to 0.79 minutes), with evidence of no heterogeneity between studies (P = 0.90, I² = 0%). Pooling of just maxillary infiltration data also suggested no evidence of a difference between formulations (MD -0.75 minutes, 95% CI -3.04 to 1.54 minutes), with no heterogeneity (P = 0.91, I² = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.75, I² = 0%).

We downgraded the outcome three levels from high to very low quality owing to study limitations (one study - Knoll-Kohler 1992a - reported an unclear method of randomization of sequence generation), imprecision (95% CI includes no effect and an appreciable benefit for both solutions, sample size of 92 participants/184 episodes of anaesthesia), and indirectness (pulp testing is repeated at intervals that are large compared with the onset times measured, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw

data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

2% lidocaine, 1:80,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 11.1). The two pooled studies included 60 participants (120 episodes of dental anaesthesia) in total (Dagher 1997; Yared 1997). Data were included for first molars using mandibular buccal infiltration (Dagher 1997), as well as IANB (Yared 1997). Pooling favoured 2% lidocaine with 1:80,000 epinephrine over 2% lidocaine with 1:100,000 epinephrine (RR 1.27, 95% CI 1.01 to 1.59), with no heterogeneity between studies (P = 0.64, I^2 = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.68, I^2 = 0%).

We downgraded the outcome by three levels from high to very low quality because of study limitations, including one trial that reported unclear methods of randomization sequence generation (Yared 1997), one trial reporting unclear methods of blinding of outcome assessors (Dagher 1997), and both trials describing unclear methods of allocation concealment. Imprecision was present (sample size of 60 participants/120 episodes of anaesthesia and 84 events) as was indirectness (clinical anaesthesia may be present at less than maximum pulp tester readings).

Primary outcome 2: speed of onset and duration of anaesthesia

No data from the included studies were available for meta-analysis.

Primary outcome 3: adverse effects: local and systemic

No data from the included studies were available.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

2% lidocaine, 1:200,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of three cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 12.1). The three pooled studies included 70 participants (140 episodes of dental anaesthesia) in total (Caldas 2015; Knoll-Kohler 1992a; Vreeland 1989). Data were included for lateral incisors and canine teeth using maxillary labial infiltration (Caldas 2015; Knoll-Kohler 1992a), as well as for first molar teeth using IANB (Vreeland 1989), using different volumes of local anaesthetic (1.8 mL of 2% lidocaine, 1:100,000 epinephrine vs 3.6 mL of 2% lidocaine, 1:200,000 epinephrine). Pooling suggested no evidence of a difference between formulations of lidocaine (RR 0.89, 95% CI 0.63 to 1.26), with evidence of substantial heterogeneity between studies (P = 0.03, I^2 = 72%). Pooling of just the maxillary infiltration data also suggested no evidence of a difference between formulations (RR 0.80, 95% CI 0.33 to 1.95), with considerable heterogeneity between studies (P = 0.0005, I^2 = 92%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.65, I^2 = 0%).

We downgraded the outcome three levels from high to very low quality because of study limitations, including reporting unclear methods of randomization sequence generation - Caldas 2015 and Knoll-Kohler 1992a - and allocation concealment - Caldas 2015. Imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations, sample size of 70 participants/140 episodes of anaesthesia and 114 events) and inconsistency (substantial heterogeneity) were present, as was indirectness (success defined in one study - Knoll-Kohler 1992a - as only one negative response, and in another study - Caldas 2015 - as two responses, to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 2: speed of onset and duration of anaesthesia

No data from the included studies were suitable for meta-analysis. We have summarized the data for these outcomes in Table 1, Table 2, and Table 3.

Primary outcome 3: adverse effects: local and systemic

No data from the included studies were available.

Secondary outcome 1: participants' experience: these include but are not limited to preference, overall experience

No data from the included studies were available.

3% mepivacaine plain versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of six cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 13.1). The six pooled studies included 208 participants (416 episodes of dental anaesthesia) in total (Abdulwahab 2009; Berberich 2009; Burns 2004; Forloine 2010; Mason 2009; McLean 1993). Data were included for first molars using maxillary buccal infiltration (Mason 2009), mandibular buccal infiltration (Abdulwahab 2009), IANB (McLean 1993), and high-tuberosity maxillary second

division nerve block (Forloine 2010). Data were also included for canine teeth using infraorbital blocks (Berberich 2009), as well as for central incisors using palatal-anterior superior alveolar injections (Burns 2004). Pooling suggested no evidence of a difference between lidocaine and mepivacaine (RR 0.92, 95% CI 0.83 to 1.02), with evidence of moderate heterogeneity between studies (P = 0.09, I^2 = 48%). The test for subgroup differences revealed evidence of little heterogeneity (P = 0.2, I^2 = 32%).

We downgraded the outcome two levels from high to low quality owing to imprecision (sample size of 208 participants/416 episodes of anaesthesia and 296 events) and indirectness (success defined in three studies - Berberich 2009; Burns 2004; Mason 2009 - as only two negative responses, and in one study - Abdulwahab 2009 - as only one negative response to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of three cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 13.2). The three pooled studies included 85 participants (170 episodes of dental anaesthesia) in total (Berberich 2009; Mason 2009; McLean 1993). Data were included for first molars using maxillary buccal infiltration (Mason 2009), canines using infraorbital nerve block (Berberich 2009), and first molars using IANB (McLean 1993). Pooling favoured mepivacaine over lidocaine (MD -1.23 minutes, 95% CI -2.31 to -0.16 minutes), with evidence of no heterogeneity between studies (P = 0.88, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.88, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (sample size of 85 participants/170 episodes of anaesthesia) and indirectness (pulp testing is repeated at intervals that are large compared with onset times measured, and clinical anaesthesia may be present at less than maximum pulp tester readings)

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

3% mepivacaine plain versus 2% lidocaine, 1:50,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of maxillary teeth with healthy pulps, tested with an electric pulp tester (Analysis 14.1). The two pooled studies included 70 participants (140 episodes of dental anaesthesia) in total (Berberich 2009; Mason 2009). Data were included for first molars using maxillary buccal infiltration (Mason 2009), and for canine teeth using infraorbital block (Berberich 2009). Pooling suggested no evidence of a difference between lidocaine and mepivacaine (RR 0.97, 95% CI 0.88 to 1.07), with evidence of no heterogeneity between studies (P = 0.58, I^2 = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.59, I^2= 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (sample size of 70 participants/140 episodes of anaesthesia and 128 events) and indirectness (success defined in two studies - Berberich 2009; Mason 2009 - as only two negative responses to maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 14.2). The two pooled studies included 58 participants (116 episodes of dental anaesthesia) in total (Berberich 2009; Mason 2009). Data were included for first molars using maxillary buccal infiltration (Mason 2009), and for canines using infraorbital nerve block (Berberich 2009). Pooling suggested no evidence of a difference between formulations (MD -0.56 minutes, 95% CI -1.54 to 0.42 minutes), with evidence of no heterogeneity between studies (P = 0.62, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.62, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (95% CI includes no effect and an appreciable benefit for 3% mepivacaine plain, sample size of 58 participants/116 episodes of anaesthesia) and indirectness (pulp testing is repeated at intervals that are large compared with onset times measured, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 3: adverse effects: local and systemic

No data from the included studies were available.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

2% mepivacaine, 1:20,000 levonordefrin versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other

appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus

No data from the included studies were available for meta-analysis. We have summarized the data for this outcome in Table 6.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two parallel studies measuring the duration of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 15.1). The two pooled studies included 458 participants (458 episodes of dental anaesthesia) in total (Albertson 1963; Sadove 1962). Types and specific sites of injection were not stated. Pooling suggested no evidence of a difference between lidocaine and mepivacaine (MD 4.43 minutes, 95% CI -10.63 to 19.48 minutes), with evidence of no heterogeneity between studies (P = 0.80, I^2 = 0%).

We downgraded the outcome three levels from high to very low quality because of study limitations (both studies had high risk of attrition bias), imprecision (95% confidence interval includes no effect and an appreciable benefit for both solutions), and indirectness (soft tissue anaesthesia is a poor indicator of duration of clinical anaesthesia).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experience: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% articaine, 1:200,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 16.1). The two pooled studies included 28 participants (56 episodes of dental anaesthesia) in total (Abdulwahab 2009; Ruprecht 1991). Data were included for first molars using mandibular buccal infiltration (Abdulwahab 2009), and for central incisors using maxillary labial infiltration (Ruprecht 1991). Pooling suggested no evidence of a difference between lidocaine and articaine (RR 1.33, 95% CI 0.33 to 5.36), with evidence of substantial heterogeneity between studies (P = 0.02, I^2= 81%). The test for subgroup differences revealed evidence of little heterogeneity (P = 0.27, I^2 = 17%).

We downgraded the outcome three levels from high to very low quality owing to study limitations, including one trial - Ruprecht 1991 - that reported unclear methods of randomization sequence generation, allocation concealment, and blinding of outcome assessors. Imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations, sample size of 28 participants/56 episodes of anaesthesia and 29 events), inconsistency (substantial heterogeneity), and indirectness (success defined in one study - Abdulwahab 2009 - as only one negative response to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings) were also present.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 16.2). The two pooled studies included 40 participants (80 episodes of dental anaesthesia) in total (Ruprecht 1991; Tortamano 2013). Data were included for central incisors using maxillary labial infiltration (Ruprecht 1991), and mandibular molars using IANB (Tortamano 2013). Pooling suggested no evidence of a difference between lidocaine and articaine (MD 0.19 minutes, 95% CI -2.06 to 2.45 minutes), with evidence of substantial heterogeneity between studies (P = 0.02, I^2 = 80%). The test for subgroup differences revealed substantial heterogeneity (P = 0.02, I^2 = 80%).

We downgraded the outcome three levels from high to very low quality because of study limitations (unclear risks of selection and detection bias - Ruprecht 1991, imprecision (95% confidence interval includes no effect and an appreciable benefit for both solutions, sample size of 40 participants/80 episodes of anaesthesia), indirectness (pulp testing is repeated at intervals that are large compared with the onset times measured, with clinical anaesthesia possibly present at less than maximum pulp tester readings), and inconsistency (substantial heterogeneity).

We pooled the results of two cross-over studies measuring the duration of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 16.3). The two pooled studies included 40 participants (80 episodes of dental anaesthesia) in total (Ruprecht 1991; Tortamano 2013). Data were included for central incisors using maxillary labial infiltration (Ruprecht 1991), and for mandibular molars using IANB (Tortamano 2013). Pooling suggested no evidence of a difference between lidocaine and articaine (MD 10.33 minutes, 95% CI -22.08 to 42.74 minutes), with evidence of considerable heterogeneity between studies (P = 0.002, I^2 = 89%). The test for subgroup differences revealed considerable heterogeneity (P = 0.002, I^2 = 89%).

We downgraded the outcome three levels from high to very low quality because of study limitations, as one trial had unclear risks of selection, performance, and detection bias (Ruprecht 1991). Imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations, sample size of 40 participants/80 episodes of anaesthesia), inconsistency (considerable heterogeneity), and indirectness (clinical anaesthesia may be present at less than maximum

pulp tester readings) were also present.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% articaine, 1:100,000 epinephrine versus 2% lidocaine, 1:80,000 epinephrine

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus

No data from the included studies were available for meta-analysis. We have summarized the data for this outcome in Table 6.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two studies measuring the onset of local anaesthesia of mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 17.1). The cross-over study - Arrow 2012 - and the parallel study - Naik 2017 - included 116 participants (125 episodes of dental anaesthesia) in total. Data were included for subjective testing of soft tissues using IANB. Pooling favoured articaine over lidocaine (MD -0.78 minutes, 95% CI -1.04 to -0.52 minutes), with evidence of little heterogeneity (P = 0.26, I^2 = 21%).

We downgraded the outcome three levels from high to very low quality owing to study limitations (unclear risk of performance and high risk of detection bias (Naik 2017), and high risk of attrition bias (Arrow 2012)), imprecision (sample size of 116 participants/125 episodes of anaesthesia), and indirectness (soft tissue anaesthesia is a poor indicator of onset of clinical anaesthesia).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% articaine, 1:200,000 epinephrine versus 4% prilocaine, 1:200,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of three cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 18.1). The three pooled studies included 97 participants (194 episodes of dental anaesthesia) in total (Abdulwahab 2009; Haas 1990; Haas 1991). Data were included for mandibular first molars (Abdulwahab 2009), and for mandibular and maxillary second molars (Haas 1991), using buccal infiltration, and for mandibular and maxillary canine teeth using buccal infiltration (Haas 1990). Pooling suggested no evidence of a difference between prilocaine and articaine (RR 1.15, 95% CI 0.93 to 1.41), with no heterogeneity between studies (P = 0.80, I^2 = 0%). No evidence of a difference was seen between formulations for maxillary infiltration (RR 1.03, 95% CI 0.83 to 1.28, P = 0.78, I^2 = 0%) and mandibular infiltration (RR 1.29, 95% CI 0.89 to 1.87, P = 0.93, I^2 = 0%). The test for subgroup differences also revealed little heterogeneity (P = 0.31, I^2 = 5%).

We downgraded the outcome three levels from high to very low quality because of study limitations, including unclear randomization sequence generation, allocation concealment, and blinding of outcome assessors (Haas 1990; Haas 1991). Indirectness (success defined in three studies - Abdulwahab 2009; Haas 1990; Haas 1991 - as only one negative response to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings) and imprecision (95% CI includes no effect and suggests an appreciable benefit for 4% articaine, 1:200,000 epinephrine, sample size of 97 participants/194 episodes of anaesthesia/118 events) were also present.

Primary outcome 2: speed of onset and duration of anaesthesia

No data from the included studies were available for meta-analysis. We summarized the data for these outcomes in Table 1 and Table 2.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% prilocaine, 1:200,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 19.1). The two pooled studies included 48 participants (96 episodes of dental anaesthesia) in total (Abdulwahab 2009; Katz 2010). Data were included for first molars using maxillary - Katz 2010 - and mandibular - Abdulwahab 2009 - buccal infiltration. Pooling suggested no evidence of a difference between lidocaine and prilocaine (RR 1.14, 95% CI 0.91 to 1.43), with no heterogeneity between studies (P = 0.76, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.80, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (95% CI includes no effect and suggests an appreciable benefit for 4% prilocaine, 1:200,000 epinephrine, sample size of 49 participants/96 episodes of anaesthesia/60 events) and indirectness (success defined in both studies as only two negative responses to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 19.2). The two pooled studies included 39 participants (76 episodes of dental anaesthesia) in total (Hinkley 1991; Katz 2010). Data were included for first molars using maxillary buccal infiltration (Katz 2010), as well as for IANB (Hinkley 1991). Pooling suggested no evidence of a difference between lidocaine and prilocaine (MD -1.19 minutes, 95% CI -3.08 to 0.70 minutes), with no heterogeneity between studies (P = 0.37, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.37, I^2 = 0%).

We downgraded the outcome two levels from high to low quality because of imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations, sample size of 39 participants/76 episodes of anaesthesia) and indirectness (pulp testing is repeated at intervals that are large compared with onset times measured, with clinical anaesthesia possibly present at less than maximum pulp tester readings).

We pooled the results of two studies measuring the speed of onset of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 19.3). Pooled results of a parallel study - Chilton 1971 - and a cross-over study - Hinkley 1991 - included 421 participants (449 episodes of dental anaesthesia) in total. Infiltrations were assumed to be pooled from both jaws in the parallel study, with IANB used in the cross-over study. Testing was done by using a gingival stick or subjective testing, depending on which occurred first, in the study by Hinkley 1991. It was assumed that subjective anaesthesia would occur before anaesthesia using gingival sticks. Subjective testing was used in the other study (Chilton 1971). Pooling suggested no evidence of a difference between lidocaine and prilocaine (MD -0.01 minutes, 95% CI -0.14 to 0.11 minutes), with evidence of no heterogeneity between studies (P = 0.86, I^2 = 0%). Pooling of just IANB data also suggested no evidence of a difference between lidocaine and prilocaine (MD -0.10 minutes, 95% CI -0.43 to 0.24 minutes), with no heterogeneity between studies (P = 0.83, I^2 = 0%). The test for subgroup differences revealed no heterogeneity (P = 0.61, I^2 = 0%).

We carried out a sensitivity analysis (Table 9) that excluded the cross-over study Hinkley 1991, whose data were not paired, which resulted in Chilton 1971 becoming an orphan study (MD -0.01, 95% CI -0.14 to 0.11).

We downgraded the outcome two levels from high to low quality because of study limitations, as one trial - Chilton 1971 - had unclear risks of selection bias, and because of indirectness (soft tissue anaesthesia is a poor indicator of onset of clinical anaesthesia).

We pooled the results of two studies measuring the duration of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 19.4). The two pooled, parallel studies included 533 participants (533 episodes of dental anaesthesia) in total (Chilton 1971; Epstein 1969). Data were included for subjective soft tissue anaesthesia using maxillary buccal infiltration (Epstein 1969), IANB (Chilton 1971; Epstein 1969), and pooled infiltrations from either jaw (Chilton 1971). Pooling suggested no evidence of a difference between lidocaine and prilocaine (MD -11.80 minutes, 95% CI -27.76 to 4.16 minutes), with evidence of substantial heterogeneity between studies (P = 0.05, I^2 = 61%). Pooling of just IANB data also suggests no evidence of a difference between lidocaine and prilocaine (MD 2.19 minutes, 95% CI -12.26 to 16.65 minutes), with no heterogeneity between studies (P = 0.49, I^2 = 0%). The test for subgroup differences revealed substantial heterogeneity (P = 0.03, I^2 = 73%).

We downgraded the outcome three levels from high to very low quality because of study limitations, with both trials having unclear methods of randomization sequence generation and allocation concealment, and high risk of attrition bias. Imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations), indirectness (soft tissue anaesthesia is a poor indicator of duration of clinical anaesthesia), and inconsistency (substantial heterogeneity and wide variation of point estimates) were also present.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis were completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% articaine plain versus 4% articaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 20.1). The two pooled studies included 134 participants (268 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006). Data were included for maxillary central incisor teeth - Kammerer 2014 - and for first premolars - Moore 2006 - using maxillary buccal infiltration, and for mandibular canine teeth using IANB (Moore 2006). Pooling favoured 4% articaine, 1:100,000 epinephrine over 4% articaine plain (RR 0.61, 95% CI 0.38 to 0.97), with substantial heterogeneity between studies (P = 0.03, I^2 = 71%). Pooling of just the maxillary infiltration data suggested no evidence of a difference between formulations of articaine (RR 0.64, 95% CI 0.34 to 1.19, P = 0.08, I^2 = 68%). The test for subgroup differences revealed no heterogeneity (P = 0.65, I^2 = 0%).

We downgraded the outcome three levels from high to very low quality owing to imprecision (sample size of 134 participants/268 episodes of anaesthesia and 166 events) and indirectness (success defined in one study - Kammerer 2014 - as only one negative response, and in another study - Moore 2006 - as only three negative responses to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings). Inconsistency (substantial heterogeneity) was also present. Study limitations were evident with one study (Moore 2006), which had unclear risk of selection bias.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 20.2). The two pooled studies included 100 participants (167 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006). Data were included for central incisors - Kammerer 2014 - and for first premolars - Moore 2006 - using maxillary buccal infiltration, and for canines using IANB (Moore 2006). Pooling suggested no evidence of a difference between formulations of articaine (MD 0.13 minutes, 95% CI -0.54 to 0.80 minutes), with evidence of no heterogeneity between studies (P = 0.52, I^2 = 0%). Pooling of just maxillary infiltration data suggested no evidence of a difference between formulations of articaine (MD 0.14, 95% CI -0.61 to 0.88, P = 0.26, I^2 = 22%). The test for subgroup differences revealed no heterogeneity (P = 0.97, I^2 = 0%).

We downgraded the outcome three levels from high to very low quality because of study limitations, with both trials having high risk of attrition bias and one - Moore 2006 - having unclear risk of selection bias. Imprecision was present (95% confidence interval includes no effect and an appreciable benefit for both solutions, sample size of 100 participants/167 episodes of anaesthesia), as was indirectness (pulp testing is repeated at intervals that are large compared with onset times measured, and clinical anaesthesia may be present at less than maximum pulp tester readings).

We pooled the results of two cross-over studies measuring the duration of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 20.3). The two pooled studies included 100 participants (167 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006). Data were included for central incisors - Kammerer 2014 - and for first premolars - Moore 2006 - using maxillary buccal infiltration, and for canines using IANB (Moore 2006). Pooling favoured 4% articaine, 1:100,000 epinephrine over 4% articaine plain (MD -37.08 minutes, 95% CI -60.95 to -13.21 minutes), with substantial heterogeneity between studies (P = 0.004, I^2 = 82%). Pooling of just maxillary infiltration data also favoured 4% articaine with 1:100,000 epinephrine over 4% articaine plain (MD -45.85 minutes, 95% CI -76.25 to -15.45 minutes, P = 0.003, I^2 = 89%). The test for subgroup differences revealed moderate heterogeneity (P = 0.12, I^2 = 58%).

We downgraded the outcome three levels from high to very low quality because of study limitations, with both trials having high risk of attrition bias and one study having unclear risk of selection bias, imprecision (sample size of 100 participants/167 episodes of anaesthesia), inconsistency (substantial heterogeneity), and indirectness (clinical anaesthesia may be present at less than maximum pulp tester readings) (Moore 2006).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% articaine plain versus 4% articaine, 1:200,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 21.1). The two pooled studies included 134 participants (268 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006). Data were included for maxillary first premolars (Moore 2006), and for central incisors (Kammerer 2014), using maxillary buccal infiltration, and for mandibular canine teeth using IANB (Moore 2006). Pooling suggested no evidence of a difference between formulations of articaine (RR 0.58, 95% CI 0.33 to 1.01), with substantial heterogeneity between studies (P = 0.006, I^2 = 80%). Pooling of just maxillary study data also suggested no evidence of a difference between formulations of articaine (RR 0.64, 95% CI 0.34 to 1.22, P = 0.07, I^2 = 69%). The test for subgroup differences revealed no heterogeneity (P = 0.44, I^2

= 0%).

We downgraded the outcome three levels from high to very low quality owing to imprecision (95% confidence interval includes no effect and an appreciable benefit for 4% articaine, 1:200,000 epinephrine, sample of 134 participants/268 episodes of anaesthesia and 169 events) and indirectness (success defined in one study - Kammerer 2014 - as only one negative response, and in another study - Moore 2006 - as only three negative responses to the maximum electric pulp tester output not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings). Inconsistency (substantial, unexplained heterogeneity) and study limitations (one study - Moore 2006 - had unclear risk of selection bias) were also present.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two cross-over studies measuring the onset of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 21.2). The two pooled studies included 102 participants (169 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006). Data were included for central incisors (Kammerer 2014), and for first premolars (Moore 2006), using maxillary buccal infiltration, and for canines using IANB (Moore 2006). Pooling suggested no evidence of a difference between formulations of articaine (MD 0.03 minutes, 95% CI -0.66 to 0.71 minutes), with evidence of little heterogeneity between studies (P = 0.23, I^2 = 32%). Pooling of just maxillary infiltration data also suggested no evidence of a difference between formulations (MD 0.14 minutes, 95% CI -0.63 to 0.91 minutes, P = 0.11, I^2 = 61%). The test for subgroup differences revealed no heterogeneity (P = 0.53, I^2 = 0%).

We downgraded the outcome three levels from high to very low quality because of study limitations (both trials had high risk of attrition bias, and one - Moore 2006 - had unclear risk of selection bias) and imprecision (95% confidence interval includes no effect and an appreciable benefit for both formulations, sample size of 102 participants/169 episodes of anaesthesia). Indirectness (pulp testing is repeated at intervals that are large compared with the onset times measured, and clinical anaesthesia may be present at less than maximum pulp tester readings) was also present.

We pooled the results of two cross-over studies measuring the duration of local anaesthesia of maxillary and mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 21.3). The two pooled studies included 102 participants (169 episodes of dental anaesthesia) in total (Kammerer 2014; Moore 2006). Data were included for central incisors (Kammerer 2014), and for first premolars (Moore 2006), using maxillary buccal infiltration, and for canines using IANB (Moore 2006). Pooling favoured 4% articaine, 1:200,000 epinephrine over 4% articaine plain (MD -28.36 minutes, 95% CI -42.06 to -14.65 minutes), with evidence of substantial heterogeneity between studies (P = 0.04, I^2 = 70%). Pooling of just maxillary infiltration data also favoured 4% articaine, 1:200,000 epinephrine over 4% articaine plain (MD -32.88 minutes, 95% CI -44.12 to -21.65 minutes, P = 0.09, I^2 = 65%).The test for subgroup differences revealed substantial heterogeneity (P = 0.05, I^2 = 75%).

We downgraded the outcome three levels from high to very low quality because of study limitations (both trials had high risk of attrition bias, and one study - Moore 2006 - had unclear risk of selection bias), imprecision (sample size of 102 participants/169 episodes of anaesthesia), inconsistency (substantial heterogeneity), and indirectness (clinical anaesthesia may be present at less than maximum pulp tester readings).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% prilocaine, 1:200,000 epinephrine versus 4% prilocaine plain

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus

No data from the included studies were available for meta-analysis. We have summarized the data for this outcome in Table 5.

Primary outcome 2: speed of onset and duration of anaesthesia

We pooled the results of two parallel studies measuring the duration of local anaesthesia of maxillary and mandibular soft tissues, using the simulated scenario testing of soft tissues (Analysis 22.1). The two pooled studies included 506 participants (506 episodes of dental anaesthesia) in total. Testing was done by using subjective self-reporting for maxillary infiltration (Epstein 1969), IANB (Chilton 1971; Epstein 1969), or buccal infiltration data combined from both jaws (Chilton 1971). Pooling favoured 4% prilocaine, 1:200,000 epinephrine over 4% prilocaine plain (MD 18.78 minutes, 95% CI 9.02 to 28.54 minutes), with evidence of no heterogeneity between studies (P = 0.62, I^2 = 0%). The test for subgroup differences revealed evidence of no heterogeneity (P = 0.70, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to study limitations (both studies had unclear methods of randomization sequence generation and allocation concealment and high risk of attrition bias) and indirectness (soft tissue anaesthesia is a poor indicator of duration of clinical anaesthesia).

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

4% prilocaine, 1:200,000 epinephrine versus 4% articaine, 1:100,000 epinephrine

Primary outcome 1: success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester

We pooled the results of two cross-over studies measuring the success of local anaesthesia of mandibular teeth with healthy pulps, tested with an electric pulp tester (Analysis 23.1). The two pooled studies included 78 participants (156 episodes of dental anaesthesia) in total (Abdulwahab 2009; Nydegger 2014). Data were included for mandibular first molars using buccal infiltration. Pooling favoured 4% articaine, 1:100,000 epinephrine over 4% prilocaine, 1:200,000 epinephrine (RR 1.74, 95% CI 1.16 to 2.60), with evidence of no heterogeneity between studies (P = 0.99, I^2 = 0%).

We downgraded the outcome two levels from high to low quality owing to imprecision (sample size of 78 participants/156 episodes of anaesthesia and 63 events). Indirectness (success defined in one study - Abdulwahab 2009 - as one negative response in 20 minutes, and in another study - Nydegger 2014 - as only two negative responses to maximum electric pulp tester output during the study not sustained over a period typical of a clinical procedure, with clinical anaesthesia possibly present at less than maximum pulp tester readings) was also present.

Primary outcome 2: speed of onset and duration of anaesthesia

No data from the included studies were available for meta-analysis. We have summarized the data for this outcome in Table 1.

Primary outcome 3: adverse effects: local and systemic

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore no meta-analysis was completed. We have summarized the data for these outcomes in Table 7.

Secondary outcome 1: participants' experiences: these include but are not limited to preference, overall experience

No data from the included studies were available.

Other comparisons with 100% success in all studies

Primary outcome 1: success of local anaesthesia, measured by the absence of pain during a procedure using a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus.

A number of outcomes measured the success of soft tissue anaesthesia using subjective self-reporting, when all studies reported 100% success for each formulation of local anaesthetic. These outcomes did not require meta-analysis to determine that there was no difference in efficacy between them. The outcomes and studies are listed below.

2% lidocaine, 1:100,000 epinephrine versus 2% lidocaine, 1:80,000 epinephrine

- Mandibular buccal infiltration (Dagher 1997): 30/30 vs 30/30
- IANB (Yared 1997): 30/30 vs 30/30

2% lidocaine, 1:100,000 epinephrine versus 2% lidocaine, 1:50,000 epinephrine

- Infraorbital nerve block (Berberich 2009): 40/40 vs 40/40
- Mandibular buccal infiltration (Dagher 1997): 30/30 vs 30/30; Yonchak 2001: 40/40 vs 40/40
- IANB (Yared 1997): 30/30 vs 30/30; Wali 2010: 30/30 vs 30/30

2% lidocaine, 1:50,000 epinephrine versus 2% lidocaine, 1:80,000 epinephrine

- Mandibular buccal infiltration (Dagher 1997): 30/30 vs 30/30
- IANB (Yared 1997): 30/30 vs 30/30

2% lidocaine, 1:100,000 epinephrine versus 3% mepivacaine plain

- Infraorbital nerve block (Berberich 2009): 40/40 vs 40/40
- IANB (Cohen 1993): 27/27 vs 34/34; McLean 1993: 30/30 vs 30/30

2% lidocaine, 1:100,000 epinephrine versus 0.5% bupivacaine, 1:200,000 epinephrine

- IANB (Sampaio 2012): 35/35 vs 35/35; Fernandez 2005: 39/39 vs 39/39

2% lidocaine, 1:100,000 epinephrine versus 2% mepivacaine, 1:100,000 epinephrine

- IANB (Allegretti 2016): 22/22 vs 22/22; Visconti 2016: 21/21 vs 21/21

Discussion

Summary of main results

The main aim of this systematic review was to evaluate the success, speed of onset, duration, and incidence of systemic and local adverse effects among patients using different local anaesthetic formulations for dental anaesthesia.

We included 123 studies (19,223 participants recruited) in the review, of which we pooled the data from 68 studies (6615 participants) for meta-analysis for the primary outcomes of success, onset, and duration of local anaesthesia. Data unsuitable for meta-analyses were derived from orphan studies (57 studies), or from those that had unusable data or paired data from cross-over studies that were not available (80 studies). The quality of outcomes ranged from moderate to very low.

Success of anaesthesia

For outcomes for which clinical study data were pooled, three comparisons showed one formulation to be superior to another when the success of anaesthesia was measured. Researchers found that 4% articaine, 1:100,000 epinephrine was superior to 2% lidocaine, 1:100,000 epinephrine when root canal treatment was performed in teeth with irreversible pulpitis. Evidence showed no difference when inferior alveolar nerve block injections (IANBs) were used to test the same formulations. When surgical procedures and surgical procedures/periodontal treatment were performed, 2% lidocaine, 1:100,000 epinephrine was superior to 3% prilocaine, 0.03 IU felypressin and 4% prilocaine plain, respectively. However, researchers found no evidence of a difference when IANBs were used in testing 2% lidocaine, 1:100,000 epinephrine versus 4% prilocaine plain.

Studies provided no evidence of a difference between 4% articaine, 1:100,000 epinephrine and both 2% mepivacaine, 1:100,000 and 4% articaine, 1:200,000 epinephrine for extracting teeth and performing surgical procedures, respectively, and between 0.5% bupivacaine, 1;200,000 epinephrine and both 4% articaine, 1:200,000 epinephrine and 2% lidocaine, 1:100,000 epinephrine for extracting teeth. Results showed no evidence of a difference between 2% lidocaine, 1:100,000 epinephrine and 2% mepivacaine, 1:100,000 when root canal treatment was performed in teeth with irreversible pulpitis.

For outcomes that pooled data from simulated scenario studies, we often downgraded quality owing to indirectness. We did this because the criteria for success in studies testing pulpal anaesthesia with an electric pulp tester or cold stimulus failed to replicate the duration of painful stimulation found in a clinical study, and because electric pulp testing may have underestimated successful anaesthesia. We also downgraded self-assessed, soft tissue anaesthesia, as it is a poor indicator of clinical anaesthetic success.

Onset and duration of anaesthesia

No clinical studies met our outcome definition. We downgraded the quality ratings of simulated scenario testing of these outcomes owing to indirectness. We did this because self-assessed soft tissue anaesthesia was a poor indicator of clinical anaesthesia, and because the intervals between testing, when an electric pulp tester was used to measure onset of anaesthesia, were relatively long when compared with the onset times measured. Also, electric pulp testing may have underestimated successful anaesthesia. When testing involved a simulated scenario, the speed of onset for the different local anaesthetics was within clinically acceptable times, while the duration of each local anaesthetic solution was variable, making them suitable for different applications.

Adverse effects

When 4% articaine, 1:100,000 epinephrine and 2% lidocaine, 1:100,000 epinephrine were compared, results showed no difference in pain on injection, while the injection of lidocaine resulted in less pain than articaine following the disappearance of anaesthesia, although clinically the difference was minor. Apart from this comparison, unwanted effects were rare. We were unable to combine data for these outcomes because of the different ways that adverse effects were measured in each study.

Participants' experience of the procedures carried out

Participants' experience of procedures was not assessed owing to lack of data.

Overall completeness and applicability of evidence

We identified 123 studies, conducted in a range of settings in 19 different countries, of which 68 were suitable for meta-analysis. Despite a thorough, structured search of bibliographic databases, handsearching of journals and bibliographies, and a search of other resources, three other published systematic reviews revealed 27 journal articles that we had not identified (Su 2014a; Su 2014b; Su 2016). These were almost certainly found in Chinese databases (the Chinese BioMedical Literature Database and the China National Knowledge Infrastructure), which were referenced in the three reviews, and to whcih we did not have access. We have included them in the Characteristics of studies awaiting classification table, and when this review is updated, we will locate, translate, and include these journal articles. Another published systematic review, Xiao 2010, referenced a further six Chinese parallel trials that were cited in Chinese. An attempt will be made to locate and translate them. Their inclusion may introduce more bias into the review, as the systematic reviews that have assessed these studies - Su 2014a and Su 2014b - have, with few exceptions - Chen 2004 and Shi 2002 - reported unclear risks of all types of bias during their assessment. Lack of access to foreign databases and problems of language may limit the number of studies that can be included in systematic reviews. However, these problems are not unique to this review, and the review authors are not aware at present of any other source of studies that could be included in this review for quantitative and qualitative assessment.

Of the 68 cross-over studies identified, three had their paired success data presented in 2 × 2 tables that could be combined with data from parallel studies (Arrow 2012; Porto 2007; Sancho-Puchades 2012). We attempted to contact authors of the remaining cross-over studies to request paired data. Of these, four study authors provided the data for five studies (Batista da Silva 2010; Bouloux 1999; Jaber 2010; Kanaa 2006; Trullenque-Eriksson 2011). Two further studies - Colombini 2006 and Laskin 1977 - had success data showing that the events in each local anaesthetic group

differed by one (19/20 vs 20/20 and 7/8 vs 8/8, respectively); therefore we were able to calculate the paired values. When no events were observed in one of the trial arms (Bouloux 1999; Colombini 2006; Jaber 2010; Kanaa 2006; Laskin 1977), cell counts of zero occurred when paired data were used. Therefore we adopted the principle recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) and added 0.5 to each cell value in the 2 × 2 table, to allow entry into Microsoft Excel. We could not use data from the remaining cross-over studies in this way; instead we treated them as parallel studies and included them in the meta-analysis.

For the outcomes of onset and duration of local anaesthesia, the data were continuous and were again present in parallel and cross-over trials. To include in the meta-analysis a cross-over study with continuous data, it is necessary to have the mean difference (A – B) and its standard error, preferably with the mean and standard error of each of A and B. This information was not available; therefore, we treated the cross-over studies as if they were parallel studies in the meta-analysis.

For both dichotomous and continuous data, it is possible to estimate the overall effect of interest in the meta-analysis by incorporating cross-over study data as if they came from parallel studies, but the standard errors are wider, and hence the confidence intervals are wider than they would be if the cross-over studies were recognized as such. For this reason, we conducted a sensitivity analysis after removing data from cross-over studies from the meta-analysis for dichotomous and continuous data, when present.

We could not use data from 80 studies for some analyses for a variety of reasons.

For dichotomous data:

- criteria for local anaesthetic success included no pain and mild pain, when it was impossible to calculate the success for just no pain;
- data calculations were unclear;
- data were presented as continuous data;
- testing methods were not reported; and
- the study provided a mixture of parallel and cross-over data (Keskitalo 1975).

For continuous data:

- standard deviations or standard errors were not reported; and
- it was unclear whether a standard error or a standard deviation was reported in the journal article.

We have listed the data for these and orphan studies in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6.

We originally asked a broad question rather than a focused one because we did not fully know the scope of our search. The 15 commercially available local anaesthetics that are available for dental use gave rise to an enormous number of different comparisons. If the comparisons are grouped, depending on the tissues or methods of testing used, and are further divided into jaw type as in Table 10, more than 2000 different comparisons were possible. However, some of the local anaesthetic formulations would not be suitable for certain clinical uses (e.g. bupivacaine, which is long-acting, would not be used for dental procedures that have a short duration). The scope of this work is huge and may be thought of as too great to be managed in a single systematic review when attempts are made to compare all commercially available local anaesthetics.

We graded no outcomes as high quality, four outcomes as moderate quality, and most outcomes as low (23) or very low quality (30). Therefore, the evidence for evaluating dental local anaesthesia in this review is very limited and should be interpreted with caution. Remaining evidence is available only in the form of orphan studies, or lacks the appropriate data to make more definitive conclusions possible.

Quality of the evidence

Using the GRADE approach resulted in four outcomes rated as moderate quality (Analysis 1.3; Analysis 1.8; Analysis 1.9; Analysis 2.1), 23 rated as low quality, and 30 rated as very low quality.

Study limitations were present in 41 outcomes, and downgrading occurred if there was high risk of bias or if unclear risks existed that may have had an impact on the outcomes. The most common reasons for this were noted in studies with unclear risk of randomization sequence generation, concealment of the allocation process, and blinding of participants, personnel, and outcome assessors. A small number of studies provided incomplete outcome data.

Eleven studies had received industry sponsorship, although we did not downgrade them owing to publication bias, as the sponsors manufactured both control and test formulations.

We often downgraded outcomes owing to imprecision because of the small overall numbers of participants and events. For dichotomous outcomes, only five out of 26 outcomes had over 300 successful dental anaesthesia events, and for continuous outcomes, only nine out of 31 outcomes had over 400 episodes of dental anaesthesia.

We downgraded outcomes owing to indirectness when measuring anaesthetic success, onset, and duration with an electric pulp tester. We did this because testing of pulp anaesthesia in this way required the maximum reading of an electric pulp tester as a sign of complete anaesthesia. Two studies have validated this (Certosimo 1996; Dreven 1987). However, clinical anaesthesia may still be present at lower readings than the maximum available, Therefore, onset times clinically may in fact be shorter than those obtained with an electric pulp tester. Clinical success and duration figures may also be greater than those measured by this method of testing, for the same reasons.

For pulpal anaesthesia onset, the shortest frequency of testing was one minute. As the onset of a number of local anaesthetic formulations was less than five minutes, this was regarded as a fairly insensitive way of determining

anaesthesia onset. However, apart from a direct clinical intervention (Kramer 1958; Mumford 1961; Nespeca 1976), which would involve stimulating dental tissues for several minutes for painful procedures before the start of clinical anaesthesia, it would be difficult to overcome this problem or suggest a better way of testing.

When measuring pulpal anaesthesia success with an electric pulp tester, many studies set their criterion for success as obtaining a negative response to the maximal output of the pulp tester within a set period of time, then maintaining this negative response for a period of time similar to the duration of a clinical procedure. However, other studies required only one (Abdulwahab 2009; Haas 1990; Haas 1991; Kammerer 2014; Kanaa 2012; Knoll-Kohler 1992a; Knoll-Kohler 1992b; Nordenram 1990; Srisurang 2011; Vahatalo 1993), two (Allegretti 2016; Batista da Silva 2010; Berberich 2009; Burns 2004; Caldas 2015; Costa 2005; Evans 2008; Forloine 2010; Gross 2007; Kanaa 2006; Katz 2010; Lawaty 2010; Maruthingal 2015; Mason 2009; McEntire 2011; Nydegger 2014; Oliveira 2004; Robertson 2007; Visconti 2016; Yonchak 2001), or three - Moore 2006 - consecutive negative responses to classify the anaesthetic as successful. As a result of this, the outcomes containing these studies were downgraded one level.

We did not include the outcome of anaesthetic success for diseased pulps with irreversible pulpitis, as a negative response to pulp testing is not a reliable indicator of pulpal anaesthesia (Dreven 1987).

We downgraded the outcomes of soft tissue anaesthesia success (Analysis 1.3; Analysis 7.2), onset (Analysis 1.6; Analysis 4.4; Analysis 5.2; Analysis 6.4; Analysis 17.1; Analysis 19.3), and duration (Analysis 1.7; Analysis 4.5; Analysis 5.3; Analysis 6.5; Analysis 15.1; Analysis 19.4; Analysis 22.1), as subjective self-assessed soft tissue anaesthesia alone is a poor indicator of clinical anaesthetic success.

We also downgraded many studies owing to inconsistency (high, unexplained heterogeneity). When possible, we attempted to investigate the cause of this by examining the factors mentioned in Assessment of heterogeneity.

Owing to the limited number of high and moderate outcomes, and the large numbers of low and very low quality outcomes presented in this review, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate for all measured outcomes,

Potential biases in the review process

There were no marginal decisions related to included studies and analysis of data that could have impacted this review. Types of interventions (infiltration and block anaesthesia), types of studies (parallel and cross-over), and subgroups used (maxillary, mandibular, both jaws combined/jaws not stated) related to primary injections of local anaesthetic were provided in all studies found in our searches. The only factor that may have excluded some data was our primary outcome: "success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus".

A number of studies defined success as the absence of pain or the presence of mild pain, which still allowed clinical procedures to be performed, albeit painfully. Study authors took the view that these findings are important to document in studies. In practice, it is common to experience a small degree of pain, despite using local anaesthetic, and still complete a dental procedure. However for this review, and from a patient perspective, any pain felt during a procedure when local anaesthetics were compared would be regarded as failure. Therefore, we used only the complete absence of pain ("no pain" or "0" on a VAS) to indicate local anaesthetic success. Outcomes of "no pain" and "0" on a VAS allow data to be pooled from different studies for meta-analysis, whereas outcomes of success from studies that include mild pain cannot be combined so easily, if mild pain is defined differently in each study. This resulted in the exclusion of data for eight studies (Hosseini 2016; Kambalimath 2013; Maniglia-Ferreira 2009; Nabeel 2014; Parirokh 2015; Pellicer-Chover 2013; Poorni 2011; Sherman 2008; Sood 2014; Yadav 2015).

Although the outcomes in our final review were slightly different from those defined in our protocol, changes were made to clarify the outcomes. Classifying outcomes in relation to the anaesthetized tissues under investigation and the method of testing used may have reduced the number of studies included in each comparison. However, the tissues and testing used were so different that review authors thought this was essential, as the individual outcomes would not be comparable. Changes did not result in any changes to studies nor to data included in the review.

A cross-over study design is often used when local anaesthetics are tested with some form of simulated scenario method, such as testing pulpal anaesthesia with an electric pulp tester. Alternatively, clinical dentistry may be performed using the same study design provided identical treatment can be provided in both arms of the study (e.g. extraction of similarly positioned third molar teeth).

The ideal approach for meta-analysis using dichotomous data from cross-over studies is to use their paired data (Elbourne 2002), which requires that success and failure for both arms of the study, for each individual, must be known. These data are rarely reported, and in this review only three cross-over studies reported the data in 2 × 2 tables to allow meta-analyses (Arrow 2012; Porto 2007; Sancho-Puchades 2012). Contacting authors for this missing data resulted in data provided for only five further studies (Batista da Silva 2010; Bouloux 1999; Jaber 2010; Kanaa 2006; Trullenque-Eriksson 2011). This meant that the anaesthetic success data for other cross-over studies could not have been pooled for meta-analyses using paired data.

For meta-analysis of cross-over studies with continuous data, it is necessary to have the mean difference between groups and its standard error, preferably along with the mean and standard error of each group. As these data were not available, we could not pool the data in that way for a number of studies.

An alternative approach is to treat cross-over studies as if they were parallel studies in the meta-analysis. It is possible to estimate the overall effect of interest using this approach in the meta-analysis, but the standard errors are larger and hence the confidence intervals wider than they would be if cross-over studies were recognized as such. We made the decision to do this while acknowledging this fact, but we also performed a sensitivity analysis, while removing the data from cross-over studies from the meta-analysis to assess the effect of their removal.

A further complication of using cross-over data is that success and failure data are needed for calculation of logs of odds ratios and hence for meta-analysis. Solutions that are 100% successful and therefore have 0% failure cannot have their data entered into the formula for calculation of odds ratios, as the numerator or denominator of the formula may contain 0, depending on which study is the control or experimental solution. This prevents their calculation in Microsoft Excel or using any other mathematical software. This would introduce bias into a review, as studies in which one or both solutions were 100% effective could not be included in meta-analyses. Although we were unable to obtain paired data for many studies, in those studies with 100% success for one solution, the paired data could be calculated. However, for the reasons stated above, their data could not be entered, unless the principle of adding 0.5 to each of the cells in the 2 × 2 table was applied (Higgins 2011b). We needed this to make this adjustment for only five studies, in three analyses: Jaber 2010 and Kanaa 2006 in Analysis 1.2, Bouloux 1999, and Laskin 1977 in Analysis 6.1, and Colombini 2006 in Analysis 7.1.

For those studies in which the success for both groups in a comparison was 100%, we entered data into the appropriate analyses. When all studies in an analysis had 100% success for both solutions, we did not complete meta-analysis. We entered the results of these studies, which looked at just the outcome of soft tissue anaesthesia success, at the end of Effects of interventions and in Table 6. We summarized in Table 6 the data from two studies - Knoll-Kohler 1992b and Ruprecht 1991 - that were meant to be added to an existing analysis (Analysis 1.2) measuring the success of pulpal anaesthesia using an electric pulp tester, when both local anaesthetics had 100% success. We did this because the data could not be entered as logs of the odds ratio (OR) and associated standard error (SE), using the 'inverse variance' method.

We reported on selection bias related to baseline characteristics of the groups being investigated. For sequence generation, among studies having low risk of bias (66), we needed clarification from their authors regarding the exact methods used to generate a random sequence in 49 studies. Although randomization was often referred to, the basic method of sequence generation was often missing, such as the use of computer software or random selection of local anaesthetic cartridges from a container. The main source of bias for this review was seen in studies for which risk was graded as high and studies for which the risk was unclear. In analyses containing any of the 54 studies with unclear risk of bias, the effect of this is unknown. Analyses containing data from these studies may have risk of selection bias, although the significance of this is unknown. One study used in meta-analysis had high risk of bias (Trullenque-Eriksson 2011), which means that we downgraded Analysis 5.1, Analysis 5.2, and Analysis 5.3 owing to study limitations.

For implementation of the randomization sequence (allocation concealment) in studies having low risk of bias (70), we needed clarification from study authors regarding the exact methods used to conceal a randomization sequence in 51 studies. Often, small but important details were missed in the report, such as how the sequence was kept hidden, and when it was eventually revealed. Therefore, Analysis 5.1, Analysis 5.2, and Analysis 5.3 have study limitations due to the inclusion of Trullenque-Eriksson 2011, which had high risk of bias; however, in those analyses containing any of the 50 studies with unclear risk of bias, the effect of this is unknown.

For performance bias (blinding of study participants and personnel), among those having low risk of bias (99), we needed clarification from study authors regarding exact methods used in 26 studies. For data analysis, one study had high risk of bias (Trullenque-Eriksson 2011). This means that Analysis 5.1, Analysis 5.2, and Analysis 5.3 have study limitations, and in those analyses containing any of the 23 studies with unclear risk of bias, the effect of this is unknown.

For blinding of outcome assessors among studies having low risk of bias (90), we needed clarification from study authors regarding exact methods used to blind outcome assessors in 25 studies. During meta-analysis, one study with high risk of bias was used (Naik 2017), which means that Analysis 17.1 has study limitations, and in those analyses containing any of the 30 studies with unclear risk of bias, the effect of this is unknown.

For randomization and blinding, the following numbers of journal articles were deficient in their reporting, which meant that we needed to seek clarification from study authors.

- Randomization sequence generation: 103/123 (84%).
- Randomization allocation concealment: 101/123 (82%).
- Blinding of participants and personnel: 49/123 (40%).
- Blinding of outcome assessors: 37/123 (30%).

These figures were surprisingly high, as 44 studies were published in journals endorsing the CONSORT guidelines for reporting of randomized trials, although some studies may have been published before the journal adopted these guidelines. Of the 49 journals represented in this review, 11 endorsed the CONSORT guidelines.

We rated the risk of attrition bias as low in 118 studies, unclear in 23 studies, and high in 12 studies.

An unclear level of reporting bias occurred in one study (Sancho-Puchades 2012), which was used for analysis owing to missing pulpal anaesthesia onset data.

We included in Analysis 4.5, Analysis 5.1, Analysis 5.2, Analysis 5.3, Analysis 15.1, Analysis 17.1, Analysis 19.4, Analysis 20.2, Analysis 20.3, Analysis 21.2, Analysis 21.3, and Analysis 22.1 studies that were graded as having high risk of bias.

Agreements and disagreements with other studies or reviews

Following our structured search, we identified nine other systematic reviews in peer-reviewed journals. Six compared articaine and lidocaine (Brandt 2011; Katyal 2010; Kung 2015; Paxton 2010; Su 2016; Xiao 2010), one compared bupivacaine with lidocaine (Su 2014a), one compared lidocaine and mepivacaine (Su 2014b), and one compared a variety of local anaesthetics and techniques to enhance local anaesthesia using an inferior alveolar nerve block for teeth with irreversible pulpitis (Corbella 2017). We identified in our search the studies included in these reviews. However, we did not include some owing to differing inclusion criteria such as looking at postoperative anaesthesia, using non-commercially available local anaesthetic solutions, and using supplemental anaesthetic techniques. A number of studies included in these systematic reviews had been screened as part of this review, but we did not include them because they did not appear to be randomized controlled trials (RCTs), or because specific data were not available (e.g. missing data for participants who had scores of zero when visual analogue scale scores were used (no pain)).

One systematic review - Xiao 2010 - found that for teeth with irreversible pulpitis, articaine anaesthetic success was superior to lidocaine when both jaws were combined (risk ratio (RR) 1.33, 95% confidence interval (CI) 1.23 to 1.44), and when maxillary anaesthesia was used (RR 1.65, 95% CI 1.38 to 1.98), but success was similar for mandibular anaesthesia (RR 1.28, 95% CI 0.97 to 1.69). Kung 2015 also found for teeth with irreversible pulpitis that articaine was more likely to achieve successful anaesthesia than lidocaine formulations for combined maxillary and mandibular injections (odds ratio (OR) 2.21, 95% CI 1.41 to 3.47) and for combined mandibular injections (OR 2.20, 95% CI1.40 to 3.44). This review also found no differences between formulations when used for maxillary infiltration (OR 3.99, 95% CI 0.50 to 31.62) or for mandibular block anaesthesia (OR 1.44, 95% CI 0.87 to 2.38). Su 2016 also favoured 4% articaine with 1:100,000 epinephrine over 2% lidocaine with 1:100,000 epinephrine in terms of success rates of anaesthesia for teeth with irreversible pulpitis (RR 1.10, 95% CI 1.10 1.19).

Despite differences in inclusion criteria, definitions of success, and anaesthetic formulations used, the Xiao 2010, Kung 2015, and Su 2016 reviews had similar results to ours. The Brandt 2011 review showed no evidence of a difference between formulations in terms of success in teeth with irreversible pulpitis (OR 1.61, 95% CI 0.74 to 3.53). This may have been due to inclusion of data from different studies and different types of included data. The Corbella 2017 review showed no evidence of a difference between formulations in terms of success when an inferior alveolar nerve block was used for teeth with irreversible pulpitis (RR 1.00, 95% CI 0.88 to 1.15, respectively). Results were similar to the results of this review, despite inclusion of data from additional studies.

When comparing 2% lidocaine, 1;100,000 epinephrine against 4% articaine, 1;100,000 epinephrine for pulpal anaesthesia, the Katyal 2010 review favoured articaine (RR 1.31, 95% CI of 1.12 to 1.54), as did the Paxton 2010 review, which was also available as the study author's master's thesis online (9.21% greater proportion of success, 95% CI 2.56% to 15.58%). The Brandt 2011 systematic review also showed the superiority of articaine over lidocaine for pulpal anaesthesia (OR 2.44, 95% CI 1.59 to 3.76). These findings were similar to ours.

In the Katyal 2010 review, the pain score (VAS) for 4% articaine, 1;100,000 epinephrine was similar to that for 2% lidocaine, 1;100,000 epinephrine during solution injection (mean difference (MD) -2.49, 95% CI -14.49 to 9.52) but favoured articaine in the Su 2016 review (MD -0.67, 95% CI -1.26 -0.08); these results differed from the findings of this review, possibly because the data for 4% articaine, 1;100,000 epinephrine from the study by Evans 2008 included in the review by Katyal 2010 were incorrect (mean = 22, rather than 44 in the journal article), and only data from an orphan study were used (Kanaa 2012) in the Su 2016 review.

In the Katyal 2010 review, injections of 4% articaine, 1;100,000 epinephrine resulted in a higher pain score (VAS) than injections of 2% lidocaine, 1;100,000 epinephrine at the injection site, when the local anaesthetic wore off (MD 6.49, 95% CI 0.02 to 12.96). Despite identical data, minor differences from this review (MD 6.41, 95% CI 1.01 to 11.80) occurred because the Katyal 2010 review used a 'random-effects' analysis model, as there were signs of statistical heterogeneity (I^2 = 30%), whereas we used a 'fixed-effect' analysis model in this review, as this level of heterogeneity might not be important.

The Su 2014a systematic review included a comparison assessing healthy pulps tested with an electric pulp tester, and showed that 0.5% bupivacaine, 1:200,000 epinephrine was less successful than 2% lidocaine, 1:100,000 epinephrine (OR 0.39, 95% CI 0.27 to 0.57). Our review showed no evidence of a difference, and this may be related to our definitions of success. There was no evidence of a difference in pulpal anaesthesia onset times between these formulations (MD 4.13, 95% CI -0.26 to 8.51), which differed from this review (MD 3.32, 95% CI 0.27 to 6.37), because that review pooled different teeth, rather than using the data for first molar teeth. Bupivacaine had a longer pulpal anaesthesia duration time than lidocaine (MD 102.59, 95% CI 87.49 to117.68). However, although this outcome used pulpal anaesthesia duration data (Fernandez 2005), the other study used soft tissue duration data (Moore 1983).

The systematic review of mepivacaine and lidocaine, when comparing pulpal anaesthetic success, reported similar findings to this review (Su 2014b). No evidence showed a difference between 3% mepivacaine plain and 2% lidocaine, 1:100,000 epinephrine (OR 0.71, 95% CI 0.51 to 1.00) or 2% lidocaine, 1:50,000 epinephrine (OR 0.82, 95% CI 0.58 to 1.17). The same was true of onset times.

When compared with 2% lidocaine, 1:100,000 epinephrine pulpal anaesthesia onset times were quicker with 3% plain mepivacaine (MD -1.13, 95% CI - 1.77 to -0.49), but no evidence suggested a difference with 2% mepivacaine with 1:20,000 levonordefrin (MD 0.20, 95% CI -2.87 to 3.27). When compared with 2% lidocaine, 1:50,000 epinephrine, 3% plain mepivacaine had a quicker pulpal anaesthesia onset time (MD -0.83, 95% CI -1.40 to -0.26), although our review found no evidence of a difference between formulations. This may be related to the data included, as numerous teeth were

investigated.

Authors' conclusions

Implications for practice

We do not have sufficient high-quality evidence to determine whether one formulation of local anaesthetic is more effective than another. The quality of our evidence ranged from very low to moderate. Only four outcomes were graded as moderate quality.

Only three outcomes showed one formulation to be superior to another when the success of anaesthesia was measured. Researchers found that 4% articaine, 1:100,000 epinephrine was superior to 2% lidocaine, 1:100,000 epinephrine when root canal treatment was performed in teeth with irreversible pulpitis (inferior alveolar nerve block injections (IANBs) showed no evidence of a difference). Study results showed that 2% lidocaine, 1:100,000 epinephrine was superior to 3% prilocaine, 0.03 IU felypressin and 4% prilocaine plain when surgical procedures and surgical procedures/periodontal treatment respectively, were performed. IANBs showed no evidence of a difference when 2% lidocaine, 1:100,000 epinephrine was compared with 4% prilocaine plain.

The only other outcomes testing clinical success showed no evidence of a difference between 4% articaine, 1:100,000 epinephrine and both 2% mepivacaine, 1:100,000 and 4% articaine, 1:200,000 epinephrine when teeth were extracted and surgical procedures were performed, respectively, nor between 0.5% bupivacaine, 1:200,000 epinephrine and both 4% articaine, 1:200,000 epinephrine and 2% lidocaine, 1:100,000 epinephrine when teeth were extracted. There was no evidence of a difference between 2% lidocaine, 1:100,000 epinephrine and 2% mepivacaine, 1:100,000 when root canal treatment was performed in teeth with irreversible pulpitis.

A large number of included trials were simulated scenario studies, which were often downgraded in quality owing to indirectness, because the testing method failed to adequately mimic what occurs in clinical practice. Therefore, their results should be interpreted with caution.

Implications for research

More studies are required that have clear reporting, low risk of bias, and an adequate sample size. Furthermore, studies should employ common validated methods with clinical outcome measures, when possible, and should provide data in a format that will allow meta-analysis.

Although studies in most comparisons showed consistent agreement in the size and direction of their effects, some showed differences between subgroups (injection types), which may be a reflection of differences in diffusion and retention of the bolus of the local anaesthetic solution when delivered in different ways. Any true differences between injection types were difficult to determine owing to the small sample sizes and therefore large confidence intervals present. For the same reasons, and because of the limited number of studies for some outcomes, it was not possible to determine whether results of any studies were outliers. This emphasises the importance of a sufficient sample size when further research is planned.

In our search, we found a substantial number of simulated scenario trials testing healthy pulps with an electric pulp tester. Although this type of study is convenient to carry out and provides a validated method of testing (Certosimo 1996; Dreven 1987), clinical anaesthesia may be present at values less than a maximum pulp tester reading, which is a common criterion for success. Also, for many clinical procedures, only a clinical intervention can be used to test the oral tissues anaesthetized. These tissues may be more successfully anaesthetized or less successfully anaesthetized than pulpal tissues tested with an electric pulp tester. The same applies to testing of soft tissues, as soft tissue anaesthesia does not necessarily reflect successful clinical anaesthesia, clinical onset, or clinical duration. However, despite the advantage of clinical procedures to test different formulations, certain outcomes such as pulpal onset and duration could be ethically measured only using a cold test or an electric pulp tester, as the alternative is to start treatment in initially unanaesthetized patients. Despite this, a few studies did adopt this latter method for measurement (Kramer 1958; Mumford 1961), although this method is unlikely to be adopted in current research.

Better reporting of randomized controlled trials is required. Although several journals have adopted the CONSORT standards, the basic information required for critical appraisal was often missing from journal articles. This occurred most commonly with randomization sequence generation and concealment and blinding of patients, personnel, and outcome assessors. Randomization is easy to perform, but actual reporting of the method used (e.g. toss of a coin, use of a computer programme) was missing in a surprisingly large number of studies. Despite this, we often were able to clarify the method used by contacting the trial author.

In older studies, blinding of local anaesthetic cartridges was poorly performed or was poorly reported, although actual masking of cartridges is relatively easy to perform.

Criteria for success varied between studies. For simulated scenario studies that tested pulps, this varied from one negative response to an electric pulp tester during the testing session (Abdulwahab 2009; Haas 1990; Haas 1991; Kammerer 2014; Kanaa 2012; Knoll-Kohler 1992a; Knoll-Kohler 1992b; Nordenram 1990; Srisurang 2011; Vahatalo 1993), to a sustained negative response for up to 60 minutes (Fernandez 2005; Haase 2008; Mikesell 2005; Wali 2010).

Differences in the criteria for success were also seen in clinical studies. Successful local anaesthesia could be classed as no pain experienced during a clinical procedure, or as no pain or mild pain experienced when a procedure could still be completed although pain was felt. Although treatment can be completed when patients experience mild pain, we took the view that successful local anaesthesia should include only those instances in which no pain is experienced. Patients receiving dental treatment do not want to experience pain, and dentists want the same for their patients; therefore including

mild pain as successful may be misleading. However in practice, a number of patients can experience pain while treatment is completed. Therefore, it is important to publish separately the results for study participants experiencing no pain or mild pain.

Criteria for success should be consistent between studies to reduce clinical heterogeneity. Testing in simulated scenario studies should be performed over a period similar to that seen in dental treatment. Journals publishing local anaesthesia research could set guidelines for this.

Some studies that gave IANB injections had participants eliminated or re-appointed for repeat testing if soft tissue anaesthesia was not achieved. This ensured that different local anaesthetics were compared for their anaesthetic properties rather than introducing other factors responsible for failure (e.g. differences in anatomy). This would seem reasonable, but dentists and patients may be unaware that repeat injections were given when success rates were stated. A local anaesthetic may fail for many reasons, and separating these out to allow better comparison of just the properties of different local anaesthetics may result in reporting of success rates that may not be achievable in clinical practice, especially when less strict criteria for success are applied.

Reporting of cross-over studies was the same as for parallel studies, in most cases using simple success and failure percentages with few exceptions (Arrow 2012; Porto 2007; Sancho-Puchades 2012). For these three studies, paired data were presented that made meta-analysis possible. Failure to publish cross-over data in this way and to obtain paired data after contacting study authors meant that many of these cross-over studies could not be used for meta-analysis by this method. Therefore, data in these studies should be comprehensively reported as paired data for inclusion in meta-analyses.

Outcomes reported in trials were varied, making combining data for meta-analysis difficult. Standardized sets of outcomes, or "core outcome sets", need to be developed as recommended in the COMET (Core Outcome Measures in Effectiveness Trials) initiative.

A poor response rate when study authors were contacted should also be mentioned. Unfortunately, this has resulted in meta-analyses that could not be completed and risk of bias that could not be clarified, leading to grading of a large number of studies as having unclear risk.

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Contributions of authors

Geoffrey St George (GST), Alyn Morgan (AM), John Meechan (JM), David R Moles (DM), Aviva Petrie (AP), Ian Needleman (IN), Yuan-Ling Ng (Y-LNg).

Conceiving the review: GST.
Co-ordinating the review: GST.
Undertaking manual searches: GST, AM.
Screening search results: GST, AM.
Organizing retrieval of papers: GST, AM.
Screening retrieved papers against inclusion criteria: GST, AM.
Appraising quality of papers: GST, AM.
Abstracting data from papers: GST, AM.
Writing to authors of papers for additional information: GST.
Providing additional data about papers: GST.
Obtaining and screening data on unpublished studies: GST, AM.
Managing data for the review: GST, AM.
Entering data into Review Manager (RevMan 2014): GST, AM.
Analysing RevMan statistical data: GST, DM, AP, Y-LNg.
Performing other statistical analysis not using RevMan: GST, DM, AP, Y-LNg.
Performing double entry of data: (data entered by person one: GST; data entered by person two: AM).
Interpreting data: GST, AM, IN, DM, AP, JM.
Performing statistical analysis: GST, DM, AP, Y-LNg.
Writing the review: GST, AM, IN, DM, JM, Y-LNg.
Securing funding for the review: GST.
Performing previous work that was the foundation of the present study: GST, JM.

Serving as guarantor for the review (one review author): GST.
Taking responsibility for reading and checking the review before submission: primarily GST, although all review authors were consulted.

Declarations of interest

Geoffrey St George: none known.

Alyn Morgan: none known.

John Meechan previously received research funding from Septodont, Astra, and Dentsply. At present, he has no research funding from any companies and will not be receiving any funding for this review. He was an author on three of the primary studies included in this review (Jaber 2010; Kanaa 2006; Kanaa 2012). Data for these studies were extracted by GSG and AM.

David R Moles: none known.

Ian Needleman: none known.

Yuan-Ling Ng: none known.

Aviva Petrie: none known.

Differences between protocol and review

We modified the title of the review from "Injectable local anaesthetics agents for operative dental anaesthesia" to “Injectable local anaesthetic agents for dental anaesthesia". Originally the word "operative" was meant to be used in relation to a surgical or non-surgical operation or intervention. As the word "operative" may confuse the reader into thinking that included studies relate only to operative dentistry and treatment of diseased teeth, we removed the word "operative" from the title.

We replaced the second author of the protocol (St George 2007), Sela Hussain, with Alyn Morgan for the full review. Also, we recruited two other authors - Yuan-Ling Ng and Aviva Petrie - to help with data handling and statistical analysis issues (pooling of cross-over study data). Contact details for David Moles have changed.

We updated the Background section of the main text to include more recent references to studies and up-to-date headings.

We included the following explanation of why the review was needed in the Why it is important to do this review section: "We are conducting this systematic review to determine which local anaesthetic solution is most successful for dental interventions owing to the current popularity of some formulations, such as those of articaine, for which growing evidence suggests that they provide more successful anaesthesia than other formulations. A rigorous systematic review of the success rate of local anaesthesia is needed to inform evidence-based practice. This review will consider only injectable agents used for dental block or infiltration, while excluding supplemental injections."

We replaced the word "experimental", used to describe studies for which outcomes were measured when treatment was not performed, with the words "simulated scenario".

In Objectives, we removed the first line, "To determine what is the most effective local anaesthetic formulation for dental anaesthesia."

In Objectives, we changed the wording of our primary objectives from:

"Our primary objectives were to test

- the adequacy of anaesthesia in patients when using different local anaesthetic formulations for operative dental anaesthesia;
- the speed of onset and duration of anaesthesia in patients when using different local anaesthetic formulations for operative dental anaesthesia;
- systemic and local adverse effects associated with dental local anaesthetic."

to:

"Our primary objectives were to compare the success of anaesthesia, the speed of onset and duration of anaesthesia, and systemic and local adverse effects amongst different local anaesthetic formulations for dental anaesthesia. We define success of anaesthesia as absence of pain during a dental procedure, or a negative response to electric pulp testing or other simulated scenario tests. We define dental anaesthesia as anaesthesia given at the time of any dental intervention"

In Objectives, we modified the primary outcome definitions:

- "We define adequacy of anaesthesia as the absence of pain during a dental procedure, or a negative response to electric pulp testing" changed to "We define success of anaesthesia as absence of pain during a dental procedure, or a negative response to electric pulp testing or other simulated scenario tests".
- "We define operative dental anaesthesia as anaesthesia at the time of an operative intervention" changed to "We define dental anaesthesia as anaesthesia given at the time of any dental intervention".

In Objectives, the secondary objective of "participants' experience of the procedures carried out" and in Secondary outcomes, the outcome of "participants' experiences: these include but are not limited to preference and overall experience" was due to be assessed. However, because of lack of data, we did not report these.

In Objectives, we removed the secondary objective of "the influence of modifying factors on efficacy of local anaesthetic

formulations", and in Secondary outcomes the outcome of "modifying factors: influence on efficacy of local anaesthetic solutions", as these were wrongly inserted into the two relative sections of the protocol in error.

In the Types of studies section, we added "When paired data, or data from the first period, were not available, we treated the data from cross-over studies as if derived from a parallel study, then performed sensitivity analysis with cross-over data removed."

In the Types of participants section, we changed "We included male and female adults and children, who were undergoing dental procedures, or volunteers who took part in experimental studies where dental local anaesthesia was tested." to "We included participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested."

In the Types of interventions section, we originally wrote "Only infiltration and block anaesthesia will be considered". To clarify that supplemental anaesthesia was not to be considered, we changed this to "We considered only primary infiltration and block anaesthesia and did not consider supplemental anaesthesia". Also, we added a paragraph giving examples of local anaesthetic formulations:

"Examples of commercial local anaesthetic solutions considered for inclusion in the review include:

- 2% lidocaine (with no epinephrine, 1:50,000 epinephrine, 1:80,000 epinephrine, 1:100,000 epinephrine, or 1:200,000 epinephrine);
- 4% articaine hydrochloride (HCl) (with no epinephrine, 1:100,000 epinephrine, 1:100,000 epinephrine, or 1:400,000 epinephrine);
- 3% prilocaine HCl (with 0.03 international units/mL (IU/mL) octapressin);
- 4% prilocaine HCl (with no epinephrine, or 1:200,000 epinephrine);
- 2% mepivacaine (with 1:20,000 levonordefrin or 1:100,000 epinephrine);
- 3% mepivacaine (with no epinephrine); and
- 0.5% bupivacaine (with 1:200,000 epinephrine)".

In Primary outcomes, we changed the wording of our primary outcomes from:

- "success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus
- speed of onset and duration of anaesthesia
- adverse effects: local and systemic"

to:

- "Success of local anaesthesia, measured by the absence of pain during a procedure via a visual analogue scale (VAS) or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia by an electric pulp tester or cold stimulus.
- Speed of onset (from time of injection to complete anaesthesia) and duration (time from onset until anaesthesia disappeared) of anaesthesia, measured by the absence of pain during a procedure seen on a VAS or other appropriate method, including self-reported patient pain or anaesthesia, or measurement of pulpal anaesthesia by an electric pulp tester or cold stimulus.
- Adverse effects: local and systemic, when the cause of the harmful effect is attributed to the local anaesthetic formulation, including:
  - pain on injection (solution deposition), measured on a VAS;
  - pain following injection, measured by VAS;
  - paraesthesia following injection; and
  - allergy to local anaesthetic".

We also added that the outcomes were classified separately into the oral tissues tested or the testing method used.

"Outcomes were classified separately by the oral tissues tested or the testing method used, which included the following.

- Clinical testing of:
  - healthy pulps - hard and soft tissues;
  - healthy pulps;
  - diseased pulps with irreversible pulpitis;
  - different tissues, pooled; and
  - tissues, when tissues tested were unclear.
- Simulated scenario testing of:
  - healthy pulps;
  - diseased pulps with irreversible pulpitis; and
  - soft tissues".

which was also mentioned in Subgroup analysis and investigation of heterogeneity.

We further modified the original primary outcome of success to one of the following outcomes, depending on the test method used, in the Effects of interventions section.

- "Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method.

- Success of local anaesthesia, by measurement of pulpal anaesthesia using an electric pulp tester.
- Success of local anaesthesia, measured by using self-reported patient pain or anaesthesia."

We did this to clarify the test method used.

In Types of interventions, one injection technique was to be compared against another injection technique. However after starting the review, we realized that this was the topic of a different review.

We had planned to search the Community of Science database but chose not to for the final review. A number of databases had their names modified while the review was performed. We updated these.

In the Selection of studies section, we changed "Two authors (GStG and SH) will independently assess the quality of the chosen randomized controlled trials" to "Two review authors (GST and AM) independently read all titles and abstracts of publications retrieved through our search".

In the Data extraction and management section, we changed "Two authors will carry out the data abstraction (GStG and SH)." to "Two review authors carried out the data abstraction independently (GST and AM)".

In the Measures of treatment effect section, we changed "For binary data, we expressed pooled outcomes as pooled odds ratios (OR) and associated 95% confidence intervals (CIs)." to "For binary data, we expressed pooled outcomes as pooled odds ratios (ORs), risk ratios (RRs), and associated 95% confidence intervals (CIs)".

"When a data and analysis had only one included study (orphan study), it was not entered into a data and analysis table. Instead, the outcome was placed in the appropriate additional table (Table 1; Table 2; Table 3; Table 4; Table 5). When an orphan study was the sole study entered into a subgroup, its data were still analysed if data were available from other studies included in other subgroups in the data and analysis table".

We added details to the Unit of analysis issues section to clarify how cross-over study data would be handled.

"The studies identified were a combination of parallel and cross-over studies. Therefore, to pool data for both types of studies, we performed the meta-analysis in several stages.

- We performed a meta-analysis on parallel-group studies only, using the ‘inverse variance’ method to generate odds ratios. We used a fixed-effect analysis or random-effects analysis model depending on whether there were signs of statistical heterogeneity from the I^2 and P value. From these values, we generated logs of the OR and standard errors (SEs).
- We used Microsoft Excel to generate the log of the OR and associated SEs for cross-over studies from the studies' paired data, if available.
- We completed the meta-analysis using Review Manager (RevMan 2014) by entering the generic inverse variance data of logs of the OR and associated SEs from both types of studies using the 'inverse variance' method. We used a fixed-effect or random-effects analysis model depending on whether there were signs of statistical heterogeneity from the I^2 and P value ($P \leq 0.05$, $I^2 \geq 50\%$ (substantial heterogeneity))".

When paired data were not available, the data from cross-over studies were used in the analysis as if they were from parallel studies, to estimate the overall effect of interest in the meta-analysis. Owing to the confidence intervals being wider when this approach is used, a sensitivity analysis was performed while removing the data from cross-over studies from the meta-analysis, when present.

In Data synthesis we originally wrote "For binary data, these were predominately pooled OR and associated 95% CI." We changed this to "For binary data, we expressed pooled outcomes as pooled odds ratios (ORs), risk ratios (RRs), and associated 95% confidence intervals (CIs)".

In Subgroup analysis and investigation of heterogeneity we planned to consider a number of subgroups for analysis:

- tooth type;
- presence of inflammation (pulpitis);
- tissue type anaesthetized;
- treatment type;
- type of injection;
- age of patient;
- type of study (treatment versus experimental); and
- pharmaceutical company sponsorship.

For the final review, we grouped outcomes depending on which dental tissues required anaesthesia, and a subgroup analysis was conducted during meta-analysis to look at the following subgroups: maxillary infiltration, maxillary block (Infraorbital block), maxillary block (palatal-anterior superior alveolar nerve block), maxillary block (high-tuberosity maxillary second division nerve block), mandibular infiltration, mandibular infiltration (buccal and lingual), mandibular block (IANB), mandibular block (mental block), mandibular block (IANB) and infiltration, mandibular testing (injection type not stated), or both jaws combined/jaw not stated.

The statistical software originally stated in the protocol for this was STATA 7, which we changed to STATA 13 following a number of updates.

Adverse effects were rare and were difficult to compare owing to differing ways of measuring each outcome and lack of raw data related to cross-over studies; therefore we completed meta-analysis for pain on injection (Analysis 1.8) and post-injection pain (Analysis 1.9), when data were available. We summarized the data for other adverse effects in Table 7. No data were available from the included studies for the secondary outcome of patient experience.

We performed Sensitivity analysis to explore the influence of study quality on our primary outcome of success of local anaesthesia in terms of those factors influencing bias: generation and concealment of the randomization sequence; blinding, attrition bias, reporting bias, or other bias as planned; and the influence of cross-over studies, when paired data were not available, on the same outcome.

We planned to investigate the possibility of publication bias but found insufficient studies to allow this.

We added a section in Data collection and analysis to describe the methods used to assess the quality of the evidence.

We planned to use the kappa statistic to assess agreement between authors, but this was not required.

We added a section entitled "Summary of findings tables and GRADE" detailing use of the GRADE approach to assess the quality of evidence and which outcomes were to be placed in the 'Summary of findings' tables:

"We used the GRADE approach to assess the quality of evidence related to each of the outcomes. We used the GRADE profiler (GRADEpro GDT) to import data from RevMan 2014 and to create 'Summary of findings' tables for the eight major comparisons in this review.

- 4% articaine, 1:100,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 1).
- 3% prilocaine, 0.03 IU felypressin versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 2).
- 4% articaine, 1:200,000 epinephrine versus 4% articaine, 1:100,000 epinephrine (Summary of findings table 3).
- 4% prilocaine plain versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 4).
- 4% articaine, 1:200,000 epinephrine versus 0.5% bupivacaine, 1:200,000 epinephrine (Summary of findings table 5).
- 0.5% bupivacaine, 1:200,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 6).
- 4% articaine, 1:100,000 epinephrine versus 2% mepivacaine, 1:100,000 epinephrine (Summary of findings table 7).
- 2% mepivacaine, 1:100,000 epinephrine versus 2% lidocaine, 1:100,000 epinephrine (Summary of findings table 8)".

When assessing the quality of evidence for each outcome, which included pooled data from RCTs, we downgraded evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias.

Two review authors (GST and AM) independently assessed the quality of evidence for each outcome. When we were unable to come to an agreement on assessment of quality, we (GST and AM) resolved disagreements initially by mutual discussion. When a difference of opinion could not be resolved, we involved a third review author - John Meechan (JM).

We included the following outcomes, for a variety of local anaesthetic comparisons, in the 'Summary of findings' tables.

- Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method, or measurement of pulpal anaesthesia using an electric pulp tester or cold stimulus.
- Speed of onset and duration of anaesthesia.
- Adverse effects: local and systemic".

Throughout the review, we carried out minor modifications of text in the Methods section.

Published notes

Characteristics of studies

Characteristics of included studies

Abdulwahab 2009

Methods	Randomized controlled simulated scenario trial, cross-over study design

Participants	**Location:** university (United States of America) **Participants:** 18 enrolled, 18 completing the study. Mean age 24.9 years, ranging from 18 to 53 years. 6 male, 12 female **Inclusion criteria** • Aged 18 to 65 years • Mandibular first molar without a dental restoration or detectable caries, normal electric pulp, and test (EPT) sensitivity value between 10 and 50 units • Ability to sign an informed consent form before undergoing any study procedures and ability to understand and agree to cooperate with study requirements **Exclusion criteria** • Evidence of soft tissue infection near the proposed injection site • Known or suspected allergies or sensitivities to sulphites or amide-type local anaesthetics • History of significant cardiac, neurological, or psychiatric disorders • Treated or untreated hypertension ≥ 140 millimetres of mercury (Hg) systolic or 90 mmHg diastolic • Bronchial asthma • Lactation or pregnancy • Current use of β blockers, monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressors, or ergot-type oxytocic drugs • Participants who had taken acetaminophen, non-steroidal anti-inflammatory drugs, opioids, or other analgesic agents within 24 hours of administration of study medication; had taken an investigational drug or participated in another study within the preceding 4 weeks; or required sedation therapy to tolerate the injection procedure They asked female participants of childbearing age to verify the specific birth control method they or their partner had used (such as abstinence, use of oral contraceptives, or use of other devices or methods) for at least 1 month before and during participation in the study. They required that female participants of childbearing potential receive negative results on a urine pregnancy test before receiving test medications
Interventions	Buccal infiltration (0.9 mL) opposite mandibular first molars using 1 of the following solutions • 2% lidocaine, 1:100,000 epinephrine (18) • 4% articaine, 1:200,000 epinephrine (18) • 4% articaine, 1:100,000 epinephrine (18) • 4% prilocaine, 1:200,000 epinephrine (18) • 3% mepivacaine, no vasoconstrictor (18) • 0.5% bupivacaine, 1:200,000 epinephrine (18)

Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: participants achieving complete pulpal anaesthesia (96/96) • Onset: tested only in cases of successful anaesthesia (28/96) • Mean change in pulp tester scores from baseline to a maximum of 80/80 Teeth tested: mandibular first molars **Soft tissue anaesthesia** (self-reported: no change in sensation, slight feeling of numbness, moderate but not complete feeling of numbness, or complete numbness on one side of the mouth) • Success: degree of numbness (a 4-point scale where 0 = no change in sensation; 1 = slight feeling of numbness; 2 = moderate but not complete feeling of numbness; 3 = complete numbness on 1 side of the mouth, although no data reported). Data for each solution not available after contacting study author • Onset: range for all solutions combined presented. Data for each solution not available after contacting study author Soft tissues tested: soft tissues on the injected side **Adverse events** (96/96) • Pain experience induced by the injection procedure (100 mm visual analogue score) • Other adverse events
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We randomly assigned participants to one of six treatment sequence allocations (6 × 6 Latin square design)" Quote (from correspondence): "Six sequences were created to assure that each formulation was administered only once per patient and that each formulation would be given during each of the six sessions. After establishing the six sequences via a Latin square, a random assignment was made in 3 blocks of six determined by using a random number chart"
Allocation concealment (selection bias)	Low risk	Quote: "He placed cartridges in coded envelopes numbered for treatment sequence. To ensure blinding, neither the research assistant, the administrator nor the patient had knowledge of the formulation used" Quote (from correspondence): "The investigator designed the study and prepared blinded cartridges. He was not present for the LA administration of subjects or for the data collection. Another person, the clinician, administered the local anaesthetic and performed the EPT testing. A research assistant recorded data and monitored the project regarding timing, etc" Comment: Participants and personnel would not be able to identify the local anaesthetic used

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "One of the authors (S.B.) removed the manufacturers' labels from the dental cartridges containing the six study formulations so that they were identical in appearance" "To ensure blinding, neither the research assistant, the administrator nor the patient had knowledge of the formulation used" Quote (from correspondence): "The investigator designed the study and prepared blinded cartridges. He was not present for the LA administration of subjects or for the data collection. Another person, the clinician, administered the local anaesthetic and performed the EPT testing. A research assistant recorded data and monitored the project regarding timing, etc" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "To ensure blinding, neither the research assistant, the administrator nor the patient had knowledge of the formulation used" Comment: Although blinding of the research assistant, the administrator, and the patient was ensured, the person administering the injections and assessing outcomes is referred to as the clinician Quote (from correspondence): "The investigator designed the study and prepared blinded cartridges. He was not present for the LA administration of subjects or for the data collection. Another person, the clinician, administered the local anaesthetic and performed the EPT testing. A research assistant recorded data and monitored the project regarding timing, etc" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 28 occasions (on those experiencing successful anaesthesia). The number assessed in each group was reasonably well balanced with some minor differences, and the reason that assessment was not possible was the same for all groups. Therefore risk of attrition bias was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	Comment: Numbers of participants assessed were not reported and individual onset data were not available for each solution. Therefore risk of attrition bias was graded as unclear
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Quote: "We found A100 to provide the highest degree of numbness and B200 to provide the lowest" for soft tissue anaesthesia Comment: Exact data were requested from first study author, but none were received
Other bias	Low risk	Comment: no other bias present

Aggarwal 2009

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** hospital (India) **Participants:** 87 enrolled, 84 completing the study (3 excluded as did not experience lip anaesthesia). Mean age 29 years, ranging from 23 to 37 years. 44 male, 40 female **Inclusion criteria** • In good health • Not taking any medication that would alter pain perception as determined by oral questioning and written questionnaire • Active pain in a mandibular molar, and prolonged response to cold testing with an ice stick and an electric pulp tester • Absence of any periapical radiolucency on radiographs, except for a widened periodontal ligament • Vital coronal pulp on access opening **Exclusion criteria** • None stated
Interventions	Inferior alveolar nerve blocks (1.8 mL) of 2% lidocaine, 1:200,000 epinephrine, followed by 1 of the following solutions: • no injections: control (25) • buccal and lingual infiltrations (1.8 mL each) of 4% articaine, 1:200,000 epinephrine (31) • buccal and lingual infiltrations (1.8 mL each) of 2% lidocaine, 1:200,000 epinephrine (31) Although a volume of 1.7 mL was used for each injection, the true volume was 1.8 mL, which included the small amount used for aspiration (e.g. "All patients received standard IANB injections using 1.8 mL of 2% lidocaine with 1:200,000 epinephrine")
Outcomes	**Clinical anaesthesia** during endodontic access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success (Heft-Parker visual analogue scale: "no pain" = 0 mm, "faint, weak, or mild" = 0 to 54 mm, "moderate" = 55 to 114 mm, "strong, intense, and maximum possible" > 114 mm), Defined as "no pain" or "weak/mild" (62/62) • Extent of access preparation and/or instrumentation ("within dentine", "within pulpal space", or "instrumentation of canals") Type of treatment: endodontic treatment of teeth with irreversible pulpitis Teeth tested: mandibular first molars and second molars **Soft tissue anaesthesia** (self-reported) • Success (60/60) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "The patients were randomly allocated to the treatment groups with the help of an online random generator which use permuted block randomization protocol (stratified) (randomization.com)"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The solutions were masked with an opaque label and were randomly assigned a three-digit alpha-numeric value. Only the alpha-numeric values were recorded on the data sheets to blind the experiment" Quote (from correspondence): "The code was broken at the end of the study and just before compilation/evaluation of results"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The solutions were masked with an opaque label and were randomly assigned a three-digit alpha-numeric value" "Only the alpha-numeric values were recorded on the data sheets to blind the experiment" Comment: Although participants and local anaesthetic administrators would know when no injection (control injection) was given, the only 2 comparisons for which data were to be used were blinded. Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the alpha-numeric values were recorded on the data sheets to blind the experiment" Comment: Outcome assessor is the same person who administered the injections. Although this person would know when no injection was given, the identities of the articaine and lidocaine cartridges for infiltration, for which data would be used, were unknown owing to masking. Outcomes are patient-reported outcomes (the outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: Numbers in each group who were tested were equal following removal of those with failed lip anaesthesia
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Quote: "After 15 minutes of the initial IANB, each patient was asked if his/her lip was numb. If profound lip numbness was not recorded within 15 minutes, the block was considered unsuccessful, and the patients were excluded from the study" Comment: Patients excluded were accounted for and used for calculation of soft tissue success
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: Outcome data were reported on, although exact data for pulpal anaesthesia success were not reported - only the statistics
Other bias	Low risk	Comment: no other bias present

Aggarwal 2014

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (India) **Participants:** 63 enrolled, 62 completing the study. Mean age 26 years, ranging from 20 to 31 years (2% lidocaine, 1:80,000 epinephrine), and mean age 27 years, ranging from 21 to 37 years (2% lidocaine, 1:200,000 epinephrine). 35 male, 27 female **Inclusion criteria** • Pain in the mandibular first or second molar • Prolonged response to cold testing with an ice stick and an electric pulp tester • Absence of any periapical radiolucency on radiographs except for a widened periodontal ligament • Vital coronal pulp on access opening • American Society of Anesthesiologists (ASA) class I medical history • Ability to understand the use of pain scales **Exclusion criteria** • Known allergy or contraindications to any content (including epinephrine) of local anaesthetic solution • Pregnant or breastfeeding • Taking any drugs that could have affected pain perception • Active pain in more than 1 mandibular/maxillary tooth
Interventions	Inferior alveolar nerve blocks of 1.8 mL of: • 2% lidocaine, 1:80,000 epinephrine (31) • 2% lidocaine, 1:200,000 epinephrine (32)
Outcomes	**Clinical anaesthesia** during endodontic access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success (Heft-Parker visual analogue scale: "no pain" = 0 mm, "faint, weak, or mild" = 1 to 54 mm, "moderate" = 55 to 114 mm, "strong, intense, and maximum possible" > 114 mm). Defined as "no pain" or "weak/mild" (63/63) Type of treatment: endodontic treatment of teeth with irreversible pulpitis Teeth tested: mandibular first and second molars **Soft tissue anaesthesia** (self-reported) • Success (63/63) Soft tissues tested: lower lip **Adverse events** reported (63/63) • Pain of injection during solution deposition (Heft-Parker visual analogue scale)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly allocated to 2 treatment groups with the help of an online random generator using permuted block stratified randomization protocol (randomization.com)"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The solutions were given an alphanumeric code, and the syringes were masked with an opaque label marked with the code. Only the code and the primary/ secondary outcomes were recorded to blind the operator. The code was broken only after completion of the study" Quote (from correspondence): "The sequence was concealed in an opaque envelope. Before initiating the treatment, the sequence was opened by a dental assistant, who loaded the cartridge in the syringe according to the sequence only. The cartridges were masked with a label with alpha-numeric code to blind the operator and the patient"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The solutions were given an alphanumeric code, and the syringes were masked with an opaque label marked with the code. Only the code and the primary/secondary outcomes were recorded to blind the operator" Quote (from correspondence): "The sequence was concealed in an opaque envelope. Before initiating the treatment, the sequence was opened by a dental assistant, who loaded the cartridge in the syringe according to the sequence only. The cartridges were masked with a label with alpha-numeric code to blind the operator and the patient" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The solutions were given an alphanumeric code, and the syringes were masked with an opaque label marked with the code. Only the code and the primary/ secondary outcomes were recorded to blind the operator" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Quote: "After 15 min, each patient was asked whether his/ her lip was numb. If profound lip numbness was not recorded, the block was considered unsuccessful, and the patients were excluded from the study" Comment: The only patient excluded was accounted for, classed as a failure, and used for calculation of clinical success
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Quote: "After 15 min, each patient was asked whether his/ her lip was numb. If profound lip numbness was not recorded, the block was considered unsuccessful, and the patients were excluded from the study" Comment: The only patient excluded was accounted for and was used for calculation of soft tissue success
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Aggarwal 2017

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (India) **Participants:** 97 enrolled, 91 completing the study. Mean age 34 years, ranging from 27 to 47 years. 57 male, 34 female **Inclusion criteria** • Active pain in a mandibular molar (> 54 mm on the HP VAS) • Presence of an extended response to pulp sensitivity tests • No appearance of a periapical radiolucency • Presence of vital pulp tissue on endodontic access preparation **Exclusion criteria** • Contraindications to any content of the local anaesthetic solution • Pregnant or breastfeeding • Requiring endodontic intervention in more than 1 mandibular tooth • Taking any medication that could alter pain perception (excluded from the study as confirmed by study author)
Interventions	Inferior alveolar nerve blocks (1.8 mL) using the following • 2% lidocaine, 1:200,000 epinephrine (32) • 4% articaine, 1:100,000 epinephrine (31) • 0.5% bupivacaine, 1:200,000 epinephrine (34)
Outcomes	**Clinical anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: ability to access and instrument the tooth without pain (VAS score of zero or weak/mild pain ≤ 54 mm) on a Heft-Parker visual analogue scale (97/97) Teeth tested: mandibular molars **Soft tissue anaesthesia** (subjective testing) • Success: numbness at 15 minutes post injection (97/97) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated to three treatment groups (lidocaine, articaine, and bupivacaine). The allocation was randomized using an online random generator (randomization.com) using a permuted block stratified randomization protocol"
Allocation concealment (selection bias)	Low risk	Quote: "The patients were allocated to three treatment groups (lidocaine, articaine, and bupivacaine). The allocation was randomized using an online random generator (randomization.com) using a permuted block stratified randomization protocol" Comment: detailed method not reported Quote (from correspondence): "The sequence was concealed in an opaque envelope. The sequence was opened just before the treatment"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "A trained dental assistant loaded the local anesthetic solutions in masked disposable syringes and coded them (three digit alpha-numeric) for treatment sequence" "To ensure blinding, neither the operator nor the assistant had knowledge of the solution tested" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A trained dental assistant loaded the local anesthetic solutions in masked disposable syringes and coded them (three digit alpha-numeric) for treatment sequence" "To ensure blinding, neither the operator nor the assistant had knowledge of the solution tested" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: No patients were excluded following re-calculation of success. Outcome data were complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: One patient each from the lidocaine and articaine groups and 4 patients from the bupivacaine group did not present lip numbness at 15 minutes and were excluded from the study. However, these were classed as failures in this review; therefore no participants were excluded. Outcome data were complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Albertson 1963

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** numbers enrolled and completing the study not clear (266; 223 without 3% mepivacaine, no vasoconstrictor) Age of participants and male:female ratio not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Injections (not specified) of • 2% lidocaine, 1:100,000 epinephrine (110) • 2% mepivacaine, 1:20,000 levonordefrin (113) • 3% mepivacaine, no vasoconstrictor (43: not included as participants for this group were not randomly chosen)
Outcomes	**Clinical anaesthesia** • Success (223/223?). ◦ Measured on a scale: grade A = complete absence of pain, grade B = some pain, but not enough to need a further injection, grade C = second injection needed) ◦ Volume of local anaesthetic used **Soft tissue anaesthesia** • Onset: assumed to be soft tissue related (218/223?) • Duration: assumed to be soft tissue related; method of measurement not stated (195/223?) Apart from success, methods were not reported Type of treatment: not stated (possibly surgery?). Teeth/soft tissues tested: not reported **Adverse effects** reported (223/223?)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In general, the method of Weil et al (2) was used (2 = Weil et al (1961). Clinical evaluation of mepivacaine hydrochloride by a new method" JADA 63:26-32) Method was as follows: "Solutions.....were supplied in identical dental cartridges marked only by a control number printed on each cartridge. At least three different code numbers were assigned to each local anaesthetic solution. All the cartridges under test were mixed indiscriminately with cartridges of the control solution, in cans of 50" Comment: only 2% lidocaine, 1:100,000 epinephrine and 2% mepivacaine, 1:20,000 levo-nordefrin were randomized. The solution of 3% mepivacaine, no vasoconstrictor was used as a comparison, without randomization; therefore data for this were not used
Allocation concealment (selection bias)	Low risk	Quote: "In general, the method of Weil et al (2) was used" (2 = Weil et al (1961). Clinical evaluation of mepivacaine hydrochloride by a new method" JADA 63:26-32) Method used was as follows: "Solutions.....were supplied on identical dental cartridges marked only by a control number printed on each cartridge. At least three different code numbers were assigned to each local anaesthetic solution. All the cartridges under test were mixed indiscriminately with cartridges of the control solution, in cans of 50" Comment: only 2% lidocaine, 1:100,000 epinephrine and 2% mepivacaine, 1:20,000 levo-nordefrin were randomized. The solution of 3% mepivacaine, no vasoconstrictor was used as a comparison, without randomization; therefore data for this were not used
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The solutions, supplied in 1.8-ml. Cartridges, were identified only by code numbers" Method used was as follows: "Solutions.....were supplied on identical dental cartridges marked only by a control number printed on each cartridge. At least three different code numbers were assigned to each local anaesthetic solution. All the cartridges under test were mixed indiscriminately with cartridges of the control solution, in cans of 50" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The solutions, supplied in 1.8-mL cartridges, were identified only by code numbers" Comment: Having a limited number of code numbers may allow identification of a solution by personnel recording the outcomes if they also administered injections, and if the properties of the solutions were markedly different. However, properties of the 2 solutions did not allow identification, and outcomes were patient-reported outcomes (the outcome assessor was the patient); therefore risk of bias was graded as low, as identification of the local anaesthetic by participants and personnel recording outcomes was not possible
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	Comment: unsure whether some patients were excluded from calculation of anaesthetic success, as the number of participants at the start of the study was not stated
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Of the total number of participants recruited who were tested, some did not have onset of soft tissue anaesthesia measured (lidocaine: 3/110 (3%), mepivacaine: 2/113 (2%)). Dropout rates were minor and balanced between groups. Therefore risk of attrition bias has been graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Of the total number of participants recruited who had successful anaesthesia and therefore had onset measured, some did not have duration of soft tissue anaesthesia measured (lidocaine: 18/107 (17%), mepivacaine: 5/111 (5%)). No dropouts would occur if the numbers of participants having duration measured were equal to those having soft tissue onset measured, assuming that all those who should have had onset measured, did. However, dropout rates of up to 17% were seen, based on those who had onset of soft tissue onset measured. Therefore attrition bias has been graded as high risk, because if dropout rates were based on soft tissue success, which was not measured, they may be higher still
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Comment: As the number of participants assessed was unclear, risk of bias was also graded as unclear
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Allegretti 2016

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Brazil) **Participants:** 66 enrolled, 66 completing the study, with a mean age of 28.7 years (articaine)/30.3 years (lidocaine)/33.9 years (mepivacaine). 25 males and 41 females **Inclusion criteria** • All patients received a clinical diagnosis of irreversible pulpitis of the first or second molar • Patients had moderate to severe spontaneous pain and exhibited a positive response to the electric pulp test and a prolonged response to cold testing with Endo-Frost (Coltène-Roeko, Langenau, Germany) • Between 18 and 50 years of age • In good health, as established by a health history questionnaire • Each participant had at least 1 adjacent molar to the tooth with irreversible pulpitis and 1 healthy contralateral canine without deep carious lesions, extensive restoration, advanced periodontal disease, history of trauma or sensitivity **Exclusion criteria** • Taking medication that could interfere with any of the anaesthetics used in the study
Interventions	Inferior alveolar nerve blocks (3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine (22) • 4% articaine, 1:100,000 epinephrine (22) • 2% mepivacaine, 1:100,000 epinephrine (22)
Outcomes	**Clinical anaesthesia** during pulpectomy of teeth with irreversible pulpitis • Success on a verbal analogue scale: 0 = no pain; 1 = mild, bearable pain; 2 = moderate, unbearable pain; 3 = severe, intense, and unbearable pain (0, 1 = success) (66/66) **Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 negative responses to maximal stimulation of the device, 80 µA (66/66) Teeth tested: mandibular first and second molars **Soft tissue anaesthesia** • Success: patient asked if lip was numb (66/66) Soft tissues tested: lower lip **Adverse events** were recorded if present (66/66)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To ensure a blind test, 2 cartridges (3.6 mL) of each anesthetic solution were sealed in envelopes. At the time of application, the researcher randomly selected 1 of the envelopes and consecutively administered the 2 anesthetic injections"
Allocation concealment (selection bias)	Low risk	Quote: "To ensure a blind test, 2 cartridges (3.6 mL) of each anesthetic solution were sealed in envelopes. At the time of application, the researcher randomly selected 1 of the envelopes and consecutively administered the 2 anesthetic injections"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "To ensure a blind test, 2 cartridges (3.6 mL) of each anesthetic solution were sealed in envelopes. At the time of application, the researcher randomly selected 1 of the envelopes and consecutively administered the 2 anesthetic injections" Comment: Despite no details of the blinding method, risk of bias was graded as low, as identification of the local anaesthetic by participants is unlikely. Also, a pre-determined method for administration was used by personnel, which minimized variation
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Electrical stimulation of the tooth pulp (RMS) and the pulpectomy (CEA) were performed by different professionals to ensure that the anesthetic solution remained unknown, thereby maintaining the double-blind nature of the study" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Arrow 2012

Methods	Randomized controlled clinical and simulated scenario trial, parallel (technique) and cross-over (local anaesthetic type) study design
Participants	**Location:** university (Australia) **Participants:** 57 enrolled, 56 completing all parts of the study. Mean age 12.7 years, ranging from 5.9 to 16.9 years. 21 male, 36 female **Inclusion criteria** • Enrolled for care with the School Dental Service of Dental Health Services, Western Australia • Children who on routine recall dental examination were deemed to require non-urgent or non-emergency restorative treatment requiring administration of a local anaesthetic on contralateral teeth in the mandibular posterior region (lower first and second permanent molars and lower second deciduous molars) • Cooperative behaviour for dental treatment under local analgesia • No history of allergy to any of the constituents in the local anaesthetic solution • No medical conditions contraindicating the use of local analgesia or need to undergo dental treatment under local analgesia • No evidence of soft tissue infection/inflammation near site of injection • Not taking any agents likely to interfere with reporting of pain (analgesics) • No neurological disorders with sensory disturbances or communication difficulties • Ability to communicate effectively in the English language • Body weight > 20 kg **Exclusion criteria** • Children requiring restorative care on teeth affected by enamel hypomineralization
Interventions	Inferior alveolar nerve block or mandibular infiltration (up to 2.2 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine (29 IANB, 28 BI) • 4% articaine, 1:100,000 epinephrine (28 IANB, 28 BI)
Outcomes	**Clinical anaesthesia** during paediatric restorative procedures • Success (111/114) ◦ Scheduled restorative treatment was completed with standard treatment management strategies after administration of the trial anaesthetic (dichotomized into 0 = 'no', 1 = 'yes') ◦ Self-report of pain using the Faces Pain Scale (dichotomized into 'no or mild pain' = 0 and 'moderate to severe pain' = 1) ◦ Assessed by the dental clinical assistant using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (dichotomized into 'no reaction' = 0, 'one or more reactions' = 1) ◦ Volume of local anaesthetic injected Teeth tested: second deciduous molar, first permanent molar, and second permanent molar **Soft tissue anaesthesia** • Onset: asking the child when the sensation of numbness started (45/114) Soft tissues tested: tongue and lower lip **Adverse events reported** (113/114) • Pain on injection: Faces Pain Scale (dichotomized into 'no or mild pain' = 0 and 'moderate to severe pain' = 1) • Postoperative pain assessed by parent (dichotomized into 'no behaviour change' = 0, 'one or more behaviour change' = 1) • Postoperative complications ('none' = 0, 'soft tissue injuries' = 1, and 'other complications' = 2)
Notes	Industry funded.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were allocated to LA technique (IANB or BI) and then to LA type (lignocaine or articaine) using a two-stage computer generated random permuted block design. The first stage was used to assign administration technique and the second stage for assignment of anaesthetic agent to be used at the first visit (each participant required two visits to complete the course of care for the study). The clinicians were advised to use clinical judgement to determine which side of the jaw to treat first and treatment visits were spaced at least one week apart"
Allocation concealment (selection bias)	Low risk	Quote: "Once a participant was registered into the trial, the clinic personnel contacted the central trial coordinator who, using a table of random numbers, selected the block for the first stage allocation of the LA technique to be used on the patient. The coordinator then used the second random block to allocate the anaesthetic drug for use at the first visit. The central trial coordinator maintained a register of trial participants and the random assignments. The coding for the anaesthetic agents was kept locked by the lead researcher at the central coordinating centre"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The clinician administering the anaesthetic, the chairside assistant and the patient receiving the anaesthetic and his/her parent were all 'blind' to the anaesthetic agent, but not to the LA technique. Each clinic was issued with two 2.2 ml cartridges of local anaesthetic (test and control) in sealed envelopes with the manufacturer's label removed and re-labelled with a researcher-generated six-digit code. The coding for the anaesthetic agents was kept locked by the lead researcher at the central coordinating centre" Comment: impossible to blind technique used, although for this review only similar techniques were compared. Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The clinician administering the anaesthetic, the chairside assistant and the patient receiving the anaesthetic and his/her parent were all 'blind' to the anaesthetic agent, but not to the LA technique. Each clinic was issued with two 2.2 ml cartridges of local anaesthetic (test and control) in sealed envelopes with the manufacturer's label removed and re-labelled with a researcher generated six-digit code. The coding for the anaesthetic agents was kept locked by the lead researcher at the central coordinating centre" Comment: impossible to blind technique used, although for this review only similar techniques were compared. Some outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: One patient was excluded but accounted for (did not attend second appointment). One hundred fourteen outcomes were scheduled to be recorded, but owing to failing 1 visit, only 113 were recorded. Of these interventions, 111 recorded the children's response to treatment (confirmed by the study author). This did not result in a large difference between groups. Therefore risk of bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	High risk	Comment: For onset of soft tissue anaesthesia, the number of participants for whom this was recorded was 9/29 (IANB lidocaine), 13/28 (BI lidocaine), 16/29 (IANB articaine), and 7/28 (BI articaine). Onset may have been measured in those with successful clinical anaesthesia but could have been measured in those with unsuccessful clinical anaesthesia (i.e. soft tissues were anaesthetised but pulps were not). Unfortunately the exact dropout rate cannot be calculated (following communication with the study author) Of the total number of participants recruited who had successful anaesthesia, some did not have onset of soft tissue anaesthesia measured: • IANB: lidocaine: 8/17 (29%), articaine: 3/19 (16%) • Infiltration: lidocaine: -8/5 (N/A), articaine: 0/7 (0%) The dropout rate in one group was as high as 29%. However, the true dropout rate could be calculated only if those having soft tissue success were known, and it is likely to be higher than the figures calculated. Therefore attrition bias was rated as high risk
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: One patient was excluded but accounted for (did not attend second appointment). One hundred fourteen outcomes were scheduled to be recorded, but owing to failing 1 visit, only 113 were recorded. This did not result in a large difference between groups; therefore risk of bias was rated as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Comment: The study author thanked Septodont Australia, which facilitated the supply of some local anaesthetic cartridges used in the study, although this was relatively minor funding

Ashraf 2013

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Iran) **Participants:** 125 enrolled, 125 completing the study. Age ranging from 20 to 60 years. Male:female ratio not reported **Inclusion criteria** • Experiencing active pain in their first or second mandibular molar • Had not taken any pain killers on the day of treatment • Prolonged response to cold testing by using an ice stick • Vital pulp tissue during access opening • Absence of periapical radiolucencies on periapical radiographs (except for periodontal ligament widening) confirmed the presence of irreversible pulpitis in the teeth **Exclusion criteria** • Younger than 20 years • Pregnant women • Systemic disease • Clinically observed lesions or swellings at the injection site
Interventions	Inferior alveolar nerve block (1.5 mL) and long buccal infiltration (0.3 mL) of: • 2% lidocaine, 1:100,000 epinephrine (numbers unclear) • 4% articaine, 1:100,000 epinephrine (numbers unclear)
Outcomes	**Pulpal anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: ability to access and instrument the tooth without pain (VAS score of zero or mild pain ≤ 54 mm) on a Heft-Parker visual analogue scale (numbers unclear) Teeth tested: first molars, second molars **Soft tissue anaesthesia** on questioning • Success: numbness at 15 minutes post injection (numbers unclear) Soft tissues tested: lower lip
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Initially, the patients were divided into 2 groups of men and women, who were then classified randomly into 2 subgroups of lidocaine or articaine by using random allocation software. One blinded nurse enrolled all participants and assigned them to intervention"
Allocation concealment (selection bias)	Low risk	Quote: "There were equal numbers of lidocaine and articaine cartridges available that had been covered and given a code. Another nurse in the department was aware of the codes and gave out the cartridges randomly and in equal numbers according to the subgroups of lidocaine or articaine. There was 1 code for each of the 2 cartridges packed together because the block and infiltration injections were supposed to be administered by using the same anaesthetic"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "There were equal numbers of lidocaine and articaine cartridges available that had been covered and given a code. Another nurse in the department was aware of the codes and gave out the cartridges randomly and in equal numbers according to the subgroups of lidocaine or articaine. There was 1 code for each of the 2 cartridges packed together because the block and infiltration injections were supposed to be administered by using the same anaesthetic" Comment: Patients and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "There were equal numbers of lidocaine and articaine cartridges available that had been covered and given a code. Another nurse in the department was aware of the codes and gave out the cartridges randomly and in equal numbers according to the subgroups of lidocaine or articaine. There was 1 code for each of the 2 cartridges packed together because the block and infiltration injections were supposed to be administered by using the same anaesthetic" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	Exact numbers of successful injections for pulpal and soft tissue anaesthesia for each local anaesthetic were not given. Therefore risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	Quote: "Patients who did not report lip numbness were excluded from the study, and their cartridges were replaced. Those who reported lip numbness were studied for data analyses" Comment: Six patients did not experience lip numbness after the IANB. However it is not clear from the journal article which group they were from, as they should have been classed as failures
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Atasoy Ulusoy 2014

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Turkey) **Participants:** 50 enrolled, 50 completing the study. Mean age 30.5 years (4% articaine, 1:100,000 epinephrine) and 30.7 years (4% articaine, 1:100,000 epinephrine bitartrate). 24 male, 26 female **Inclusion criteria** • Pulp diagnosis was made by a dentist who was not involved in the study • Pain in the maxillary first molar • Prolonged symptomatic response to cold stimuli • Absence of a periapical lesion other than widened lamina dura • All included patients fulfilled the criteria for a clinical diagnosis of irreversible pulpitis **Exclusion criteria** • Younger than 18 or older than 60 years • Pregnant females • History of medical conditions that contraindicated the use of local anaesthetics and use of analgesics within the last 12 hours
Interventions	Maxillary buccal infiltration (1.5 mL) of 1 of the following: • 4% articaine, 1:100,000 epinephrine (25) • 4% articaine, 1:100,000 epinephrine bitartrate (25)
Outcomes	**Pulpal anaesthesia** tested with Endo-Ice (Coltene/Whaledent) • Success (50/50) **Pulpal anaesthesia** during endodontic access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success: Heft-Parker visual analogue scale: "no pain" = 0 mm, "faint, weak, or mild" = 0 to 54 mm, "moderate" = 55 to 114 mm, "strong, intense, and maximum possible" > 114 mm), Defined as "no pain" or "weak/mild" pain (50/50) Type of treatment: endodontic treatment of teeth with irreversible pulpitis Teeth tested: maxillary first molars **Adverse events and heart rate** were measured (50/50)
Notes	No funding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "For the randomization process, the two anaesthetic formulations were randomly assigned 4-digit numbers from a random table by a graduate student who was not involved in the trial. The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered" Comment: Detailed methods were not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "For the randomization process, the two anaesthetic formulations were randomly assigned 4-digit numbers from a random table by a graduate student who was not involved in the trial. The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered" "Only the random numbers were recorded on the data collection sheets" Comment: Detailed methods were not reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Only the random numbers were recorded on the data collection sheets. Patients were blinded to the type of anaesthetic solution" Comment: Despite no details of the blinding method, risk of bias was graded as low, as identification of the local anaesthetic by participants is unlikely. Also, a pre-determined method for administration was used by personnel, which minimized variation
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Only the random numbers were recorded on the data collection sheets. Patients were blinded to the type of anaesthetic solution" Comment: No details of the blinding method were reported, and it is not clear whether the person recording the patient outcomes was a different person than the person administering the local anaesthetic, who may have been able to influence the participant's response (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Batista da Silva 2010

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 40 enrolled, 40 completing the study. Ages ranging from 18 to 35 years (no mean). 20 male, 20 female **Inclusion criteria** • Volunteers presented with mandibular premolars, canines, and lateral incisors, all responsible to the pulp tester **Exclusion criteria** • Pregnancy • Systemic disease • Intake of medicines other than contraceptives • History of allergy to components of the local anaesthetic solutions • Local anaesthesia in the region at least 1 week before the experiment • Caries, large restorations, periodontal disease, or a history of trauma or sensitivity in the target teeth
Interventions	Incisive/mental nerve blocks (0.6 mL) of 1 of the following solutions: • 2% lidocaine, 1:100,000 epinephrine (40) • 4% articaine, 1:100,000 epinephrine (40)
Outcomes	**Pulpal anaesthesia** tested using an electric pulp tester • Success (80/80) • Onset (50/80) • Duration (50/80) Teeth tested: right mandibular lateral incisors, canines, first premolars, second premolars, and contralateral canines **Soft tissue anaesthesia** tested by asking volunteers to palpate the inferior lip • Onset (80/80) • Duration (80/80) Soft tissues tested: lower lip on the affected side **Adverse events** reported (80/80) • Pain associated with needle insertion and anaesthetic solution deposition (100 mm visual analogue scale: 0 = "no pain" to 100 = "unbearable pain") • Postoperatively after soft tissues returned to normal sensation (100 mm visual analogue scale: 0 = "no pain" to 100 = "unbearable pain") • Other adverse events: 24 hours after the injection
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Volunteers randomly received two incisive/mental nerve blocks according to the technique described by Malamed (10) at 2 separate appointments spaced at least 2 weeks apart in a repeated-measures design" Quote (from correspondence): "The randomization was performed prior to the study by using an Excel sheet in order to sort the injection sequence. Volunteers were assigned to the injection code in the first visit"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Volunteers randomly received two incisive/mental nerve blocks according to the technique described by Malamed (10) at 2 separate appointments spaced at least 2 weeks apart in a repeated-measures design" Quote (from correspondence): "The participants and also the clinician were not aware of the cartridges since those cartridges were colour coded (no brand or other names on them). Those responsible for all analysis (statistics, graphics, etc) just received the data described by colour codes. After the end of all procedure, the main investigator revealed the codes and the name of colours in the graphics were changed for the real names of solutions"
Blinding of participants and personnel (performance bias)	Low risk	Quote: All pulp testing was performed by a trained person who was blinded to the anaesthetic solutions administered Quote (from correspondence): "The participants and also the clinician were not aware of the cartridges since those cartridges were colour coded (no brand or other names on them)" Comment: Coding the cartridges of each formulation with the same colour could allow identification of a solution by the personnel administering injections in a cross-over study if properties of the solutions were markedly different. Participants may comment about long duration, poor anaesthesia, etc., at their second visit. However, the properties of the 2 solutions would not allow identification, and a pre-determined method for administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All the pulp testing was performed by a trained person who was blinded to the anaesthetic solutions administered" Quote (from correspondence): "Those responsible for all analysis (statistics, graphics, etc.) just received the data described by colour codes" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant); therefore risk of bias was graded as low, as identification of the local anaesthetic by participants is unlikely
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 50 occasions with mandibular second premolar teeth (on those experiencing successful anaesthesia: 28 cases of lidocaine, 32 cases of articaine) and was confirmed by the study author. Both groups were equally balanced; therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: All 40 participants (80 episodes of successful anaesthesia) had onset of soft tissue anaesthesia measured (confirmed by study author)

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: Onset of pulpal anaesthesia was tested on 50 occasions with mandibular second premolar teeth (on those experiencing successful anaesthesia: 28 cases of lidocaine, 32 cases of articaine) and was confirmed by the study author. Both groups were equally balanced; therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: All 40 participants (80 episodes of successful anaesthesia) had duration of soft tissue anaesthesia measured (confirmed by study author)
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Berberich 2009

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 40 enrolled, 40 completing the study. Mean age 26 years, ranging from 23 to 33 years. 34 male, 6 female **Inclusion criteria** • Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity **Exclusion criteria** • Younger than 18 or older than 65 years of age • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions • Taking any medications that may affect anaesthetic assessment • Active sites of pathosis in the area of injection • Inability to give informed consent
Interventions	Intraoral infraorbital nerve blocks of 1 cartridge (1.8 mL; confirmed by study author) of: • 2% lidocaine, 1:100,000 epinephrine (40) • 2% lidocaine, 1:50,000 epinephrine (40) • 3% mepivacaine, no vasoconstrictor (40)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset (90/120) • Short duration: Patient achieved 2 consecutive 80 readings, lost the 80 reading, and never regained it within the 60-minute period • Success: when 2 consecutive 80 readings were obtained (120/120) Teeth tested: maxillary anterior teeth, premolars, and first molars **Soft tissue anaesthesia** (palpation of soft tissues) • Success: to determine whether a block was a failure after 20 minutes (120/120) Soft tissues tested: lip, side of nose, and lower eyelid **Adverse effects** reported (120/120) • Pain on injection. • Pain following injection (after numbness wore off and each morning on arising for 3 days) (scale: 0 = no pain, 1 = mild pain that was recognizable but not discomforting, 2 = moderate pain that was discomforting but bearable, 3 = severe pain that caused considerable discomfort and was difficult to bear) • Other adverse events
Notes	Non-industry funding (confirmed by study author)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, the 3 anaesthetic formulations were randomly assigned 4-digit numbers from a random number table. Each subject was randomly assigned to 1 of the 3 anaesthetic formulations to determine which anaesthetic was to be administered at each appointment" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The anaesthetic formulations ..... were masked with opaque labels, and the cartridge caps and plungers were masked with a black felt tip marker. The corresponding 4-digit codes were written on each cartridge label" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the random numbers were recorded on the data collection and post-injection survey sheets to blind the experiment" "Trained personnel, who were blinded to the type of injection technique used, performed all preinjection and post-injection tests" Quote (from correspondence): "The master code list was not available to the investigator. The data sheets to record the pulp test results only had the random number on each sheet for each random number/subject" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Thirty sets of available matched pair data (from participants experiencing anaesthetic success) were used to assess onset of pulpal anaesthesia. Local anaesthetic groups were balanced. Therefore risk was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Bhagat 2014

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (India) **Participants:** 209 male, 151 female • 2% lidocaine with 1:100,000 epinephrine group: 180 enrolled, 180 completing the study. Mean age 29.33 years ± 7.537 (SD) • 4% articaine with 1:100,000 epinephrine group: 180 enrolled, 180 completing the study. Mean age 28.42 years ± 6.849 (SD) **Inclusion criteria** • Without systemic disorders or antecedents of complications associated with local anaesthetics • Presenting with impacted lower third molars requiring ostectomy and tooth sectioning for extraction **Exclusion criteria** • Younger than 15 years, older than 50 years • Pregnancy • Concomitant cardiac disease, neurological disease, liver or renal disease, hyperthyroidism, diabetes mellitus, and immunosuppression • Evidence of soft tissue infection near the proposed injection site (localized periapical or periodontal infections permitted) • Reduced mouth opening (mouth opening > 30 mm was considered normal)
Interventions	Inferior alveolar nerve blocks (volume not stated) using the following: • 2% lidocaine, 1:100,000 epinephrine (180) • 4% articaine, 1:100,000 epinephrine (180)
Outcomes	**Clinical anaesthesia** during surgical removal of mandibular third molars • Success (360/360) ◦ Quality of anaesthesia during surgery (visual analogue scale: 0 = absolutely no pain, 1 = very mild pain, 2 to 4 = mild pain, 5 to 7 = moderate pain, 8 to 9 = severe pain, 10 = unbearable pain) ◦ Self-report of pain using the Faces Pain Scale Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: when child reported the sensation of numbness starting (360/360) • Duration: recorded via telephone interview (326/360) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomized, double-blinded, controlled clinical trial comparing the efficacy of 4% articaine (Articaine 4% Inibsa®, Inibsa, Barcelona, Spain) and 2% lignocaine for the surgical removal of the mandibular third molar" Comment: detailed methods not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "A randomized, double-blinded, controlled clinical trial comparing the efficacy of 4% articaine (Articaine 4% Inibsa®, Inibsa, Barcelona, Spain) and 2% lignocaine for the surgical removal of the mandibular third molar" Comment: detailed methods not reported

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "A randomized, double-blinded, controlled clinical trial comparing the efficacy of 4% articaine (Articaine 4% Inibsa®, Inibsa, Barcelona, Spain) and 2% lignocaine for the surgical removal of the mandibular third molar" Comment: Despite no details of the blinding method, risk of bias was graded as low, as identification of the local anaesthetic by participants is unlikely. Also, a pre-determined method of administration was used by personnel, which minimized variation
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "A randomized, double-blinded, controlled clinical trial comparing the efficacy of 4% articaine (Articaine 4% Inibsa®, Inibsa, Barcelona, Spain) and 2% lignocaine for the surgical removal of the mandibular third molar" Comment: No details of the blinding method were reported, and it is not clear if the person recording participants' outcomes was a different person than the person administering the local anaesthetic, who may have been able to influence the participant's response (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Soft tissue duration was tested on 164/180 participants in the lidocaine group and 162/180 participants in the articaine group. As the groups were balanced, risk was graded as low
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Bortoluzzi 2009

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 25 enrolled, 24 completing the study. Mean age 22.6 ± 2.3 years. 10 male, 14 female **Inclusion criteria** • Healthy patients between 20 and 30 years old and owning a watch **Exclusion criteria** • Presence of infection at the anaesthesia site • Pregnancy and any known allergy to local anaesthetics or components of their formulations
Interventions	Mandibular buccal infiltration (0.18 mL) using 1 of the following solutions: • 4% articaine, 1:100,000 epinephrine (24) • 2% mepivacaine, 1:100,000 epinephrine (24)
Outcomes	**Soft tissue anaesthesia** (VAS ranging from zero (deep or total anaesthesia with no sensibility) to 10 (no anaesthesia or lower lip with normal sensibility) • Success: using a little scrub over the anaesthetized area with a standardized piece of cotton; using a needle and a controlled continuous pressure device (48/50) • Duration: self-reported by the patient using a form (48/50) • Lateral spread of anaesthesia in mm Soft tissues tested: centre of the lower lip **Adverse events** (48/50) • Patients were instructed to describe and record any problems that they experienced
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated through a raffle to receive the anaesthetic ME (Drug 1) or AR (Drug 2)" Quote (from correspondence): the patients "just picked up a card yellow (drug 1) or green (drug 2)" "It was done at the same time as the first injection"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Both patient and operator were blind (double-blind) to which anaesthetic were receiving or using. For this, in a separate room and under aseptic conditions, the commercial anaesthetic solutions were transferred from the original container to disposable insulin syringes in an amount of 0.18 mL (10% of an anaesthetic cartridge) (authors 1&2)" Quote (from correspondence): "The second research assistant kept a research instrument in order to collect data. A third research assistant conducted the injections. Both assistants didn't know which drug was to be administered, since I prepared the insulin syringes with the anaesthetic solutions in a separated room. With time they tried to guess which drug was being administered but it was only supposition. Patients and assistants had no access to the anaesthetic packs, garbage, or other information that could reveal the drugs" "This code was maintained during all research"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both patient and operator were blind (double-blind) to which anaesthetic were receiving or using. For this, in a separate room and under aseptic conditions, the commercial anaesthetic solutions were transferred from the original container to disposable insulin syringes in an amount of 0.18 mL (10% of an anaesthetic cartridge) (authors 1&2)" Comment: Participants and personnel would not be able to identify the local anaesthetic used
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Both patient and operator were blind (double-blind) to which anaesthetic were receiving or using. For this, in a separate room and under aseptic conditions, the commercial anaesthetic solutions were transferred from the original container to disposable insulin syringes in an amount of 0.18 mL (10% of an anaesthetic cartridge) (authors 1&2)" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was npt possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Quote: "One subject was excluded due to a possibly delayed-type hypersensitivity to articaine", but accounted for. Groups remained equal in numbers; therefore risk was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Quote: "One subject was excluded due to a possibly delayed-type hypersensitivity to articaine", but accounted for. Duration of soft tissue anaesthesia measured for all 24 participants (confirmed by study author). Groups remained balanced; therefore risk was graded as low
Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "One subject was excluded due to a possibly delayed-type hypersensitivity to articaine", but accounted for. Groups remained equal in numbers; therefore risk was graded as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Bouloux 1999

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Australia) **Participants:** 23 enrolled, 23 completing the study. Mean age 24 years, ranging from 18 to 41 years. 9 male, 14 female **Inclusion criteria** • Required elective surgical removal of 2 or 4 bilaterally symmetrical, impacted third molars **Exclusion criteria** • Known allergy to local anaesthetic agents • History of cardiovascular disease • Thyrotoxicosis • Immunosuppression • Diabetes mellitus • Liver disease
Interventions	Patients received the following injections: • Mandibular third molars: inferior alveolar nerve block (3.4 mL), lingual nerve block (0.5 mL), infiltration for the long buccal nerve (0.5 mL) • Maxillary third molars: buccal infiltration (2.0 mL), greater palatine nerve block (0.2 mL) with either: • 2% lidocaine, 1:100,000 epinephrine (23) • 0.5% bupivacaine, 1:200,000 epinephrine (23)
Outcomes	**Clinical anaesthesia** during third molar removal • Depth of anaesthesia: VAS score determined after contact with study author (VAS = 100 mm horizontal line with no pain to the left and worst pain imaginable to the right). Global pain scale: none, a little, some, a lot, and worst possible (46/46) **Soft tissue anaesthesia** • Success: pain on probing (46/46) Tissues tested: mucosa adjacent to tooth **Adverse effects** reported (46/46) • Changes in blood pressure and heart rate measured • Postoperative pain/infection measured in terms of medication consumed (400 mg ibuprofen tablet and phenoxymethyl penicillin consumption) and visual analogue/global pain scales detailed
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The choice of local anaesthetic and the side to be operated on was decided by the toss of a coin"
Allocation concealment (selection bias)	Low risk	Quote: "The choice of local anaesthetic and the side to be operated on was decided by the toss of a coin" Quote (from correspondence): "The randomization of the side to be operated and the choice of local anaesthetic were both made with a coin toss on the same day as the procedure several hours before the patient arrived. This was done by a research coordinator. The operator (myself) was blinded to the local anaesthetic but was informed of the side to be operating on"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The dental anaesthetic cartridges (2.2 mL) used were marked only as 'A' or 'B'" Quote (from correspondence): "The labels were removed from the cartridges by the research coordinator and were supplied to the investigator (myself) only labelled as A or B. The outcome assessor was myself and I was blinded to all data except surgical side" Comment: Labelling all cartridges containing similar local anaesthetic with a similar code (A or B) may allow identification of a solution by personnel recording the outcomes and the administrator in a cross-over study if he or she also recorded outcomes, if properties of the solutions were markedly different. However, properties of the 2 solutions did not allow identification (only success - not duration - was measured). Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person. Identification of the local anaesthetic by participants was not possible. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The dental anaesthetic cartridges (2.2 mL) used were marked only as 'A' or 'B'" Quote (from correspondence): "The labels were removed from the cartridges by the research coordinator and were supplied to the investigator (myself) only labelled as A or B. The outcome assessor was myself and I was blinded to all data except surgical side" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Bradley 1969

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Australia) **Participants:** 254 enrolled, 254 completing the study. Ages ranging from 5 to 14 years. 131 male, 123 female **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Infiltration or "mandibular" injection of the following solutions: • 2% lidocaine, 1:100,000 epinephrine (138) • 3% mepivacaine, no vasoconstrictor (116) Volume of solution was observed to range from 0.8 mL to 3.6 mL, with 1.8 mL given in: • 53% of infiltrations • 82% of mandibular injections
Outcomes	**Clinical anaesthesia** during various dental procedures including restorative (65%), surgical (19%), root extirpation (10%), miscellaneous (5%) • Success: graded as Grade A: complete elimination of pain at the site of operation; Grade B: presence of some pain or discomfort but a second injection was not necessary; Grade C: anaesthesia was unsatisfactory and a second injection was necessary (254/254) **Soft tissue anaesthesia** • Onset: method of measurement not reported but assumed to be onset of soft tissue anaesthesia (number assessed not clear) • Median duration: measured from onset time until all symptoms of anaesthesia in the tissues were gone (number assessed not clear) Teeth/soft/hard tissues tested: All tissues were tested, depending on what procedure was being performed **Adverse effects** reported (254/254)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The drug used for each injection was administered in a randomized double-blind procedure" Comment: detailed methods not reported
Allocation concealment (selection bias)	Unclear risk	Comment: detailed methods not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: detailed methods not reported. Although participants were unlikely to identify the local anaesthetic because it was contained in a syringe, there was no mention of whether the administrator was blinded, or whether a specific pre-determined method was used to inject the solution and minimize variation. Therefore risk was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: detailed methods not reported Comment: no details of the blinding method reported; not clear if the person recording participants' outcomes was a different person than the person administering the local anaesthetic, who may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	The number of participants who had onset measured is not known. Therefore, attrition bias was judged as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	The number of participants who had duration measured is not known. Therefore, attrition bias was judged as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Burns 2004

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 40 enrolled, 40 completing the study. Average age 27 years, ranging from 19 to 47 years. 20 male, 20 female **Inclusion criteria:** All participants were in good health (written health history and oral questioning) and were not taking any medication that would alter pain perception **Exclusion criteria:** not reported
Interventions	Palatal-anterior superior alveolar injections (1.4 mL) of either: • 2% lidocaine, 1:100,000 epinephrine (40) • 3% mepivacaine, no vasoconstrictor (40)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset (insufficient numbers for matched pair comparison; therefore onset presented as a range) • Success: percentage of successfully anaesthetized teeth (80/80) • Incidence of anaesthesia: number of 80 readings over time Teeth tested: maxillary central incisors, lateral incisors, and canines
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, we randomly assigned the two anaesthetic solutions six-digit numbers from a random number table. We assigned the random numbers to a subject to designate which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Each solution had a six-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Two blinded cartridges of the same anaesthetic solution were placed in letter-sized envelopes that were labelled with the six-digit code, so the code would not have to be broken in the event of a broken or dropped cartridge. Only the random numbers were recorded on the data collection sheets to further blind the experiment" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Two blinded cartridges of the same anaesthetic solution were placed in letter-sized envelopes that were labelled with the six-digit code, so the code would not have to be broken in the event of a broken or dropped cartridge. Only the random numbers were recorded on the data collection sheets to further blind the experiment" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Onset presented as a range of values for participants with successful anaesthesia
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Caldas 2015

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 30 enrolled, 30 completing the study. Mean age of females 22.6 ± 3.7 years and of males 24.3 ± 4.7 years. 12 male, 18 female **Inclusion criteria** • Having a right upper canine tooth without decay or extensive restorations, trauma, endodontic treatment, and responsive to electric stimulation (pulp tester) • Not having used any drug that could change pain perception (anti-inflammatory, analgesic, anxiolytic, anti-depressant) **Exclusion criteria** • Pregnancy • History of hypersensitivity to studied drugs (lidocaine) and to preservatives of tested solutions (sodium bisulphite) • Evidence of organic dysfunction or significant deviation from normal • History of psychiatric disease that could impair the ability to give written consent • History of drug addiction or abusive alcohol consumption
Interventions	Maxillary buccal infiltration (1.8 mL) using the following: • 2% lidocaine, 1:100,000 epinephrine (30) • 2% lidocaine, 1:200,000 epinephrine (30)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive lack of responses within the initial 10 minutes (60/60) • Onset: time between end of anaesthetic injection until lack of stimulation perception (60/60) • Duration: return to response baseline threshold (60/60) Teeth tested: maxillary right canine **Soft tissue anaesthesia** • Duration: tested using a 30-gauge needle (60/60) Soft tissues tested: vestibular mucosa **Adverse events** (60/60) • Pain on injection (VAS 0–10) • Pain following injection (VAS 0–10) (scale: 0 = no pain, 10 = most severe pain) • Other adverse events (blood pressure, partial oxygen concentration, and heart rate measured)
Notes	Non-industry funding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Volunteers were submitted to two more clinical sessions, with a previously defined randomized order for the application of both tested solutions and with a minimum interval of two weeks between anesthesias" Comment: detailed methods not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Volunteers were submitted to two more clinical sessions, with a previously defined randomized order for the application of both tested solutions and with a minimum interval of two weeks between anesthesias" Comment: detailed methods not reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The investigator-operator was not involved in the evaluation of anesthetic parameters, characterizing a double-blind study" Comment: Despite no details of the blinding method, risk of bias was graded low, as identification of the local anaesthetic by participants was unlikely. Also, a pre-determined method for administration was used by personnel, which minimized variation
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The investigator-operator was not involved in the evaluation of anesthetic parameters, characterizing a double-blind study" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants is unlikely. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Chapman 1988

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Australia) **Participants:** 20 enrolled, 20 completing the study. Mean age 22 years, ranging from 17 to 33 years. 14 male, 6 female **Inclusion criteria:** not stated, although healthy patients requiring removal of both impacted mandibular third molar teeth participated in the study **Exclusion criteria:** not stated
Interventions	Inferior alveolar nerve block (2.0 mL) and buccal infiltration (1.0 mL) of either: • 2% lidocaine, 1:80,000 epinephrine (20) • 0.5% bupivacaine, 1:200,000 epinephrine (20)
Outcomes	**Clinical anaesthesia** during extraction of teeth • Success: "Satisfactory depth of anaesthesia was established within a further five minutes with both agents" (40/40) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: lower lip anaesthesia in minutes (40/40) • Duration: mental anaesthesia in minutes (number assessed not clear) Soft tissues tested: lower lip/mental region. Methods of testing unclear **Adverse effects** related to extractions were reported (number assessed not clear) • Postoperative pain (100 mm VAS, 0 at one end and 10 at the other, representing 'no pain' and 'the worst pain imaginable') • Analgesic requirements
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The order of use of anaesthetics was randomly selected before the first operation" Comment: exact method of generation of randomized sequence not stated

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "The order of use of anaesthetics was randomly selected before the first operation" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The survey was conducted as a double-blind cross-over study" Comment: No details of the blinding method were reported (bupivacaine was loaded into a 10-mL syringe), although identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The survey was conducted as a double-blind cross-over study" Comment: No details of the blinding method were reported, and it is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, who may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	The number of participants who had duration measured was not reported. This was probably measured by participants at home, but it is not clear whether all participants provided data. Therefore, attrition bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	The number of participants who had adverse events measured is not known. It is not clear whether all participants returned to provide the data. Therefore, attrition bias is graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Chilton 1971

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** private practice (United States of America) **Participants:** 821 enrolled, 821 completing the study. Average age 39 years. 304 male, 517 female. 424 (52%) required periodontal treatment; 397 (48%) required endodontic treatment **Inclusion criteria:** none **Exclusion criteria** • May have objected for medical or personal reasons to participate • History of cardiovascular disease and patient's physician thought that a vasoconstrictor was contraindicated • Emergency patients already receiving a local anaesthetic from their dentist
Interventions	Infiltration: average volume for periodontal procedures = 1.5 mL (greater volume for endo procedures). Inferior alveolar nerve block: average volume for periodontal procedures = 1.8 mL (including supplemental injections) of either: • 2% lidocaine, 1:100,000 epinephrine (204) • 4% prilocaine, 1:200,000 epinephrine (202) • 4% prilocaine, 1:300,000 epinephrine: not commercially available (210) • 4% prilocaine, no epinephrine (205)
Outcomes	**Clinical anaesthesia** during endodontic and periodontal procedures (821/821) • Grade of anaesthesia (at the end of the procedure, the operator classified the anaesthesia as complete, complete but worn off, partial no reinjection, partial reinjection, failure) • Overall performance (assessed as excellent, adequate, poor) Hard/soft tissues tested: various **Soft tissue anaesthesia** • Onset: time to sensation of numbness or tingling (788/821) • Duration: Participants returned a postcard with time when "sense of numbness" disappeared (566/821) Soft tissues tested: those relevant to the type of injection **Adverse effects** were measured (821/821)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Cartridges of local anaesthetic were provided by the manufacturer and coded randomly with a sealed copy of the code" Comment: method of randomization not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Cartridges of local anaesthetic were provided by the manufacturer and coded randomly with a sealed copy of the code" Comment: method of randomization not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Cartridges of local anaesthetic were provided by the manufacturer and coded randomly with a sealed copy of the code" Comment: Despite limited details of the blinding method, risk of bias was graded as low, as identification of the local anaesthetic by participants and personnel is unlikely
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Cartridges of local anaesthetic were provided by the manufacturer and coded randomly with a sealed copy of the code" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient); therefore risk of bias was graded as low, as identification of the local anaesthetic by participants and personnel recording the outcomes is unlikely
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	The true dropout rate could be calculated only if those having soft tissue success were known, as successful soft tissue anaesthesia is required to measure onset. Soft tissue anaesthesia may have been present in those who had failure of anaesthesia during endodontic and periodontal treatment, or may have been absent, meaning it was not measured. As this measurement was performed in a clinic, immediately before treatment, the only minor differences in proportions between groups would be due to differences in soft tissue success. Therefore attrition bias has been graded as low risk
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Of the total number of participants recruited who had onset of soft tissue anaesthesia measured, some did not have duration of soft tissue anaesthesia measured **Inferior alveolar nerve block** • Duration: 2% lidocaine, 1:100,000 epinephrine: 17/67 (25%); 4% prilocaine, 1:200,000 epinephrine: 18/68 (26%); 4% prilocaine, no epinephrine: 25/72 (35%) **Infiltration** • Duration: 2% lidocaine, 1:100,000 epinephrine: 26/124 (21%); 4% prilocaine, 1:200,000 epinephrine: 45/134 (34%); 4% prilocaine, no epinephrine: 33/113 (29%) For duration of soft tissue anaesthesia, no dropouts would occur if the number of participants having duration measured was equal to the number having soft tissue onset measured. However, dropout rates of up to 35% were seen. This was probably due to lack of compliance of patients returning postcards with time when "sense of numbness" disappeared. Therefore attrition bias was graded as high risk
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Claffey 2004

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** 25 male, 47 female • 2% lidocaine with 1:100,000 epinephrine group: 40 enrolled, 35 completing the study. Age 31 years ± 8.0 (SD), ranging from 20 to 48 years. Initial pain: 96 ± 31 • 4% articaine with 1:100,000 epinephrine group: 39 enrolled, 37 completing the study. Age 31 years ± 8.3 (SD), ranging from 21 to 53 years. Initial pain: 96 ± 32 **Inclusion criteria** • Teeth given an initial diagnosis of irreversible pulpitis (based on standard endodontic criteria such as spontaneous pain, prolonged sensitivity to thermal changes, sensitivity to pressure or percussion, and pulpal exposure). Only teeth that could respond to cold were included in this study **Exclusion criteria** • Teeth that were non-responsive to cold, or whose pain was relieved by cold, were not included in the study • Patients whose medical condition contraindicated the use of vasoconstrictor were not included
Interventions	Inferior alveolar nerve blocks (2.2 mL) of: • 2% lidocaine, 1:100,000 epinephrine (40) • 4% articaine, 1:100,000 epinephrine (39)
Outcomes	**Clinical anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: ability to access and instrument the tooth without pain (VAS score of zero or mild pain ≤ 54 mm) on a Heft-Parker visual analogue scale (79/79) • Extent of access achieved when the patient felt pain (within dentine, entering the pulp chamber, or initial file placement) Teeth tested: mandibular first premolars, second premolars, first molars, second molars **Soft tissue anaesthesia** on questioning • Success: numbness at 15 minutes post injection (79/79) Soft tissues tested: lower lip
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each patient was randomly assigned a five-digit random number to determine which anaesthetic solution was administered" Quote (from correspondence): "Each solution had a five-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The appropriate five digit random number was placed on a label, which was affixed to the outside of the Luer-Lok syringe. Only the random number was used on the data collection sheets to further blind the experiment" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The appropriate five digit random number was placed on a label, which was affixed to the outside of the Luer-Lok syringe. Only the random number was used on the data collection sheets to further blind the experiment" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Quote: "At 15-min post-injection, the patient was questioned regarding lip numbness. If profound lip numbness was not recorded, the block was considered missed and the patient was eliminated from the study" "A total of 7 patients, two using the articaine solution and five using the lidocaine solution, did not have profound lip numbness at 15 min and were not included in the data analysis of the 72 patients. The number of these missed blocks was not statistically different between the articaine and lidocaine solutions (P = 0.43). One hundred percent of the subjects used for data analysis had subjective lip anaesthesia with either the articaine and lidocaine solutions" Comment: Patients excluded were accounted for and used for calculation of overall failure
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Cohen 1993

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** endodontic specialist practice (United States of America) **Participants** • 2% lidocaine, 1:100,000 epinephrine group: 27 enrolled, 27 completing the study • 3% mepivacaine, no vasoconstrictor group: 34 enrolled, 34 completing the study Proportion of male and female patients, age and initial pain not reported Quote (from correspondence): "We did not record age or sex for the purposes of the study. The overwhelming number of our patients are adults past school age" **Inclusion criteria** • Teeth with an initial diagnosis of irreversible pulpitis (based on standard endodontic criteria such as spontaneous pain, prolonged sensitivity to thermal changes, sensitivity to pressure or percussion, and pulpal exposure). Only teeth that could respond to cold were included in this study **Exclusion criteria** • Teeth that were non-responsive to cold, or whose pain was relieved by cold • Patients whose medical condition contraindicated the use of vasoconstrictor
Interventions	Inferior alveolar nerve blocks (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine (27) • 3% mepivacaine, no vasoconstrictor (34)
Outcomes	**Clinical anaesthesia** during pulpotomy in teeth with irreversible pulpitis • Success: Participant reported any discomfort felt on access to pulp chamber (61/61) **Pulpal anaesthesia** tested with dichlorodifluoromethane • Success (61/61) Teeth tested: mandibular molars **Soft tissue anaesthesia** on questioning (61/61) • Success: Patient reported that the lower lip was "all numb" (61/61) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomly, 27 subjects were injected with 2% lidocaine HCl with 1:100,000 epinephrine and 34 subjects were injected with 3% mepivacaine HCl with no vasoconstrictor" Quote (from correspondence): "Forty sealed envelopes for each of the two treatment modalities were prepared. At each case an envelope was opened. Thus the treatment choice was decided by lottery"
Allocation concealment (selection bias)	Low risk	Quote: "Randomly, 27 subjects were injected with 2% lidocaine HCl with 1:100,000 epinephrine and 34 subjects were injected with 3% mepivacaine HCl with no vasoconstrictor" Quote (from correspondence): "Forty sealed envelopes for each of the two treatment modalities were prepared. At each case an envelope was opened. Thus the treatment choice was decided by lottery"
Blinding of participants and personnel (performance bias)	Low risk	Quote (from correspondence): "There was no blinding. Since we were following our normal protocol for treatment of emergencies in our office, the patients were not informed that we were involved in a study" Comment: Despite no attempt to blind the local anaesthetic cartridges, risk of bias was graded as low, as identification of the local anaesthetic by participants is unlikely. Also, a pre-determined method of administration was used by personnel, which minimized variation
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (from correspondence): "There was no blinding. Since we were following our normal protocol for treatment of emergencies in our office, the patients were not informed that we were involved in a study" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by the local anaesthetic administrator. Identification of the local anaesthetic by participants is unlikely, and whether the clinician recording the outcomes influenced patients is not clear. Therefore risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Colombini 2006

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 20 enrolled, 20 completing the study. Mean age 23.1 years, ranging from 18 to 37 years. 13 male, 7 female **Inclusion criteria** • Symmetrically positioned full bony impacted lower third molars in patients with no systemic illness and no signs of inflammation or infection at extraction sites **Exclusion criteria** • Medical history of cardiovascular and kidney diseases; gastrointestinal bleeding or ulceration; allergic reaction to local anaesthetic; allergy to aspirin, ibuprofen, or any similar drugs; and pregnancy or current lactation
Interventions	Inferior alveolar nerve block (1.8 mL) and local infiltration (0.9 mL) of: • 2% mepivacaine, 1:100,000 epinephrine (20) • 4% articaine, 1:100,000 epinephrine (20)
Outcomes	**Clinical anaesthesia** during impacted lower third molar removal (40/40) • Total volume of anaesthetic solution used during surgery • Number of participants who required additional local anaesthesia along with the initial amount Teeth tested: mandibular third molars **Soft tissue anaesthesia** (loss of sensibility of the soft tissues) • Onset determined by loss of sensibility of the inferior lip, the corresponding half of the tongue, and the mucosa (40/40) • Duration of postoperative anaesthesia Soft tissues tested: inferior lip, tongue, and mucosa **Adverse effects** were reported (40/40)
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "For local anaesthesia, in the first appointment the patients were randomly selected to receive either 2% mepivacaine or 4% articaine (both with 1:100,000 epinephrine). In the second appointment, the local anaesthetic not used previously was then administered in a crossed manner" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "For local anaesthesia, in the first appointment the patients were randomly selected to receive either 2% mepivacaine or 4% articaine (both with 1:100,000 epinephrine). In the second appointment, the local anaesthetic not used previously was then administered in a crossed manner" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "This was a double-blind study; neither the surgeon nor the patients were aware of the local anaesthetic being tested at the 2 different appointments" Comment: No details of the blinding method were reported, and it is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "This was a double-blind study; neither the surgeon nor the patients were aware of the local anaesthetic being tested at the 2 different appointments" Comment: No details of the blinding method were reported, and it is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, who may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Costa 2005

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 20 enrolled, 20 completing the study. Ages ranging from 18 to 31 years. 5 male, 15 female **Inclusion criteria:** healthy individuals with 3 maxillary posterior teeth on the same side with initial stage occlusal caries or indication for occlusal sealant **Exclusion criteria:** none
Interventions	Maxillary buccal infiltration (of 1.8 mL) of each of the following: • 2% lidocaine, 1:100,000 epinephrine (20) • 4% articaine, 1:100,000 epinephrine (20) • 4% articaine, 1:200,000 epinephrine (20)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset (60/60) • Duration (60/60) This was performed while patients were having restorative dentistry treatment of low capacity Teeth tested: maxillary posterior teeth
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The tooth that would be treated randomly received 1.8 ml of one of three local anaesthetics" Quote (from correspondence): "Three cartridges for local anaesthetic (2% lidocaine with 1:100.000 epinephrine; 4% articaine with 1:200.000 epinephrine and 4% articaine with 1:100.000 epinephrine) were placed in 20 sealed envelopes, so we had one envelope for each patient. The anaesthetic was always administered by the same researcher, who placed the hand inside the envelope and randomly chose one cartridge to be used in each session, leaving the remaining cartridges inside the envelope to be used in the next sessions, until the last application of sealant in the last tooth. The tooth where the sealant was going to be applied in each appointment was also chosen randomly"
Allocation concealment (selection bias)	Low risk	Quote: "The tooth that would be treated randomly received 1.8 ml of one of three local anaesthetics" Quote (from correspondence): "Three cartridges for local anaesthetic (2% lidocaine with 1:100.000 epinephrine; 4% articaine with 1:200.000 epinephrine and 4% articaine with 1:100.000 epinephrine) were placed in 20 sealed envelopes, so we had one envelope for each patient. The anaesthetic was always administered by the same researcher, who placed the hand inside the envelope and randomly chose one cartridge to be used in each session, leaving the remaining cartridges inside the envelope to be used in the next sessions, until the last application of sealant in the last tooth. The tooth where the sealant was going to be applied in each appointment was also chosen randomly" Quote (from correspondence): “In the Costa research where there were 3 cartridges inside the envelopes, some masking tape was put around the cartridges after they were used in order to identify appointment 1,2, or 3, and they were transferred to another envelope that had the number of the patient. These envelopes were only opened at the end of the experiments by a third researcher, too. The ink was removed with 70% alcohol and thus could see the identification of articaine solution with 1:100,000 or 1:200,000 epinephrine. The lidocaine solution presented rubber different colour (orange)"
Blinding of participants and personnel (performance bias)	Low risk	Quote (from correspondence): "In this case, only one cartridge per appointment was used and the infiltration injection delivered by myself in all cases. All cartridges were masked and in every experiment I chose one randomly from an envelope before using it to administer the injection to that patient. After that, I left the workstation and immediately after the researcher (Costa) would enter to apply the electric tests and sealant" Comment: Identification of the local anaesthetic by participants and administrator was not possible, and a pre-determined method for administration was used by personnel, which minimized variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote (from correspondence): "In this case, only one cartridge per appointment was used and the infiltration injection delivered by myself in all cases. All cartridges were masked and in every experiment I chose one randomly from an envelope before using it to administer the injection to that patient. After that, I left the workstation and immediately after the researcher (Costa) would enter to apply the electric tests and sealant" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete (confirmed by study author)
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete (confirmed by study author)
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Dagher 1997

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Lebanon) **Participants:** 30 enrolled, 30 completing the study. Mean age 32 years, range 22 to 50 years. 22 male, 8 female **Inclusion criteria** • Participants were in good health and were not taking any medications that would alter pain perception • Clinical examinations indicated that all teeth were free of caries, large restorations, and periodontal disease, and that none had a history of trauma or sensitivity **Exclusion criteria:** none stated
Interventions	Inferior alveolar nerve blocks (1.8 mL) of each of the following: • 2% lidocaine, 1:50,000 epinephrine (30) • 2% lidocaine, 1:80,000 epinephrine (30) • 2% lidocaine, 1:100,000 epinephrine (30)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Slow onset of anaesthesia (participant achieved 2 consecutive 80 readings after 16 minutes) • Anaesthesia of short duration (participant achieved 2 consecutive 80 readings, lost the 80 readings, and never regained them within the 50-minute period) • Non-continuous anaesthesia (participant achieved 2 consecutive 80 readings, lost the 80 readings, and then regained the 80 readings during the 50 minutes) • Success: 80 reading achieved within 16 minutes and sustained for the remainder of the 50-minute test period (90/90) • Failure (participant never achieved 2 consecutive 80 readings during the 50 minutes) • Incidence at each time interval Teeth tested: mandibular first molar, first premolar, and lateral incisor **Soft tissue anaesthesia** (feeling of numbness/response to mucosal sticks) • Success: Participant felt numbness within 20 minutes and/or did not respond to mucosal sticks (90/90) Soft tissues tested: labial and lingual to the premolar and buccal to the first molar
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The sequence of solution administration was determined randomly" Comment: exact method of generation of randomized sequence not stated Quote (from correspondence: conversation with author, P. Machtou): "Randomization sequence was generated from random number tables"
Allocation concealment (selection bias)	Unclear risk	Quote: "The sequence of solution administration was determined randomly" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All of the injections were given blindly by one operator" Comment: Despite no details of the blinding method, risk of bias was graded as low, as identification of the local anaesthetic by participants is unlikely. Also, a pre-determined method for administration was used by personnel, which minimized variation
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "All preinjection and post-injection tests were done by a trained person who was blinded to the solutions injected" Comment: No details of the blinding method were reported, and it is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, who may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Bias	Authors' judgement	Support for judgement
Other bias	Low risk	Comment: no other bias present

Donaldson 1987

Methods	Randomized controlled simulated scenario trial (treatment carried out but anaesthesia determined with a pulp tester), cross-over study design
Participants	**Location:** university (Canada) **Participants:** 81 enrolled, 71 completing the study. Mean age 20.91 years. 23 male, 48 female **Inclusion criteria** • Requiring contralateral injections for restorative dental treatment • Bilateral teeth in identical condition requiring identical treatment • Aged as follows: children: 6 to 16 years of age; adults: 18 to 40 years of age **Exclusion criteria** • Sensitivity to any of the product contents • Previous sensitivity to local anaesthetics of the amide group • Pregnancy or suspected pregnancy • Taking medication that could influence the analgesic assessment such as narcotic or non-narcotic analgesics, anti-inflammatory, anxiolytic, antipsychotic, and antihistamine agents • Sepsis near the proposed injection site • Any degree of heart block, existing neurological disease, severe hypertension, diabetes, or thyrotoxicosis, and those undergoing orthodontic treatment
Interventions	Inferior alveolar nerve block (1.8 mL) or maxillary infiltration (0.6 mL) of 1 of the following: • 4% articaine, 1:200,000 epinephrine (71) • 4% prilocaine, 1:200,000 epinephrine (71)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset of anaesthesia (134/142) • Duration of anaesthesia (presented in life tables; therefore data not used) • Success (percentage of successful anaesthesia: presented only graphically) Teeth tested: not stated
Notes	Industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized into two groups" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized into two groups" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Cartridges were blinded so that neither the patient nor the investigator was aware of which product was being given (Fig. 3)" Comment: A photograph of the coded cartridge is shown in the journal article, which would prevent participants, personnel, and outcome assessors from identifying the local anaesthetic used. Risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Cartridges were blinded so that neither the patient nor the investigator was aware of which product was being given (Fig. 3)" Comment: A photograph of the coded cartridge is shown in the journal article, which would prevent participants, personnel, and outcome assessors from identifying the local anaesthetic used. Risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Of 142 possible episodes of anaesthesia, onset was measured only in those with successful pulpal anaesthesia (134 times). Therefore, 3% (1/38) of prilocaine infiltrations, 6% (2/33) of prilocaine IANBs, 5% (2/38) of articaine infiltrations, and 9% (3/33) of articaine IANBs were not measured. Attrition bias was graded as low risk, as losses were balanced across groups and for the same reasons
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Comment: Study was supported by Astra Pharmaceuticals

Elbay 2016

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Turkey) **Participants:** 60 enrolled, 60 completing the study Pulpotomy: • Mean age 7.5 ± 0.8 years • 14 male, 16 female Extraction: • Mean age 9.93 ± 1.3 years • 11 male, 19 female **Inclusion criteria** • 6 to 12 years of age • Required similar procedures (extraction or pulpotomy) bilaterally on primary molars with similar operative difficulties and demonstrated positive or definitely positive behaviour (Frankl scale 3 or 4) during pre-treatment behavioural assessment **Exclusion criteria** • Allergies to local anaesthetics or sulphites • History of significant medical conditions or dental treatment • Site of active pathosis in the area of injection • Taking any medication that might affect anaesthetic assessment
Interventions	Inferior alveolar nerve blocks (0.9 mL) of each of the following: • 2% lidocaine, 1:80,000 epinephrine (60) • 3% mepivacaine, no vasoconstrictor (60)

Outcomes	**Clinical anaesthesia** during extraction or pulpotomy • Success: percentage of successful anaesthesia, using the Face, Legs, Activity, Cry, Consolability (FLACC) behavioural pain assessment scale (1: Face; 2: Legs; 3: Activity; 4: Crying; 5: Consolability), each given a pain score of 0–2, for a total behavioural pain score in the range of 0–10, as follows: 0 = relaxed and comfortable (no pain); 1–3 = mild discomfort; 4–6 = moderate pain; and 7–10 = severe discomfort and/or pain (120/120) These were recorded for: • Stages of pulpotomy ◦ During use of the high-speed handpiece on enamel ◦ During use of the low-speed handpiece on dentine ◦ During removal of the coronal pulp ◦ During placement of matrix band ◦ During tooth restoration • Stages of extraction ◦ During probing of the buccal and lingual gingival sulci ◦ During gingival elevation and elevation ◦ During extraction Teeth tested: mandibular primary molars **Soft tissue anaesthesia** • Success: probing of the buccal and lingual gingival sulci, tested as part of the extraction procedure (120/120) • Duration: details recorded on a form, given postoperatively (number assessed not clear) Soft tissues tested: relevant soft tissues (success) and lower lip and soft tissues (duration) **Adverse events reported** (120/120) • Pain on injection: FLACC behavioural pain assessment scale • Local postoperative complications (none, mild, moderate); details recorded on a form, given postoperatively
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The local anesthetic used in a patient at the first appointment was randomly selected using a computer-generated list"
Allocation concealment (selection bias)	Unclear risk	Quote: "The local anesthetic used in a patient at the first appointment was randomly selected using a computer-generated list" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "A dental assistant put the anesthetic solution in the device, so both the practitioner and the rater were blinded to the local anesthetic solution being tested" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A dental assistant put the anesthetic solution in the device, so both the practitioner and the rater were blinded to the local anesthetic solution being tested" "A single practitioner who had 6 months of experience using the CCDS performed all injections and operations and a single rater who was not the practitioner evaluated the anesthetic solutions" Comment: Outcomes were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	The number of participants who had duration measured was not reported. This was probably measured by participants at home, but it is not clear whether all participants provided data. Therefore, attrition bias is graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Epstein 1965

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** hospital (United States of America) **Participants:** 420 enrolled, 420 completing the study (277 without 3% prilocaine, 1:300,000 epinephrine). Mean age 33 years, range 10 to 75 years. 128 male, 255 female **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Maxillary buccal infiltration (1.2 mL) and inferior alveolar nerve block (1.5 mL) of: • 2% lidocaine, 1:100,000 epinephrine (133) • 3% prilocaine, 1:300,000 epinephrine (not commercially available) • 4% prilocaine, no vasoconstrictor (144)
Outcomes	**Clinical anaesthesia** during extraction (18/18), restorative dentistry (246/246) or other procedures (13/13) (total = 277/277) • Grade of anaesthesia (incidence of complete, complete but worn off, partial, or failure) • Overall impression (incidence of excellent, adequate, or poor) Teeth tested: various (individual teeth not stated) **Soft tissue anaesthesia** • Duration: self-reported by questionnaire (191/277) Soft tissues tested: lower lip and adjacent hard/soft tissues **Adverse effects** were reported (278/278?)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The solutions were distributed in a completely randomized sequence" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "The solutions were distributed in a completely randomized sequence" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "In the present study, the anaesthetic cartridges were coded by the manufacturer. A sealed copy of the code was provided to the investigator" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "In the present study, the anaesthetic cartridges were coded by the manufacturer. A sealed copy of the code was provided to the investigator" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording the outcomes was not possible. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Of the total number of participants recruited who had complete, completely worn off, or partial anaesthesia, when soft tissue anaesthesia may occur, some did not have duration of soft tissue anaesthesia measured: **Inferior alveolar nerve block** • 2% lidocaine, 100,000 epinephrine: 11/62 (18%); 4% prilocaine, no vasoconstrictor: 8/57 (14%) **Infiltration** • 2% lidocaine, 100,000 epinephrine: 28/68 (41%); 4% prilocaine, no vasoconstrictor: 34/85 (40%) For duration of soft tissue anaesthesia, the dropout rate could be calculated only if those having soft tissue success were known. No dropouts would occur if the number of participants having duration measured was equal to the number having soft tissue anaesthetic success. Soft tissue anaesthesia may have been present in those who had failure of anaesthesia during treatment, or may have been absent, meaning it was not measured. However, even with these difficulties in measuring attrition rate, dropout rates of up to 41% were seen. Therefore attrition bias has been graded as high risk
Incomplete outcome data (attrition bias) Adverse events	Low risk	The total number of injections administered is mentioned throughout the journal article (277 for the solutions commercially available). However in Table 9, which presents data related to adverse events, the total is 278, which is possibly due to a typographical error. However, all patients appear to have been assessed; therefore risk was graded as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Epstein 1969

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** hospital (United States of America) **Participants:** 816 enrolled, 816 completing the study (610 participants, not including the 4% prilocaine, 1:300,000 epinephrine group). Median age 32 years. 272 male, 544 female **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Maxillary buccal infiltration (average = 1.2 mL) and inferior alveolar nerve block (average = 1.4 mL) of: • 2% lidocaine, 1:100,000 epinephrine (197) • 4% prilocaine, 1:200,000 epinephrine (209) • 4% prilocaine, 1:300,000 epinephrine (not commercially available) • 4% prilocaine, no vasoconstrictor (204)
Outcomes	**Clinical anaesthesia** during extraction or restorative dentistry, including restorations, endodontic and periodontal procedures (610/610) • Grade of anaesthesia (incidence of complete, complete but worn off, partial, or failure) • Overall impression (incidence of excellent, adequate, or poor) Teeth tested: various (individual teeth not stated) **Soft tissue anaesthesia** • Duration: self-reported by questionnaire (359/610) Soft tissues tested: relevant soft tissues **Adverse effects** were reported (599/610)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eight hundred and sixteen injections were administered from single-coded cartridges, about equally divided among the four solutions in randomized sequence" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Eight hundred and sixteen injections were administered from single-coded cartridges, about equally divided among the four solutions in randomized sequence" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The anaesthetic cartridges were coded by the manufacturer, and a sealed copy of the code was provided" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The anaesthetic cartridges were coded by the manufacturer, and a sealed copy of the code was provided" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Of the total number of participants recruited who had complete, completely worn off, or partial anaesthesia, when soft tissue anaesthesia may occur, some did not have duration of soft tissue anaesthesia measured **Inferior alveolar nerve block** • 2% lidocaine, 1:100,000 epinephrine: 26/78 (33%); 4% prilocaine, 1:200,000 epinephrine: 26/72 (36%); 4% prilocaine, no vasoconstrictor: 24/75 (32%) **Infiltration** • 2% lidocaine, 1:100,000 epinephrine: 46/113 (41%); 4% prilocaine, 1:200,000 epinephrine: 51/132 (39%); 4% prilocaine, no vasoconstrictor: 65/127 (51%) For duration of soft tissue anaesthesia, the dropout rate could be calculated only if those having soft tissue success were known. No dropouts would occur if the number of participants having duration measured was equal to the number having soft tissue anaesthetic success. Soft tissue anaesthesia may have been present in those who had failure of anaesthesia during treatment, or may have been absent, meaning it was not measured. However, even with these difficulties in measuring attrition rate, dropout rates of up to 51% were seen. Therefore attrition bias has been graded as high risk
Incomplete outcome data (attrition bias) Adverse events	Low risk	Dropouts were few and occurred in similar numbers over all groups

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Evans 2008

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 80 enrolled, 80 completing the study Lateral incisor: • Mean age 25 years, ranging from 20 to 36 years • 25 male, 15 female First molar: • Mean age 24 years, ranging from 20 to 33 years • 21 male, 19 female **Inclusion criteria:** All participants were in good health and were not taking any medication that would alter pain perception **Exclusion criteria** • Younger than 18 or older than 65 years of age • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions • Taking any medications that may affect anaesthetic assessment • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	Maxillary buccal infiltration (1.8 mL) of each of the following: • 2% lidocaine, 1:100,000 epinephrine (80) • 4% articaine, 1:100,000 epinephrine (80)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset of anaesthesia (lateral incisors and first molars: 60/80) • Success: percentage of successful anaesthesia (lateral incisors and first molars: 80/80) • Incidence: number of maximum pulp tester readings (80) over time Teeth tested: maxillary lateral incisors and first molars **Adverse effects** were reported (lateral incisors and first molars: 80/80) • Pain of injection (Heft-Parker visual analogue scale) • Post-injection pain (Heft-Parker visual analogue scale) • Post-injection complications
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The two anaesthetic solutions were randomly assigned six-digit numbers from a random number table. The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Each solution had a six-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The two anaesthetic solutions were randomly assigned six-digit numbers from a random number table. The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The lidocaine and articaine cartridges were masked with opaque labels, and the cartridge caps and plungers were masked with a black felt-tip marker. The corresponding six-digit codes were written on each cartridge label" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The lidocaine and articaine cartridges were masked with opaque labels, and the cartridge caps and plungers were masked with a black felt-tip marker. The corresponding six-digit codes were written on each cartridge label" "Trained personnel who were blinded to the anaesthetic solutions administered all preinjection and post-injection tests" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Onset of pulpal anaesthesia was tested on 60 occasions (for those experiencing successful anaesthesia: 29 cases of lidocaine, 31 cases of articaine). As numbers assessed were balanced across groups, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Fernandez 2005

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 39 enrolled, 39 completing the study. Mean age 24 years, ranging from 20 to 30 years. 26 male, 13 female **Inclusion criteria:** Participants were in good health and were not taking any medications that would alter their perception of pain **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks (1.8 mL) of each of the following: • 2% lidocaine, 1:100,000 epinephrine (39) • 0.5% bupivacaine, 1:200,000 epinephrine (39)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset of anaesthesia (68/78) • Duration of anaesthesia (68/78) • Success (78/78) • Incidence (number of maximum pulp tester readings (80) over time) Teeth tested: mandibular lateral incisor, first premolar, second premolar, first molar, second molar **Soft tissue anaesthesia** tested by pinching/palpating lip + completing post-injection questionnaire • Onset (78/78) • Duration (78/78) • Success (78/78) Soft tissues tested: lower lip
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The two anaesthetic solutions were randomly assigned six digit numbers from a random number table. Each subject was randomly assigned to one of the two solutions to determine which anaesthetic solution was to be administered at each appointment" "Forty IAN block injections were administered on the right side and 38 injections were administered on the left side. The same side randomly chosen for the first injection was used again for the second injection" Quote (from correspondence): "Each solution had a six-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote: "The two anaesthetic solutions were randomly assigned six digit numbers from a random number table. Each subject was randomly assigned to one of the two solutions to determine which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Masking the appropriate cartridges with opaque tape, which were labelled with the six-digit numbers, blinded the anaesthetic solutions administered" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the random numbers were recorded on the data collection and post-injection survey sheets to blind the experiment" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Onset of pulpal anaesthesia was tested on 68 occasions (for those experiencing successful pulpal anaesthesia: 36 cases of lidocaine, 32 cases of articaine). As numbers assessed were balanced across groups, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Duration of pulpal anaesthesia was tested on 68 occasions (for those experiencing successful pulpal anaesthesia: 36 cases of lidocaine, 32 cases of articaine). As numbers assessed were balanced across groups, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Fertig 1968

Methods	Randomized controlled clinical trial (treatment carried out but soft tissue duration determined in a simulated scenario). Study design not reported, although appears to be a parallel design from the data presented
Participants	**Location:** private practice (United States of America) **Participants:** 79 enrolled, 79 completing the study (62 excluding 4% prilocaine, 1:300,000 epinephrine). Mean age, age range, and male:female ratio not reported **Inclusion criteria:** none reported **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks (1.8 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine (17) • 4% prilocaine, no vasoconstrictor (23) • 4% prilocaine, 1:200,000 epinephrine (22) • 4% prilocaine, 1:300,000 epinephrine (not commercially available)
Outcomes	**Soft tissue anaesthesia** tested by the patient reporting disappearance of anaesthesia • Duration: postal questionnaire (62/62) Soft tissues tested: soft tissues on injected side
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The solutions were randomly assigned to all patients for whom local anaesthesia was indicated for a particular endodontic procedure or for periodontic surgery" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "The solutions were randomly assigned to all patients for whom local anaesthesia was indicated for a particular endodontic procedure or for periodontic surgery" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: exact method of blinding not stated Comment: Despite no details of the blinding method, risk of bias was graded as low, as identification of the local anaesthetic by participants is unlikely. Also, a pre-determined method of administration was not used by personnel, which would minimize variation. Therefore, risk of bias was graded as unclear

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: exact method of blinding not stated Comment: No details of the blinding method were reported, and it is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, who may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Forloine 2010

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 50 enrolled, 50 completing the study. Mean age 25 years, ranging from 18 to 57 years. 27 male, 23 female **Inclusion criteria:** Participants were in good health **Exclusion criteria** • Younger than 18 or older than 65 years of age • Allergies to local anaesthetics or sulphites • Pregnancy; history of significant medical conditions (ASA II or higher) • Taking any medications that might affect anaesthetic assessment (over-the-counter analgesic medications, opioids, antidepressants, alcohol) • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	High-tuberosity maxillary second division nerve blocks (4.0 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine (50) • 3% mepivacaine, no vasoconstrictor (50)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset of anaesthesia (92/100) • Anaesthesia of short duration (participant achieved 2 consecutive 80 readings, lost the 80 readings, and never regained them within the 60-minute period) • Success (100/100) • Incidence (number of maximum pulp tester readings (80) over time) Teeth tested: maxillary molars, premolars, canines, lateral incisors, and central incisors **Soft tissue anaesthesia** (participants questioned regarding subjective numbness) • Success (figures could not be calculated) Soft tissues tested: lip, side of nose, and lower eyelid **Adverse effects** were reported (100/100) • Pain of injection (Heft-Parker visual analogue scale) • Post-injection pain (Heft-Parker visual analogue scale) • Other adverse events
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, the 2 anaesthetic formulations were randomly assigned 5-digit numbers from a random number table. Each subject was randomly assigned to the right or left side. The order of the anaesthetic solutions was also randomly assigned to determine which solutions were to be administered at each appointment" Quote (from correspondence): "Each solution had a five-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Before the experiment, the 2 anaesthetic formulations were randomly assigned 5-digit numbers from a random number table. Each subject was randomly assigned to the right or left side. The order of the anaesthetic solutions was also randomly assigned to determine which solutions were to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Each syringe was masked with an opaque label, and the corresponding 5-digit code was written on each label" "Only the random numbers were recorded on the data collection and post-injection survey sheets to blind the experiment" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the random numbers were recorded on the data collection and post-injection survey sheets to blind the experiment" "Trained personnel who were blinded to the type of anaesthetic solution used performed all preinjection and post-injection tests" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Quote: "If the subject did not obtain any signs of subjective anaesthesia after 20 minutes, the block was considered a failure, and the subject was dismissed and reappointed for 1 week later" "Twelve percent (6 of 50) of the subjects did not achieve soft issue anaesthesia within 20 minutes of the injection but did achieve soft tissue anaesthesia at a subsequent appointment. Five subjects (3 lidocaine and 2 mepivacaine) were eliminated from the study because they did not attain soft tissue anaesthesia after 2 attempts. Five additional subjects were recruited to replace these subjects" Comment: Two attempts were made to anaesthetize some participants, and additional participants were recruited when a second attempt to anaesthetize them also failed. It was not possible to re-calculate success accounting for these participants. However, the numbers involved were small compared with total group sizes, and those eliminated were well balanced across groups. Therefore risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Onset of pulpal anaesthesia was tested on 92 occasions (for those experiencing successful anaesthesia: 46 cases of lidocaine, 46 cases of mepivacaine). As numbers assessed were equal across groups, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Gangarosa 1967

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** hospital/private practice (United States of America) **Participants:** 542 enrolled, 542 completing the study? Mean age, age range, and male:female ratio not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Mandibular block and infiltration (volume not stated) of each of the following: • 2% lidocaine, 1:100,000 epinephrine (112?) • 2% lidocaine, 1:300,000 epinephrine (not commercially available) • 4% prilocaine, no vasoconstrictor (57?) • 3% prilocaine, 1:100,000 epinephrine (not commercially available) • 3% prilocaine, 1:300,000 epinephrine (not commercially available)
Outcomes	**Clinical anaesthesia** during various general practice, oral surgery, and periodontal procedures • Success: satisfactory or unsatisfactory (number assessed not clear) Teeth tested: not reported **Soft tissue anaesthesia** • Onset of anaesthesia: rapid, medium, slow, re-injection needed (exact method and number assessed not clear, but assumed to be onset of soft tissue anaesthesia) • Duration: post-injection postcard (number assessed not clear) Soft tissues tested: not reported **Adverse effects** were reported (number assessed not clear)
Notes	Industry and non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each cartridge of anaesthetic was supplied in a randomly numbered coin-envelope" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Each cartridge of anaesthetic was supplied in a randomly numbered coin-envelope" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The anaesthetics were kindly supplied in blinded cartridges by Astra Pharmaceuticals, Inc" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The anaesthetics were kindly supplied in blinded cartridges by Astra Pharmaceuticals, Inc" Comment: Limited details of the blinding method were reported, and it is not clear whether the person recording participant outcomes was a different person from the one administering the local anaesthetic, who may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	Comment: Total number of participants is not the same as those in Figures 1 and 2 attached to the graphs in the journal article. Therefore some participants may have been excluded, but this is not clear
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	The number of participants who had onset of soft tissue anaesthesia measured was not stated; therefore risk of bias was rated as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	The number of participants who had duration of soft tissue anaesthesia measured was not stated; therefore risk of attrition bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	The number of participants who had adverse events measured was not stated; therefore risk of attrition bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Quote: "The anaesthetics were kindly supplied in blinded cartridges by Astra Pharmaceuticals, Inc"

Gazal 2015

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Saudi Arabia) **Participants:** 25 enrolled, 23 completing the study. Mean age 29.9 years, ranging from 17 to 60 years. 25 male, 0 female (determined following correspondence) **Inclusion criteria** • 17 to 60 years of age • Intact first molar teeth • American Society of Anesthesiologists (ASA) I patients (ASA, 1994) **Exclusion criteria** • Allergy to local anaesthetics • Bilateral non-vital or missing lower first molar teeth, with bilateral composite or amalgam fillings of lower first molar teeth • Inability to complete the trial • Taking medications (determined following correspondence)
Interventions	Inferior alveolar nerve block (1.8 mL) of 2% mepivacaine, 1:100,000 epinephrine, followed by mandibular buccal infiltration (1.8 mL) of 1 of the following solutions: • 2% mepivacaine, 1:100,000 epinephrine (23) • 4% articaine, 1:100,000 epinephrine (23)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success (46/46) • Onset of anaesthesia (46/46) • Duration of anaesthesia (46/46) Teeth tested: mandibular first molars
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was achieved by an independent researcher (KHA)" Quote (from correspondence): "For allocation of the participants, a computer-generated list of random numbers was used by the study coordinator, who was not involved in the treatments or assessments"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was achieved by an independent researcher (KHA)" Quote (from correspondence): "The treatment alternative was placed in envelopes, numbered in accordance with the randomization list and concealed. An independent dental assistant consequently revealed the allocation and made preparation for local anesthetic injection"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both volunteers and the researcher testing anesthetic effectiveness (American Medical Association) were not aware to which local anesthetic buccal infiltration regimen was administered" Quote (from correspondence): "The local anesthetic cartilages were covered with opaque stickers to hide the type of local anesthetic which will be used. Dental Surgeon and assessors involved in treatment were blinded to which type of local anesthetic the patient was allocated" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Both volunteers and the researcher testing anesthetic effectiveness (American Medical Association) were not aware to which local anesthetic buccal infiltration regimen, was administered" Quote (from correspondence): "The local anesthetic cartilages were covered with opaque stickers to hide the type of local anesthetic which will be used. Dental Surgeon and assessors involved in treatment were blinded to which type of local anesthetic the patient was allocated" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Quote: "Two volunteers were excluded due to faint following first local anesthetic IANB injection (one volunteer from mepivacaine regimen and one from articaine regimen) and were excluded consequently according to study protocol and official clearances" Comment: Patients excluded were accounted for, were used for calculation of pulp anaesthesia success, and were balanced across groups
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Quote: "Two volunteers were excluded due to faint following first local anesthetic IANB injection (one volunteer from mepivacaine regimen and one from articaine regimen) and were excluded consequently according to study protocol and official clearances" Comment: Patients excluded were accounted for, were few, and were balanced across groups
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Quote: "Two volunteers were excluded due to faint following first local anesthetic IANB injection (one volunteer from mepivacaine regimen and one from articaine regimen) and were excluded consequently according to study protocol and official clearances" Comment: Patients excluded were accounted for, were few, and were balanced across groups
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Gazal 2017

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Saudi Arabia) **Participants:** 94 enrolled, 90 completing the study. Age ranging from 16 to 70 years. All participants were male **Inclusion criteria** • Males 16 to 70 years of age • Scheduled for extraction of upper tooth • American Society of Anesthesiology I or II patients • Ability to understand and co-operate with requirements of the protocol; ability and willingness to exercise an appropriate written informed consent **Exclusion criteria** • Allergy to local anaesthesia • Needing multiple upper teeth extracted • Having a vomiting reflex
Interventions	Maxillary buccal infiltration (1.4 mL) and palatal infiltration (0.4 mL) using the following: • 2% mepivacaine, 1:100,000 epinephrine (45) • 4% articaine, 1:100,000 epinephrine (45)
Outcomes	**Clinical anaesthesia** during extraction of teeth • Success: absence of pain (90/90) • Onset: Tooth and bone were tested by applying percussion with a mirror after just the buccal infiltration – confirmed by study author (90/90) Teeth tested: various maxillary teeth **Soft tissue anaesthesia** • Onset: measured by probing; tested after just buccal infiltration – confirmed by study author (90/90) Soft tissues tested: adjacent soft tissues in the maxilla **Adverse effects** were reported (90/90) • Pain of injection (0–100 mm VAS)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Prior to the study, a researcher allocated the sequence of patient identity numbers to either the test or control group" Comment: detailed methods not reported. Following contact with study author, it was confirmed that "Slips of paper with test group or control group were placed in opaque envelopes and sealed. This was done by a secretary who was not associated with the study" Envelopes were then randomly chosen and allocated to each patient by the main study author
Allocation concealment (selection bias)	Low risk	Quote: "Slips of paper with 4% articaine (test group) or 2% mepivacaine (control group) were placed in opaque envelopes and sealed by a secretary who was not associated with the study. These envelopes had been numbered sequentially on their outside with the patient identity number and were attached to the patient's dental hospital treatment record"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both patients and the researcher testing anesthetic effectiveness were not aware to which local anesthetic BI regimen was administered" Comment: detailed methods not reported. Following contact with the study author, it was determined that the cartridges were masked and the syringe was loaded by a dental assistant. Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Both patients and the researcher testing anesthetic effectiveness were not aware to which local anesthetic BI regimen was administered" Comment: detailed methods not reported. Following contact with the study author, it was confirmed that the assessor was not present when the injections were administered. In addition, the cartridges were masked. Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Gregorio 2008

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 50 enrolled, 50 completing the study. Mean age 21.84 ± 0.65 years, ranging from 18 to 35 years. 21 male, 29 female **Inclusion criteria:** good health and not taking any medication that would alter pain perception **Exclusion criteria:** references given for eligibility/exclusion criteria within the study
Interventions	Inferior alveolar nerve block (1.8 mL) and local infiltration (0.9 mL) of each of the following: • 4% articaine, 1:200,000 epinephrine (50) • 0.5% bupivacaine, 1:200,000 epinephrine (50)
Outcomes	**Clinical anaesthesia** during surgical removal of lower third molars • Total volume of anaesthetic solution used during surgery • Quality of anaesthesia used during surgery evaluated by the surgeon (3-point category rating scale: no discomfort reported by the patient during the surgery; any discomfort reported by the patient during the surgery, without the need for additional anaesthesia; any discomfort reported by the patient during the surgery, with the need for additional anaesthesia) (100/100) Patients were divided into 2 categories: • Surgeries requiring osteotomy (28 patients) • Surgeries not requiring osteotomy (22 patients) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset of anaesthesia: "loss of sensibility of the inferior lip, the corresponding half of the tongue and the mucosa" (100/100) Soft tissues tested: inferior lip, corresponding half of the tongue, and mucosa **Adverse effects** were reported (100/100)
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "For local anaesthesia, in the first appointment, the patients randomly received A200 or B200 solutions" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "For local anaesthesia, in the first appointment, the patients randomly received A200 or B200 solutions" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This was a double-blind study, that is, neither the surgeon nor the patients were aware of the local anaesthetic being used at the two different appointments, since the labels of both anaesthetics were pulled off and the cartridges were coded by someone not directly involved in data collection prior to the patient visit" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "This was a double-blind study, that is, neither the surgeon nor the patients were aware of the local anaesthetic being used at the two different appointments, since the labels of both anaesthetics were pulled off and the cartridges were coded by someone not directly involved in data collection prior to the patient visit" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Gross 2007

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 65 enrolled, 65 completing the study Lateral incisor: • 20 males and 12 females. Mean age 24 years, ranging from 18 to 36 years First molar: • 20 males and 13 females. Mean age 24 years, ranging from 18 to 36 years **Inclusion criteria:** good health and not taking any medication that would alter pain perception **Exclusion criteria** • Younger than 18 years or older than 60 years • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions • Use of any medications that may affect anaesthetic assessment • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	Maxillary buccal infiltration (1.8 mL) of each of the following: • 2% lidocaine, 1:100,000 epinephrine (65) • 0.5% bupivacaine, 1:200,000 epinephrine (65)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset (104/130) • Success (130/130) • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: maxillary lateral incisors and first molars **Soft tissue anaesthesia** tested by palpation • Onset: data not available and measured only at 15 minutes (communication with study author) • Duration (130/130) Soft tissues tested: upper lip and buccal gingiva
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, the two anaesthetic solutions were randomly assigned four-digit numbers from a random number table. The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered and which side (right or left) was to be used at each appointment" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Before the experiment, the two anaesthetic solutions were randomly assigned four-digit numbers from a random number table. The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered and which side (right or left) was to be used at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Each anaesthetic cartridge had its label removed and was masked with an opaque label. The random number was written on the label. Only the random numbers were recorded on the data collection sheets to further blind the experiment" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Each anaesthetic cartridge had its label removed and was masked with an opaque label. The random number was written on the label. Only the random numbers were recorded on the data collection sheets to further blind the experiment" "Trained personnel, who were blinded to the anaesthetic solutions, administered all pre-injection and post-injection tests" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 48 occasions on first molar teeth (for those experiencing successful anaesthesia: 27 cases of lidocaine, 21 cases of bupivacaine). As numbers were reduced in both groups for the same reason and were fairly balanced across groups, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Haas 1990

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Canada) **Participants:** 20 enrolled, with 20 completing the study. Mean age 25 years, ranging from 22 to 32 years. Male:female ratio not reported **Inclusion criteria** • Between 18 and 50 years of age • In good medical health • Teeth 13, 23, 33, and 43 present in satisfactory condition with no restorations • Must give informed written consent before participation **Exclusion criteria** • Allergies to amide local anaesthetics or any of the ingredients in the cartridges • Pregnant females • History of any significant medical conditions • Taking any medications that may influence the anaesthetic assessment, such as analgesics, anti-inflammatories, or sedative drugs • Active oral or dental pathology or undergoing treatment at tested sites • Presence of restorative dental work at tested sites • Inability to provide informed consent
Interventions	Mandibular and maxillary infiltration (1.5 mL) of each of the following: • 4% prilocaine, 1:200,000 epinephrine (20) • 4% articaine, 1:200,000 epinephrine (20)
Outcomes	**Pulpal anaesthesia** and **soft tissue anaesthesia** (both tested with an electric pulp tester) • Success (40/40) • Time course of anaesthesia (degree of anaesthesia over time) Teeth tested: all maxillary and mandibular canine teeth
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was double blind, with the order of drug administration randomized" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "This study was double blind, with the order of drug administration randomized" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This study was double blind, with the order of drug administration randomized" "The cartridges were covered with an adhesive paper label, leaving only a 4 mm window adjacent to the cap to allow visualization of the aspiration results, yet concealing the type of anaesthetic. The cartridge was loaded by a nurse assistant so that neither the subject nor the dentist administering the anaesthetic was aware of which preparation was being injected" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "This study was double blind, with the order of drug administration randomized" "The cartridges were covered with an adhesive paper label, leaving only a 4 mm window adjacent to the cap to allow visualization of the aspiration results, yet concealing the type of anaesthetic. The cartridge was loaded by a nurse assistant so that neither the subject nor the dentist administering the anaesthetic was aware of which preparation was being injected" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants was not possible. It is not clear whether the person recording participant outcomes was blinded and was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Haas 1991

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Canada) **Participants:** 20 enrolled, 20 completing the study. Mean age 26 years, ranging from 23 to 41 years. Male:female ratio not reported **Inclusion criteria** • Between 18 and 50 years of age • In good medical health • Teeth 17, 27, 37, and 47 present in satisfactory condition with no restorations • Must give informed written consent before participation **Exclusion criteria** • Allergies to amide local anaesthetic or any of the ingredients in the cartridges • Pregnant females • History of any significant medical condition • Taking any medication that may influence the anaesthetic assessment, such as analgesics, anti-inflammatories, or sedative drugs • Active oral or dental pathology or undergoing treatment at tested sites • Presence of restorative dental work at tested sites • Inability to provide informed consent
Interventions	Mandibular and maxillary infiltration (1.5 mL) of each of the following: • 4% prilocaine, 1:200,000 epinephrine (20) • 4% articaine, 1:200,000 epinephrine (20)
Outcomes	**Pulpal anaesthesia** and **soft tissue anaesthesia** (tested with an electric pulp tester) • Success (40/40) • Time course of anaesthesia (degree of anaesthesia over time) Teeth tested: all maxillary and mandibular second molar teeth
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was double blind, with the order of drug administration randomized" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "This study was double blind, with the order of drug administration randomized" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This study was double blind, with the order of drug administration randomized" "The cartridges were covered with an adhesive paper label, leaving only a 4-mm window adjacent to the cap to allow visualization of the aspiration results, yet concealing the type of anaesthetic. The cartridge was loaded by a nurse assistant so that neither the subject nor the dentist administering the anaesthetic was aware of which preparation was being injected" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "This study was double blind, with the order of drug administration randomized" "The cartridges were covered with an adhesive paper label, leaving only a 4 mm window adjacent to the cap to allow visualization of the aspiration results, yet concealing the type of anaesthetic. The cartridge was loaded by a nurse assistant so that neither the subject nor the dentist administering the anaesthetic was aware of which preparation was being injected" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants was not possible. It is not clear whether the person recording participant outcomes was blinded and was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Haase 2008

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 73 enrolled, 73 completing the study. Mean age 27 years, ranging from 20 to 36 years. 46 male, 27 female **Inclusion criteria:** in good health and not taking any medications that would alter their perception of pain **Exclusion criteria** • Younger than 18 years, older than 60 years • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions • Taking any medications that may affect anaesthetic assessment • Active sites of pathosis in the area of injection • Inability to give informed consent
Interventions	Inferior alveolar nerve blocks (1.8 mL) of: • 4% articaine, 1:100,000 epinephrine followed by additional mandibular buccal infiltration (1.8 mL) of: • 4% articaine, 1:100,000 epinephrine (73) • 2% lidocaine, 1:100,000 epinephrine (73)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success (146/146) • Incidence (number of maximum pulp tester readings (80) over time) Teeth tested: mandibular first molars **Adverse effects** were reported (146/146) • Pain at each stage of injection (Heft-Parker visual analogue scale) • Post-injection pain (Heft-Parker visual analogue scale) • Post-injection complications
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, we randomly assigned to the two anaesthetic solutions six-digit numbers from a random number table. In addition, we randomly assigned each subject to each of the two formulations to determine which anaesthetic formulation was to be administered at each appointment" Quote (from correspondence): "Each solution had a six-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote: "Before the experiment, we randomly assigned to the two anaesthetic solutions six-digit numbers from a random number table. In addition, we randomly assigned each subject to each of the two formulations to determine which anaesthetic formulation was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "We recorded only the random numbers on the data collection sheets to further blind the experiment" "Research personnel masked the lidocaine and articaine cartridges with opaque labels and the cartridge caps and rubber plungers with a black felt-tip marker. The research personnel wrote the corresponding six-digit codes on each cartridge label" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "We recorded only the random numbers on the data collection sheets to further blind the experiment" "Research personnel masked the lidocaine and articaine cartridges with opaque labels and the cartridge caps and rubber plungers with a black felt-tip marker. The research personnel wrote the corresponding six-digit codes on each cartridge label" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Hellden 1974

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Sweden) **Participants:** 420 enrolled, 420 completing the study. 280 excluding 0.25% bupivacaine, 1:200,000 epinephrine. Mean age 26.7 ± 0.6 years (standard error). 198 male, 222 female **Inclusion criteria:** healthy outpatients **Exclusion criteria:** none reported
Interventions	Mandibular block (1.8 mL) and local infiltration (1.8 mL) of each of the following: • 2% lidocaine, 1:80,000 epinephrine (140) • 0.25% bupivacaine, 1:200,000 epinephrine (140 - not commercially available) • 3% mepivacaine, no vasoconstrictor (140) An additional 1.8 mL was used if supplemental anaesthesia was required
Outcomes	**Clinical anaesthesia** during surgical removal of lower third molars • Need for supplemental injections • Anaesthetic effect: "good" when treatment could be carried out without any additional injection; "poor" when supplementary injection was necessary; and "acceptable" when the patient felt some pain but no additional anaesthetic injection was necessary (280/280) Teeth tested (and adjacent soft and hard tissues): mandibular third molars **Soft tissue anaesthesia** tested by self-assessment • Duration: Patients also received questionnaires in which they stated the time at which anaesthesia wore off (number assessed not clear) Soft tissues tested: lower lip and adjacent soft tissues **Adverse effects** were reported (280/280)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The test solutions were delivered as a random series of code-marked cartridges of 1.8 mL" Comment: exact method of generation of randomized sequence not stated Quote (from correspondence): "Sorry. I cannot answer your question. The 'Bofors coordinating person' (pharmacist + statistician) was (now dead) extremely strict"
Allocation concealment (selection bias)	Low risk	Quote: "The test solutions were delivered as a random series of code-marked cartridges of 1.8 ml" Comment: exact method of allocation concealment not stated Quote (from correspondence): "The nurses followed a consecutive list/table (from Bofors) telling which one of the 'code-numbered boxes' they should 'serve' the surgeon. Thus, neither the nurse nor the surgeon had any knowledge about the type of anaesthetics that was used in the individual case" "The surgeon had to use the substance that was served"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study was performed as a double blind test" "The test solutions were delivered as a random series of code-marked cartridges of 1.8 ml. Three cartridges of each anaesthetic type were marked with the same code and corresponded to one of the patients and to one of the operators. In this way each operator treated an equal number of patients from each test group" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The study was performed as a double blind test" "The test solutions were delivered as a random series of code-marked cartridges of 1.8 ml. Three cartridges of each anaesthetic type were marked with the same code and corresponded to one of the patients and to one of the operators. In this way each operator treated an equal number of patients from each test group" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	The exact number of participants who had duration of soft tissue anaesthesia measured is not clear. It is likely that it would have been possible to measure this for all participants, but the compliance of participants in returning questionnaires was not mentioned in the study. Attrition bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Hersh 1995

Methods	Randomized controlled simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** 60 enrolled, 60 completing the study • Lidocaine: 20 enrolled, 20 completing the study. Mean age 26.1 years. 14 male, 6 female • Mepivacaine: 21 enrolled, 21 completing the study. Mean age 27 years. 11 male, 10 female • Prilocaine: 19 enrolled, 19 completing the study. Mean age 26.7 years. 13 male, 6 female **Inclusion criteria:** had to be in good general health and to have no contraindications to local anaesthetics or vasoconstrictors **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks.(1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine (20) • 4% prilocaine, no vasoconstrictor (21) • 3% mepivacaine, no vasoconstrictor (19)
Outcomes	**Soft tissue anaesthesia** (visual analogue scale: 100 mm bar connecting the words "not numb" and "completely numb") • Success: score ≥ 50 mm (60/60) • Onset: represented graphically; exact figures not presented (number assessed not clear) • Duration: represented graphically; exact figures not presented (number assessed not clear) • Mean lip numbness over time • Peak numbness effects Soft tissues tested: lower lip and tongue
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Study participants were randomly assigned to receive a single cartridge (1.8 mL) of 2 percent lido-epi, 3 percent mepivacaine or 4 percent prilocaine" Quote (from correspondence): "Randomization I believe was in blocks of three"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Study participants were randomly assigned to receive a single cartridge (1.8 mL) of 2 percent lido-epi, 3 percent mepivacaine or 4 percent prilocaine" Quote (from correspondence): "Randomization code broken at end of study and after all queries addressed"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "To maintain double-blind conditions, we instructed a dental assistant who was not directly involved in the study to remove the product identification label from each cartridge before loading it into a syringe" Quote (from correspondence): "Label of identifying local anaesthetic removed by research assistant and replaced by code # which she kept. Person injecting and subject blinded to treatment. Randomization code broken at end of study and after all queries addressed" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "To maintain double-blind conditions, we instructed a dental assistant who was not directly involved in the study to remove the product identification label from each cartridge before loading it into a syringe" Quote (from correspondence): "Label of identifying local anaesthetic removed by research assistant and replaced by code # which she kept. Person injecting and subject blinded to treatment. Randomzation code broken at end of study and after all queries addressed" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	The number of participants who had onset of anaesthesia measured was not stated; therefore risk of attrition bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	The number of participants who had duration of anaesthesia measured was not stated; therefore risk of attrition bias was graded as unclear. Data were not used for meta-analysis

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Hinkley 1991

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 30 enrolled, 28 completing the study. Mean age 27 years, ranging from 23 to 42 years. 19 male, 11 female **Inclusion criteria:** in good health and not taking any medications that would alter pain perception **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks (1.8 mL) of • 4% prilocaine, 1:200,000 epinephrine (28) • 2% mepivacaine, 1:20,000 levonordefrin (28) • 2% lidocaine, 1:100,000 epinephrine (28)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 80 reading achieved within 16 minutes and sustained for the remainder of the 50-minute test period (84/84) • Failure: Participant never achieved 2 consecutive 80 readings during the 50 minutes • Onset (44/84) • Slow onset: Participant achieved 2 consecutive 80 readings after 16 minutes • Anaesthesia of short duration: Participant achieved 2 consecutive 80 readings, lost the 80 readings, and never regained them within the 50-minute period • Incidence: number of maximum pulp tester readings (80) over time • Mean elevation of pulp test readings above baseline readings for all participants with anaesthetic failures Teeth tested: mandibular first molars, first premolars, and lateral incisors **Soft tissue anaesthesia** (participant felt numbness upon sticking of the alveolar mucosa with a sharp explorer) • Success (84/84) • Onset (84/84) Tissues tested: lower lip, tongue, and mucosa
Notes	Non-industry funding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each subject randomly received each anaesthetic solution on three successive appointments spaced at least 1 week apart" "The subjects were randomly assigned to one of six letter (ABC) combinations to determine the sequence of solution administration" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The three cartridges for each subject were placed in an autoclave bag with the numbers recorded on the outside showing the injection order" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Each anaesthetic cartridge label was removed and masked with tape. A four-digit random number, corresponding to the letter designation, was written on each cartridge" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All pre- and post-injection tests were done by trained personnel who were blinded to the solutions injected" "Each anaesthetic cartridge label was removed and masked with tape, A four-digit random number, corresponding to the letter designation, was written on each cartridge" Quote (from correspondence): "The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Quote: "Two of 30 subjects achieved lip numbness only after 20 min and were excluded from the data analysis. All of the remaining 28 subjects had subjective lip and tongue numbness" Comment: It was not stated which solution this was with, or whether the other 2 solutions were tested. The study author was contacted, but the identity of the solutions used for the 2 cases of failed lip anaesthesia was not known. However, as the study used a cross-over design, the groups remained balanced. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Quote: "Two of 30 subjects achieved lip numbness only after 20 min and were excluded from the data analysis. All of the remaining 28 subjects had subjective lip and tongue numbness" Comment: It was not stated which solution this was with, or whether the other 2 solutions were tested. The study author was contacted, but the identity of the solutions used for the 2 cases of failed lip anaesthesia was not known. However, as the study used a cross-over design, the groups remained balanced. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 44 occasions on first molar teeth (for those experiencing successful anaesthesia: 15 cases of lidocaine, 16 cases of mepivacaine, and 13 cases of prilocaine). As numbers were reduced in all groups for the same reasons and were fairly balanced across groups, risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Quote: "Two of 30 subjects achieved lip numbness only after 20 min and were excluded from the data analysis. All of the remaining 28 subjects had subjective lip and tongue numbness" Comment: It was not stated which solution this was with, or whether the other 2 solutions were tested. The study author was contacted, but the identity of the solutions used for the 2 cases of failed lip anaesthesia was not known. However, as the study used a cross-over design, the groups remained balanced. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Hosseini 2016

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (Iran) **Participants:** 50 enrolled, 47 completing the study. Mean age/age range not stated. Proportion of male and female patients not reported **Inclusion criteria** • Healthy adult patients • Over 18 years of age • Having a first maxillary molar with asymptomatic irreversible pulpitis and normal periapical radiographic appearance (pulp vitality was determined by a positive response to EPT (SybronEndo, Glendora, CA) and cold tests (Roeko Endo Frost, Roeko, Hangenav, Germany), and a diagnosis of asymptomatic irreversible pulpitis was made if prolonged response to cold (longer than 10 seconds) was noted) **Exclusion criteria** • Presence of systemic disorders • Any known sensitivity to 2% lidocaine or 4% articaine or epinephrine • Widening of periodontal ligament space, or presence of a periapical radiolucency • Pregnancy • Using any type of analgesic 12 hours before treatment • Moderate to severe spontaneous pain; tenderness to percussion • Having a tooth not suitable for simple restorative treatment because of extensive caries or periodontal problems
Interventions	Maxillary buccal infiltration (1.8 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine (25) • 4% articaine, 1:100,000 epinephrine (25)
Outcomes	**Pulpal anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success: ability to access and instrument the tooth without pain (VAS score of zero or mild pain < 54 mm) on a Heft-Parker visual analogue scale (47/50) Teeth tested: maxillary first molars **Adverse events** reported (47/50)
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly divided into two groups of 25 patients each. In order to randomize the patients, the number of patients in each group were written on paper and kept in a sealed box. The practitioner who administrated the local anesthesia chose one of the papers and based on the number, the patient was assigned to one of the groups"
Allocation concealment (selection bias)	Low risk	Quote: "The patients were randomly divided into two groups of 25 patients each. In order to randomize the patients, the number of patients in each group were written on paper and kept in a sealed box. The practitioner who administrated the local anesthesia chose one of the papers and based on the number, the patient was assigned to one of the groups"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "A trained dental assistant loaded the local anesthetic solutions in masked disposable syringes and coded them (three digit alpha-numeric) for treatment sequence" "To ensure blinding, neither the operator nor the assistant had knowledge of the solution tested" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A trained dental assistant loaded the local anesthetic solutions in masked disposable syringes and coded them (three digit alpha-numeric) for treatment sequence" "To ensure blinding, neither the operator nor the assistant had knowledge of the solution tested" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: Only patients for whom a different, definitive diagnosis was determined during treatment were excluded (23 assessed in the lidocaine group (1 pulp was not exposed, another pulp was necrotic) and 24 assessed in the articaine group (pulp not exposed in 1 case)). As numbers were reduced in both groups for similar reasons and were fairly balanced across groups, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: Only patients for whom a different, definitive diagnosis was determined during treatment were excluded (23 assessed in the lidocaine group (1 pulp was not exposed, another pulp was necrotic) and 24 assessed in the articaine group (pulp not exposed in 1 case)). As numbers were reduced in both groups for similar reasons and were fairly balanced across groups, risk of attrition bias was rated as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Jaber 2010

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United Kingdom) **Participants:** 31 enrolled, 31 completing the study. Mean age 24.4 years, standard deviation 4.4 years. 11 male, 20 female **Inclusion criteria:** healthy adult volunteers 18 years of age and older **Exclusion criteria** • Younger than 18 years of age • Unable to give informed consent • Bleeding disorder • Facial anaesthesia or paraesthesia • Allergies to local anaesthetic drugs • Pregnant at the time of the study • Teeth that responded negatively to baseline pulp testing or with key test teeth missing
Interventions	Injections were given as: • 1 buccal (0.9 mL) and 1 lingual infiltration (0.9 mL) • 1 buccal infiltration (1.8 mL) and 1 dummy lingual infiltration of the following • 4% articaine with 1:100,000 epinephrine (31) • 2% lidocaine with 1:100,000 epinephrine (31)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 80 reading within 15 minutes and maintained for 45 minutes post injection (62/62) • Onset (number assessed not clear) • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: mandibular central incisor and contralateral mandibular lateral incisor **Adverse effects** reported (62/62) • Discomfort associated with each of the injections reported (100 mm visual analogue scale)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Local anaesthetic regimens were applied in randomized order determined by a web-based program (http://department.obg.cuhk.edu.hk/researchsupport/random_integer.asp)"
Allocation concealment (selection bias)	Low risk	Quote: "Local anaesthetic regimens were applied in randomized order determined by a web-based program (http://department.obg.cuhk.edu.hk/researchsupport/random_integer.asp)" Quote (from correspondence): "The researcher recording the outcome measures who also did the data analyses was blinded till the last data collection – he was given the code after completion of data collection"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Dummy injections were administered to blind the volunteers to the method of anaesthesia used" Comment (from correspondence): There was no blinding for participants and personnel to the type of local anaesthetic used Comment: Despite no blinding of participants and personnel administering the local anaesthetic, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore, risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Efficacy of anaesthesia was determined by electronic pulp testing (Analytic Technology) by an investigator blinded to the injections administered" Quote (from correspondence): "The researcher recording the outcome measures who also did the data analyses was blinded till the last data collection – he was given the code after completion of data collection" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	Comment: Exact number of participants having onset of pulpal anaesthesia measured was not stated. Data were not used in meta-analysis
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Jain 2016

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (India) **Participants:** 70 enrolled, 70 completing the study. Age ranging from 18 to 45 years. Proportion of male and female patients not reported **Inclusion criteria** • Between 18 and 45 years of age • Prophylactic removal of third molars • Acute pericoronitis in relation to lower third molar region • Dental decay in relation to third molars **Exclusion criteria** • Any known or suspected allergies or sensitivities to any of the local anaesthetic solutions included in the study or to any ingredients in anaesthetic solutions • Pregnancy and lactation • Single isolated impacted tooth • Systemic disorder like diabetes, hypertension, or cardiac or neurological disorder • Reduced mouth opening (mouth opening > 30 mm was considered normal)
Interventions	Inferior alveolar nerve block and buccal infiltration (1.7 mL in total) using the following: • 2% lidocaine, 1:100,000 epinephrine (35) • 4% articaine, 1:100,000 epinephrine (35)
Outcomes	**Clinical anaesthesia** during surgical removal of mandibular third molars • Success: VAS from 0 = no pain to 10 = worst pain imaginable (70/70) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: measured subjectively and objectively, although the exact method was not stated (70/70) • Postoperative duration: Patients recorded the moment that all soft tissue sensation returned to normal Soft tissues tested: inferior lip, corresponding half of the tongue, and buccal mucosa **Adverse effects** were reported • Subjective pain during local anaesthetic administration and pain after procedure evaluated on VAS (70/70)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly administered one of the two local anesthetics" Comment: detailed methods not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly administered one of the two local anesthetics" Comment: detailed methods not reported

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The anesthetic used was unknown for the patient and the observer who performed the measurements" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation, or if they were blinded. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The anesthetic used was unknown for the patient and the observer who performed the measurements" Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (patient-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Kalia 2011

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (India) **Participants:** 100 enrolled, 100 completing the study. Mean age/age range not stated. 51 male, 49 female **Inclusion criteria** • Undergoing minor oral surgical procedures • 12 to 60 years of age • Agreed to participate in the study protocol after submitting a written informed consent **Exclusion criteria** • Known or suspected allergies or sensitivities to sulphites and/or amide-type local anaesthetics or any ingredients in anaesthetic solutions • Concomitant cardiac, neurological, respiratory disease; uncontrolled diabetes; bleeding disorder; pregnancy • Evidence of soft tissue infection near the proposed injection site • Concomitant use of monoamine oxidase inhibitors and tricyclic antidepressants
Interventions	Inferior alveolar nerve blocks, inferior alveolar nerve blocks and long buccal nerve blocks, infraorbital and greater palatine nerve blocks (volumes not stated) using the following: • 2% lidocaine, 1:100,000 epinephrine (100) • 4% articaine, 1:100,000 epinephrine (100)

Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester
	• Onset of anaesthesia (172/200)
	Teeth tested: various pairs of mandibular and maxillary teeth
	Soft tissue anaesthesia
	• Onset (200/200):
	  ◦ Subjectively by loss of sensation of the lip, buccal mucosa, tongue, and palate
	  ◦ Objectively by presence/absence of pain to prick of sharp dental probe applied about 7 mm from buccal gingival margin
	• Duration of postoperative anaesthesia: Patients recorded the time when anaesthesia had worn off, subjectively
	Soft tissues tested: lip, buccal mucosa, tongue and palate (subjective), and attached gingiva, 7 mm from gingival margin (objective)

Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "100 individuals participated in this single centre, randomized, controlled, single blind, single operator, cross over study design" Comment: detailed methods not reported

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "100 individuals participated in this single centre, randomized, controlled, single blind, single operator, cross over study design" Comment: detailed methods not reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "100 individuals participated in this single centre, randomized, controlled, single blind, single operator, cross over study design" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method for administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "100 individuals participated in this single centre, randomized, controlled, single blind, single operator, cross over study design" Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: onset of pulpal anaesthesia tested on 172 occasions on teeth (for those experiencing successful anaesthesia: 86 cases of lidocaine, 86 cases of articaine). As numbers were reduced in both groups for the same reasons and are exactly balanced across groups, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Kambalimath 2013

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (India) **Participants:** 38 enrolled, 30 completing the study. Mean age 25.8 years, ranging from 18 to 48 years. 13 male, 17 female **Inclusion criteria** • Absence of systemic illness • No signs of inflammation or infection at the extraction site **Exclusion criteria** • Medical history of cardiovascular and kidney diseases, gastrointestinal bleeding or ulceration • Allergic reaction to local anaesthetic; allergy to aspirin, ibuprofen, or any similar drugs • Pregnancy or current lactation • Given instructions not to take any other pain medication before removal of the third molars
Interventions	Inferior alveolar nerve block and buccal infiltration (volume not stated) using the following: • 2% lidocaine, 1:100,000 epinephrine (30) • 4% articaine, 1:100,000 epinephrine (30)
Outcomes	**Clinical anaesthesia** during surgical removal of mandibular third molars • Success: graded as success (patient felt no pain during surgery or had a short duration of pain sensation when tooth was sectioned), partial success, and failure (60/76) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: measured subjectively and objectively, although exact methods were not stated (60/76) • Duration: time from initial patient perception of the anaesthetic effect to the moment in which the effect began to fade (60/76) Soft tissues tested: lower lip and adjacent soft tissues **Adverse effects** were reported (60/76) • Blood pressure, oxygen saturation, and heart rate were recorded • Any signs of systemic toxicity were noted
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "For local anesthesia, in the first appointment the patients were randomly selected to receive either 2 % lidocaine (Lignospan, Indore, India) or 4% Articaine (Articaine 4% Septanest, Indore, India) both with 1:100,000 epinephrine. In the second appointment, the local anesthetic not used previously was then administered in a crossed manner" Comment: detailed methods not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "For local anesthesia, in the first appointment the patients were randomly selected to receive either 2 % lidocaine (Lignospan, Indore, India) or 4% Articaine (Articaine 4% Septanest, Indore, India) both with 1:100,000 epinephrine. In the second appointment, the local anesthetic not used previously was then administered in a crossed manner" Comment: detailed methods not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "This was a double-blind study; neither the surgeon nor the patients were aware of the local anesthetic being tested at the two different appointments" Comment: detailed methods not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation, or if they were blinded. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "This was a double-blind study; neither the surgeon nor the patients were aware of the local anesthetic being tested at the two different appointments" Comment: detailed methods not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: Originally 38 patients were scheduled for treatment, but 8 were withdrawn (1 owing to transient inferior alveolar nerve paraesthesia, 1 because of transient paraesthesia of the lingual nerve, and 6 because of voluntary dropout from the study). Because the study had a cross-over design, the reduction in numbers across groups and reasons for reduction were identical. Therefore risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: Originally 38 patients were scheduled for treatment, but 8 were withdrawn (1 owing to transient inferior alveolar nerve paraesthesia, 1 because of transient paraesthesia of the lingual nerve, and 6 because of voluntary dropout from the study). Because the study had a cross-over design, the reduction in numbers across groups and reasons for the reduction were identical. Therefore risk of attrition bias was rated as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: Originally 38 patients were scheduled for treatment, but 8 were withdrawn (1 owing to transient inferior alveolar nerve paraesthesia, 1 because of transient paraesthesia of the lingual nerve, and 6 because of voluntary dropout from the study). Because the study had a cross-over design, the reduction in numbers across groups and the reasons for reduction were identical. Therefore risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: Originally 38 patients were scheduled for treatment, but 8 were withdrawn (1 owing to transient inferior alveolar nerve paraesthesia, 1 because of transient paraesthesia of the lingual nerve, and 6 because of voluntary dropout from the study). Because the study had a cross-over design, the reduction in numbers across groups and the reasons for reduction were identical. Therefore risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Kammerer 2012

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Moldova) **Participants:** 88 enrolled, 88 completing the study. Mean age 36.7 years, ranging from 18 to 80 years. 43 male, 45 female **Inclusion criteria:** all who required single tooth extractions in the mandibular arch **Exclusion criteria** • Cardiovascular instability, including unstable angina pectoris, recent myocardial infarction (< 6 months), and refractory dysrhythmias • Untreated or uncontrolled hypertension • Uncontrolled diabetes mellitus • Sulfite sensitivity or allergy to any part of the solution • Steroid-dependent asthma • Pheochromocytoma, tricyclic antidepressant treatment • History of psychiatric illness • Requiring open surgical extractions and having infected teeth
Interventions	Inferior alveolar nerve blocks and additional buccal nerve blocks using a variable amount (2.2 mL was available in each syringe) of: • 4% articaine, 1:100,000 epinephrine (41) • 4% articaine, no vasoconstrictor (47)
Outcomes	**Clinical anaesthesia** during extraction of mandibular posterior teeth (88/88) • Quality of anaesthesia during surgery: pain rated by a visual analogue scale from 0 (no pain) to 10 (worst pain) (88/88) • Volume of local anaesthetic injected • Need for supplemental injections Teeth tested: mandibular posterior teeth **Soft tissue anaesthesia** • Onset of anaesthesia: tested by probing (88/88) • Duration: self-reported by patient (calculated for participants who received 1 injection and 2 injections: 88/88. Data only for those given 1 injection: 70/88) Soft tissues tested: vestibular mucosa and oral gingivae **Adverse effects** were reported (88/88) • Pain on injection (pain rated by a visual analogue scale from 0 (no pain) to 10 (worst pain)) • Bleeding complications (not reported) • Other adverse effects
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Equal randomization was achieved with the use of a computer-generated random number list"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Equal randomization was achieved with the use of a computer-generated random number list" "A dental nurse gave the different solutions in identical syringes (2 mL) marked with the patient's randomization number only. The blinding was rendered when evaluating the data. The same LA was used in second and repeated injections" Quote (from correspondence): "The list was organized by a nurse only. It was not shown to any clinician. She chose the solution and gave it to the assistant helping the respective dentist"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "A dental nurse gave the different solutions in identical syringes (2 mL) marked with the patient's randomization number only. The blinding was rendered when evaluating the data. The same LA was used in second and repeated injections" Comment: Participants and personnel would not be able to identify the local anaesthetic used. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A dental nurse gave the different solutions in identical syringes (2 mL) marked with the patient's randomization number only. The blinding was rendered when evaluating the data. The same LA was used in second and repeated injections" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: Duration of soft tissue anaesthesia was tested on 70 occasions (for those experiencing successful anaesthesia: 34 cases of 4% articaine, 1:100,000 epinephrine and 36 cases of 4% articaine, no vasoconstrictor). Because the reduction in numbers across groups was well balanced and reasons were identical, risk of bias was rated as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Kammerer 2014

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Germany) **Participants:** 10 enrolled, 10 completing the study. Mean age 30 years ranging from 24 to 34 years. 10 men and 0 women **Inclusion criteria** • Signed informed consent • Male gender • 18 to 35 years of age • Body weight > 50 kg • No concomitant diseases • Anamnestic and vital maxillary central incisors without pathological findings and without caries and/or prior filling therapy. The periodontium of each tooth had to be free of pathological signs as well **Exclusion criteria** • ASA III to IV • Contraindications to the use of articaine and/or epinephrine • Allergy to sodium bisulphite • Use of nicotine; alcohol and/or drug abuse • At the time of the examinations, no volunteer was allowed to use painkillers and/or tranquilizers
Interventions	Maxillary buccal infiltration (1.7 mL) of: • 4% articaine, no vasoconstrictor (10) • 4% articaine, 1:100,000 epinephrine (10) • 4% articaine, 1:200,000 epinephrine (10) • 4% articaine, 1:300,000 epinephrine (not commercially available) • 4% articaine, 1:400,000 epinephrine (10)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 1 consecutive maximal reading with the pulp tester (40/40) • Onset (34/40) • Duration (34/40) Teeth tested: right maxillary central incisors **Soft tissue anaesthesia** • Success: visual analogue scale (0–10; 0 = no anaesthesia, 10 = full anaesthesia) (40/40) • Post-experimental duration: tested by probing the gingivae around each tooth every 15 minutes; method confirmed by study author Soft tissues tested: gingivae around each tooth **Adverse effects** reported (40/40) • Heart rate frequency • Systolic and diastolic blood pressures • Oxygen saturation
Notes	No funding reported. One of the study authors is a member of the scientific advisory board of the local anaesthetic manufacturer, 3M ESPE

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: detailed method not reported Quote (from correspondence): "For randomization, the old program 'Clinstat' was used (MS-DOS). The injections were carried out as indicated by the program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Comment: detailed method not reported Quote (from correspondence): "For randomization, the old program 'Clinstat' was used (MS-DOS). The injections were carried out as indicated by the program"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All solutions were supplied by 3M ESPE (Seefeld, Germany) and delivered in similar coded glass carpules containing 1.7 ml colorless fluid" "In order to obtain a double-blinded design, the code on the carpule was noted for each injection and unblinded after the whole study was completed" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All solutions were supplied by 3M ESPE (Seefeld, Germany) and delivered in similar coded glass carpules containing 1.7 ml colorless fluid" "In order to obtain a double-blinded design, the code on the carpule was noted for each injection and unblinded after the whole study was completed" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group (4% articaine, 1:100,000 epinephrine vs 4% articaine, 1:200,000 epinephrine). No patients were excluded. Outcome data were complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: Duration of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group (4% articaine, 1:100,000 epinephrine vs 4% articaine, 1:200,000 epinephrine). No patients were excluded. Outcome data were complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	High risk	Comment: Onset of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group except 4% articaine, no vasoconstrictor, when only 4/10 were measured (those who achieved anaesthetic success). Risk of bias was rated as high owing to differences in numbers and small numbers measured
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	High risk	Comment: Duration of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group except 4% articaine, no vasoconstrictor, when only 4/10 were measured (those who achieved anaesthetic success). Risk of bias was rated as high owing to differences in numbers and small numbers measured
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Comment: One of the study authors is a member of the scientific advisory board of the local anaesthetic manufacturer, 3M ESPE

Kanaa 2006

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United Kingdom) **Participants:** 31 enrolled, 31 completing the study. Mean age 22.8 years, ranging from 20 to 30 years of age; standard deviation 2.1 years. 15 male, 16 female **Inclusion criteria:** healthy adult volunteers between 20 and 30 years of age **Exclusion criteria:** none reported
Interventions	Mandibular buccal infiltration (1.8 mL) of: • 4% articaine, 1:100,000 epinephrine (31) • 2% lidocaine, 1:100,000 epinephrine (31)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: no response to the maximum stimulation (80 µA) on ≥ 2 consecutive episodes of testing (62/62) • Incidence: percentage of maximum pulp tester readings (80 µA) over time • Change in pulp tester reading at first sensation from baseline Teeth tested: mandibular first molars **Soft tissue anaesthesia** • Success: participant's feelings of anaesthesia (62/62) • Onset: participant's feelings of anaesthesia (62/62) Soft tissues tested: lower lip and lingual mucosa **Adverse effects** reported (62/62) • Pain on injection (100 mm visual analogue scale)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was determined using a computer-generated sequence of random numbers by one of the authors who was not involved in delivering the local anaesthetic"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization was determined using a computer-generated sequence of random numbers by one of the authors who was not involved in delivering the local anaesthetic" Quote (from correspondence): "The researcher recording the outcome measures who also did the data analyses was blinded till the last data collection – he was given the code after completion of data collection"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The investigator who enrolled the volunteers was blinded to the order of injection" "Both the volunteer and the investigator of anaesthetic efficacy were blinded to the drug being used" Quote (from correspondence): "Volunteers always had the same type of injection and did not see the solution. Administrator was not blinded" Comment: Despite no blinding of the local anaesthetic administrator, identification of the local anaesthetic by participants was unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Both the volunteer and the investigator of anaesthetic efficacy were blinded to the drug being used" Quote (from correspondence): "The outcome measurer was not in the room during LA administration and was blinded (did not get the code broken till study completed)" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Kanaa 2012

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United Kingdom) **Participants:** 100 enrolled, 73 completing the study. Mean age 33.4 years, ranging from 16 to 62 years of age. Standard deviation 10.6 years. 66 male, 34 female **Inclusion criteria** • Over 16 years of age • Presented at a dental emergency clinic with irreversible pulpitis in 1 tooth and an asymptomatic vital tooth on the opposite side of the arch (which acted as an internal control of pulp tester function) **Exclusion criteria** • Medical history contraindicating the use of epinephrine-containing local anaesthetics (e.g. unstable angina) or showing compromised data collection (e.g. facial paraesthesia) • Self-reported allergies or sensitivities to lidocaine, articaine, or other ingredients in the anaesthetic solutions
Interventions	Maxillary buccal infiltration (2.0 mL) of the following: • 4% articaine, 1:100,000 epinephrine (50) • 2% lidocaine,1:80,000 epinephrine (50) Patients for extraction received a supplementary palatal injection of 0.2 mL 2% lidocaine, 1:80,000 epinephrine
Outcomes	**Clinical anaesthesia** during extraction or pulp extirpation • Success: ability to complete treatment without any sensation (100/100) Tissues tested: pulp (+ bone and gingivae in the case of extractions) **Pulpal anaesthesia** tested with an electric pulp tester • Success: The pulp tester reached its maximum (80 reading) without sensation, within 10 minutes of the injection (100/100) • Onset: time to first stimulation reaching the maximum (80 reading) without sensation (73/100) Teeth tested: maxillary teeth **Adverse effects** reported (100/100) • Pain on injection: 100 mm visual analogue scale: "ranging from no pain" (0 mm) and "unbearable pain" (100 mm)
Notes	No funding reported.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization of drug allocation was determined by a web-based program"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization codes were held by researchers (JGM and JMW) who were responsible for syringe preparation but had no involvement in drug administration or in assessing outcomes"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Blinding of drugs was achieved by drawing local anaesthetic solutions from their 2.2-mL cartridges into coded 2.5 mL sterile standard syringes" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Blinding of drugs was achieved by drawing local anaesthetic solutions from their 2.2-mL cartridges into coded 2.5 mL sterile standard syringes" "Randomization codes were held by researchers (JGM and JMW) who were responsible for syringe preparation but had no involvement in drug administration or in assessing outcomes" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Quote: "Patients who did not secure successful pulpal anaesthesia within 10 minutes were withdrawn from the trial, categorized as failure of pulp anaesthesia, and managed according to the local best clinical practice, with further supplementary injections as needed" Comment: Participants who were excluded were accounted for, which allowed overall failure to be calculated
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 73 occasions (for those experiencing successful anaesthesia: 38 cases of 4% articaine, 1:100,000 epinephrine and 35 cases of lidocaine, 1:80,000 epinephrine). Because the reduction in numbers across groups was well balanced and the reasons identical, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Karm 2017

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Republic of Korea) **Participants:** 65 enrolled, 51 completing the study. Mean age 24.1 ± 5.0 (SD) years. 34 male, 31 female **Inclusion criteria** • Age over 19 years • Physical grade I or II according to the American Society of Anesthesiologists (ASA) • Requirement of bilateral surgical extraction of impacted mandibular third molars (mesio-angular or horizontal angulation of Winter's classification) and similar degree of impaction on both sides • Agreed and signed written informed consent **Exclusion criteria** • History of hypersensitivity to lidocaine or to this group of drugs • Presence of active infection or abscess at the time of extraction • Coagulation disorder, hyperthyroidism, atherosclerosis, heart failure, convulsions, uncontrolled hypertension, or diabetes mellitus • Current use of vasoconstrictors, ergot alkaloids, phenothiazines, butyrophenones, tricyclic antidepressants, monoamine oxidase inhibitors, sedatives, or anxiolytics • Use of anticoagulants or antiplatelets, including aspirin, systemic corticosteroids, or non-steroidal anti-inflammatory drugs within 7 days before the extraction date • Use of analgesics within 24 hours before the extraction • Requirement for sedatives or anti-anxiolytic drugs during the extraction • Other operative plans requiring general or local anaesthesia during the clinical trial period • Other medical history that might affect the clinical trial (e.g. malignant tumour, immunodeficiency, kidney disease, liver disease, lung disease, unstable psychiatric condition) • Pregnancy or breastfeeding • Planned pregnancy or intention of using contraception during the clinical trial period • Use of other investigated products or medical devices within 4 weeks before the extraction date • History of prior oral or maxillofacial surgery
Interventions	Inferior alveolar nerve block and buccal infiltration (1.8 mL in total) using the following: • 2% lidocaine, 1:80,000 epinephrine (51) • 2% lidocaine, 1:200,000 epinephrine (51)

Outcomes	**Clinical anaesthesia (success)** during surgical removal of mandibular third molars • VAS measured immediately after surgical extraction: 100-mm horizontal row of light-emitting diodes labelled (102/102): ◦ "minimum" = no pain at all (left end) ◦ "maximum" = maximum imaginable pain (right end) • Total volume of anaesthetic solution used • Operator's overall satisfaction and participant's overall satisfaction (Likert scale: scale scores from 1 (very dissatisfied) to 5 (very satisfied)) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: loss of sensibility of the lower lip, corresponding half of the tongue, and mucosa (102/102) • Duration: lack of sensibility of the lower lip, tongue, and mucosa. Participants recorded the moment that the anaesthesia had worn off (102/102) Soft tissues tested: lower lip, corresponding half of the tongue, and mucosa **Other adverse events** (102/102) • Systolic and diastolic blood pressure and pulse rate measured • Perioperative bleeding • Other adverse events including post-injection pain
Notes	Industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The statistician randomly assigned the participants using the block randomization method with SAS (SAS Institute, Cary, NC)"
Allocation concealment (selection bias)	Low risk	Quote: "The statistician delivered a list of random assignment codes to the pharmacy packager" Comment: No details were given of where the key to the coding was stored Quote (from correspondence): "An independent statistician generated random codes and provided them to the factory of Huons company. The company's random assignment officer removed the labels from both products and labeled them the same while keeping a thorough secret. Random numbers and information needed for clinical trials were written on the label. Boxed and provided to research institutions (hospitals).The research institute provided a local anesthetic cartridge to the operator while maintaining double blindness"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This study was double blinded; neither the operator nor the participant was aware of which anesthetic was administered" "2% lidocaine with 1:200,000 epinephrine…. and 2% lidocaine with 1:80,000 epinephrine…. were packaged so that they could not be recognized and were distributed to the trial institutes" Quote (from correspondence): "An independent statistician generated random codes and provided them to the factory of Huons company. The company's random assignment officer removed the labels from both products and labeled them the same while keeping a thorough secret. Random numbers and information needed for clinical trials were written on the label. Boxed and provided to research institutions (hospitals).The research institute provided a local anesthetic cartridge to the operator while maintaining double blindness" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "This study was double blinded; neither the operator nor the participant was aware of which anesthetic was administered" "2% lidocaine with 1:200,000 epinephrine…. and 2% lidocaine with 1:80,000 epinephrine…. were packaged so that they could not be recognized and were distributed to the trial institutes" Quote (from correspondence): "An independent statistician generated random codes and provided them to the factory of Huons company. The company's random assignment officer removed the labels from both products and labeled them the same while keeping a thorough secret. Random numbers and information needed for clinical trials were written on the label. Boxed and provided to research institutions (hospitals). The research institute provided a local anesthetic cartridge to the operator while maintaining double blindness" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Quote: "Ten participants dropped out because of randomization error. Four participants were omitted because the study drugs were not administered or the inclusion or exclusion criteria were violated" Comment: Study used a cross-over design. Despite errors producing dropouts, the reduction in numbers across groups resulted in study numbers that were still above the sample size required (23), with groups exactly balanced and reasons for reduction in numbers identical. Risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Quote: "Ten participants dropped out because of randomization error. Four participants were omitted because the study drugs were not administered or the inclusion or exclusion criteria were violated" Comment: Study used a cross-over design. Despite errors producing dropouts, the reduction in numbers across groups resulted in study numbers that were still above the sample size required (23), with groups exactly balanced and reasons for reduction in numbers identical. Risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Quote: "Ten participants dropped out because of randomization error. Four participants were omitted because the study drugs were not administered or the inclusion or exclusion criteria were violated" Comment: Study used a cross-over design. Despite errors producing dropouts, the reduction in numbers across groups resulted in study numbers that were still above the sample size required (23), with groups exactly balanced and reasons for reduction in numbers identical. Risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "Ten participants dropped out because of randomization error. Four participants were omitted because the study drugs were not administered or the inclusion or exclusion criteria were violated" Comment: Study used a cross-over design. Despite errors producing dropouts, the reduction in numbers across groups resulted in study numbers that were still above the sample size required (23), with groups exactly balanced and reasons for reduction in numbers identical. Risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Comment: Study was supported by Huons Co. Ltd. Pharmaceutical Company

Katz 2010

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 60 enrolled, 60 completing the study • Lateral incisor, 30 enrolled, 30 completed the study; aged ranged from 22 to 31 years, with mean age of 25 years. 25 male, 5 female • First molar, 30 enrolled, 30 completed the study; age ranged from 22 to 33 years, with mean age of 25 years. 20 male, 10 female **Inclusion criteria** • In good health and not taking any medication that would alter pain perception **Exclusion criteria** • Younger than 18 or older than 65 years of age • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions (American Society of Anesthesiology (ASA) II or higher) • Taking any medications that may affect anaesthetic assessment (over-the-counter pain-relieving medications, narcotics, sedatives, antianxiety or antidepressant medications) • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	Maxillary buccal infiltration using 1.8 mL of: • 2% lidocaine, 1:100,000 epinephrine (60) • 4% prilocaine, 1:200,000 epinephrine (60) • 4% prilocaine, no vasoconstrictor (60)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings with the pulp tester were obtained within 10 minutes after infiltration (120/120) • Onset (72/120) • Anesthesia of short duration: Participant achieved 2 consecutive 80 readings, lost the 80 readings, and never regained them within the 60-minute period • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: maxillary first molars and lateral incisors
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment was begun, the 3 anaesthetic solutions were randomly assigned 4- digit numbers from a random number table generated by Microsoft Office Excel (Microsoft Corporation, Redmond, Wash). The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Before the experiment was begun, the 3 anaesthetic solutions were randomly assigned 4- digit numbers from a random number table generated by Microsoft Office Excel (Microsoft Corporation, Redmond, Wash). The random numbers were assigned to a subject to designate which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The 2% lidocaine cartridges ..... were masked with opaque labels, and the cartridge caps and plungers were masked with a black felt tip marker. Corresponding 4-digit codes were written on each cartridge label" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The 2% lidocaine cartridges ..... were masked with opaque labels, and the cartridge caps and plungers were masked with a black felt tip marker. Corresponding 4-digit codes were written on each cartridge label." "Trained personnel,who were blinded to the anaesthetic solutions, administered all preinjection and post-injection tests" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 72 occasions with first molar teeth (for those experiencing successful anaesthesia (matched pairs): 24 cases of 2% lidocaine, 1:100,000 epinephrine, 24 cases of 4% prilocaine, 1:200,000 epinephrine and 24 cases of 4% prilocaine, no vasoconstrictor). Because numbers were reduced across groups and reasons for reduction were identical, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Keskitalo 1975

Methods	Randomized controlled clinical trial, part parallel and part cross-over study design
Participants	**Location:** university (Sweden) **Participants:** 439 enrolled, 298 completing the study. 379 teeth were removed. Age ranged from 18 to 62 years. 193 teeth were removed from males, 186 teeth from females **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Inferior alveolar nerve block and buccal infiltration (3.6 mL initially) of: • 2% lidocaine, 12.5 µg/mL (1:80,000) epinephrine (188) • 3% prilocaine, 0.03 IU/mL felypressin (191)
Outcomes	**Clinical anaesthesia** during extraction of impacted mandibular third molars • Success: complete anaesthetic effect: no pain during the operation; partial anaesthetic effect: patient-reported pain, which according to the patient did not require supplementary anaesthetic; unsuccessful anaesthetic effect: pain produced required a supplemental anaesthetic (379/379) Teeth tested: mandibular third molars **Adverse events** reported (379/379)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The anaesthetic agents were randomly varied between the two operations in the bilateral cases. In the unilateral cases the anaesthetic agents were randomly varied between the patients" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The anaesthetic agents were randomly varied between the two operations in the bilateral cases. In the unilateral cases the anaesthetic agents were randomly varied between the patients" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The investigation was planned as a double blind study" Comment: detailed methods not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation, or if they were blinded. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The investigation was planned as a double blind study" Comment: Detailed methods were not reported. It is not clear whether the person recording participants' outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Quote: "141 cases were not included" Comment: These were accounted for and were due to teeth not having closed apices, administrative reasons, or teeth not likely to produce postoperative symptoms. This is high (47%), as only 298 cases were enrolled in the trial. However, most of these were initially entered into the study but were removed from the trial before treatment was performed, probably following radiographic examination when incomplete apices were detected. Because numbers across groups were reduced and reasons for reduction were balanced, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "141 cases were not included" Comment: These were accounted for and were due to teeth not having closed apices, administrative reasons, or teeth not likely to produce postoperative symptoms. This is high (47%), as only 298 cases were enrolled in the trial. However, most of these were initially entered into the study but were removed from the trial before treatment was performed, probably following radiographic examination when incomplete apices were detected. Because numbers across groups were reduced and the reasons for reduction were balanced, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Khoury 1991

Methods	Randomized controlled clinical and simulated scenario trial, parallel design
Participants	**Location:** university (Germany) **Participants:** 1700 enrolled, 1518 completing the study. Participants aged 18 years and older. 755 males, 763 females completed the study **Inclusion criteria:** none reported **Exclusion criteria:** contraindications to using the different local anaesthetic solutions, mentioned in the local anaesthetic packaging insert
Interventions	Varying doses of local anaesthetic were given depending on the procedure undertaken. Techniques used were described as "conduction and infiltration anaesthesia". Most used volumes of 2.0 mL, with a range from 0.8 mL to 5.0 mL. Further injections of 0.5 mL to 2.0 mL were given if required: • 3% prilocaine, 0.03 IU/mL felypressin (364) • 4% articaine, 1:100,000 epinephrine (408) • 4% articaine, 1:200,000 epinephrine (382) • 2% lidocaine, 1:100,000 epinephrine (363)
Outcomes	**Clinical anaesthesia** during surgical procedures (1518/1700) • Success: procedure completed with standard volume of local anaesthetic or no pain during the procedure • Duration: data for solutions not reported Hard and soft tissues tested: various **Adverse events** reported (1518/1700)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: detailed methods not reported
Allocation concealment (selection bias)	Unclear risk	Comment: detailed methods not reported
Blinding of participants and personnel (performance bias)	Low risk	Comment: The similar looking 2 mL ampoules did not bear the name of the anaesthetic but consecutive numbers. Detailed methods were not reported. The sequence of numbering is not clear, but it may have allowed identification of the formulations used if properties between the local anaesthetics were markedly different and all ampoules of a formulation were labelled in a similar way (e.g. 1 formulation was labelled with even numbers and the other formulation was labelled with even numbers). However, properties of the 2 solutions did not allow identification. Identification of the local anaesthetic by participants was not possible. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	Comment: Data for 282 patients were not included, which represents 17% of those enrolled. Reasons for the dropouts and whether these were equal amongst groups were not clear, although the final numbers in groups were not too dissimilar. Risk of bias was therefore graded as unclear

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Comment: Data on 282 patients were not included, which represents 17% of those enrolled. Reasons for the dropouts and whether these were equal amongst groups were not clear, although the numbers in groups were not too dissimilar. Risk of bias was therefore graded as unclear
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Knoll-Kohler 1992a

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Germany) **Participants:** 10 enrolled, 10 completing the study. Aged 26 years ± 1 year. 10 male, 0 female **Inclusion criteria** • Aged 26 ± 1 year • Weighing 76 ± 9 kg • Normotensive • Non-smoker • Had no problems with alcohol or drug dependence • No signs of acute or chronic disease • No allergy to any component of the anaesthetic solution • Had a current radiograph showing no restoration or caries in the right maxillary incisor or evidence of periodontal disease **Exclusion criteria:** not reported
Interventions	Maxillary buccal infiltration injections using 0.5 mL of: • 2% lidocaine, no vasoconstrictor (not commercially available) • 2% lidocaine, 1:50,000 epinephrine (10) • 2% lidocaine, 1:100,000 epinephrine (10) • 2% lidocaine, 1:200,000 epinephrine (10)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Failure (30/30) • Onset (26/30) • Duration (26/30) Teeth tested: right maxillary incisor
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "0.5 ml of one of the anaesthetic solutions compiled in Table I was injected into the mucobuccal aspect adjacent to the apex of the maxillary right incisor in a random manner with a double-blind crossover design" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Low risk	Quote: "0.5 ml of one of the anaesthetic solutions compiled in Table I was injected into the mucobuccal aspect adjacent to the apex of the maxillary right incisor in a random manner with a double-blind crossover design" "The ampoules were coded with serial numbers" "After data collection the code was broken for statistical analysis"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The investigation was carried out as a double-blind study with coded cartridges" "The ampoules were coded with serial numbers" "After data collection the code was broken for statistical analysis" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The investigation was carried out as a double-blind study with coded cartridges" "The ampoules were coded with serial numbers" "After data collection the code was broken for statistical analysis" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group (2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine). No patients were excluded. Outcome data were complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: Duration of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group (2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine). No patients were excluded. Outcome data were complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	High risk	Comment: Onset of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group except 2% lidocaine, 1:200,000 epinephrine, when only 6/10 were measured (those who achieved anaesthetic success). Risk of bias was rated as high owing to differences in numbers assessed and the few participants involved. Data were not used for meta-analysis

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	High risk	Comment: Duration of pulpal anaesthesia was tested on all 10 participants in each local anaesthetic group except 2% lidocaine, 1:200,000 epinephrine, when only 6/10 were measured (those who achieved anaesthetic success). Risk of bias was rated as high owing to differences in numbers assessed and the few participants involved. Data were not used for meta-analysis
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Knoll-Kohler 1992b

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Germany) **Participants:** 12 enrolled, 12 completing the study. Aged 26 years ± 1 year. 12 male, 0 female **Inclusion criteria** • Male sex. • Age 26 ± 1 year • Body weight 76 ± 9 kg • Normotension • Non-smoker • No alcohol or drug dependence • No signs of acute or chronic disease • No allergy to any component of the anaesthetic solution • Current radiograph showing no restoration or caries in the right maxillary incisor or evidence of periodontal disease **Exclusion criteria:** not reported
Interventions	Maxillary buccal infiltration injection (0.5 mL) of: • 2% (74 mM) lidocaine, 1:100,000 (54.5 µm) epinephrine (12) • 3.4% (125 mM) lidocaine, 1:100,000 (54.5 µm) epinephrine (not commercially available) • 2.4% (74 mM) articaine, 1:100,000 (54.5 µm) epinephrine (not commercially available) • 4% (125 mM) articaine, 1:100,000 (54.5 µm) epinephrine (12)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success (24/24) • Onset (24/24) • Duration (24/24) Teeth tested: right maxillary incisor
Notes	Industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Thereafter, 0.5 ml of one of the anaesthetic solutions.....were injected into the mucobuccal aspect adjacent to the apex of the maxillary right incisor in a random manner using a double blind crossover design" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Low risk	Quote: "Thereafter, 0.5 ml of one of the anaesthetic solutions.....were injected into the mucobuccal aspect adjacent to the apex of the maxillary right incisor in a random manner using a double blind crossover design" "The ampoules were coded with serial numbers" "After data collection the code was broken for statistical analysis"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The ampoules were coded with serial numbers" "After data collection the code was broken for statistical analysis" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The ampoules were coded with serial numbers" "After data collection the code was broken for statistical analysis" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Espe GmbH & Co KG (Seefeld, Germany) was responsible for preparation and supply of the anaesthetic solutions

Kolli 2017

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (India) **Participants:** 90 enrolled, 90 completing the study. Mean age 9.74 ± 1.9 years. 45 male, 45 female **Inclusion criteria** • Co-operative children • Children with definite indications for extraction of primary first or second maxillary molars • No history of intraoral injections • Maxillary molars for which 2/3 of root should be present • Children who can fully understand given instructions **Exclusion criteria** • Children whose parents or caregivers did not give consent for the study • Children allergic to lidocaine/articaine • Children with underlying vascular or immunological disease
Interventions	Maxillary buccal infiltration (1.7 mL) of: • 2% lidocaine, 1:80,000 epinephrine (30) • 4% articaine, 1:100,000 epinephrine (30) Epinephrine concentrations assumed to be 1:80,000 for lidocaine (same as control injection, below) and 1:100,000 epinephrine for articaine (most common formulation), as these were not included in the journal article. Attempts to clarify this were unsuccessful, as contact with the study author via email was unsuccessful. Maxillary buccal/palatal infiltration (1.7 mL in total) of: • 2% lidocaine, 1:80,000 epinephrine (30)
Outcomes	**Clinical anaesthesia** during extraction of primary maxillary molars • Success (90/90) • Faces Pain Scale - Revised (FPS-R) score was recorded after the extraction • Face Legs Activity Cry Consolability (FLACC) score was recorded perioperatively Teeth tested: primary first or second maxillary molars **Adverse effects** were reported (90/90) • Heart rate was recorded • Other adverse events were recorded
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The treatment allocation was predetermined by generating randomization list using GraphPad StatMate version 1.01i (GraphPad Software, Inc., Armonk, NY: IBM Corp). Children were allocated sequentially into one of the three groups"
Allocation concealment (selection bias)	Unclear risk	Quote: "The treatment allocation was predetermined by generating randomization list using GraphPad StatMate version 1.01i (GraphPad Software, Inc., Armonk, NY: IBM Corp). Children were allocated sequentially into one of the three groups" Comment: method used for concealment not reported

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "An experienced pediatric dentist performed all the injections who was blinded to the anesthetic solutions while another experienced pediatric dentist performed the extraction procedure" Comment: detailed methods not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "An experienced pediatric dentist performed all the injections who was blinded to the anesthetic solutions while another experienced pediatric dentist performed the extraction procedure" Comment: detailed methods not reported. Some outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Kramer 1958

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Canada) **Participants:** 3703 injections given, although the numbers of participants in each group (success) were not known. Mean age and range and male:female ratio not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Mandibular and maxillary buccal injections (1 or more cartridges if required) of: • 2% procaine, 1:60,000 epinephrine (not commercially available) • 2% lidocaine, 1:50,000 epinephrine (number of injections not clear) • 2% lidocaine, 1:100,000 epinephrine (number of injections not clear) • 1.5% metabutoxycaine, 1:60,000 epinephrine (not commercially available) • 1.5% metabutoxycaine, 1:125,000 epinephrine (not commercially available) • 0.4% propoxycaine/2% procaine, 1:30,000 levarterenol (not commercially available) • 0.15% tetracaine/2% procaine, 1:10,000 nordefrin (not commercially available)
Outcomes	**Clinical anaesthesia** during operative dentistry procedures • Onset: from time of injection to when cutting of dentine could be archived without pain (3061/3703) • Success: grade of anaesthesia: A - complete elimination of pulpal pain during operative procedures; B - some pain reported but another injection was not required; C – reinjection was necessary (number assessed not clear: 3703?) Teeth tested: not stated **Soft tissue anaesthesia** from time of injection to time participant reported soft tissues returning to normal, or was given a postcard to record duration • Duration (2434/3703) Soft tissues tested: relevant soft tissues, depending on injection and jaw **Adverse events** reported (3703/3703)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "These seven test solutions were issued at random from a central dispensary" "The dental assistant issuing the solutions maintained a record so that each solution was distributed equally to all operators" Comment: exact method of generation of randomized sequence not reported

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "These seven test solutions were issued at random from a central dispensary and were identified only by a code in which the identifying digit was placed in a certain location in a varying four digit number. None of the operators knew the identity of the compound being used when he received a prepared syringe" "The dental assistant issuing the solutions maintained a record so that each solution was distributed equally to all operators"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "These seven test solutions were issued at random from a central dispensary and were identified only by a code in which the identifying digit was placed in a certain location in a varying four digit number. None of the operators knew the identity of the compound being used when he received a prepared syringe" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Seven test solutions were issued at random from a central dispensary and were identified only by a code in which the identifying digit was placed in a certain location in a varying four digit number. None of the operators knew the identity of the compound being used when he received a prepared syringe" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	Comment: The total number of participants was 3703 according to the journal article. The percentages of participants having successful anaesthesia were given, but not the numbers in each group; therefore it was impossible to determine whether there had been any dropouts. Attrition bias was therefore graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comment: The total number of participants was 3703 according to the journal article. The number of participants having duration of soft tissue anaesthesia measured was 2434, but without information on how many in each group had successful soft tissue anaesthesia, it was impossible to determine whether there had been any dropouts. Attrition bias was therefore graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Comment: The total number of participants was 3703 according to the journal article. The number of participants having numbers of adverse events measured was not stated; therefore it was impossible to determine whether there had been any dropouts. Attrition bias was therefore graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	Comment: The total number of participants was 3703 according to the journal article. The number of participants having onset of pulpal anaesthesia measured was 3061, but without information on how many in each group had successful anaesthesia, it was impossible to determine whether there had been any dropouts. Attrition bias was therefore graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Lasemi 2015

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Iran) **Participants:** 20 enrolled, 20 completing the study. Mean age 38.3 ± 11.3 years, ranging from 18 to 50 years. 20 male, 20 female **Inclusion criteria** • Requiring extraction of both of the first mandibular molars **Exclusion criteria** • Systemic conditions in which injection of articaine with epinephrine is contraindicated • Pregnancy • Use of medications (over-the-counter pain-relieving medications, narcotics, sedatives, antianxiety, or antidepressants) that could affect anaesthetic assessment • History of psychiatric illness • Allergy to components of the local anaesthetic solutions • Local anaesthesia in same region < 2 weeks before the experiment
Interventions	Inferior alveolar nerve blocks (volume not stated) using the following: • 4% articaine, 1:100,000 epinephrine (20) • 4% articaine, 1:200,000 epinephrine (20)
Outcomes	**Soft tissue anaesthesia** • Onset: tingling or numbness of the lower lip (40/40) • Duration: recorded using a stop watch (40/40) Soft tissues tested: lower lip **Other adverse events** (40/40) • Systolic and diastolic blood pressure and pulse rate measured
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The procedures were performed during 2 separate appointments. In the first session, the side of the mouth for administering the IANB (right or left) and the type of anesthetic solution (A100 and A200) (Primacaine, Pierre Rolland, Bordeaux, France) were chosen randomly" Comment: detailed methods not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The procedures were performed during 2 separate appointments. In the first session, the side of the mouth for administering the IANB (right or left) and the type of anesthetic solution (A100 and A200) (Primacaine, Pierre Rolland, Bordeaux, France) were chosen randomly" Comment: detailed methods not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The surgeon and patient were blinded about the type of anesthetic solution administered" Comment: detailed methods not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was not used by personnel to minimize variation. Therefore, risk of bias was graded as unclear

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The surgeon and patient were blinded about the type of anesthetic solution administered" Comment: detailed methods not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Laskin 1977

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 25 enrolled, 25 completing the study. 50 teeth were reported. Age ranging from 18 to 35 years old, with mean age of 23 years. 11 males, 14 females **Inclusion criteria** • All teeth were caries free clinically and radiographically • All teeth were class IIa or B according to Pell and Gregory's classification of impacted third molars **Exclusion criteria:** not reported
Interventions	1.8 mL for each quadrant: mandibular nerve block (1.6 mL), long buccal nerve (0.2 mL) initially, then a further dose of up to 1.8 mL was administered if required of: • 0.25% bupivacaine (not commercially available) • 0.5% bupivacaine (not commercially available) • 0.75% bupivacaine (not commercially available) • 0.25% bupivacaine, 1:200,000 epinephrine (not commercially available) • 0.5% bupivacaine, 1:200,000 epinephrine (8) • 2% lidocaine, 1:100,000 epinephrine (8)
Outcomes	**Clinical anaesthesia** during extraction • Success: sensation with incision, sensation with reflection of flap, sensation when bur was introduced into the pulp within 3 minutes of the start of surgery, necessity for supplemental doses of local anaesthetic, anaesthetic failure (16/16) Teeth tested: impacted mandibular third molars **Soft tissue anaesthesia** • Onset: patient-recorded time sensation started (16/16) • Duration: patient-recorded time sensation returned to normal (16/16) Soft tissues tested: lower lip **Adverse events** reported (16/16)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The first six preparations were administered randomly without knowledge of what the syringe contained; the seventh preparation was known and was reserved for use in anaesthetic failures. Random sampling was used for determination of which side of the jaw was treated at the first appointment" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Low risk	Quote: "The local anaesthetics were supplied by the pharmacy, prepackaged, and labelled for each patient, following a random pattern that had been predetermined and unknown to the operator"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Each patient had a specific 'number' and the drugs were identified as 'number' right and 'number' left. The local anaesthetics were supplied by the pharmacy, prepackaged, and labelled for each patient, following a random pattern that had been predetermined and unknown to the operator" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Each patient had a specific 'number' and the drugs were identified as 'number' right and 'number' left. The local anaesthetics were supplied by the pharmacy, prepackaged, and labelled for each patient, following a random pattern that had been predetermined and unknown to the operator" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Lawaty 2010

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 60 enrolled, 60 completing the study • Central incisor: 30 enrolled, 30 completing the study; mean age of 25 years ranging from 22 to 31 years. 15 men and 15 women • First molar: 30 enrolled, 30 completing the study; mean age of 24 years ranging from 21 to 29 years, 15 men and 15 women **Inclusion criteria:** in good health and not taking any medication that would alter pain perception **Exclusion criteria** • Older than 65 years of age • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions (American Society of Anesthesiologists classification II or higher) • Taking any medications that may affect anaesthetic assessment (over-the-counter pain-relieving medications, narcotics, sedatives, or antianxiety or antidepressant medications) • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	Maxillary buccal infiltration (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine (60) • 2% mepivacaine, 1:20,000 levonordefrin (60)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings with the pulp tester were obtained (120/120) • Anaesthesia of short duration: Participant achieved 2 consecutive 80 readings, lost the 80 readings, and never regained them within the 60-minute period • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: maxillary first molars and lateral incisors
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 2 anaesthetic solutions were randomly assigned 4-digit numbers from a random number table. Each subject was randomly assigned to the right or left side infiltration grouping. The order of the anaesthetic solutions was also randomly assigned to determine which solutions were to be administered at each appointment" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote: "The 2 anaesthetic solutions were randomly assigned 4-digit numbers from a random number table. Each subject was randomly assigned to the right or left side infiltration grouping. The order of the anaesthetic solutions was also randomly assigned to determine which solutions were to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: The local anaesthetic cartridges "were masked with opaque labels. The corresponding 4-digit codes were written on each cartridge label" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the random numbers were recorded on the data collection sheets to help blind the experiment" "Trained personnel, who were blinded to the anaesthetic solutions, administered all preinjection and post-injection tests" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no participants excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Lima 2009

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (Brazil) **Participants:** 100 enrolled, 100 completing the study (200 teeth), with age ranging from 15 to 46 years. Male:female ratio not reported, although confirmed as 50 male and 50 female by the first study author following email communication **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Maxillary buccal infiltration (1.8 mL) of: • 4% articaine, 1:100,000 epinephrine (100) • 4% articaine, 1:200,000 epinephrine (100)
Outcomes	**Clinical anaesthesia** during each surgical phase of extraction (presence or absence of pain) • Success: this was determined at either: ◦ 5 minutes post injection (100/100) ◦ 10 minutes post injection (100/100) Teeth tested: maxillary third molars
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "The randomization was done in "blocks" of predetermined size, 25 patients per group. We used a program which selected in 5 of 5 patients per group, where the size of each group was 25 patients"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "The surgeon did not know the patients nor the data and operated five patient groups selected by the program and coordinated by staff (interns)" "The syringes were sealed with tape, preventing the visualization of the applicator, only the appraiser who prepared the syringes knew the division of anaesthesia and groups"
Blinding of participants and personnel (performance bias)	Low risk	Quote (from correspondence): "The syringes were sealed with tape, preventing the visualization of the applicator, only the appraiser who prepared the syringes knew the division of anaesthesia and groups. The patient also had no knowledge of type of anaesthetic used. Only one person made all anaesthesia to avoid variation or deviation of the anaesthetic technique" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote (from correspondence): "The syringes were sealed with tape, preventing the visualization of the applicator, only the appraiser who prepared the syringes knew the division of anaesthesia and groups. The patient also had no knowledge of type of anaesthetic used. Only one person made all anaesthesia to avoid variation or deviation of the anaesthetic technique" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Linden 1986

Methods	Randomized controlled simulated scenario trial (following a clinical intervention), cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 20 enrolled, 20 completing the study. Age ranging from 20 to 65 years of age. Male:female ratio not reported **Inclusion criteria:** none reported **Exclusion criteria** • History of systemic illness • Taking medications that could interact with the local anaesthetic agents
Interventions	One or more of the following injections: • mandible: inferior alveolar nerve blocks, lingual and long buccal injections • maxilla: posterior superior alveolar nerve blocks, local and palatal infiltrations using either 1.5 Carpule (2.7 mL) for block injections or 1 Carpule (1.8 mL) for other injections (including palatal blocks) of 1 of the following solutions: • 2% lidocaine, 1:100,000 epinephrine (20) • 0.5% bupivacaine, 1:200,000 epinephrine (20)
Outcomes	**Soft tissue anaesthesia** following periodontal surgery • Duration: Participants were asked when did anaesthesia wear off, in a questionnaire (40/40) Soft tissues tested: relevant soft tissues **Adverse effects** reported (38/40) • Postoperative pain (10-point VAS) • Haemostasis
Notes	Industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Identical Carpules were used and placed in containers labelled A or B. 8 of each were removed and placed in identical envelopes with a coded number on the outside, which was not available to the investigator" Each patient was assigned 2 envelopes "The second party then randomly assigned the anaesthetic given, the quadrant to be treated surgically, and the order of the surgeries (i.e. left or right side), so that the first anaesthetic given to a patient and order of the surgeries varied" Quote (from correspondence): “We had a third party not involved randomize the anaesthetic given which was placed in a sterile bag, (blank Carpules) so we didn't know what we were giving the patient. In addition, the quadrant was also randomly assigned until the patient was seated. In summary we didn't know until we were given the instructions of the quadrant, side of the mouth, anaesthetic blank Carpules and location to treat before the patient arrived" "The entire process was randomized by a independent third party who literally pulled numbers blindly out of a box with anaesthetic, locations or quadrants, and order"
Allocation concealment (selection bias)	Low risk	Quote: "Identical Carpules were used and placed in containers labelled A or B. 8 of each were removed and placed in identical envelopes with a coded number on the outside, which was not available to the investigator" Each patient was assigned 2 envelopes "The second party then randomly assigned the anaesthetic given, the quadrant to be treated surgically, and the order of the surgeries (i.e. left or right side), so that the first anaesthetic given to a patient and order of the surgeries varied" Quote (from correspondence): "We had a third party not involved randomize the anaesthetic given which was placed in a sterile bag, (blank Carpules) so we didn't know what we were giving the patient"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Identical Carpules were used and placed in containers labelled A or B. 8 of each were removed and placed in identical envelopes with a coded number on the outside, which was not available to the investigator" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Identical Carpules were used and placed in containers labelled A or B. 8 of each were removed and placed in identical envelopes with a coded number on the outside, which was not available to the investigator" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: One patient failed to respond when asked for preference of local anaesthetic solution. This was balanced across groups because the study used a cross-over design. Also, haemostasis was assessed during surgery. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Quote: "Cooke Waite donated a small amount of money to our dental clinic. There were no stipends or bonuses"

Malamed 2000a

Methods	Randomized controlled clinical trial, parallel study design, carried out at 27 sites
Participants	**Location:** United States of America, United Kingdom **Participants:** 1325 enrolled, 1325 completing the study: • Articaine: 882 enrolled, 882 completing the study. Mean age 36.2 years ± 0.52 SEM. 50 participants were 4 to 12 years of age. 464 males, 418 females • Lidocaine: 443 enrolled, 443 completing the study. Mean age 36.5 years ± 0.73 SEM. 20 participants 4 to 12 years of age. 259 males, 184 females **Inclusion criteria:** not reported **Exclusion criteria** • Pregnancy • Bony, fully impacted teeth or maxillofacial surgery • Known or suspected allergies or sensitivities to sulphites, amide-type local anaesthetics, or any ingredients in the anaesthetic solutions • Concomitant cardiac or neurological disease • History of severe shock, paroxysmal tachycardia, frequent dysrhythmia, severe untreated hypertension, or bronchial asthma • Evidence of soft tissue infection near the proposed injection site (localized periapical or periodontal infections were permitted) • Concomitant use of monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs, or ergot-type oxytocic drugs • Requiring chloroform, halothane, cyclopropane, trichloroethylene, or related anaesthetics during the treatment visit • Expected to require nitrous oxide if anxious or any topical or general anaesthesia (topical anaesthesia allowed in the United Kingdom study) • Had taken aspirin, acetaminophen, non-steroidal anti-inflammatory drugs, or other analgesic agents within 24 hours before administration of study medication
Interventions	Standard infiltration or nerve block of the following mean volumes: • **Simple procedures:** 2.5 mL ± 0.07 SEM of 4% articaine, 1:100,000 epinephrine (675) 2.6 mL ± 0.09 SEM of 2% lidocaine, 1:100,000 epinephrine (338) • **Complex procedures:** 4.2 mL ± 0.15 SEM of 4% articaine, 1:100,000 epinephrine (207) 4.5 mL ± 0.21 SEM of 2% lidocaine, 1:100,000 epinephrine (105)
Outcomes	**Clinical anaesthesia** during various procedures • Efficacy: visual analogue scale, ranging from 0 = "no pain" to 10 = "worst pain imaginable". Participant and investigator rated pain during the procedure (1323/1325) "Simple" group included single extractions with no complications, routine operative procedures, single apical resections, single crown procedures "Complex" group included multiple extractions, multiple crowns, bridge procedures or both, multiple apical resections, alveolectomies; mucogingival operations, other osseous surgical procedures Teeth tested: not reported **Adverse events** reported (1323/1325)
Notes	No funding stated. Study authors thanked Septodont

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We randomized subjects in a 2:1 ratio to receive articaine or lidocaine" Comment: The difference in group size was deliberate and was related to safety issues. Exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "We randomized subjects in a 2:1 ratio to receive articaine or lidocaine" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: detailed methods not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method for administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: detailed methods not reported. The person recording participants' outcomes also administered the local anaesthetic, so they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: Data were missing for 2 participants. As missing data were minor, risk of bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: Data were missing for 2 participants. As missing data were minor, risk of bias was rated as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Unsure whether study was sponsored by Septodont

Malamed 2000b

Methods	Randomized controlled clinical trial, parallel study design, carried out at 7 sites
Participants	**Location:** United States of America and United Kingdom **Participants:** 70 enrolled, 70 completing the study • Articaine: 50 enrolled, 50 completing the study. Participants were 4 to 12 years of age. 29 males, 21 females • Lidocaine: 20 enrolled, 20 completing the study. Participants 4 to 12 years of age. 7 males, 13 females **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Standard infiltration or nerve block of the following mean volumes: • **Simple procedures:** 1.9 mL ± 0.10 SEM of 4% articaine, 1:100,000 epinephrine (43) 1.9 mL ± 0.23 SEM of 2% lidocaine, 1:100,000 epinephrine (18) • **Complex procedures:** 2.5 mL ± 0.43 SEM of 4% articaine, 1:100,000 epinephrine (7) 2.6 mL ± 0.00 SEM of 2% lidocaine, 1:100,000 epinephrine (2)
Outcomes	**Clinical anaesthesia** during various procedures • Efficacy (visual analogue scale, ranging from 0 = "it didn't hurt" to 10 = "worst hurt imaginable"). Participant and investigator rated pain during the procedure (70/70) "Simple" group included single extractions with no complications, routine operative procedures, single apical resections, single crown procedures "Complex" group included multiple extractions, multiple crowns, bridge procedures or both, multiple apical resections, alveolectomies; mucogingival operations, other osseous surgical procedures Teeth tested: not reported **Adverse events** reported along with vital signs (70/70)
Notes	No funding reported. Study authors thanked Septodont

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All subjects were randomized in a 2:1 ratio to receive articaine or lidocaine, with the paediatric population ultimately receiving the anaesthetics in a 2.5:1 ratio" Comment: The difference in group size was deliberate and was related to safety issues. Exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "All subjects were randomized in a 2:1 ratio to receive articaine or lidocaine, with the pediatric population ultimately receiving the anaesthetics in a 2.5:1 ratio" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: detailed methods not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: detailed methods not reported. It is not clear whether the person recording participants' outcomes also administered the local anaesthetic, as he or she may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Unsure whether study was sponsored by Septodont

Maniglia-Ferreira 2009

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Brazil) **Participants:** 60 enrolled, 60 completing the study. Age ranging from 21 to 48 years. Male:female ratio not reported **Inclusion criteria** • All patients had irreversible pulpitis of a mandibular molar and had to undergo inferior alveolar nerve block • All teeth were vital and had to undergo endodontic treatment because of irreversible pulpitis **Exclusion criteria** • Hypersensitive to any of the anaesthetics used in the study or had any systemic disease (hypertension or cardiopathy)
Interventions	Inferior alveolar nerve blocks (1 cartridge) of: • 2% lidocaine, 1:2,500 phenylephrine (20: not commercially available) • 2% mepivacaine, 1:100,000 epinephrine (20) • 4% articaine, 1:100,000 epinephrine (20)
Outcomes	**Clinical anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: ability to access and instrument the tooth without pain (VAS score of zero or mild pain ≤ 54 mm) on a Heft-Parker visual analogue scale (60/60) • The number of cartridges necessary to achieve anaesthesia Teeth tested: mandibular molars **Soft tissue anaesthesia** • Duration: method of measuring not reported (number tested was unclear) Soft tissues tested: unclear. Lower lip?
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to three groups of 20 participants each" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to three groups of 20 participants each" Comment: methods of concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel, to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Detailed methods were not reported. It is not clear whether the person recording participants' outcomes also administered the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comment: The number of participants who had duration of anaesthesia measured was not stated; therefore risk of attrition bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Martinez-Rodriguez 2012

Methods	Randomized controlled simulated scenario (before and following a clinical intervention), parallel study design
Participants	**Location:** university (Spain) **Participants:** 96 enrolled, 96 completing the study (48 in each group). Mean age or range of ages and male:female ratio not reported **Inclusion criteria** • Male and female patients who provide their consent to participate in the study • Ages between 18 and 45 years • Presence of retained lower third molar that is susceptible to surgical extraction • Capable of understanding and carrying out instructions given by the investigators **Exclusion criteria** • Women found to be pregnant or nursing • Cardiovascular problems, renal and/or liver failure, and/or blood dyscrasias • History of hypersensitivity to the anaesthetics under study • Deformities that may interfere with injections or evaluations • Participation in another study with drugs that are under investigation in the previous 3 months • Inability to follow instructions or co-operate during the study
Interventions	Inferior alveolar nerve block (1.8 mL) and mandibular buccal infiltration (0.9 mL) of: • 4% articaine, 1:100,000 epinephrine (48) • 2% lidocaine, 1:100,000 epinephrine (48)
Outcomes	**Soft tissue anaesthesia** (self-reported) • Onset (96/96) • Duration (96/96) Soft tissues tested: lower lip Teeth extracted: mandibular third molars **Adverse effects** were reported (96/96) • Mild, moderate, or severe
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "....designed as a parallel, simple blind, single-site study with randomization in four-element blocks or two treatments" "6 blocks of 4 possible treatments were established; Test-A and reference-B (Table 2)" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "....designed as a parallel, simple blind, single-site study with randomization in four-element blocks or two treatments" "6 blocks of 4 possible treatments were established; Test-A and reference-B (Table 2)" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The study was open to the investigators and blind to the patients" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The study was open to the investigators and blind to the patients" Comment: Detailed methods were not reported. It is not clear whether the person recording participants' outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Maruthingal 2015

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (India) **Participants:** 32 enrolled, 32 completing the study. Mean age 18.2 years ranging from 15 to 35 years. 7 male, 25 female **Inclusion criteria** • Age ranging from 15 to 35 years • Initial occlusal caries confirmed by intraoral periapical radiograph **Exclusion criteria** • Known or suspected allergies • Sensitivities to sulphites and amide-type local anaesthetics or to any ingredient in the anaesthetic solution • Concomitant cardiac disease • Neurological disease. • Pregnant women or lactating mothers • Concomitant use of monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, vasodepressor drugs, or ergot-type oxytocic drugs • Taking sedatives or had taken aspirin, acetaminophen, or NSAIDs 24 hours before administration of local anaesthetic. The teeth tested as non-vital were not included in the study
Interventions	Mandibular buccal infiltration (1.7 mL) using the following: • 2% lidocaine, 1:100,000 epinephrine (32) • 4% articaine, 1:100,000 epinephrine (32)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive lack of responses (64/64) • Onset: time from end of anaesthetic injection until lack of response (45/64) Teeth tested: mandibular first molars **Soft tissue anaesthesia** • Success: sensation of numbness (64/64) • Onset: first feeling of numbness reported (64/64) Soft tissues tested: lip and lingual mucosa
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Study was designed as a prospective randomized double-blind crossover trial" "They were treated as Group I to receive 2% lidocaine with 1:100,000 epinephrine……in the first visit and the same individuals were treated as Group II to receive 4% articaine with 1:100,000 epinephrine……local anesthesia in the second visit" Comment: Although the trial was described as randomized, the order of local anaesthetics administered was pre-determined for everyone in a non-randomized way. Attempts were made to contact the study author to clarify this, but no contact could be made

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Quote: "Study was designed as a prospective randomized double-blind crossover trial" "They were treated as Group I to receive 2% lidocaine with 1:100,000 epinephrine……in the first visit and the same individuals were treated as Group II to receive 4% articaine with 1:100,000 epinephrine……local anesthesia in the second visit" Comment: Although the trial was described as randomized, the order of local anaesthetics administered was pre-determined for everyone in a non-randomized way. Attempts were made to contact the study author to clarify this, but no contact could be made
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both the subjects, and the dentist and dental nurse were blinded for the drug being used and had no involvement with testing the outcome" "They were treated as Group I to receive 2% lidocaine with 1:100,000 epinephrine……in the first visit and the same individuals were treated as Group II to receive 4% articaine with 1:100,000 epinephrine……local anesthesia in the second visit" Comment: The order of local anaesthetics administered was pre-determined for everyone in a non-randomized way; therefore the local anaesthetic used would be known. A pre-determined method of administration was used by personnel to minimize variation. Despite no blinding, identification of the local anaesthetic by participants would be possible only if they were informed of the order of formulations administered. Attempts were made to contact the study author to clarify this, but no contact could be made. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	High risk	Quote: "Both the subjects, and the dentist and dental nurse were blinded for the drug being used and had no involvement with testing the outcome" "They were treated as Group I to receive 2% lidocaine with 1:100,000 epinephrine……in the first visit and the same individuals were treated as Group II to receive 4% articaine with 1:100,000 epinephrine ……local anesthesia in the second visit" Comment: The order of local anaesthetics administered was pre-determined for everyone in a non-randomized way; therefore the local anaesthetic used would be known, although a separate outcome assessor was used. Attempts were made to contact the study author to clarify this, but no contact could be made. Risk of bias was graded as high
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	Comment: The number of participants who had onset of pulpal anaesthesia measured is not clear. Numbers of participants for lidocaine and articaine were likely to be 17 and 28, respectively, based on those who had successful pulpal anaesthesia. As this could not be clarified by the study author, risk of attrition bias was graded as unclear. Data were not used for meta-analysis

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Mason 2009

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 60 enrolled, 60 completing the study • Lateral incisor: 30 enrolled, 30 completing the study, with mean age of 25 years ranging from 19 to 43 years. 15 men and 15 women • First molar: 30 enrolled, 30 completing the study, with mean age of 25 years, ranging from 20 to 42 years, 16 men and 14 women **Inclusion criteria:** in good health and not taking any medication that would alter pain perception **Exclusion criteria** • Younger than 18 or older than 65 years of age • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions • Taking any medications that may affect aesthetic assessment • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	Maxillary buccal infiltration (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine (60) • 2% lidocaine, 1:50,000 epinephrine (60) • 3% mepivacaine, no vasoconstrictor (60)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings with the pulp tester were obtained within 10 minutes of infiltration (180/180) • Onset (84/90: first molar, 84/90: lateral incisor) • Anaesthesia of short duration: Participant achieved 2 consecutive 80 readings, lost the 80 readings, and never regained them within the 60-minute period • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: maxillary first molars and lateral incisors
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, the three anaesthetic solutions were randomly assigned to designate which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Each solution had a random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote: "Before the experiment, the three anaesthetic solutions were randomly assigned to designate which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: The cartridges "were masked with opaque labels, and the cartridge caps and plungers were masked with a black felt tip marker. The corresponding random code number was written on each cartridge label" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Trained personnel, who were blinded to the anaesthetic solutions, administered all preinjection and post-injection tests" "Only the random numbers were recorded on the data-collection sheets to further blind the experiment" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 84 occasions on first molar teeth and on 84 occasions on lateral incisors (for those experiencing successful anaesthesia (matched pairs): 28 cases of 2% lidocaine, 1:100,000 epinephrine; 28 cases of 2% lidocaine, 1:50,000 epinephrine; and 28 cases of 3% mepivacaine, no vasoconstrictor). As numbers were reduced in all groups equally and for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

McEntire 2011

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 86 enrolled, 86 completing the study. Mean age 26 years, ranging from 18 to 43 years. 43 male, 43 female **Inclusion criteria:** in good health and not taking any medication that would alter pain perception **Exclusion criteria** • Younger than 18 or older than 65 years of age • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions (American Society of Anesthesiologists class II or higher) • Taking any medications (over-the-counter pain-relieving medications) • Narcotics, sedatives, antianxiety or antidepressant medications that might affect anaesthetic assessment • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	Mandibular buccal infiltration (1.8 mL) of • 4% articaine, 1:100,000 epinephrine (86) • 4% articaine, 1:200,000 epinephrine (86)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings with the pulp tester were obtained within 10 minutes of the initial injection (172/172) • Onset (90/172) • Incidence: number of maximum pulp tester readings (80) over time Teeth tested: mandibular first molars **Adverse events** reported (172/172) • Pain at each stage of injection (Heft-Parker visual analogue scale) • Post-injection pain (Heft-Parker visual analogue scale) • Other adverse events
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 2 anaesthetic formulations were randomly assigned 6-digit numbers from a random number table. Each subject was randomly assigned to each of the 2 anaesthetic formulations to determine which formulation was to be administered at each appointment" Quote (from correspondence): "Each solution had a six-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote: "The 2 anaesthetic formulations were randomly assigned 6-digit numbers from a random number table. Each subject was randomly assigned to each of the 2 anaesthetic formulations to determine which formulation was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The anaesthetic cartridges were masked with opaque labels, and the corresponding 6-digit codes were written on each cartridge" "Only the random numbers were recorded on the data collection sheets to further blind the experiment" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Trained personnel who were blinded to the anaesthetic formulations administered all preinjection and post-injection tests" "Only the random numbers were recorded on the data collection sheets to further blind the experiment" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 90 occasions (for those experiencing successful anaesthesia (matched pairs): 45 cases of 4% articaine, 1:100,000 epinephrine and 45 cases of 4% articaine, 1:200,000 epinephrine). As numbers were reduced in both groups equally and for the same reasons, risk of bias was rated as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

McLean 1993

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 30 enrolled, 30 completing the study. Mean age 28 years, ranging from 24 to 43 years. 24 male, 6 female **Inclusion criteria:** in good health and not taking any medication that would alter pain perception **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks (1.8 mL) of • 2% lidocaine, 1:100,000 epinephrine (30) • 4% prilocaine, no vasoconstrictor (30) • 3% mepivacaine, no vasoconstrictor (30)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 80 reading was achieved within 16 minutes, and this reading was sustained for the remainder of the 50-minute test period (90/90) • Failure: Participant never achieved 2 consecutive 80 readings during the 50 minutes • Onset (82/90) • Anaesthesia of slow onset: Participant achieved 2 consecutive 80 readings after 16 minutes • Anaesthesia of short duration: Participant achieved 2 consecutive 80 readings, lost the 80 readings, and never regained them within the 50-minute period • Non-continuous anaesthesia: Participant achieved 2 consecutive 80 readings, lost the 80 readings, and then regained the 80 readings during the 50 minutes • Incidence: number of maximum pulp tester readings (80) over time Teeth tested: mandibular first molars, first premolars, and lateral incisors **Soft tissue anaesthesia** sticking the alveolar mucosa (labial and lingual to the premolar and buccal to the first molar) with a sharp explorer • Success: Participant felt numbness within 20 minutes and/or did not respond to mucosal sticks (90/90) • Onset (90/90) Soft tissues tested: lower lip/tongue (participant felt numbness) and labial and lingual to the premolar and buccal to the first molar (mucosal sticks)
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were randomly assigned to one of six letter (ABC) combinations to determine the sequence of solution administration" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "A four-digit random number, corresponding to the letter designation, was written on each cartridge, and the three cartridges for each subject were placed in an autoclave bag with the numbers recorded on the outside showing the injection order" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an autoclave bag for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment etc was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Each anaesthetic cartridge label was removed and masked with tape. A four-digit random number, corresponding to the letter designation, was written on each cartridge, and the three cartridges for each subject were placed in an autoclave bag with the numbers recorded on the outside showing the injection order" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All pre- and post-injection tests were done by trained personnel who were blinded to the solutions injected" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 82 occasions (for those experiencing successful anaesthesia: 27 cases of 2% lidocaine, 1:100,000 epinephrine; 28 cases of 4% prilocaine, no vasoconstrictor; and 27 cases of 3% mepivacaine, no vasoconstrictor). As numbers in both groups were well balanced and were reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Mikesell 2005

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 57 enrolled, 57 completing the study. Mean age 28 years, ranging from 19 to 60 years. 30 male, 27 female **Inclusion criteria:** in good health and not taking any medications that would alter their perception of pain **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine (57) • 4% articaine, 1:100,000 epinephrine (57)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings were obtained within 15 minutes and 80 readings were continuously sustained for 60 minutes (114/114) • Failure: Participant never achieved 2 consecutive 80 readings during the 60 minutes • Anaesthesia of slow onset: Participant achieved 2 consecutive 80 readings after 15 minutes • Incidence: number of maximum pulp tester readings (80) over time Teeth tested: mandibular second molars, first molars, second premolars, first premolars, lateral incisors, and central incisors **Soft tissue anaesthesia** • Success: Lip numbness was recorded within 15 minutes. Participant was asked whether lip/tongue was numb every minute for 15 minutes (114/114) Soft tissues tested: lower lip and tongue **Adverse events** reported (114/114) • Pain at each stage of injection (Heft-Parker visual analogue scale) • Post-injection pain (Heft-Parker visual analogue scale) • Other adverse events
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 57 blinded subjects randomly received an IAN block injection of either an articaine or lidocaine solution at two separate appointments" "Before the experiment, the two anaesthetic solutions were randomly assigned six-digit numbers from a random number table. Each subject was randomly assigned to one of the two solutions to determine which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Each solution had a six-digit random number for each subject and for each solution. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The 57 blinded subjects randomly received an IAN block injection of either an articaine or lidocaine solution at two separate appointments" "Before the experiment, the two anaesthetic solutions were randomly assigned six-digit numbers from a random number table. Each subject was randomly assigned to one of the two solutions to determine which anaesthetic solution was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an autoclave bag for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment etc was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The anaesthetic solutions administered were blinded by masking the appropriate cartridges with opaque labels, which were labelled with the six-digit numbers" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the random numbers were recorded on the data collection and post-injection survey sheets to blind the experiment" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Quote: "If profound lip numbness was not recorded within 15 min, the block was considered unsuccessful; the subject was then reappointed" "A total of eight patients, two using the articaine solution and six using the lidocaine solution, did not have profound lip numbness at 15 min (unsuccessful blocks) and were reappointed. One hundred percent of the subjects used for data analysis had profound lip anaesthesia with both the articaine and lidocaine solutions" Comment: Participants who were re-appointed had successful pulpal anaesthesia; therefore it was possible to re-calculate overall success
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Quote: "If profound lip numbness was not recorded within 15 min, the block was considered unsuccessful; the subject was then reappointed" "A total of eight patients, two using the articaine solution and six using the lidocaine solution, did not have profound lip numbness at 15 min (unsuccessful blocks) and were reappointed. One hundred percent of the subjects used for data analysis had profound lip anaesthesia with both the articaine and lidocaine solutions" Comment: Participants who were re-appointed had failed lip anaesthesia; therefore it was possible to re-calculate overall success
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: Two participants using articaine and 6 using lidocaine were re-allocated, after initial failure of lip anaesthesia. Adverse events in the journal article represent those from participants initially having successful anaesthesia and 8 participants following re-allocation. The numbers re-allocated were relatively low in number; therefore as numbers in both groups were well balanced and reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Mittal 2015

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (India) **Participants:** 104 enrolled, 104 completing the study. Age ranging from 5 to 12 years. 68 male, 36 female **Inclusion criteria** • Children who were physically and mentally healthy and assessed as being co-operative, having behavioural ratings positive or definitely positive, according to the Frankl Behaviour Classification Scale • All required primary maxillary molar extraction • Not treated under nitrous oxide sedation or receiving any treatment that could modify behaviour or awareness of pain **Exclusion criteria** • Children younger than 4 years old • Allergies to local anaesthetics or sulphites • History of significant medical conditions • Taking any medications that might affect anaesthetic assessment • Active state of pathosis in the area of injection
Interventions	Maxillary buccal infiltration using the following: • 1.8 mL of 2% lidocaine, 1:80,000 epinephrine (52) • 1.7 mL of 4% articaine, 1:100,000 epinephrine (52)
Outcomes	**Clinical anaesthesia** during extraction of primary maxillary molars • Success (104/104): ◦ Subjective evaluation: Wong Baker Facial Pain Scale (subjective) ◦ Objective evaluation: Modified Behavioural Pain Scale (facial display, hand/leg movements, torso movements, crying) Teeth/soft tissues tested: primary maxillary molars **Soft tissue anaesthesia** • Success: no pain on probing (104/104) Soft tissues tested: soft tissues, buccal and palatal to the tooth to be extracted **Adverse events** reported (104/104) • Haemodynamic parameters of heart rate and blood pressure recordings were used
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Children were randomly selected employing the envelope method to receive buccal infiltration using either 1.8 ml lidocaine HC1 two percent with epinephrine 1:80,000 (Lignospan special, Septodont, Saint-Maur-des-Fosses, France) (Group A) or 1.7 ml articaine HC1 four percent with epinephrine 1:100,000 (Septanest, Septodont, France; Group B)" Quote (from correspondence): "The name of the anesthetic agent to be used was written on multiple slips (equal number of slips for both the agents), which were kept in an envelope. Patient picked one of the slips without seeing the name, the slips were folded"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Children were randomly selected employing the envelope method to receive buccal infiltration using either 1.8 ml lidocaine HC1 two percent with epinephrine 1:80,000 (Lignospan special, Septodont, Saint-Maur-des-Fosses, France) (Group A) or 1.7 ml articaine HC1 four percent with epinephrine 1:100,000 (Septanest, Septodont, France; Group B)" Quote (from correspondence): "The name of the anesthetic agent to be used was written on multiple slips (equal number of slips for both the agents), which were kept in an envelope. Patient picked one of the slips without seeing the name, the slips were folded"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The clinician administering the anesthetic, chairside assistant, patient receiving the anesthetic, and his/her parent were all blinded to the anesthetic agent being used" Quote (from correspondence): "The cartridge or the Wand assembly was loaded by a person different from clinician, assistant, patient or parent. There is a very slight colour difference between the two anesthetic cartridges. The clinician could see the cartridge if he saw carefully. The cartridge was loaded and given to him just before injection" Comment: Identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Facial display followed Craig's behavioral description of facial actions. Only two of the four of Craig's most descriptive facial actions were evident (eyebrow bulge or eye squeeze), as the mouth was open and the nose was partly covered by the operator's hand during the procedure. These behavioural parameters were evaluated during the extraction procedure by a trained dental assistant who did not participate in the treatment and was blind to the agent being used" Comment: Outcomes were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Moore 1983

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States) **Participants:** 32 enrolled, 32 completing the study. 14 male, 18 female. Mean age of bupivacaine patients: 40.3 years, ranging from 21 to 64 years. Mean age of lidocaine patients: 41.4 years, ranging from 22 to 66 years **Inclusion criteria:** none reported **Exclusion criteria** • Pregnancy • History of allergic reactions to any of the study medications • Maxillofacial deformities that might interfere with injections or evaluations • Concurrent oral or intravenous sedation medication • Treatments not restricted and including initial canal instrumentation appointments as well as canal obturation and apical surgery
Interventions	Maxillary and mandibular injections (blocks and infiltrations), 2 cartridges (2 × 1.8 mL) used for each procedure of: • 2% lidocaine, 1:100,000 epinephrine (16) • 0.5% bupivacaine, 1:200,000 epinephrine (16)
Outcomes	**Clinical anaesthesia** during non-surgical and surgical endodontic treatment • Profundity of anaesthesia: excellent, satisfactory, or unsatisfactory on the basis of whether 2 cartridges were sufficient, whether supplemental injections were necessary, or whether complete anaesthesia was not possible (32/32) Teeth tested: maxillary or mandibular teeth, but no specific details **Soft tissue anaesthesia** • Onset: method of measurement clarified by study author: measured by self-report of lip numbness (32/32) • Duration: questionnaire asking when the local anaesthetic began to wear off (a "pins and needles" feeling (32/32)) Soft tissues tested: lip **Adverse events** reported (32/32) • Postoperative pain
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (from correspondence): "We used a random number table and sealed envelopes to assure blinding"
Allocation concealment (selection bias)	Low risk	Quote (from correspondence): "We used a random number table and sealed envelopes to assure blinding" "Double-blind conditions were maintained by coding identically appearing unlabeled cartridges of the two agents. The code was available in a sealed envelope if needed"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Double-blind conditions were maintained by coding identically appearing unlabeled cartridges of the two agents. The code was available in a sealed envelope if needed" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Double-blind conditions were maintained by coding identically appearing unlabeled cartridges of the two agents. The code was available in a sealed envelope if needed" Comment: Identification of the local anaesthetic by participants and personnel was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Moore 2006

Methods	Randomized controlled simulated scenario trial, cross-over study design

Participants	**Location:** university (United States of America) **Participants** • Trial 1 (mandible): 63 enrolled, 62 completing the study. Mean age 30.4 years (SD ± 10.0), ranging from 19 to 60 years. 36 male, 27 female • Trial 2 (maxilla): 63 enrolled, 62 completing the study. Mean age 30.4 years (SD ± 8.4), ranging from 20 to 55 years. 28 male, 35 female One person withdrew, who had successfully received an injection of 4% articaine, 1:100,000 epinephrine in trial 1 and trial 2 **Inclusion criteria** • 18 to 65 years of age • Females of childbearing potential to engage in an acceptable method of birth control (such as abstinence, use of oral contraceptive steroids, or use of an intrauterine device) for at least 1 month before and throughout the study. They required a negative urine pregnancy test at screening and at all subsequent treatment visits. Lactating women were not eligible **Exclusion criteria** • Known or suspected allergies or sensitivities to sulphites or amide-type local anaesthetics • Significant history of cardiac or neurological disease • Severe or frequent cardiac arrhythmias • Treated or untreated hypertension ≥ 140 millimetres of mercury (Hg) systolic or 90 mmHg diastolic pressure • Severe or currently symptomatic bronchial asthma • Severe psychiatric condition or evidence of soft tissue infection near the proposed injection site • Current use of specific medications (non-selective beta blockers, monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs, aspirin, acetaminophen, non-steroidal anti-inflammatory drugs, opioids, or other analgesic agents within 24 hours of administration of study medication) and/or having taken an investigational drug or participated in another study within the 4 weeks preceding initiation of treatment • Required sedation therapy (oral, inhalational, or intravenous) to tolerate the injection procedure
Interventions	Either inferior alveolar nerve block (1.7 mL; trial 1) or maxillary buccal infiltration anaesthesia (1.0 mL; trial 2) using: • 4% articaine, 1:200,000 epinephrine (62 in trial 1, 62 in trial 2) • 4% articaine, 1:100,000 epinephrine (63 in trial 1, 63 in trial 2) • 4% articaine, with no vasoconstrictor (62 in trial 1, 62 in trial 2)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 3 consecutive tests (at 30-second intervals) above the maximum threshold (EPT ≥ 80) (187/189 in trial 1, 187/189 in trial 2) • Onset (80/189 in trial 1, 165/189 in trial 2) • Duration (80/189 in trial 1, 165/189 in trial 2) • Self-report of anaesthesia characteristics: no change or alteration in sensation, slight feeling of numbness, moderate but not complete feeling of numbness, and complete numbness on 1 side of the mouth Note: 189 is the total number of expected measurements, but owing to 1 dropout in each trial, the number of participants was reduced in each group by 1, except the 4% articaine, 1:100,000 epinephrine group, for which measurements had already been recorded before dropout Teeth tested: mandibular canines (trial 1) and maxillary first premolars (trial 2) **Adverse events** reported (187/189 in trial 1, 187/189 in trial 2)
Notes	Industry funded (first study author is a paid consultant, and another study author is an employee of the study sponsor)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the first treatment visit, we enrolled subjects and assigned them to a randomized sequence for drug allocation" Quote (from correspondence): "Randomized by sponsor, sealed in a box labelled with subject code and not visually different"
Allocation concealment (selection bias)	Low risk	Quote: "At the first treatment visit, we enrolled subjects and assigned them to a randomized sequence for drug allocation" "The study sponsor (Novocol Pharmaceutical, Cambridge, Ontario, Canada) prepared identical-appearing dental cartridges of the three study formulations and coded them properly to ensure blinded administration" Quote (from correspondence): "Randomized by sponsor, sealed in a box labelled with subject code and not visually different"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study sponsor (Novocol Pharmaceutical, Cambridge, Ontario, Canada) prepared identical-appearing dental cartridges of the three study formulations and coded them properly to ensure blinded administration" Comment: Participants and personnel would not be able to identify the local anaesthetic used, and a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The study sponsor (Novocol Pharmaceutical, Cambridge, Ontario, Canada) prepared identical-appearing dental cartridges of the three study formulations and coded them properly to ensure blinded administration" Comment: Identification of the local anaesthetic by participants and personnel was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Quote: "One subject was not included in the second and third treatment session owing to an error in the EPT protocol. At the conclusion of the trial, data were available for 63 subjects who received A100, 62 who received A200 and 62 who received Aw/o" Comment: excluded participant accounted for. Different groups were well balanced. Therefore risk was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 165 occasions in the maxilla (for those experiencing successful anaesthesia: 58 cases of 4% articaine, 1:200,000 epinephrine; 60 cases of 4% articaine, 1:100,000 epinephrine; and 47 cases of 4% articaine, with no vasoconstrictor) Onset of pulpal anaesthesia was tested on 80 occasions in the mandible (for those experiencing successful anaesthesia: 34 cases of 4% articaine, 1:200,000 epinephrine; 30 cases of 4% articaine, 1:100,000 epinephrine; and 16 cases of 4% articaine, with no vasoconstrictor) As numbers in all groups were well balanced and were reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: Duration of pulpal anaesthesia was tested on 165 occasions in the maxilla (for those experiencing successful anaesthesia: 58 cases of 4% articaine, 1:200,000 epinephrine; 60 cases of 4% articaine, 1:100,000 epinephrine; and 47 cases of 4% articaine, with no vasoconstrictor) Duration of pulpal anaesthesia was tested on 80 occasions in the mandible (for those experiencing successful anaesthesia: 34 cases of 4% articaine, 1:200,000 epinephrine; 30 cases of 4% articaine, 1:100,000 epinephrine; and 16 cases of 4% articaine, with no vasoconstrictor) As numbers in all groups were well balanced and were reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "One subject was not included in the second and third treatment session owing to an error in the EPT protocol. At the conclusion of the trial, data were available for 63 subjects who received A100, 62 who received A200 and 62 who received Aw/o" Comment: excluded participant accounted for. Different groups were well balanced. Therefore risk was graded as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	High risk	Comment: Onset of pulpal anaesthesia was tested on 165 occasions in the maxilla (for those experiencing successful anaesthesia: 58 cases of 4% articaine, 1:200,000 epinephrine; 60 cases of 4% articaine, 1:100,000 epinephrine; and 47 cases of 4% articaine, with no vasoconstrictor) Onset of pulpal anaesthesia was tested on 80 occasions in the mandible (for those experiencing successful anaesthesia: 34 cases of 4% articaine, 1:200,000 epinephrine; 30 cases of 4% articaine, 1:100,000 epinephrine; and 16 cases of 4% articaine, with no vasoconstrictor) Onset of pulpal anaesthesia was measured in similar numbers of participants in each local anaesthetic group except 4% articaine, no vasoconstrictor, when only 47/62 were measured in the maxilla and 16/62 in the mandible (those who achieved anaesthetic success). Risk of bias was rated as high owing to differences in numbers measured in each group
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	High risk	Comment: Duration of pulpal anaesthesia was tested on 165 occasions in the maxilla (for those experiencing successful anaesthesia: 58 cases of 4% articaine, 1:200,000 epinephrine; 60 cases of 4% articaine, 1:100,000 epinephrine; and 47 cases of 4% articaine, with no vasoconstrictor) Duration of pulpal anaesthesia was tested on 80 occasions in the mandible (for those experiencing successful anaesthesia: 34 cases of 4% articaine, 1:200,000 epinephrine; 30 cases of 4% articaine, 1:100,000 epinephrine; and 16 cases of 4% articaine, with no vasoconstrictor) Duration of pulpal anaesthesia was measured in similar numbers of participants in each local anaesthetic group, except 4% articaine, no vasoconstrictor, when only 47/62 were measured in the maxilla and 16/62 in the mandible (those who achieved anaesthetic success). Risk of bias was rated as high owing to differences in numbers measured in each group

Bias	Authors' judgement	Support for judgement
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Quote: industry funded (first study author is a paid consultant, and another study author is an employee of the study sponsor)

Moore 2007

Methods	Randomized controlled clinical trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 42 enrolled, 42 completing the study. Mean age 46.3 (SD ± 9.7), ranging from 22 to 65 years. 26 male, 16 female **Inclusion criteria** • 21 to 65 years of age • Diagnosis of moderate to severe periodontal disease requiring bilateral • Gingival flap surgery (equal numbers of teeth involved (± 1 tooth) and equal mean levels of attachment loss (± 2 mm)). Free gingival graft procedures were not permitted • Must have had clinical laboratory values within the normal range at screening **Exclusion criteria** • Any known or suspected allergies or sensitivities to sulphites or amide-type local anaesthetics or any of the ingredients in the test solutions • Significant history of cardiac or neurological disease • Severe or frequent cardiac arrhythmias • Treated or untreated hypertension (> 140/90 mmHg) • Severe or currently symptomatic bronchial asthma • Severe psychiatric disability • Evidence of acute soft tissue infection near proposed injection sites • Current drug therapy included non-selective beta blockers, monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs, warfarin, dicumarol, heparin, aspirin, or any medication that inhibits blood coagulation • Participants had taken an investigational drug, participated in another study within 4 weeks of their screening visit, or consumed more than 3 alcoholic beverages per day or 21 alcoholic beverages per week on a regular basis • Could not be pregnant or lactating (a urine pregnancy test for females of childbearing potential was completed at screening and at each treatment visit before drug administration). Females of childbearing potential must have been using an adequate method of birth control (e.g. abstinence, oral contraceptive steroids, intrauterine device) for ≤ 1 month before and during the study
Interventions	Maxillary buccal infiltration (buccal and palatal if required) techniques using the following: • 4% articaine, 1:200,000 epinephrine: 4.1 ± 1.3 mL (42) • 4% articaine, 1:100,000 epinephrine: 4.1 ±1.2 mL (42) Volumes varied depending on procedure (minimum used, with a maximum of 4 cartridges)
Outcomes	**Clinical anaesthesia** during periodontal surgery • Descriptive report of anaesthesia: 1 = normal sensation; 2 = slight feeling of numbness; 3 = moderate, but not complete, feeling of numbness; and 4 = side of mouth is completely numb (84/84) • Volume of local anaesthetic injected • Failure: need to administer an alternative anaesthetic agent for pain control or visualization of the surgical field Teeth tested: maxillary teeth/soft tissues **Adverse events** reported (84/84)
Notes	Industry funded (1 study author is an employee of the study sponsor) (first study author was a paid consultant for the study sponsor in a previous study (Moore 2006), although this is not declared in the current study)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomized to one of the two drug sequence groups: A200 at the first surgical appointment and A100 at the second surgical appointment or A100 at the first surgical appointment and A200 at the second surgical appointment" Comment: exact method of generation of randomized sequence not reported Quote (from correspondence): "Randomized by sponsor, sealed in a box, labelled with subject code and not visually different"
Allocation concealment (selection bias)	Low risk	Quote: "Subjects were randomized to one of the two drug sequence groups: A200 at the first surgical appointment and A100 at the second surgical appointment or A100 at the first surgical appointment and A200 at the second surgical appointment" Quote (from correspondence): "Randomized by sponsor, sealed in a box, labelled with subject code and not visually different"
Blinding of participants and personnel (performance bias)	Low risk	Quote (from correspondence): "Cartridges were unlabelled and dispensed in an investigator container with only subject number" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote (from correspondence): "Cartridges were unlabelled and dispensed in an investigator container with only subject number" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Quote: industry funded (1 study author is an employee of the study sponsor) (first study author was a paid consultant for the study sponsor in a previous study (Moore 2006), although this is not declared in the current study)

Mumford 1961

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United Kingdom) **Participants:** 300 enrolled, 300 completing the study (200 without 2% mepivacaine, 1:80,000 epinephrine). Mean age 21.3 to 25.4 years, ranging from 11 to 59 years. Exact number of male and female participants not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	"Regional" and infiltration injections (1.5 and 1.0 mL, respectively) of: • 2% lidocaine, 1:80,000 epinephrine (100) • 3% mepivacaine, no epinephrine (100) • 2% mepivacaine, 1:80,000 epinephrine (100: not commercially available)
Outcomes	**Clinical anaesthesia** during routine tooth cavity preparation • Success (200/200) • Onset: Bur was applied every 30 seconds until no pain was felt (167/200) • Duration: until dentine cutting produced no pain, or until cavity preparation finished before this - minimum duration (164/200) Teeth tested: maxillary lateral incisors, canines, first premolars, mandibular molars **Soft tissue anaesthesia** • Duration: when soft tissues returned to normal. Self-reported and written on a postcard, which was returned (number assessed not clear) Soft tissues tested: soft tissues relevant to the procedure **Adverse events** reported (number assessed not clear) • Quality of soft tissue anaesthesia • Other adverse effects
Notes	Possibly industry funded, as study authors thank Bayer and Astrapharm

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The materials were randomized and coded for double blind testing" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The materials were randomized and coded for double blind testing" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The materials were randomized and coded for double blind testing" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The materials were randomized and coded for double blind testing" Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comment: Of 300 participants, 209 were given postcards for soft tissue duration. Of these, 192 were returned. It is not clear how many postcards were given to each local anaesthetic group's participants, or why these were not given to every participant. Therefore risk was graded as unclear

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Comment: Of 300 participants, 209 were given postcards to record adverse events. Of these, 192 were returned. It is not clear how many postcards were given to each local anaesthetic group's participants, or why these were not given to every participant. Therefore risk was graded as unclear
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 82 occasions for those experiencing successful anaesthesia for infiltration (40 cases of 2% lidocaine, 1:80,000 epinephrine; 42 cases of 3% mepivacaine, no epinephrine) and on 85 occasions for IANBs (43 cases of 2% lidocaine, 1:80,000 epinephrine; 42 cases of 3% mepivacaine, no epinephrine). As numbers in both groups were well balanced and were reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Low risk	Comment: Duration of pulpal anaesthesia was tested on 80 occasions for those experiencing successful anaesthesia for infiltration (39 cases of 2% lidocaine, 1:80,000 epinephrine; 41 cases of 3% mepivacaine, no epinephrine) and on 84 occasions for IANBs (42 cases of 2% lidocaine, 1:80,000 epinephrine; 42 cases of 3% mepivacaine, no epinephrine) Of the total number of participants recruited who had successful pulpal anaesthesia, a few did not have duration of pulpal anaesthesia measured: • **IANB:** ◦ 2% lidocaine, 80,000 epinephrine: not measured in 1/43 (2%) ◦ 3% mepivacaine, no epinephrine: not measured in 0/42 (0%) • **Infiltration:** ◦ 2% lidocaine, 80,000 epinephrine: not measured in 1/40 (0%) ◦ 3% mepivacaine, no epinephrine: not measured in 1/42 (2%) As numbers in both groups were well balanced and were reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Comment: possibly industry funded, as study authors thank Bayer and Astrapharm

Nabeel 2014

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (Pakistan) **Participants:** 76 enrolled, 76 completing the study. Age ranging from 18 to 67 years. 33 male, 43 female **Inclusion criteria** • Diagnosis of irreversible pulpitis of maxillary first premolars **Exclusion criteria** • Taking any drugs that could alter pain perception • Suffering from any allergy, heart disease, or diabetes mellitus • Expecting and lactating mothers
Interventions	Maxillary buccal infiltration (1.7 mL) using the following: • 2% lidocaine, 1:100,000 epinephrine (38) • 4% articaine, 1:100,000 epinephrine (38)
Outcomes	**Pulpal anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: ability to access and instrument the tooth without pain (score of 0 to 3, on a VAS of 0 to 10) (76/76) Teeth tested: maxillary first premolars
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were assigned group 1 or 2 by using a computer-generated list of random numbers with randomization ratio of 1:1 produced by random allocation software (version 1.0)"
Allocation concealment (selection bias)	Unclear risk	Quote: "They were assigned group 1 or 2 by using a computer-generated list of random numbers with randomization ratio of 1:1 produced by random allocation software (version 1.0)" Comment: detailed methods not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: detailed methods not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear if a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Naik 2017

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (India) **Participants:** 49 male, 51 female • 2% lidocaine with 1:80,000 epinephrine group: 50 enrolled, 50 completing the study. Mean age 28.6 years ± 6.52, ranging from 18 to 40 years • 4% articaine with 1:100,000 epinephrine group: 50 enrolled, 50 completing the study. Mean age 28.6 years ± 6.52, ranging from 18 to 40 years **Inclusion criteria** • 18 to 40 years of age • Without any systemic disorders or antecedents of complications associated with local anaesthetics • Impacted lower third molars requiring removal when patients were included irrespective of sex, caste, religion, and socioeconomic status **Exclusion criteria** • Existence of acute infection and/or swelling at the time of surgery • Allergic to lignocaine or articaine • ASA III, IV, V category
Interventions	Inferior alveolar nerve blocks (2 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine (50) • 4% articaine, 1:100,000 epinephrine (50) Followed by 0.5 mL long buccal infiltration for extraction and measurement of success/duration (confirmed by study author)
Outcomes	**Clinical anaesthesia** during surgical removal of third molars • Success: graded by the volume of local anaesthetic used (100/100) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: methods confirmed by study author - measured before long buccal infiltration (100/100): ◦ Subjective: time from administration of local anaesthetic to appearance of numbness of the lower lip ◦ Objective: symptoms checked with a metallic straight probe on the labial gingiva over the mandibular canine region • Duration: Patients were asked to record the time of complete disappearance of numbness (100/100) Soft tissues tested: lip and associated tissues **Adverse effects** (100/100) • Postoperative pain (VAS from 0 cm = no pain to 10 cm = worst pain, and consumption of analgesics measured)
Notes	No funding reported.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated to one of two possible treatment groups according to a randomized list on the visit for surgery" Comment: detailed methods not reported Quote (from correspondence): "We had prepared 2 small chits one with lignocaine and one with articaine. We would pick one chit and allot the patient to whichever group it came"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The patients were allocated to one of two possible treatment groups according to a randomized list on the visit for surgery" Comment: detailed methods not reported Quote (from correspondence): "We had prepared 2 small chits one with lignocaine and one with articaine. We would pick one chit and allot the patient to whichever group it came"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "As articaine 4% is available in only 2ml cartridges in India, before the administration of local anesthetic, it was aspirated in a plastic syringe from the articaine cartridges (SEPTANEST® 4%, SEPTODONT) whereas lignocaine was aspirated in a plastic syringe from lignocaine vials (LIGNOX 2% A, INDOCO REMEDIES LTD). The patients were thus blinded with respect to the type of local anaesthetic treatment given on each occasion" Quote (from correspondence): "Only the patients were blinded" Comment: Participants would not be able to identify the local anaesthetic used. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Study author was emailed to see if this was done, but no reply. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	High risk	Quote: "As articaine 4% is available in only 2ml cartridges in India, before the administration of local anesthetic, it was aspirated in a plastic syringe from the articaine cartridges (SEPTANEST® 4%, SEPTODONT) whereas lignocaine was aspirated in a plastic syringe from lignocaine vials (LIGNOX 2% A, INDOCO REMEDIES LTD). The patients were thus blinded with respect to the type of local anaesthetic treatment given on each occasion" Quote (from correspondence): "Outcome assessor was not blinded" Comment: If the outcome assessor was not blinded, he or she may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as high
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Nespeca 1976

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** military base (United States of America) **Participants:** 143 enrolled, 143 completing the study (100, excluding 0.25% bupivacaine, 1:200,000 epinephrine, which is not commercially available). Mean age 26 years, ranging from 16 to 65 years. Numbers of male and female participants not reported **Inclusion criteria** • ASA I and ASA II **Exclusion criteria:** not reported
Interventions	Inferior alveolar nerve block and infiltration injections (1.5 to 2.0 mL) of: • 2% lidocaine, 1:100,000 epinephrine (40) • 0.25% bupivacaine, 1:200,000 epinephrine (43) • 0.5% bupivacaine, 1:200,000 epinephrine (60)
Outcomes	**Cinical anaesthesia** during maxillofacial procedures • Onset: earliest time after injection that the surgeon was able to begin operating - exact method of testing not reported (100/100) Teeth/soft tissues tested: not stated **Soft tissue anaesthesia:** method of testing not stated: lip numbness, sensitivity in the vestibular gum • Duration: self-reported (100/100) Soft tissues tested: soft tissues relevant to the procedure **Adverse events** reported (100/100) • Postoperative pain (visual analogue scale) • Other adverse effects
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The proposed agents....were randomly selected by the dental assistant, who blindly chose a lettered marker corresponding to one of the six agents" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The proposed agents....were randomly selected by the dental assistant, who blindly chose a lettered marker corresponding to one of the six agents" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The operator was not aware of the contents of the anaesthetic syringe" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The operator was not aware of the contents of the anaesthetic syringe" Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Nordenram 1990

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Sweden) **Participants:** 40 enrolled, 40 completing the study. Mean age 71 years, ranging from 65 to 81 years (elderly group); mean age 24 years, ranging from 17 to 33 years (young group). 19 male, 21 female **Inclusion criteria** • No history of adverse reactions to amino-amide-type local anaesthetics • One group 65 years or older (elderly group) • One group 32 years of age or younger (young group) **Exclusion criteria:** not stated
Interventions	Maxillary buccal infiltration of 0.6 mL of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine (40) • 3% mepivacaine, no vasoconstrictor (40) • 3% prilocaine, 0.03 IU/mL felypressin (40)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success (120/120) • Onset (106/120) • Duration (106/120?) Teeth tested: central incisors, lateral incisors, cuspids **Soft tissue anaesthesia** • Duration: volunteers instructed to register the time for complete recovery from soft tissue numbness (number assessed unclear) Soft tissues tested: upper lip **Adverse effects** were reported (120/120)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was carried out in a double-blind design according to a randomized pattern" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "The study was carried out in a double-blind design according to a randomized pattern" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study was carried out in a double-blind design according to a randomized pattern" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method for administration was used by personnel to minimize variation. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The study was carried out in a double-blind design according to a randomized pattern" Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia measured on 106 occasions (for those experiencing successful anaesthesia: 38 cases of 2% lidocaine, 1:80,000 epinephrine; 34 cases of 3% mepivacaine, no epinephrine; and 34 cases of 3% prilocaine, 0.03 IU/mL felypressin). As numbers in the groups were well balanced and were reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: The number of participants who had the duration of pulpal anaesthesia measured was not stated but was probably the same as for onset of pulpal anaesthesia, as this was recorded at the same visit as onset. As numbers in the groups were well balanced and were reduced for the same reasons, risk of bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comments: The number of participants in each group who had the duration of soft tissue anaesthesia measured was not stated. Therefore risk of bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Bias	Authors' judgement	Support for judgement
Other bias	Low risk	Comment: no other bias present

Nydegger 2014

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 60 enrolled, 60 completing the study. Mean age 26 years, ranging from 20 to 38 years. 30 male, 30 female **Inclusion criteria** • In good health and not taking any medication that would alter pain perception, as determined by a written health history and oral questioning • All test teeth were free of caries, large restorations, crowns, and periodontal disease, and none had a history of trauma or sensitivity **Exclusion criteria** • Younger than 18 or older than 65 years of age • Allergies to local anaesthetics or sulphites • History of significant medical conditions (American Society Anesthesiologist classification II or higher) • Taking any medications (over-the-counter pain-relieving medications, narcotics, sedatives, or anti-anxiety or antidepressant medications) that could affect anaesthetic assessment • Active sites of pathosis in the area of injection • Inability to give informed consent • if pregnant, with suspected pregnancy, trying to become pregnant, or lactating
Interventions	Buccal infiltration (1.8 mL) opposite the mandibular first molars using: • 4% lidocaine, 1:100,000 epinephrine (60 - not commercially available) • 4% articaine, 1:100,000 epinephrine (60) • 4% prilocaine, 1:200,000 epinephrine (60)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: participants achieving complete pulpal anaesthesia (120/120) Teeth tested: mandibular first molars **Adverse events** reported (120/120) • Pain at each stage of injection (Heft-Parker visual analogue scale) • Post-injection pain (Heft-Parker visual analogue scale) • Other adverse events
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, the 3 anesthetic formulations were randomly assigned 6-digit numbers from a random number table. Each subject was randomly assigned to each of the 3 anesthetic formulations to determine which formulation was to be administered at each appointment" Quote (from correspondence): "We did use a computer to assign the anesthetic solutions to the subjects"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "A master list with the 6-digit numbers and the order in which the subject received the anesthetic formulations was accessible to a research assistant who prepared the anesthetic formulations for injection. Only the random numbers were recorded on the data collection sheets to further blind the experiment"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Formulations were loaded by trained personnel into a separate, sterile 5-mL Luer-Lok disposable syringe (Becton-Dickinson & Co, Rutherford, NJ) by aspirating the standard cartridge contents into an appropriate 6-digit, labelled syringe. A master list with the 6-digit numbers and the order in which the subject received the anesthetic formulations was accessible to a research assistant who prepared the anesthetic formulations for injection. Only the random numbers were recorded on the data collection sheets to further blind the experiment" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A master list with the 6-digit numbers and the order in which the subject received the anesthetic formulations was accessible to a research assistant who prepared the anesthetic formulations for injection. Only the random numbers were recorded on the data collection sheets to further blind the experiment" "Trained personnel, who were blinded to the anesthetic formulations, administered all preinjection and postinjection tests" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Odabas 2012

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Turkey) **Participants:** 50 enrolled, 50 completing the study. 25 male, 25 female. Mean age of patients 11.3 years, ranging from 7 to 13 years **Inclusion criteria** • Healthy and co-operative • Similar operative procedure needs in symmetrical primary teeth **Exclusion criteria** • Allergies to local anaesthetics or sulphites • History of significant medical conditions • Taking any medications that might affect anaesthetic assessment • Active site of pathosis in the area of injection
Interventions	Maxillary buccal infiltration, using 1 cartridge (1.8 mL) of: • 4% articaine, 1:200,000 epinephrine (50) • 3% mepivacaine, no epinephrine (50)
Outcomes	**Clinical anaesthesia** while performing operative dentistry procedures in deciduous teeth • Success: no pain and feeling of numbness (100/100) **Soft tissue anaesthesia** • Onset: when they could not feel their upper lip (100/100) • Duration: Parents asked their child to record the time when feeling of numbness disappeared (100/100) Soft tissues tested: upper lip **Adverse events** reported (100/100) • Pain on injection (modified behavioural pain scale (a) facial display; (b) arm/leg movements; (c) torso movements; (d) crying) • Pain immediately after injection, then 1 hour and 2 hours later (Wong-Baker FACES Pain Rating Scale)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomized, double-blind, split-mouth design was used" "For local infiltration anaesthesia, in the first appointment, subjects were randomly selected to receive either a cartridge of Articaine 4% with 1:200,000 epinephrine.....or mepivacaine 3%" Quote (from correspondence): "Our nurse randomly selected a masked cartridge from a box and gave it to the operator. They were coded. We gave code 1 to articaine, code 2 to mepivacaine. In the first visit, the nurse recorded which code was used then at the second visit she gave the other coded cartridge. The cartridge was chosen randomly. Interestingly, when we checked the order of administration (first or second visit) we found equality for both solutions"
Allocation concealment (selection bias)	Low risk	Quote: "A randomized, double-blind, split-mouth design was used" "For local infiltration anaesthesia, in the first appointment, subjects were randomly selected to receive either a cartridge of Articaine 4% with 1:200,000 epinephrine.....or mepivacaine 3%" Quote (from correspondence): "Our nurse randomly selected a masked cartridge from a box and gave it to the operator. They were coded. We gave code 1 to articaine, code 2 to mepivacaine. In the first visit, the nurse recorded which code was used then at the second visit she gave the other coded cartridge. The cartridge was chosen randomly. Interestingly, when we checked the order of administration (first or second visit) we found equality for both solutions"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Trained personnel, who were blind to the anaesthetic solutions, administered all preinjection and post-injection tests" Quote (from correspondence): "We used our dental nurse for this procedure. She prepared the cartridges of local anaesthetic. We masked the cartridges with tape. They were coded. We gave code 1 to articaine, code 2 to mepivacaine" Comment: Labelling all cartridges containing the same local anaesthetic with the same number could allow identification of a solution by personnel administering injections in a cross-over study if the properties of the solutions were markedly different. Patients may comment about long duration, poor anaesthesia, etc., at their second visit. However, the properties of the 2 solutions would not allow identification, and a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Trained personnel, who were blind to the anaesthetic solutions, administered all preinjection and post-injection tests" Quote (from correspondence): "We used our dental nurse for this procedure. She prepared the cartridges of local anaesthetic. We masked the cartridges with tape. They were coded. We gave code 1 to articaine, code 2 to mepivacaine" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator (confirmed in correspondence). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete. Onset of anaesthesia was measured for all 50 participants (confirmed by study author)
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete. Duration of anaesthesia was measured for all 50 participants (confirmed by study author)
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Oliveira 2004

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 20 enrolled, 20 completing the study. Mean age 26 years, ranging from 20 to 39 years. 4 male, 16 female **Inclusion criteria:** healthy adults not taking any pain perception-altering medication **Exclusion criteria:** none reported
Interventions	Maxillary infiltration buccally (1.8 mL) and palatally (0.35 mL) of: • 4% articaine, 1:100,000 epinephrine (20) • 2% lidocaine, 1:100,000 epinephrine (20)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset (40/40) • Duration (40/40) Teeth tested: right maxillary canines **Soft tissue anaesthesia** • Duration: determined by the patient (40/40) Soft tissues tested: upper lip **Adverse events** reported (40/40) • Pain on injection (visual analogue scale ranging from 0 = 'no pain' to 10 = 'worst pain imaginable')
Notes	Non-industry funding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "During two separate appointments the subjects randomly received an infiltration" Quote (from correspondence): "The order of administration was randomized by a coin toss, previously to the beginning of the study. Each volunteer that entered the study was assigned to a number in the list, in sequence, following the order of entrance in the study"
Allocation concealment (selection bias)	Low risk	Quote: "During two separate appointments the subjects randomly received an infiltration" Quote (from correspondence): "The cartridges were coded (nail polish with different colours) by a person not related to the study. The codes were opened after statistical analysis, which was performed by another researcher, not involved in the administration or in the pulp testing. The researchers and the subjects could just see the colours of the cartridges, with no knowledge of their content"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (from correspondence): "The cartridges were coded (nail polish with different colours) by a person not related to the study. The codes were opened after statistical analysis, which was performed by another researcher, not involved in the administration or in the pulp testing. The researchers and the subjects could just see the colours of the cartridges, with no knowledge of their content" Comment: Disguising the cartridges of each formulation with the same nail polish could allow identification of a solution by personnel administering injections in a cross-over study if the properties of the solutions were markedly different. Patients may comment about long duration, poor anaesthesia, etc., at their second visit. However, the properties of the 2 solutions would not allow identification, and a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote (from correspondence): "The cartridges were coded (nail polish with different colours) by a person not related to the study. The codes were opened after statistical analysis, which was performed by another researcher, not involved in the administration or in the pulp testing. The researchers and the subjects could just see the colours of the cartridges, with no knowledge of their content" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator (confirmed in correspondence). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded (confirmed by study author); outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded (confirmed by study author); outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded (confirmed by study author); outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Ozec 2010

Methods	Randomized controlled simulated scenario trial, intraindividual study design
Participants	**Location:** university (Turkey) **Participants:** 30 enrolled, 30 completing the study. Mean age 22.6, ranging from 21 to 27 years. 14 male, 16 female **Inclusion criteria** • Healthy with no history of any medical conditions • All maxillary teeth present and free of caries, large restorations, and periodontal disease **Exclusion criteria** • Allergic to local anaesthetics • Taking any medications that could affect anaesthetic assessment • Active sites of pathology in the area of injection
Interventions	Maxillary buccal infiltration (1.7 mL) using the following: • 4% articaine, 1:200,000 epinephrine (30) • 4% articaine, 1:100,000 epinephrine (30)
Outcomes	**Soft tissue anaesthesia** • Success: presence or absence of pain tested by needle-prick stimulation of palatal tissues on a Heft-Parker visual analogue scale (60/60) Tissues tested: palatal tissues of maxillary first molars and first premolars
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 30 volunteers were divided randomly into 2 groups" "The teeth were randomized according to epinephrine doses. In the second group the same procedure was applied to the first molars" Comment: exact method of generation of randomized sequence not reported

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "The 30 volunteers were divided randomly into 2 groups" "The teeth were randomized according to epinephrine doses. In the second group the same procedure was applied to the first molars" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "All local anaesthetic injections were given by the same surgeon (U.T.), who had no involvement in assessing outcome" "The volunteers and the investigators of anaesthetic outcome were blinded to the epinephrine dose used" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The volunteers and the investigators of anaesthetic outcome were blinded to the epinephrine dose used" Comment: Detailed methods were not reported. Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Parirokh 2015

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Iran) **Participants** • 2% lidocaine with 1:80,000 epinephrine group: 30 enrolled, 29 completing the study. Mean age 26.7 years ± 7.2 (SD). 15 male, 14 female • 0.5% bupivacaine with 1:200,000 epinephrine group: 30 enrolled, 30 completing the study. Mean age 26.7 years ± 8.6 (SD). 9 male, 21 female **Inclusion criteria** • Healthy patients over 18 years old who had a first or second mandibular molar tooth in need of root canal treatment with irreversible pulpitis • Clinical diagnosis of irreversible pulpitis confirmed by a positive response to an electric pulp tester (The Element Diagnostic Unit: SybronEndo, Glendora, CA, USA) and a prolonged response longer than 10 seconds with moderate to severe pain to a cold test (Roeko Endo-Frost, Roeko, Langenau, Germany) applied with a size 2 cotton pellet **Exclusion criteria** • Presence of systemic disorders, sensitivity to lidocaine with 1:80,000 epinephrine, or sensitivity to bupivacaine • Presence of a widening of the periodontal ligament space, or presence of a periapical radiolucency • Lactation, pregnancy, and/or using any type of analgesic medication in the preceding 12 hours before treatment • Teeth that were unsuitable for restoration, teeth with full crowns, and teeth associated with spontaneous severe pain that needed emergency treatment
Interventions	Inferior alveolar nerve blocks (1.8 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine (29) • 0.5% bupivacaine, 1:200,000 epinephrine (30)
Outcomes	**Pulpal anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: ability to access and instrument the tooth without pain (VAS score of zero or mild pain ≤ 54 mm) on a Heft-Parker visual analogue scale (59/60) Teeth tested: first or second mandibular molars **Soft tissue anaesthesia** • Success: patients questioned regarding subjective numbness (59/60) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All patients who agreed to participate in the study were randomly divided into two groups of 30 patients each. Patients were randomly assigned to the groups by selecting a sealed opaque envelope with the group number concealed inside it"
Allocation concealment (selection bias)	Low risk	Quote: "All patients who agreed to participate in the study were randomly divided into two groups of 30 patients each. Patients were randomly assigned to the groups by selecting a sealed opaque envelope with the group number concealed inside it"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Only the clinician who administered the anesthetic solution was aware of the type of anesthetic technique used" Comment: Detailed methods were not reported. The clinician administering the injections was aware of the formulation injected. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Two clinicians performed the clinical procedures, one administered the IANB injection and the other prepared the endodontic access cavity 15 minutes following the injection. Only the clinician who administered the anesthetic solution was aware of the type of anesthetic technique used" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: One patient dropped out of the 2% lidocaine, 1:80,000 epinephrine group. As the 2 groups were still well balanced, risk of bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: One patient dropped out of the 2% lidocaine, 1:80,000 epinephrine group. As the 2 groups were still well balanced, risk of bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Pellicer-Chover 2013

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Spain) **Participants:** 36 enrolled, 36 completing the study. Mean age 23.1 ± 6 years, ranging from 18 to 37 years. 12 male, 24 female **Inclusion criteria** • Adults requiring bilateral impacted lower third molar extraction with similar levels of surgical difficulty according to the Alemany-Martinez et al scale **Exclusion criteria** • Systemic disease • Pharmacological treatment (except oral contraceptives) • Patients allergic to the drugs used in the trial
Interventions	Inferior alveolar nerve block (1.8 mL) and buccal infiltration (1.8 mL) using the following: • 0.5% bupivacaine, 1:200,000 epinephrine (36) • 4% articaine, 1:100,000 epinephrine (36)
Outcomes	**Clinical anaesthesia** during surgical removal of third molars • Success: graded as no discomfort, slight discomfort but not requiring additional anaesthesia, and moderate to severe discomfort needing additional anaesthetic (72/72) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: measured subjectively as the first sign of numbness in the lower lip (72/72) • Duration: Patients were asked to record the time of complete recovery of feeling in the tongue and lower lip (number assessed unclear) Soft tissues tested: lower lip and tongue **Adverse effects** (72/72) • Systolic/diastolic blood pressure and cardiac rate • Bleeding during the procedure (classified as minimum, normal, and abundant) • Postoperative analgesia (time from the end of the surgical procedure to ingestion of the first ibuprofen tablet) • Postoperative pain (VAS from 0 = no pain to 10 = worst pain and the percentage of participants consuming analgesics)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The articaine and bupivacaine carpules (1.8 ml) were marked as “1” or “2” by an individual unrelated to the study. The local anesthetic used and the side of the intervention were allotted randomly using a predefined random numbers table and enclosed in envelopes"
Allocation concealment (selection bias)	Unclear risk	Quote: "The articaine and bupivacaine carpules (1.8 ml) were marked as “1” or “2” by an individual unrelated to the study. The local anesthetic used and the side of the intervention were allotted randomly using a predefined random numbers table and enclosed in envelopes" Comment: clarification of the method of concealment needed; unsure whether coding the cartridges as 1 or 2 is related to their order of use or is used as an identifier. In this latter case, it would be possible to determine the identity of the local anaesthetic used through their differing properties
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The articaine and bupivacaine carpules (1.8 ml) were marked as '1' or '2' by an individual unrelated to the study. The local anesthetic used and the side of the intervention were allotted randomly using a predefined random numbers table and enclosed in envelopes" Comment: Coding the cartridges as 1 or 2 may allow identification of a solution by personnel administering injections in a cross-over study if the properties of the solutions were markedly different. Patients may comment about long duration, poor anaesthesia, etc., at their second visit. The properties of these 2 solutions may have allowed identification (related to duration). However it is not clear whether this occurred or whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "The articaine and bupivacaine carpules (1.8 ml) were marked as '1' or '2' by an individual unrelated to the study. The local anesthetic used and the side of the intervention were allotted randomly using a predefined random numbers table and enclosed in envelopes" Comment: It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes) if the identity of the local anaesthetic had been determined. Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comments: The number of participants in each group who had the duration of soft tissue anaesthesia measured was not stated (patients were asked to record the time of recovery - unsure of compliance). Therefore risk of bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Poorni 2011

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** dental college and hospital (India) **Participants:** 156 enrolled, 156 completing the study. 90 male, 60 female. Age (mean ± standard deviation in years): • IANB (articaine) 24.40 ± 4.19 • Buccal infiltration (articaine) 23.46 ± 3.7 • IANB (lidocaine) 24.13 ± 4.21 (overall mean = 24) **Inclusion criteria** • Healthy adult volunteers • 18 to 30 years of age • Active pain of ≥ 54 mm on Heft-Parker visual analogue scale in a mandibular molar • Prolonged response to cold testing with an ice stick (1,1,1,2 tetrafluoroethane; Hygenic Corp, Akron Ohio) and an electric pulp tester (Digitest; Parkell, Farmingdale, New York) • Absence of any periapical radiolucency on radiographs except for a widened periodontal ligament and a vital coronal pulp on access opening **Exclusion criteria** • American Society of Anesthesiologists IV classification of systemic disorders • Complications associated with local anaesthetics • Pregnant and lactating women • Under medication to alter pain perception
Interventions	1.8 mL of 1 of the following: • 4% articaine, 1:100,000 epinephrine, given as inferior alveolar nerve block (52) • 4% articaine, 1:100,000 epinephrine, given as mandibular buccal infiltration (52) • 2% lidocaine, 1:100,000 epinephrine, given as inferior alveolar nerve block (52)
Outcomes	**Clinical anaesthesia** during pulpotomy of teeth with irreversible pulpitis • Success: Heft-Parker visual analogue scale: pain < mild pain was classified as success (156/156) Teeth tested: mandibular molar teeth **Soft tissue anaesthesia** (self-reported) • Success (156/156) Soft tissues tested: lower lip
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "For allocation of the subjects, a computer-generated list of random numbers was used with a randomization ratio of 1:1:1 by using random allocation software (version 1.0, May 2004)"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation sequence was concealed from the researchers who were a part of the study to reduce selection bias" Quote (from correspondence): "A case sheet was filled for every patient by the operator who enrolled the patients. The case sheet had a column which carried the group name to which the patient belonged to. Hence the sequence was concealed to the clinicians administering LA and recording outcomes" "The sequence was generated and was available to only one person and [was] hidden"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All local anaesthetic injections were given by a single operator who was not a part of the study process. This operator had no involvement with the study outcome. The trial adhered to established procedures to maintain separation among the operators" Quote (from correspondence): "The cartridges were concealed from the patients as they were masked" Comment: Participants and personnel would not be able to identify the local anaesthetic used, and a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All local anaesthetic injections were given by a single operator who was not a part of the study process. This operator had no involvement with the study outcome. The trial adhered to established procedures to maintain separation among the operators" Quote (from correspondence): "The cartridges were hidden before the assessor entered" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Porto 2007

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 35 enrolled, 35 completing the study. Age ranging from 13 to 27 years. 10 male, 25 female **Inclusion criteria** • Classified as ASA I by the American Society of Anesthesiology • Without a history of significant systemic pathology • Had to have 2 lower third molars in a similar position by the Pell & Gregory classification and classified as mesioangular and vertical by the Winter classification **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve block and buccal infiltration (minimum of 3.6 mL in total) of: • 2% lidocaine, 1:100,000 epinephrine (35) • 2% mepivacaine, 1:100,000 epinephrine (35)
Outcomes	**Clinical anaesthesia** during extraction of lower third molars • Success: tested by recording teeth requiring re-anaesthesia (70/70) Teeth/soft tissues tested: mandibular wisdom teeth and associated soft tissues **Pulpal anaesthesia** • Success: tested with Endofrost (cold test) (70/70) Teeth tested: mandibular wisdom teeth **Soft tissue anaesthesia** tested by recording the time of return of normal sensation • Duration (number assessed was unclear) Soft tissues tested: lower lip **Adverse effects** (number assessed was unclear) • Postoperative pain (VAS from 0 = no pain to 100 = worst pain)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Two groups were established (n = 35 each) on a randomized basis (by allotment), according to the anaesthetic solution" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Two groups were established (n = 35 each) on a randomized basis (by allotment), according to the anaesthetic solution" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comment: The number of participants in each group who had the duration of soft tissue anaesthesia measured was not stated. Therefore risk of bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Comment: The number of participants in each group who had adverse events measured was not stated. Therefore risk of bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Pässler 1996

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (Germany) **Participants:** 3 parts to the study, 2 suitable for this review: • Second part: 180 enrolled, 180 completing the study. Mean age, age range, and male:female ratio not reported • Third part: 40 enrolled, 40 completing the study. Age range greater than 18 years and younger than 60 years. Male:female ratio not reported **Inclusion criteria** • Second part: not reported • Third part: age not younger than 18 and not older than 60 years, body weight ≤ 50 kg; no contraindications to articaine, epinephrine, or pyrosulphite **Exclusion criteria** • Second part: not reported • Third part: acute inflammation in the extraction area; the tooth extraction should proceed without possible complications; extractions requiring flap procedures; on the day of the extraction, the patient should have received no local anaesthesia
Interventions	Second part: injections of 1 cartridge of either 2 mL (extractions) or 4 mL (apicectomies) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine (93) • 3% prilocaine, 0.03 IU felypressin (87) Third part: Injections of 1.7 mL of either: • 4% articaine, 1:100,000 adrenaline (21) • 4% articaine, 1:200,000 adrenaline (19)
Outcomes	**Clinical anaesthesia** during tooth removal and apicectomy • Success (second part: method not stated; third part: success = no pain, partial success = additional local anaesthetic given and anaesthesia achieved, failure = anaesthesia not achieved) (220/220) Teeth/tissues tested: second part: apicectomy - anterior teeth, extraction - not stated. Third part: extraction of mandibular anterior and premolar teeth **Adverse effects** were reported (220/220)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The distribution of the patients was carried out according to a randomization code which was known during the double-blind experiment, by only the investigator" Comment: detailed method not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The distribution of the patients was carried out according to a randomization code which was known during the double-blind experiment, by only the investigator" An assistant prepared the syringes, and vials were labelled and concealed Comment: detailed method not reported
Blinding of participants and personnel (performance bias)	Low risk	Comment: "The distribution of the patients was carried out according to a randomization code which was known during the double-blind experiment, by only the investigator" An assistant prepared the syringes, and vials were labelled and concealed Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Comment: An assistant prepared the syringes, and vials were labelled and concealed. Exact details of blinding were not given Comment: The outcome is a participant-reported outcome (outcome assessor is the participant) and was recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Ram 2006

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Israel) **Participants:** 62 enrolled, 62 completing the study. Mean age 8.4 years, ranging from 5 to 13 years. 28 male, 34 female **Inclusion criteria** • Need for at least 2 clinical sessions for similar operative procedures with local anaesthesia in the same arch, not as emergency procedures • Healthy children, with none needing a sedative or other pharmacological support to receive dental treatment **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve block and maxillary buccal infiltration (up to 1 cartridge) using the following: • 2% lidocaine, 1:100,000 epinephrine (62) • 4% articaine, 1:200,000 epinephrine (62)
Outcomes	**Clinical anaesthesia** during paediatric operative dental procedures • Success (124/124): ◦ Re-injection required ◦ Modified behavioural pain scale (facial display, arm/leg movements, torso movements, crying) ◦ Craig's behavioural description of facial actions (eyebrow bulge or eye squeeze) Teeth tested: not stated **Soft tissue anaesthesia** • Onset: asking the child when the sensation of numbness started (124/124) • Duration: Parents asked the child when the feeling of numbness disappeared (number assessed was unclear) Soft tissues tested: not stated **Adverse events** reported (124/124) • Pain on injection: ◦ Modified behavioural pain scale (facial display, arm/leg movements, torso movements, crying) ◦ Craig's behavioural description of facial actions (eyebrow bulge or eye squeeze) ◦ Subjective evaluation of feeling after the injection (Wong–Baker FACES Pain Rating Scale) • Other adverse events
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A random cross-over design was used and each child served as his or her own control" "Each patient was randomly assigned to receive either lidocaine HCl 2% with 1:100 000 epinephrine ..... or articaine HCl 4% with 1:200 000 epinephrine ..... for the first visit, with the other solution administered during the second visit" Quote (from correspondence): "Closed envelopes were kept by the dental assistant (one in Jerusalem and other in Tel Aviv), inside there was written: lidocaine or articaine. The envelopes were mixed up before starting the study, and no one knew what was inside the envelope. The dental assistant (who was the only one who gave the operator the syringe) was the only one who knew which solution was delivered, and of course that she wrote the solution in a special file in order to know which solution should be administered in the second visit"
Allocation concealment (selection bias)	Low risk	Quote: "A random cross-over design was used and each child served as his or her own control" "Each patient was randomly assigned to receive either lidocaine HCl 2% with 1:100 000 epinephrine ..... or articaine HCl 4% with 1:200 000 epinephrine ..... for the first visit, with the other solution administered during the second visit" Quote (from correspondence): "Closed envelopes were kept by the dental assistant (one in Jerusalem and other in Tel Aviv), inside there was written: lidocaine or articaine. The envelopes were mixed up before starting the study, and no one knew what was inside the envelope. The dental assistant (who was the only one who gave the operator the syringe) was the only one who knew which solution was delivered, and of course that she wrote the solution in a special file in order to know which solution should be administered in the second visit"
Blinding of participants and personnel (performance bias)	Low risk	Quote (from correspondence): "The only person who knew which local anaesthesia was delivered was the dental assistant. The cartridge was 'hidden' in the syringe with aluminium foil, therefore no one other that the dental assistant knew which local anaesthetic solution was delivered" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A trained dental assistant, who did not participate in the treatment and was blinded to the agent being used, recorded the behavioural parameters in each centre" Quote (from correspondence): "The only person who knew which local anaesthesia was delivered was the dental assistant. The cartridge was 'hidden' in the syringe with aluminium foil, therefore no one other that the dental assistant knew which local anaesthetic solution was delivered" Comment: Identification of the local anaesthetic by personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comment: The numbers of participants in each group who had the duration of anaesthesia measured were not stated. Therefore, risk of bias was graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Robertson 2007

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 60 enrolled, 60 completing the study. Mean age 27 years, ranging from 19 to 51 years. 26 men and 34 women **Inclusion criteria:** in good health and not taking any medications that would alter the perception of pain **Exclusion criteria** • Younger than 18 years or older than 60 years of age • Allergic to local anaesthetics or sulphites • Pregnant • History of significant medical conditions • Taking any medications that could affect anaesthetic assessment • Active sites of pathosis in the area of injection • Inability to give informed consent
Interventions	Mandibular buccal infiltration (1.8 mL) of either: • 4% articaine, 1:100,000 epinephrine (60) • 2% lidocaine, 1:100,000 epinephrine (60)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive readings of 80 with the electric pulp tester (120/120) • Onset (66/120) • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: mandibular first molars, second molars, first premolars, and second premolars **Adverse events** reported (120/120) • Pain at each stage of injection (Heft-Parker visual analogue scale) • Pain after injection (Heft-Parker visual analogue scale) • Other adverse events
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, we randomly assigned the two anaesthetic formulations six-digit numbers from a random number table. We randomly assigned each subject to one of the two formulations to determine which anaesthetic formulation was to be administered at each appointment" Quote (from correspondence): "Each solution had a six-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Before the experiment, we randomly assigned the two anaesthetic formulations six-digit numbers from a random number table. We randomly assigned each subject to one of the two formulations to determine which anaesthetic formulation was to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "To further blind the experiment, we recorded only the random numbers on the data collection sheets" "We masked the lidocaine and articaine cartridges with opaque labels and wrote the corresponding six-digit codes on each cartridge" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "To further blind the experiment, we recorded only the random numbers on the data collection sheets" "We masked the lidocaine and articaine cartridges with opaque labels and wrote the corresponding six-digit codes on each cartridge" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Only those participants with successful pulpal anaesthesia could have pulpal onset measured. Study authors used 33 matched pairs from the 2 groups, so both groups were equal in size. As the groups were equal in size, risk of attrition bias was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Ruprecht 1991

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Germany) **Participants:** 10 enrolled, 10 completing the study. Age ranging from 25 ± 5 years. 10 male, 0 female **Inclusion criteria** • Over 25 ± 5 years of age • Weighing 70 kg ± 10 kg • Non-smoking • Normotension • No alcohol dependence • No clinical signs of acute or chronic disease • No allergy against a component of the solution • Radiographically confirmed, caries-free incisors and free from periodontal inflammation **Exclusion criteria:** none stated
Interventions	Maxillary labial infiltrations (0.5 mL) of: • 4% articaine, 1:200,000 epinephrine (10) • 4% articaine, 1:100,000 epinephrine (10) • 2.4% articaine, 1:100,000 epinephrine (10 - not commercially available) • 3.4% lidocaine, 1:200,000 epinephrine (10 - not commercially available) • 3.4% lidocaine, 1:100,000 epinephrine (10 - not commercially available) • 2% lidocaine, 1:100,000 epinephrine (10)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: method of measurement not stated (30/30) • Onset: time to first -167 V impulse, to produce no response from the patient (30/30) • Duration: time between first -167 V pulse without a positive patient response and first re-perception of the stimulus (30/30) Teeth tested: maxillary central incisors
Notes	Industry funding (local anaesthetic provided by Espe)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: detailed method not reported
Allocation concealment (selection bias)	Unclear risk	Comment: detailed method not reported
Blinding of participants and personnel (performance bias)	Low risk	Comment: Vials were coded by consecutive numbers. Detailed methods were not reported. Labelling all cartridges containing the same local anaesthetic with consecutive numbers could allow identification of a solution by personnel administering injections in a cross-over study if the properties of the solutions were markedly different. It would depend on how the cartridges were numbered (e.g. 1 to 10 for one solution and 11 to 20 for another solution, etc.). Participants may comment about long duration, poor anaesthesia, etc., at their second visit. However, the properties of these solutions would not allow identification by participants and personnel, and a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Vials were coded by consecutive numbers. Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Industry funding, as local anaesthetic provided by Espe

Sadove 1962

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** The journal article says approximately 700 completed the study. Actual total is 687 (343, excluding those not commercially available). Age range and mean age not reported. Male:female ratio not reported **Inclusion criteria:** not reported **Exclusion criteria** • Medical history that contraindicated use of vasoconstrictors
Interventions	Various types of dental block and infiltration of: • 2% lidocaine, 1:100,000 epinephrine (174) • 2% mepivacaine, 1:20,000 levonordefrin (169) • 2% lidocaine, no vasoconstrictor (not commercially available) • 2% mepivacaine, no vasoconstrictor (not commercially available)
Outcomes	**Pulpal anaesthesia** tested during restorative and surgical procedures • Success: A: profound anaesthesia, patient did not experience any discomfort; B: adequate anaesthesia, patient experienced only slight discomfort; C: inadequate anaesthesia, patient needed re-injection (343/343) Teeth tested: various **Soft tissue anaesthesia** • Onset: determined by a gingival pinprick or by stripping the gingival attachment with a blunt instrument (318/343) • Duration: tested by recording time of return of normal sensation (263/343) Soft tissues tested: various
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each solution in cartridges were assigned three different code numbers, and these cartridges were packed and used at random"
Allocation concealment (selection bias)	Low risk	Quote: "Each solution in cartridges were assigned three different code numbers, and these cartridges were packed and used at random"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This rigidly controlled double-blind investigation was designed to eliminate all possible bias by using specially manufactured, coded dental anaesthetic cartridges, a sealed coding system, and a statistical evaluation of the collected data" "All the anaesthetic cartridges were identical in appearance, had no markings except for the numerical code" "Each solution in cartridges were assigned three different code numbers, and these cartridges were packed and used at random" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "This rigidly controlled double-blind investigation was designed to eliminate all possible bias by using specially manufactured, coded dental anaesthetic cartridges, a sealed coding system, and a statistical evaluation of the collected data." "All the anaesthetic cartridges were identical in appearance, had no markings except for the numerical code" "Each solution in cartridges were assigned three different code numbers, and these cartridges were packed and used at random" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: Of the total number of participants recruited who had profound and adequate clinical anaesthesia, some did not have onset of soft tissue anaesthesia measured: lidocaine: -4/157 (% N/A), mepivacaine: -6/151 (% N/A) Negative values were obtained for dropouts (i.e. numbers of participants having soft tissue onset measured were greater than the numbers having clinical anaesthetic success measured). This is to be expected. The dropout rate, if present, could be calculated only if participants having soft tissue success were known. Soft tissue anaesthesia may have been present in those who had failure of clinical anaesthesia, or it may have been absent, meaning that it was not measured. As this measurement was performed in a clinic immediately before treatment, and as groups were fairly well balanced in numbers, it is highly unlikely that there was any significant attrition bias. Therefore risk of bias has been graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Comment: Of the total number of participants recruited who had profound and adequate clinical anaesthesia, some did not have duration of soft tissue anaesthesia measured: lidocaine: 39/161 (24%), mepivacaine: 16/157 (10%) No dropouts would occur if the numbers of participants who had duration measured were equal to the numbers having soft tissue onset measured, assuming there were no incomplete onset data. However, even with these difficulties in measuring attrition rate, dropout rates of up to 24% were seen, which are likely to be conservative estimates if true soft tissue success figures are higher. Therefore risk of bias has been graded as high
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Sampaio 2012

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Brazil) **Participants:** 32 male, 38 female • 2% lidocaine, 1:100,000 epinephrine group: 35 enrolled, 35 completing the study. Average age 32.3 years. Initial pain: 96 ± 31 • 0.5% bupivacaine, 1:200,000 epinephrine group: 35 enrolled, 35 completing the study. Average age 29.4 years. Initial pain: 96 ± 32 **Inclusion criteria** • Patients admitted to the Emergency Center of the School of Dentistry at the University of Sao Paulo with a clinical diagnosis of irreversible pulpitis in the first or second lower molar • Moderate to severe spontaneous pain and exhibiting a positive response to the electric pulp test and prolonged response to cold testing with Endo-Frost (Coltene-Roeko, Langenau, Germany) • Between 18 and 50 years old • In good health as established by a health history questionnaire • Each participant had at least 1 molar adjacent to a molar presenting irreversible pulpitis and a healthy contralateral canine with no deep carious lesions, extensive restoration, advanced periodontal disease, a history of trauma, or sensitivity **Exclusion criteria** • Use of medication that could potentially interact with any of the anaesthetics used in the study
Interventions	Inferior alveolar nerve blocks (3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine (35) • 0.5% bupivacaine, 1:200,000 epinephrine (35)
Outcomes	**Clinical anaesthesia** during access cavity preparation and instrumentation • Success: ability to access the pulp chamber without the patient reporting pain (pain scores 0 or 1) on a verbal analogue scale (0, no pain; 1, mild, bearable pain; 2, moderate, unbearable pain; 3, severe, intense, and unbearable pain (70/70)) **Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive negative responses to the maximum pulp stimulus (70/70) Teeth tested: mandibular first molars and second molars **Soft tissue anaesthesia** • Success on questioning: numbness at 10 minutes post injection (70/70) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Seventy adult patients (n = 70) were included in this prospective, randomized, double-blind clinical study. To ensure the blindness of the study, 2 cartridges (3.6 mL) of either anaesthetic solution were sealed in envelopes. At the time of application, the senior researcher who administered the 2 consecutive anaesthesia injections chose 1 of the envelopes at random"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Seventy adult patients (n = 70) were included in this prospective, randomized, double-blind clinical study. To ensure the blindness of the study, 2 cartridges (3.6 mL) of either anaesthetic solution were sealed in envelopes. At the time of application, the senior researcher who administered the 2 consecutive anaesthesia injections chose 1 of the envelopes at random"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Seventy adult patients (n = 70) were included in this prospective, randomized, double-blind clinical study. To ensure the blindness of the study, 2 cartridges (3.6 mL) of either anaesthetic solution were sealed in envelopes. At the time of application, the senior researcher who administered the 2 consecutive anaesthesia injections chose 1 of the envelopes at random" Quote (from correspondence): "I was administering the anaesthetic injections in all cases and the cartridges were masked. However, as it could still be possible (unlikely but possible) to identify the rubber bungs, we have always used a different researcher to deliver the electric test and pulpectomy, to eliminate this risk" Comment: Although the bung of the cartridge may have been visible and allowed the person administering the local anaesthetic to identify the solution, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Electric pulp stimulations to assess pulpal anaesthesia and the pulpectomy were performed by a different professional to guarantee that the anaesthetic solution remained unknown, thus maintaining the double blindness of the study" Quote (from correspondence): "We have always used a different researcher to deliver the electric test and pulpectomy, to eliminate this risk. The other researcher (Sampaio) was not present during the anaesthetic procedure and only 10 minutes after the anaesthetic procedure was completed (and I had left the workstation) Sampaio would enter to carry on the electric tests and pulpectomy. Therefore, the patients, as well as the post-graduation student who was administering the electric tests and making the pulpectomy (Sampaio), were not aware of the identity of the cartridges" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Sancho-Puchades 2012

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Spain) **Participants:** 20 enrolled, 18 completing the study. Mean age 23.8 years (SD 5.0 years; ranging from 18 to 35 years). 7 male, 11 female **Inclusion criteria** • ASA I or II patients • Between 18 and 40 years of age • Presented bilaterally impacted lower third molars, which required for their removal flap elevation, bone removal, and tooth sectioning **Exclusion criteria** • Allergy to local anaesthetics or any other medication • Pregnancy or current lactation, heart rate > 110 bpm or < 60 bpm, systolic arterial pressure > 150 mmHg or < 100 mmHg, diastolic arterial pressure > 100 mmHg or < 60 mmHg, oxygen saturation < 96% • Pain, swelling, or infectious signs associated with the third molar site immediately before surgery • Any drug intake during the 15 days before surgery • Surgeries lasting less than 15 minutes or longer than 45 minutes

Interventions	Inferior alveolar nerve block (1.8 mL: 1.3 mL injected at the mandibular foramen, 0.5 mL injected on withdrawal) and buccal infiltration (0.9 mL) of: • 4% articaine, 1:200,000 epinephrine (18) • 0.5% bupivacaine, 1:200,000 epinephrine (18) A further inferior alveolar nerve block (1.8 mL) was given if thermal testing was positive on the mandibular second molar on the injected side Additional intraligamental injections (0.2 mL) or inferior alveolar nerve blocks (1.8 mL) were given if pain was felt during surgery
Outcomes	**Clinical anaesthesia** during extraction of lower third molars • Total volume of anaesthetic solution used during surgery and need for additional anaesthetic infiltrations (time, volume, and anaesthetic technique used for re-anaesthesia) • Intraoperative global pain judged by the patient and by the surgeon at the end of surgery: 5-point scale: no pain, light pain, moderate pain, strong pain, or unbearable pain (36/36) Teeth/soft tissues tested: mandibular wisdom teeth and associated hard/soft tissues **Pulpal anaesthesia** tested with tetrafluoroethane (cold test) • Success (36/36) • Onset (results not reported) Teeth tested: mandibular wisdom teeth **Soft tissue anaesthesia** • Onset: sensibility to pricking (number assessed was unclear) • Duration: time at which lip and tongue sensibility had totally returned to normality - unsure whether this time is total duration or postoperative duration (number assessed was unclear) Soft tissues tested: lower lip.and tongue (+ retromolar trigone mucosa with onset) **Adverse events** reported (36/36) • Postoperative pain (VAS scale from 0 to 100: 0 is no pain and 100 is the worst pain imaginable) • Amount of rescue analgesic medication needed during the first 4 postoperative days • Systolic and diastolic arterial pressure, heart rate, and oxygen saturation • Adverse reactions during surgery or during the first postoperative week
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Study design: triple-blind crossover randomized clinical trial" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Study design: triple-blind crossover randomized clinical trial" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study design comprised a triple-blind scheme. All anaesthetic Carpules were equally manufactured and were encoded. The patient, the surgeon and the statistician who performed the data analysis did not know which anaesthetic solution had been used" Comment: Despite the method of encoding not being reported, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The study design comprised a triple-blind scheme. All anaesthetic Carpules were equally manufactured and were encoded. The patient, the surgeon and the statistician who performed the data analysis did not know which anaesthetic solution had been used" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: Only 18 participants completed the study from 20 who started it, as 2 of the participants were withdrawn from the study because they did not attend the second surgical appointment. Excluded participants were accounted for when success was calculated. Because the study used a cross-over design, groups remained exactly balanced. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: Only 18 participants completed the study from 20 who started it, as 2 of the participants were withdrawn from the study because they did not attend the second surgical appointment. Excluded participants were accounted for when success was calculated. Because the study used a cross-over design, groups remained exactly balanced. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	Comment: The number of participants in each group who had the onset of soft tissue anaesthesia measured was not stated. As it is not clear how many participants had successful soft tissue anaesthesia, so that onset could be measured, risk of attrition bias has been graded as unclear
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comment: The number of participants in each group who had the duration of soft tissue anaesthesia measured was not stated. It is not clear how many participants were compliant with reporting the duration. Therefore risk of attrition bias has been graded as unclear

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: Only 18 participants completed the study from 20 who started it, as 2 of the participants were withdrawn from the study because they did not attend the second surgical appointment. Excluded participants were accounted for when success was calculated. Because the study used a cross-over design, groups remained exactly balanced. Therefore, risk of attrition bias was graded as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	Comment: All expected outcomes, apart from onset data, were reported. The study author could not be contacted. Therefore risk was rated as unclear
Other bias	Low risk	Comment: no other bias present

Santos 2007

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 50 enrolled, 50 completing the study. Mean age 21.8 years, ranging from 18 to 40 years. 18 male and 32 female **Inclusion criteria** • Symmetrically positioned full bony impacted lower third molars, as observed in panoramic radiographs • Absence of systemic illness • No signs of inflammation or infection at the extraction sites **Exclusion criteria** • Medical history of cardiovascular and kidney diseases; gastrointestinal bleeding or ulceration; allergic reaction to local anaesthetic; allergy to aspirin, ibuprofen, or any similar drugs; and pregnancy or current lactation
Interventions	Inferior alveolar nerve block (1.8 mL) and mandibular buccal infiltration (0.9 mL) of: • 4% articaine, 1:100,000 epinephrine (50) • 4% articaine, 1:200,000 epinephrine (50)
Outcomes	**Clinical anaesthesia** during tooth removal • Quality: 3-point scale: 1 - no discomfort reported by the patient during surgery; 2 - any discomfort reported by the patient during surgery, without the need for additional anaesthesia; and 3 - any discomfort reported by the patient during surgery, with the need for additional anaesthesia (100/100) • Total volume of anaesthetic solution used during surgery Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: loss of sensibility (number assessed was unclear) • Duration of postoperative anaesthesia: Patients recorded the moment that the anaesthetic wore off Soft tissues tested: inferior lip, tongue, and mucosa **Adverse effects** were reported (100/100)
Notes	No funding was reported, but the study authors thanked Dixtal Biomédica Ind e Com Ltda, Marília/SP, Brazil, for providing the DX2010 monitoring system

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "For local anaesthesia, in the first appointment, the patients randomly received A100 or A200. In the second appointment, the local anaesthetic not used previously was administered in a crossed manner" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "For local anaesthesia, in the first appointment, the patients randomly received A100 or A200. In the second appointment, the local anaesthetic not used previously was administered in a crossed manner" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "This was a double-blind study; that is, neither the surgeon nor the patients were aware of the local anaesthetic being used at the 2 different appointments" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "This was a double-blind study; that is, neither the surgeon nor the patients were aware of the local anaesthetic being used at the 2 different appointments" Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	Comment: The number of participants in each group who had the onset of soft tissue anaesthesia measured was not stated. As it is not clear how many participants had successful soft tissue anaesthesia, so that onset could be measured, risk of attrition bias has been graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Sherman 1954

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** 191 enrolled, 191 completing the study. 700 injections given in total. Age ranging from 9 to 75 years. 63 male, 128 female **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Mandibular and maxillary injections: • Inferior alveolar block: 2.2 mL • Zygomatic injection: 2.2 mL • Infraorbital block: 1.1 mL • Infiltration: 1.1 mL of 1 of the following solutions: • 2% procaine, 0.15% tetracaine with 1:10,000 nordefrin (100 - not commercially available) • 0.75% ravocaine, 1:30,000 levoarterenol (100 - not commercially available) • 2% lidocaine, 1:50,000 epinephrine (100) • 2% lidocaine, 1:100,000 epinephrine (100) • 2% butethamine, 1:50,000 epinephrine (100 - not commercially available) • 3.8% unacaine, 1:60,000 epinephrine (100 - not commercially available) 2% procaine, 1:50,000 epinephrine used as a standard
Outcomes	**Clinical anaesthesia** during operative dentistry procedures • Success: grade of anaesthesia: A - complete elimination of pulpal pain during operative procedures; B - some pain reported but another injection was not required; C – reinjection was necessary (200/200) Teeth tested: various **Soft tissue anaesthesia** • Onset: method of measurement not stated: onset presumed to be subjective, self-reported soft tissue onset, as operative procedures started 5 minutes after injection and onset was recorded as less than this (1 to 2 minutes) (number assessed was unclear) • Duration: postcard filled in and returned (number tested was unclear) Soft tissues tested: various **Adverse events** reported (200/200)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A double code system was used, so that each solution was represented by two different code numbers. The cartridges were packaged in boxes of six, so that each box contained cartridges representing all six solutions" "the cartridges were selected by dental assistants who loaded the syringes for the operators"
Allocation concealment (selection bias)	Low risk	Quote: "A double code system was used, so that each solution was represented by two different code numbers. The cartridges were packaged in boxes of six, so that each box contained cartridges representing all six solutions" "the cartridges were selected by dental assistants who loaded the syringes for the operators"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "In order to make this study as objective as possible, the six test solutions were placed in identical cartridges and codified. Thus, the characteristic metal or rubber caps and the distinctive Coloured plungers were not present" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote:"In order to make this study as objective as possible, the six test solutions were placed in identical cartridges and codified. Thus, the characteristic metal or rubber caps and the distinctive Coloured plungers were not present" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	Comment: The number of participants in each group who had the onset of soft tissue anaesthesia measured was not stated. As it is not clear how many participants had successful soft tissue anaesthesia, so that onset could be measured, risk of attrition bias has been graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Comment: The number of participants in each group who had the duration of soft tissue anaesthesia measured was not stated. As it is not clear how many participants had successful soft tissue anaesthesia, so that duration could be measured, risk of attrition bias has been graded as unclear. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Sherman 2008

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** 42 enrolled, 40 completing the study. Age and age range not reported • 2% lidocaine group: male 12, female 8. Pre-treatment pain: 89.1 ± 16.1 • 4% articaine group: male 7, female 13. Pre-treatment pain: 93.1 ± 18.3 **Inclusion criteria** • In good health without any contraindications to local anaesthetic with epinephrine • Each patient had to present to the endodontic clinic with a symptomatic, vital, posterior tooth. Each tooth in question satisfied the criteria for a diagnosis of irreversible pulpitis **Exclusion criteria:** none reported
Interventions	Gow-Gates alveolar nerve block and maxillary buccal infiltration of 1 of the following: • 4% articaine, 1:100,000 epinephrine (1.7 mL) (20) • 2% lidocaine, 1:100,000 epinephrine (1.8 mL) (20)
Outcomes	**Clinical anaesthesia** during pulpotomy of teeth with irreversible pulpitis • Success: Heft-Parker visual analogue scale: pain < mild pain = success (40/42) **Pulpal anaesthesia** • Success: no pulpal response with Endo-Ice after 15 minutes (42/42) Teeth tested: maxillary and mandibular posterior teeth
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Preceding the experiment, the 2 anaesthetic solutions were randomly assigned 3-digit numbers from a random number table. The random numbers were subsequently assigned to a subject designating which anaesthetic solution the patient was to receive" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Preceding the experiment, the 2 anaesthetic solutions were randomly assigned 3-digit numbers from a random number table. The random numbers were subsequently assigned to a subject designating which anaesthetic solution the patient was to receive" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Preceding the experiment, the 2 anaesthetic solutions were randomly assigned 3-digit numbers from a random number table. The random numbers were subsequently assigned to a subject designating which anaesthetic solution the patient was to receive" "The cartridges of anaesthetic solution were 'blinded' by completely masking the aluminium caps with a permanent black marker and masking the appropriate cartridges with an opaque label" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Preceding the experiment, the 2 anaesthetic solutions were randomly assigned 3-digit numbers from a random number table. The random numbers were subsequently assigned to a subject designating which anaesthetic solution the patient was to receive" "The cartridges of anaesthetic solution were 'blinded' by completely masking the aluminium caps with a permanent black marker and masking the appropriate cartridges with an opaque label" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Quote: "One patient with LE and one with AE did not have a negative response to cold stimuli at the 15-minute mark and were not included in this study" Comment: One patient dropped out of each group. As the 2 groups were still equal in size and reasons for dropping out were the same (still positive to the cold test following local anaesthesia), risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Sierra Rebolledo 2007

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Spain) **Participants:** 30 enrolled, 27(?) completing the study. Mean age 23.72 years, ranging from 18 to 36 years. 13 male, 17 female **Inclusion criteria** • Over the age of 18 • Without systemic disorders or antecedents of complications associated with local anaesthetics • With impacted symmetrical lower third molars requiring ostectomy and tooth sectioning for extraction **Exclusion criteria** • Existence of acute infection and/or swelling at the time of surgery • Interventions in which anaesthetic latency exceeded 5 minutes • Operations lasting longer than 60 minutes • Presenting intraoperative or postoperative complications such as paraesthesia or dysaesthesia of the inferior alveolar nerve
Interventions	Inferior alveolar nerve block (1.8 mL) and buccal infiltration (1.8 mL) of either: • 4% articaine, 1:100,000 epinephrine (30) • 2% lidocaine, 1:100,000 epinephrine (24)
Outcomes	**Clinical anaesthesia** during tooth removal • Depth of anaesthesia: visual analogue scale from 0 to 100 mm (53/60) • Need for re-injection Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset: from full needle withdrawal until the patient referred the first evidence of Vincent's sign (anaesthesia of lower lip) (54/60) • Duration: time from initial patient perception of the anaesthetic effect to the moment in which the effect began to fade (54/60) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to one of the two anaesthetic groups" "The anaesthetic techniques were performed on a random basis by one of the two operators" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to one of the two anaesthetic groups" "The anaesthetic techniques were performed on a random basis by one of the two operators" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	Quote: "three were excluded from the study: one due to the development of transient inferior alveolar nerve paraesthesia, another because of transient paraesthesia of the lingual nerve, and the third as a result of voluntary dropout from the study" Comment: Results were based only on those who were not excluded. However, it is not clear from the journal article how the final figures for those completing the study were derived. Although 3 participants dropped out, these were in the lidocaine group and there were 6 dropouts in this group. Six dropouts would occur only if the study used a parallel design and 2 teeth in each of the 3 dropouts would have been extracted. Risk of attrition bias was therefore graded as unclear
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	Quote: "three were excluded from the study: one due to the development of transient inferior alveolar nerve paraesthesia, another because of transient paraesthesia of the lingual nerve, and the third as a result of voluntary dropout from the study" Comment: Results were based only on those who were not excluded. However, it is not clear from the journal article how the final figures for those completing the study were derived. Although 3 participants dropped out, these were in the lidocaine group and there were 6 dropouts in this group. Six dropouts would occur only if the study used a parallel design and 2 teeth in each of the 3 dropouts should have been extracted. Risk of attrition bias was therefore graded as unclear
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	Quote: "three were excluded from the study: one due to the development of transient inferior alveolar nerve paraesthesia, another because of transient paraesthesia of the lingual nerve, and the third as a result of voluntary dropout from the study" Comment: Results were based only on those who were not excluded. However, it is not clear from the journal article how the final figures for those completing the study were derived. Although 3 participants dropped out, these were in the lidocaine group and there were 6 dropouts in this group. Six dropouts would occur only if the study used a parallel design and 2 teeth in each of the 3 dropouts should have been extracted. Risk of attrition bias was therefore graded as unclear
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Silva 2012

Methods	Randomized controlled clinical and simulated scenario trial, intraindividual study design, although the study is described by the authors as using "a prospective, randomized, controlled, parallel group" design
Participants	**Location:** university (Brazil) **Participants:** 24 enrolled, 20 completing the study. Mean age 23.25 ± 3.94 years, ranging from 18 to 30 years. 6 men and 18 women **Inclusion criteria** • Undergoing removal of bilateral lower jaw third molar surgery in a symmetrical position requiring ostectomy and/or tooth sectioning for extraction • Third molar had to be class A or B and position 1 or 2, according to Pell & Gregory classification, based on the space relationship of the tooth to the ascending ramus of the mandible and to the occlusal plane of the lower second molar. Winter's classification was considered for vertical and/or mesioangular position (orthopantomographic radiograms were taken to ensure the similarity of tooth inclinations and angulations) **Exclusion criteria** • Systemic disorders or previous complications associated with local anaesthetic • Under the use of any types of drugs and presenting any condition that contraindicated the use of sodium dipyrone
Interventions	Inferior alveolar nerve block (3.6 mL) and mandibular buccal infiltration (0.9 mL) of: • 4% articaine, 1:100,000 epinephrine (20) • 2% lidocaine, 1:100,000 epinephrine (20)
Outcomes	**Clinical anaesthesia** during tooth removal • Total volume of anaesthetic solution used during surgery (40/48) Teeth tested: mandibular third molars **Soft tissue anaesthesia** • Onset time: exact method not stated - assumed to be soft tissue anaesthesia (40/48) Soft tissues tested: not stated **Adverse effects** were reported (40/48) • Postoperative pain (VAS scale from 0 to 100: 0 is no pain and 100 is the worst pain imaginable) • McGill pain questionnaire • Analgesic consumption
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The choice of the first side to be operated and the group of anaesthetic solutions used had been randomly distributed, after a random drawing using the envelope method" Comment: exact method of generation of randomized sequence not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "The choice of the first side to be operated and the group of anaesthetic solutions used had been randomly distributed, after a random drawing using the envelope method" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Detailed methods were not reported. It is not clear whether the person recording participant outcomes was a different person than the one administering the local anaesthetic, as they may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as unclear
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: Only 20 participants completed the study from 24 who started it, as 2 were excluded from the analysis because of an incomplete pain diary form, and the other 2 did not return for the second surgery. Excluded participants were accounted for when success was calculated. Because the study used a cross-over design, groups remained exactly balanced. Therefore, risk of attrition bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: Only 20 participants completed the study from 24 who started it, as 2 were excluded from the analysis because of an incomplete pain diary form, and the other 2 did not return for the second surgery. Excluded participants were accounted for when success was calculated. Because the study used a cross-over design, groups remained exactly balanced. Therefore, risk of attrition bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: Only 20 participants completed the study from 24 who started it, as 2 were excluded from the analysis because of an incomplete pain diary form, and the other 2 did not return for the second surgery. Excluded participants were accounted for when adverse events were studied. Because the study used a cross-over design, groups remained exactly balanced. Therefore, risk of attrition bias was graded as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Sood 2014

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (India) **Participants:** 100 enrolled, 100 completing the study. Age ranging from 18 to 50 years. 47 male, 53 female **Inclusion criteria** • Clinical diagnosis of irreversible pulpitis • At least 1 adjacent tooth plus a healthy contralateral canine or, alternatively, a contralateral canine without deep carious lesions, extensive restoration, advanced periodontal disease, history of trauma, or sensitivity • Positive response on electric pulp testing of the diseased tooth • Prolonged response with moderate to severe pain to cold testing using Roeko Endo-Frost (Roeko, Langenau, Germany) **Exclusion criteria** • Took medication potentially interacting with any of the anaesthetics or with systemic disorders • History of sensitivity to anaesthetic agents • Presence of periodontal ligament (PDL) widening or periapical radiolucency • Pregnancy
Interventions	Inferior alveolar nerve blocks (1.8 mL) of: • 2% lidocaine, 1:80,000 epinephrine (100) • 4% articaine, 1:100,000 epinephrine (100)
Outcomes	**Clinical anaesthesia** during pulpectomy of teeth with irreversible pulpitis • Success: visual analogue scale: 0 = no pain; 1 = mild, bearable pain; 2 = moderate, unbearable pain; 3 = severe, intense, and unbearable pain (0, 1 = success) (200/200) **Pulpal anaesthesia** tested with an electric pulp tester • Success: negative response to electric stimuli generated with an electric pulp tester (200/200) Teeth tested: mandibular first premolars, second premolars, first molars, second molars, and third molars **Soft tissue anaesthesia** • Success: numbness at 10 minutes post injection on questioning (200/200) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "1 cartridge [1.8 mL] of either anesthetic solution was sealed in envelopes. At the time of application, one researcher, who administered the anesthesia injections, chose one of the envelopes at random"
Allocation concealment (selection bias)	Low risk	Quote: "1 cartridge [1.8 mL] of either anesthetic solution was sealed in envelopes. At the time of application, one researcher, who administered the anesthesia injections, chose one of the envelopes at random"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "To ensure the blindness of the study, the label on the cartridges was removed and the cartridges were coded" Comment: Participants and personnel would not be able to identify the local anaesthetic used.. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "To ensure the blindness of the study, the label on the cartridges was removed and the cartridges were coded" "Electric pulp stimulations to assess pulpal anesthesia were performed by a colleague to guarantee that the anesthetic solution remained unknown and thus maintain the double blindness of the study" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Srinivasan 2009

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (India) **Participants:** 40 enrolled, 40 completing the study First premolar: • 2% lidocaine group: mean age 29.1 years ± 6.35 (SD); male 5, female 5. Pre-treatment pain: 6.7 ± 1.42 • 4% articaine group: mean age 29.4 years ± 6.72 (SD); male 6, female 4. Pre-treatment pain: 6.5 ± 1.43 First molar: • 2% lidocaine group: mean age 29.3 years ± 6.96 (SD); male 4, female 6. Pre-treatment pain: 6.6 ± 1.26 • 4% articaine group: mean age 29.6 years ± 7.01 (SD); male 5, female 5. Pre-treatment pain: 6.4 ± 1.43 **Inclusion criteria** • In good health as determined by a health history questionnaire and verbal questioning • A vital maxillary posterior tooth (first molar or first premolar) was actively experiencing pain • Prolonged response to cold testing with Endo-Ice (1,1,1,2 tetrafluoroethane, Hygenic Corp., Akron, OH) **Exclusion criteria** • No response to cold testing • Periradicular pathosis (other than a widened periodontal ligament) • No vital coronal pulp tissue on access
Interventions	Maxillary buccal infiltration (1.7 mL) of 2 of the following: • 2% lidocaine, 1:100,000 epinephrine (20) • 4% articaine, 1:100,000 epinephrine (20)
Outcomes	**Clinical anaesthesia** during access cavity preparation in teeth with irreversible pulpitis • Success: visual analogue scale from 0 cm = no pain to 10 cm = unbearable pain (40/40) Teeth tested: maxillary first premolars and first molars
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "These 40 patients were randomly divided into 4 study groups" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "These 40 patients were randomly divided into 4 study groups" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All the patients and investigator were blinded to the type of anaesthetic solution used" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore, risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A single operator gave all local anaesthetic injections using standard dental aspirating syringe fitted with a 27-gauge, 1.5-inch needle and this operator had no involvement with testing the outcome" "All the patients and investigator were blinded to the type of anaesthetic solution used" Comment: The outcome is a patient-reported outcome (outcome assessor is the patient) and was recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Srisurang 2011

Methods	Randomized controlled simulated scenario trial, parallel study design
Participants	**Location:** university (Thailand) **Participants:** 33 enrolled, 33 completing the study (48 teeth extracted). Mean age 18.2 years, ranging from 13 to 45 years. Male:female ratio not reported **Inclusion criteria** • No patients were taking medications that would alter pain perception • Extracted teeth were vital, were in normal alignment, and had no periodontal pathology **Exclusion criteria** • Younger than 13 years or older than 60 years of age • Allergies to local anaesthetics or sulphite • Pregnancy
Interventions	Maxillary buccal (0.9 mL) and palatal (0.3 mL) infiltrations of: • 2% lidocaine, 1:100,000 epinephrine (16) • 4% articaine, 1:100,000 epinephrine (16) • 2% mepivacaine, 1:100,000 epinephrine (16)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: no response at the maximum output of the pulp tester (a reading of 80) (48/48) • Duration: measured at 60 minutes only Teeth tested: maxillary lateral incisors, canines, first and second premolars, and first molars **Soft tissue anaesthesia** • Extent of anaesthetized soft tissue (measured by probing: soft tissues tested: at 5 mm above the cervical margin (through a template) and at the marginal gingiva of both the buccal and palatal sites) **Adverse effects** (48/48) • Pain on injection: 100-mm VAS with endpoints of "no pain" and "worst pain imaginable"
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each patient was randomly assigned to one of the following three anesthetic solution groups: 2% lidocaine (lidocaine HCl 2%; Cook-Waite, Abbott Laboratories, KS, USA), 2% mepivacaine (Scandonest 2% special; Septodont, Kent, UK) or 4% articaine (Ubistesin 3M ESPE; ESPE Platz, Seefeld, Germany), all with 1:100 000 epinephrine" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Each patient was randomly assigned to one of the following three anesthetic solution groups: 2% lidocaine (lidocaine HCl 2%; Cook-Waite, Abbott Laboratories, KS, USA), 2% mepivacaine (Scandonest 2% special; Septodont, Kent, UK) or 4% articaine (Ubistesin 3M ESPE; ESPE Platz, Seefeld, Germany), all with 1:100 000 epinephrine" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All cartridges were unidentified, with their stickers removed and the volume of the solution labelled with a permanent marker" Comment: Exact details of blinding methods were not reported. However, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All cartridges were unidentified, with their stickers removed and the volume of the solution labelled with a permanent marker" "Soft tissues: One trained person, blinded to the anesthetic solutions, performed all pre-injection and post-injection tests" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Stibbs 1964

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** 751 enrolled, 751 completing the study (512 excluding 2% procaine/1.5% tetracaine, 1:20,000 levonordefrin). Age and sex distribution not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Various mandibular and infiltration injections of 1 of the following (varying volumes): • 2% mepivacaine, 1:20,000 levonordefrin (248: 107 mandibular, 99 infiltration, and 42 other injections) • 2% lidocaine, 1 50,000 epinephrine (264: 114 mandibular, 102 infiltration, and 48 other injections) • 2% procaine/1.5% tetracaine, 1:20,000 levonordefrin (239: 126 mandibular, 79 infiltration, and 34 other injections - not commercially available)
Outcomes	**Pulpal anaesthesia** during restorative procedures • Success during "restorative operations": grade A = no discomfort when the bur was applied to the dentin; grade B = the patient seemed apprehensive about feeling pain but in the opinion of the student more anaesthetic was not required; grade C = it was obvious, to both the patient and the student, that anaesthesia was unsatisfactory and another injection was required (512/512) • Loss of operating anaesthesia: time recorded if tooth became sensitive during the operation Teeth tested: not reported **Soft tissue anaesthesia** • Onset: self-reported by patients, verbally (491/512) • Duration: self-reported by patients, by postcard (431/512) Soft tissues tested: not reported **Adverse events** reported (512/512)
Notes	Industry funding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The numbered cartridges were jumbled and packed in lots of 50 in sealed cans, thus assuring randomized use"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The numbered cartridges were jumbled and packed in lots of 50 in sealed cans, thus assuring randomized use" "The identity of each code was not revealed until the data were to be assembled for analysis"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Three sterile isotonic local anesthetic solutions were provided in identical dental cartridges. Each cartridge was identified only by a control number. To assure the blindness of the study, three different numbers were assigned to each solution which made a total of nine code numbers. The identity of each code was not revealed until the data were to be assembled for analysis" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Three sterile isotonic local anesthetic solutions were provided in identical dental cartridges. Each cartridge was identified only by a control number. To assure the blindness of the study, three different numbers were assigned to each solution which made a total of nine code numbers. The identity of each code was not revealed until the data were to be assembled for analysis" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: Of the total number of participants recruited who had successful anaesthesia, some did not have onset of soft tissue anaesthesia measured **Mandibular injection:** • Lidocaine: -17/96 (N/A), mepivacaine: -6/97 (N/A) **Infiltration:** • Lidocaine: -11/90 (N/A), mepivacaine: -8/90 (N/A) For onset of soft tissue anaesthesia, small values and even negative values were obtained for dropouts (i.e. numbers of participants having onset measured were greater than numbers having anaesthetic success measured). This is to be expected. However, the dropout rate if present could be calculated only if those having soft tissue success were known. Soft tissue anaesthesia may have been present in those who had failure of anaesthesia during endodontic and periodontal treatment, or it may have been absent, meaning that it was not measured. As this measurement was performed in a clinic immediately before treatment, and as groups were fairly well balanced in numbers, it is highly unlikely that there was any attrition bias. Therefore risk of attrition bias has been graded as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Of the total number of participants recruited who had successful anaesthesia, some did not have duration of soft tissue anaesthesia measured **Mandibular injection:** • Lidocaine: 12/113 (11%), mepivacaine: 10/103 (10%) **Infiltration:** • Lidocaine: 21/101 (21%), mepivacaine: 17/98 (17%) No dropouts would occur if the numbers of participants having duration measured were equal to the numbers having soft tissue onset measured, assuming there were no incomplete onset data. However, even with these difficulties in measuring attrition rate, dropout rates of up to 21% were seen, which are likely to be conservative estimates if true soft tissue success figures are higher. Therefore risk of attrition bias has been graded as high
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Unclear risk	Study was supported by a grant from Cook-Waite Laboratories, Inc.

Thakare 2014

Methods	Randomized controlled clinical trial, cross-over study design
Participants	**Location:** hospital (India) **Participants:** 40 enrolled, 40 completing the study (160 teeth in total). Ages ranging from 10 to 18 years (no mean). Male:female ratio not reported **Inclusion criteria** • Systemically healthy individuals • No reported allergy to local anaesthetics • Requiring extraction of premolars for orthodontic reasons **Exclusion criteria** • None reported
Interventions	Maxillary labial infiltration (1.4 mL) of either: • 4% articaine, 1:200,000 epinephrine (80) • 0.5% bupivacaine, 1:200,000 epinephrine (80)
Outcomes	**Clinical anaesthesia** during premolar removal • Success: intraoperative pain or postoperative pain (VAS scale from 0 to 100 mm) (160/160) • Onset: method not stated but assumed to be onset of soft tissue anaesthesia (160/160) • Duration of postoperative analgesia: method not stated Teeth tested: maxillary and mandibular premolars (one side of the face) **Adverse effects** were reported (160/160) • Time to first rescue medication
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A computer-generated list was used to allocate each patient into either 4% articaine or 0.5% bupivacaine groups" Comment: exact method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "A computer-generated list was used to allocate each patient into either 4% articaine or 0.5% bupivacaine groups" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	Low risk	Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: Self-assessment of onset of soft tissue anaesthesia may have been the method used. No patients were excluded. Outcome data were complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Tofoli 2003

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 20 enrolled, 20 completing the study. Mean age 23 years, ranging from 20 to 35 years. 7 male, 13 female **Inclusion criteria:** healthy individuals who did not use any medication 1 week before or during the experiment, having the right inferior first premolars free of caries and restorations **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks (1.8 mL) of: • 4% articaine, 1:100,000 epinephrine (20) • 4% articaine, 1:200,000 epinephrine (20)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset (40/40) • Duration of complete anaesthesia: no response to maximal output of the pulp tester (80 reading) (40/40) • Duration of partial anaesthesia: interval between the first reading below 80 and return to basal levels Teeth tested: right mandibular first premolars **Soft tissue anaesthesia** • Duration: Participants reported numbness (40/40) Soft tissues tested: lower lip
Notes	Study authors acknowledge the financial support of CNPQ-PIBIC

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Both solutions were randomly applied to the subjects at 2 different sessions" Quote (from correspondence): "The order of administration was randomized by a tossed coin, prior to the beginning of the study. Each volunteer that entered the study was assigned to a number in the list, in sequence, following the order of entrance in the study (Heads: code 1; Tails: code 2. Code 1: First anaesthesia: blue solution; Code 2: First anaesthesia: red solution)"
Allocation concealment (selection bias)	Low risk	Quote: "Both solutions were randomly applied to the subjects at 2 different sessions" Quote (from correspondence): "The solutions were administered by a senior [researcher]; a clinician previously trained to use the pulp tester evaluated anaesthesia parameters. Another [researcher] performed the statistical analysis before the codes were revealed"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "In this double blind random study, the solutions were codified by an individual involved neither in the administration of the anaesthetic solutions nor in pulp testing procedures" Quote (from correspondence): "The identification on the cartridges was removed with alcohol and gauze, and each solution was assigned a colour (a strip of adhesive tape). This procedure was conducted by a person not involved in the administration or evaluation of anaesthesia parameters (pulp testing and statistical analysis). Therefore, the person who administered the solutions, the one that evaluated the anaesthesia parameters and the volunteers were able just to see the colour assigned to the solutions (tape strip)" Comment: Disguising the cartridges of each formulation with the same coloured tape could allow identification of a solution by personnel administering injections in a cross-over study if the properties of the solutions were markedly different. Participants may comment about long duration, poor anaesthesia, etc., at their second visit. However, the properties of the 2 solutions are unlikely to allow identification, and a pre-determined method of administration was used by personnel, to minimize variation. Therefore, risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "In this double blind random study, the solutions were codified by an individual involved neither in the administration of the anaesthetic solutions nor in pulp testing procedures" Quote (from correspondence): "The identification on the cartridges was removed with alcohol and gauze, and each solution was assigned a colour (a strip of adhesive tape). This procedure was conducted by a person not involved in the administration or evaluation of anaesthesia parameters (pulp testing and statistical analysis). Therefore, the person who administered the solutions, the one that evaluated the anaesthesia parameters and the volunteers were able just to see the colour assigned to the solutions (tape strip)" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded (confirmed by study author); outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded (confirmed by study author); outcome data complete

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded (confirmed by study author); outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: Study authors acknowledge the financial support of CNPQ-PIBIC

Tortamano 2009

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Brazil) **Participants:** 40 enrolled, 40 completing the study, with mean age of 29.9 years (articaine)/34.1 years (lidocaine). 16 males and 24 females **Inclusion criteria** • Clinical diagnosis of irreversible pulpitis • Between 18 and 50 years old • In good health as determined by a health history questionnaire • Each participant had at least 1 adjacent tooth plus a healthy contralateral canine or, alternatively, a contralateral canine without deep carious lesions, extensive restoration, advanced periodontal disease, history of trauma, or sensitivity **Exclusion criteria** • Taking medication that potentially interacts with any of the anaesthetics used
Interventions	Inferior alveolar nerve blocks (3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine (20) • 4% articaine, 1:100,000 epinephrine (20)
Outcomes	**Clinical anaesthesia** during pulpectomy of teeth with irreversible pulpitis • Success: verbal analogue scale: 0 = no pain; 1 = mild, bearable pain; 2 = moderate, unbearable pain; 3 = severe, intense, and unbearable pain (0, 1 = success) (40/40) Teeth tested: mandibular second premolars, first molars, second molars, and third molars **Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings with the pulp tester obtained (40/40) **Soft tissue anaesthesia** • Success: patient asked if lip was numb (40/40) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To ensure the blindness of the study, 2 cartridges (3.6 mL) of either anaesthetic solution were sealed in envelopes" "At the time of application, the senior researcher, who administered the 2 consecutive anaesthesia injections, chose 1 of the envelopes at random"
Allocation concealment (selection bias)	Low risk	Quote: "To ensure the blindness of the study, 2 cartridges (3.6 mL) of either anaesthetic solution were sealed in envelopes" "At the time of application, the senior researcher, who administered the 2 consecutive anaesthesia injections, chose 1 of the envelopes at random"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "To ensure the blindness of the study, 2 cartridges (3.6 mL) of either anaesthetic solution were sealed in envelopes" Quote (from correspondence): "Apart from placing the cartridges inside the envelopes and sealing them, we also masked (painted) the cartridges. However, during the pilot tests, we realized that, as the rubber of the cartridges had different colours, it might be possible still to identify the cartridges. Therefore, we did not mention the painted cartridges and decided to have a different researcher performing the electric tests and making the pulpectomy, so that we could ensure that the testing was blind and relevant" Comment: Although the bung of the cartridge may have been visible and allowed the person administering the local anaesthetic to identify the solution, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "To ensure the blindness of the study, 2 cartridges (3.6 mL) of either anaesthetic solution were sealed in envelopes" "Electric pulp stimulations to assess pulpal anaesthesia were performed by a postgraduate student to guarantee that the anaesthetic solution remained unknown and thus maintain the double-blindness of the study" Quote (from correspondence): "Apart from placing the cartridges inside the envelopes and sealing them, we also masked (painted) the cartridges. However, during the pilot tests, we realized that, as the rubber of the cartridges had different colours, it might be possible still to identify the cartridges. Therefore, we did not mention the painted cartridges and decided to have a different researcher performing the electric tests and making the pulpectomy, so that we could ensure that the testing was blind and relevant" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Tortamano 2013

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Brazil) **Participants:** 30 enrolled, 30 completing the study. Mean age 24.63 years, ranging from 18 to 40 years. 15 male, 15 female **Inclusion criteria** • Between 18 and 40 years old • Presenting at least 3 vital asymptomatic mandibular posterior molars • Diagnosed occlusal caries in enamel, without restoration, pulpal calcification, and periodontal disease (which were clinically and radiographically confirmed), and were selected at the Emergency Center of the School of Dentistry at the University of Sao Paulo • Exhibited healthy contralateral canine teeth (i.e. without presence of deep cavities, extensive restorations, or periodontal disease, and no history of trauma or sensitivity) • In good health as established according to a health history questionnaire **Exclusion criteria:** taking medication that can potentially interact with any of the anaesthetics used in the study
Interventions	Inferior alveolar nerve blocks (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine (30) • 4% articaine, 1:100,000 epinephrine (30) • 4% articaine, 1:200,000 epinephrine (30)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Onset (90/90) • Duration (90/90) Teeth tested: mandibular molars
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 30 blinded subjects randomly received an IAN block injection..." "Three cartridges of each local anesthetic solution were sealed in 30 envelopes (one for each patient). During application, the main investigator who administered the three injections (one *per* appointment) randomly removed one cartridge from the envelope. Only one cartridge was randomly chosen and administered *per* appointment. The initial tooth to be restored was randomly selected" Quote (from correspondence): "Although the cartridges were all painted with black ink, the rubber in lidocaine solution is orange which, if observed against a bright light, could eventually be identified. To avoid this risk, the main investigator (myself) personally took out of the envelope (blind) one of the cartridges, inserted it into the carpule syringe and applied the injection on the patient. Then, I would leave the patient to the Graduate student, who applied all the electric tests" "The remaining cartridges would stay in the same envelope, ready to be randomly selected and used in the next appointment of that specific patient. For cross check, the used cartridge was identified (e.g. 'C1' referred to 'appointment 1') and placed in another brown envelope, with the same patient identification number. The same procedure was used in appointment 2 and 3"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Three cartridges of each local anesthetic solution were sealed in 30 envelopes (one for each patient). During application, the main investigator who administered the three injections (one *per* appointment) randomly removed one cartridge from the envelope. Only one cartridge was randomly chosen and administered *per* appointment. The initial tooth to be restored was randomly selected" Quote (from correspondence): "Although the cartridges were all painted with black ink, the rubber in Lidocaine solution is orange which, if observed against a bright light, could eventually be identified. To avoid this risk, the main investigator (myself) personally took out of the envelope (blind) one of the cartridges, inserted it into the carpule syringe and applied the injection on the patient. Then, I would leave the patient to the Graduate student, who applied all the electric tests" "The remaining cartridges would stay in the same envelope, ready to be randomly selected and used in the next appointment of that specific patient. For cross check, the used cartridge was identified (e.g. 'C1' referred to 'appointment 1') and placed in another brown envelope, with the same patient identification number. The same procedure was used in appointment 2 and 3"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "These tests were conducted by a blinded researcher to ensure that the anesthetic solution remained unknown, thus maintaining the double-blindness of the study" Quote (from correspondence): "Although the cartridges were all painted with black ink, the rubber in Lidocaine solution is orange which, if observed against a bright light, could eventually be identified. To avoid this risk, the main investigator (myself) personally took out of the envelope (blind) one of the cartridges, inserted it into the carpule syringe and applied the injection on the patient. Then, I would leave the patient to the Graduate student, who applied all the electric tests" Comment: Although the bung of the cartridge may have been visible and allowed the person administering the local anaesthetic to identify the solution, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore, risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "These tests were conducted by a blinded researcher to ensure that the anesthetic solution remained unknown, thus maintaining the double-blindness of the study" Quote (from correspondence): "Although the cartridges were all painted with black ink, the rubber in lidocaine solution is orange which, if observed against a bright light, could eventually be identified. To avoid this risk, the main investigator (myself) personally took out of the envelope (blind) one of the cartridges, inserted it into the carpule syringe and applied the injection on the patient. Then, I would leave the patient to the Graduate student, who applied all the electric tests" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Trieger 1979

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** 69 enrolled, 69 completing the study. Age ranging from 14 to 55 years. Male:female ratio not reported **Inclusion criteria** • Healthy adults • ASA I or II **Exclusion criteria:** not reported
Interventions	Mandibular nerve block and infiltration anaesthesia, using variable volumes of: • 0.5% bupivacaine, no epinephrine (15 - not commercially available) • 0.5% bupivacaine, 1:200,000 epinephrine (32) • 3% mepivacaine, no epinephrine (22) Note - Some patients received a general anaesthetic, and injections were given at the end of surgery
Outcomes	**Clinical anaesthesia** and postoperative analgesia during extraction • Success: measured in terms of the volume injected per quadrant to obtain anaesthesia (54/54) Teeth tested: mandibular third molars and teeth requiring bone removal at time of extraction **Soft tissue anaesthesia** • Onset: pricking the operative site with a sharp instrument (54/54) Soft tissues tested: those at the site of extraction **Adverse effects** were reported (54/54)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Assignment to the three drug groups was randomized based on the alphabet" Quote (from correspondence): "Random sampling was done by dividing up the alphabet into three segments and assigning each patient to a group, based on the family name of each subject. For example: a to i made one group; j to r another and s to z a third" Comment: The randomisation process, which was based on the alphabet, resulted in imbalance in group size: • 0.5% bupivacaine, no epinephrine (15 participants) • 0.5% bupivacaine, 1:200,000 epinephrine (32 participants) • 3% mepivacaine, no epinephrine (22 participants)
Allocation concealment (selection bias)	High risk	Quote: "Assignment to the three drug groups was randomized based on the alphabet" Quote (from correspondence): "Random sampling was done by dividing up the alphabet into three segments and assigning each patient to a group, based on the family name of each subject. For example: a to i made one group; j to r another and s to z a third" "Once that selection was made the dental assistant was requested to put the specific disposable loaded syringe on the surgical tray for the surgeon to administer"

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (from correspondence): "Blinding as to which anaesthetic was used for a given case was not possible since the dental assistant who was directed to provide the drug, the surgeon and the recorder all were aware. However the patient was unaware as to which agent was used" Comment: Participants undergoing testing were blinded but the clinician administering local anaesthetic was not. Identification of the local anaesthetic by participants is unlikely. It is not clear whether a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as unclear
Blinding of outcome assessment (detection bias)	High risk	Quote (from correspondence): "Blinding as to which anaesthetic was used for a given case was not possible since the dental assistant who was directed to provide the drug, the surgeon and the recorder all were aware. However the patient was unaware as to which agent was used" Comment: Detailed methods were not reported. The person recording participant outcomes knew the identity of the formulations and may have been able to influence participants' responses (participant-reported outcomes). Therefore, risk of bias was graded as high
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; success outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Trullenque-Eriksson 2011

Methods	Randomized controlled clinical and simulated scenario trial, cross-over study design
Participants	**Location:** university (Spain) **Participants:** 35 enrolled, 19 completing the study. Mean age 24.47 years. 6 male and 13 female **Inclusion criteria** • Planned to undergo extraction of bilaterally symmetrical mandibular third molars when both were of similar surgical difficulty and similar estimated duration of the intervention **Exclusion criteria** • Allergy or hypersensitivity to local anaesthetics, antibiotics, or analgesics used • Pregnancy • Cardiovascular, liver, or renal disease; hyperthyroidism, diabetes mellitus, immunosuppression, or chronic pain • Had taken drugs (except oral contraceptives)
Interventions	Inferior alveolar nerve block and mandibular buccal infiltration (1.8 mL) of: • 0.5% bupivacaine, 1:200,000 epinephrine (19) • 4% articaine, 1:200,000 epinephrine (19)
Outcomes	**Clinical anaesthesia** during tooth removal • Success: need for local anaesthetic reinforcement: absence of pain (confirmed with study author) (38/70) Teeth/soft tissues tested: mandibular third molars and adjacent tissues .**Soft tissue anaesthesia:** Lip numbness was self-reported; sensitivity in the vestibular gum was measured with a sharp instrument • Onset (number assessed was unclear) • Duration (number assessed was unclear) Soft tissues tested: inferior alveolar nerve: lip; buccal nerve: vestibular gum **Adverse events** reported (38/70) • Postoperative pain: visual analogue scale • Other adverse effects
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The patients were randomly administered one of the two local anaesthetics in the first surgery, and the other one in the following" Quote (from correspondence): "Several surgeons participated in our study. They were told to randomly choose an anaesthetic for the first surgery. They were not offered both anaesthetics in a container to blindly pick one. Both were in the same container (drawer) but they were able to see their choice. The observer however was not able to see what anaesthetic had been chosen / was being used"
Allocation concealment (selection bias)	High risk	Quote: "The patients were randomly administered one of the two local anaesthetics in the first surgery, and the other one in the following" Quote (from correspondence): "Several surgeons participated in our study. They were told to randomly choose an anaesthetic for the first surgery. They were not offered both anaesthetics in a container to blindly pick one. Both were in the same container (drawer) but they were able to see their choice. The observer however was not able to see what anaesthetic had been chosen / was being used"
Blinding of participants and personnel (performance bias)	High risk	Quote: "The anaesthetic used was unknown for the patient and the observer who performed the measurements. At the time of the surgery this information was only known by the surgeon who administered the anaesthesia and the surgeon who assisted him, who recorded the anaesthetic and dose in the patient's medical history and a collection sheet in an opaque envelope, which were not consulted until the data analysis." "The double-blind contributed to avoid bias, as the observer and the patient ignored the anaesthetic used in each surgery" Comment: Identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was not used by personnel to minimize variation. The surgeon administering local anaesthetic was not blinded and was allowed to vary the dose depending on what he or she thought was necessary. Therefore, risk of bias was graded as high
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The anaesthetic used was unknown for the patient and the observer who performed the measurements. At the time of the surgery this information was only known by the surgeon who administered the anaesthesia and the surgeon who assisted him, who recorded the anaesthetic and dose in the patient's medical history and a collection sheet in an opaque envelope, which were not consulted until the data analysis" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Clinical success	High risk	Quote: "Of the thirty-five patients selected, nineteen were included in the study" Quote (from correspondence): "Due to not fulfilling inclusion criteria: • 9 patients did not want / could not undertake the second surgery during the study period • In 1 case double blind was not achieved • In 2 cases the same anaesthetic was administered in both surgeries by mistake • In 2 cases it was not possible for the same surgeon to perform the second surgery • In 2 cases one of the surgeries was more complicated than expected rendering their surgeries non-comparable" Comment: Although accounted for, 46% were excluded and reasons for exclusion varied. Therefore risk of attrition bias was graded as high
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	High risk	Quote: "Of the thirty-five patients selected, nineteen were included in the study" Quote (from correspondence): "Due to not fulfilling inclusion criteria: • 9 patients did not want / could not undertake the second surgery during the study period • In 1 case double blind was not achieved • In 2 cases the same anaesthetic was administered in both surgeries by mistake • In 2 cases it was not possible for the same surgeon to perform the second surgery • In 2 cases one of the surgeries was more complicated than expected rendering their surgeries non-comparable" Comment: Although accounted for, 46% were excluded and reasons for exclusion varied. Therefore risk of attrition bias was graded as high
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Quote: "Of the thirty-five patients selected, nineteen were included in the study" Quote (from correspondence): "Due to not fulfilling inclusion criteria: • 9 patients did not want/could not undertake the second surgery during the study period • In 1 case double blind was not achieved • In 2 cases the same anaesthetic was administered in both surgeries by mistake • In 2 cases it was not possible for the same surgeon to perform the second surgery • In 2 cases one of the surgeries was more complicated than expected rendering their surgeries non-comparable" Comment: Although accounted for, 46% were excluded and reasons for exclusion varied. Therefore risk of attrition bias was graded as high
Incomplete outcome data (attrition bias) Adverse events	High risk	Quote: "Of the thirty-five patients selected, nineteen were included in the study" Quote (from correspondence): “Due to not fulfilling inclusion criteria: • 9 patients did not want/could not undertake the second surgery during the study period • In 1 case double blind was not achieved • In 2 cases the same anaesthetic was administered in both surgeries by mistake • In 2 cases it was not possible for the same surgeon to perform the second surgery • In 2 cases one of the surgeries was more complicated than expected rendering their surgeries non-comparable" Comment: Although accounted for, 46% were excluded and reasons for exclusion varied. Therefore risk of attrition bias was graded as high
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Vahatalo 1993

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Finland) **Participants:** 20 enrolled, 20 completing the study. Mean age 23.8 years. 8 male, 12 female **Inclusion criteria** • No history of allergic reaction to amide-type anaesthetic agents • Not taking medications regularly • Only intact lateral incisors included **Exclusion criteria:** none reported
Interventions	Maxillary buccal infiltration (0.6 mL) of: • 2% lidocaine, 1:80,000 epinephrine (20) • 4% articaine, 1:200,000 epinephrine (20)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: no response to maximum output of the stimulator (40/40) • Onset (40/40) • Duration (40/40) Teeth tested: maxillary lateral incisors
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study protocol was double-blind. The code was not broken until the statistical analysis of the data. The dental assistant was the only person aware of which preparation was being injected" Quote (from correspondence): "The one and only research nurse loaded 1 ml tuberculin syringes by aspiration with 0.6ml test solution from commercially available cartridges" "She had lists of tested study persons who were coded and was aware what solution (A or B) used in second visit" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The study protocol was double-blind. The code was not broken until the statistical analysis of the data. The dental assistant was the only person aware of which preparation was being injected" Quote (from correspondence): "The one and only research nurse loaded 1 ml tuberculin syringes by aspiration with 0.6ml test solution from commercially available cartridges" "She had lists of tested study persons who were coded and was aware what solution (A or B) used in second visit" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Vilchez-Perez 2012

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Spain) **Participants:** 33 enrolled, 20 completing the study. Mean age 22.75 years (SD = 2.15). 5 male, 15 female **Inclusion criteria** • Healthy volunteers (ASA I) • 18 to 30 years old • Absence of systemic disease • No background of medication, hypersensitivity, or pregnancy • No toxic habits (including alcohol abuse, smoking or regular cannabis smoking, or other drug use) • Absence of routine medication use • Absence of adverse reaction to local anaesthetics • Absence of dental disease (tooth decay or other abnormalities), tooth restorations, traumatic lesions, dental hypersensitivity, or periodontal disease for all teeth under study • Positive pulp vitality tests in all teeth under study • Absence of acute or chronic infection in the oral and maxillofacial area **Exclusion criteria** • Use of any medication for 15 days before the study • Use of local anaesthetics in the oral and maxillofacial area for 15 days before the study • Heart rate lower than 50 or higher than 90 beats/min • Latency time longer than 3 minutes during infiltration. In this case, infiltration is repeated in another session to rule out the possibility of error in anaesthesia administration if a volunteer drops out
Interventions	Maxillary labial infiltration (0.9 mL) of: • 4% articaine, 1:200,000 epinephrine (20) • 0.5% bupivacaine, 1:200,000 epinephrine (20)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Incidence: percentage of successful anaesthesia over time Teeth tested: right and left maxillary lateral incisors **Soft tissue anaesthesia** • Onset: first reported sensation of numbness (classified as immediate after needle removal, less than 30 seconds, after 30 or more seconds; measured with a probe) (40/40) • Duration: self-reported (40/40) • Incidence: percentage of successful anaesthesia over time Soft tissues tested: • Onset: upper lip • Duration: upper lip • Incidence: attached gingiva, alveolar mucosa, upper lip mucosa, and lip skin **Adverse events** reported (40/40) • Haemodynamic parameters
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was based on a sequence generated by Laboratorios Inibsa, Barcelona, Spain" Quote (from correspondence): "Randomization was based on a sequence generated by Laboratorios Inibsa, Barcelona, Spain. There was an individual envelope for each volunteer with information about which solution (solution A or solution B) had to be infiltrated in each side (right side or left side). The solutions A or B were different in each envelope. The list of treatment implemented (articaine or bupivacaine) was saved by Laboratorios Inibsa" Comment: exact method of generation of randomized sequence needing clarification
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was based on a sequence generated by Laboratorios Inibsa, Barcelona, Spain" Quote (from correspondence): "Randomization was based on a sequence generated by Laboratorios Inibsa, Barcelona, Spain. There was an individual envelope for each volunteer with information about which solution (solution A or solution B) had to be infiltrated in each side (right side or left side). The solutions A or B were different in each envelope. Both solutions were encoded so that the surgeon performing the anaesthesia infiltration, the monitor recording the variables and the volunteer could not identify the anaesthetic solution used. The code of solutions was given to us after the statistical analysis by Laboratorios Inibsa"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both solutions were encoded so that the surgeon performing the anaesthesia infiltration, the monitor recording the variables and the volunteer could not identify the anaesthetic solution used" Quote (from correspondence): "The code of solutions was given to us after the statistical analysis by Laboratorios Inibsa" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore, risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Both solutions were encoded so that the surgeon performing the anaesthesia infiltration, the monitor recording the variables and the volunteer could not identify the anaesthetic solution used" Quote (from correspondence): "The code of solutions was given to us after the statistical analysis by Laboratorios Inibsa" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Visconti 2016

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Brazil) **Participants** • 2% lidocaine with 1:100,000 epinephrine group: 21 enrolled, 21 completing the study. Mean age 28 years. 6 male, 15 female (confirmed by study author) • 2% mepivacaine with 1:100,000 epinephrine group: 21 enrolled, 21 completing the study. Mean age 26 years. 3 male, 18 female **Inclusion criteria** • Age from 18 to 50 years • Currently feeling pain • In good health and not taking any medication that would alter perception of pain (determined by verbal questioning and a written questionnaire) • Had to receive clinical diagnosis of irreversible pulpitis on the basis of moderate to severe spontaneous pain and prolonged response exhibited to cold testing with Endo-Frost (Coltene-Roeko, Langenau, Germany) and a positive response to the electric pulp test (Vitality Scanner 2006; SybronEndo, Orange, CA) • Each participant had at least 1 adjacent tooth plus a healthy contralateral canine or, alternatively, a contralateral canine without deep caries damage, extensive restoration, advanced periodontal disease, history of trauma, or sensitivity **Exclusion criteria** • None
Interventions	Inferior alveolar nerve blocks (1.8 mL or 3.6 mL) using the following: • 2% lidocaine, 1:100,000 epinephrine (21) • 2% mepivacaine, 1:100,000 epinephrine (21)
Outcomes	**Clinical anaesthesia** during access cavity preparation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: 4-point scale: 0 = no pain; 1 = mild pain (pain that was recognizable but did not cause discomfort); 2 = moderate pain (pain that was causing discomfort but was bearable); 3 = severe pain (pain that caused considerable discomfort and was difficult to bear). Pain was that graded as 0 or 1 (32/42) **Pulpal anaesthesia** tested with an electric pulp tester • Success (42/42) Teeth tested: mandibular molars **Soft tissue anaesthesia** • Success: Patients were asked whether their lip was numb (42/42) Soft tissues tested: lower lip
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Blinding was achieved as follows: 3 cartridges (1.8 mL each) of each anesthetic solution were sealed in 42 envelopes by the first author. The senior researcher, who was not involved in the endodontic procedure, administered the anaesthesia injection after choosing 1 of the envelopes at random"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Blinding was achieved as follows: 3 cartridges (1.8 mL each) of each anesthetic solution were sealed in 42 envelopes by the first author. The senior researcher, who was not involved in the endodontic procedure, administered the anaesthesia injection after choosing 1 of the envelopes at random"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Blinding was achieved as follows: 3 cartridges (1.8 mL each) of each anesthetic solution were sealed in 42 envelopes by the first author. The senior researcher, who was not involved in the endodontic procedure, administered the anaesthesia injection after choosing 1 of the envelopes at random" Quote (from correspondence): "We assembled 21 envelopes with three cartridges of 2% lidocaine with 1:100,000 epinephrine another 21 envelopes with three cartridges of 2% mepivacaine with 1:100,000 epinephrine. The 42 envelopes were stored in a box where the anesthesia applicator (senior operator) randomly, took one of the envelopes. It should be noted that all injections were administered by the same operator (senior operator), since the electrical tests and the opening were performed by another operator. So the patient was blind, as well as the operator of the electrical tests. The only person who knows the anesthesia was the senior operator (who did the injections)" Comment: Identification of the local anaesthetic by participants is unlikely. Although the operator administering the local anaesthetic knew the identity of the formulation used, a pre-determined method of administration was used by the operator to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Electric pulp stimulations to assess pulpal anesthesia and the pulpectomy were performed by a postgraduate student to guarantee that the anesthetic solution remained unknown and thus maintain the double-blindness of the study. All pre-injection and post-injection tests were conducted by trained personnel who were blinded to the anesthetic volumes administered" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: Only 32 participants were tested clinically from 42 who started it, as 3 were eliminated from the mepivacaine group and 7 were eliminated from the lidocaine group following failure of anaesthesia tested with the electric pulp tester. Excluded participants were accounted for when success was calculated; groups remained balanced (18 vs 14) and reasons for dropout were the same. Therefore risk of attrition bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Vreeland 1989

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 30 enrolled, 30 completing the study. Mean age 25.5 years, ranging from 22 to 32 years. 27 male, 3 female **Inclusion criteria** • Judged to be in good health • Currently taking no medications • Had never had an allergic or toxic reaction to a local anaesthetic agent **Exclusion criteria** • Caries, large restorations, crowns, previous endodontic therapy, exposed dentin, or periodontal disease associated with test teeth • History of trauma or sensitivity
Interventions	Inferior alveolar nerve blocks of: • 1.8 mL 2% lidocaine, 1:100,000 epinephrine (30) • 3.6 mL 2% lidocaine, 1:200,000 epinephrine (30) • 1.8 mL 4% lidocaine, 1:100,000 epinephrine (30 - not commercially available)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: patients who achieved an 80 reading within 16 minutes and continuously sustained this reading for 55 minutes (60/60) • Failure: patients who never achieved 2 consecutive 80 readings at any time interval up to 55 minutes • Onset: time of the first of 2 consecutive 80 readings of the pulp tester (52/60) • Anaesthesia of slow onset: patients who achieved an 80 reading after 16 minutes • Incidence: number of maximum pulp tester readings (80) over time • Short duration: patients who achieved 2 consecutive 80 readings, lost the 80 readings, and never regained the readings within 55 minutes • Non-continuous anaesthesia: patients who achieved 2 consecutive 80 readings, lost the 80 readings, and then regained the 80 readings during the 55 minutes Teeth tested: mandibular first molars, canines, and lateral incisors **Soft tissue anaesthesia** (alveolar mucosal sticks labial and lingual to the test canine and buccal to the test molar; patient was asked if the lip and tongue were numb) • Success: profound lip numbness on questioning and negative response to mucosal sticks (60/60) • Onset: patient questioning: occurred at the first of 2 consecutive positive responses. Mucosal sticks: lip, tongue, and buccal anaesthesia occurred when the patient responded negatively to the first of 2 consecutive alveolar mucosal sticks (60/60) Soft tissues tested: soft tissues labial and lingual to the test canine and buccal to the test contralateral canine/first molar
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each subject was randomly assigned to one of six letter combinations in order to determine the sequence of solution administration. A four digit random number was assigned prior to the experiment for each subject and recorded on a master code list" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "Each subject was randomly assigned to one of six letter combinations in order to determine the sequence of solution administration. A four digit random number was assigned prior to the experiment for each subject and recorded on a master code list" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetics solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All injections, as timed with a watch, took 2 min to complete so the subject was unaware of which solution he or she received" Comment: The participant may be aware of a difference in injections, as double the volume of 2% lidocaine, 1:200,000 epinephrine was injected, which may feel different. However, the participant would not necessarily know the identity of the formulation at each visit. The clinician delivering this solution would know which solution was being injected, but a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All pre- and post-injection tests were done by trained personnel who had no knowledge of the solutions injected" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 52 occasions (for those not experiencing anaesthetic failure: 25 cases of 2% lidocaine, 1:100,000 epinephrine (1.8 mL) and 27 cases of 2% lidocaine, 1:200,000 epinephrine (3.6 mL)). Because the reduction in numbers across groups was well balanced and the reasons identical, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Wali 2010

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (United States of America) **Participants:** 30 enrolled, 30 completing the study. Mean age 28 years, ranging from 22 to 44 years. 22 male and 8 female **Inclusion criteria:** in good health and not taking any medications that would alter the perception of pain **Exclusion criteria** • Younger than 18 years • Older than 65 years • Allergies to local anaesthetics or sulphites • Pregnancy • History of significant medical conditions • Taking any medications that might affect anaesthetic assessment (non-steroidal anti-inflammatory drugs, opioids, antidepressants, alcohol) • Active sites of pathosis in area of injection • Inability to give informed consent
Interventions	Inferior alveolar nerve blocks of: • 1.8 mL of 2% lidocaine, 1:100,000 epinephrine (30) • 1.8 mL of 2% lidocaine, 1:50,000 epinephrine (30) • 3.6 mL of 2% lidocaine, 1:50,000 epinephrine (30 - data not used)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings were obtained within 15 minutes, and 80 readings were continuously sustained through the 60th minute (60/60) • Onset (48/60 - molar teeth, 52/60 - first premolar teeth, 36/60 - lateral incisor teeth) • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: mandibular first molars, first premolars, lateral incisors **Soft tissue anaesthesia** (patient was asked if his/her lip was numb) • Success (60/60) • Onset (60/60) Soft tissues tested: lower lip
Notes	Non-industry funding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The 3 solutions were randomly assigned 4-digit numbers from a random number table. Each subject was randomly assigned to the right or left side for the set of injections. The order of the anaesthetic solutions was also randomly assigned to determine which solutions were to be administered at each appointment" Quote (from correspondence): "Each solution had a four-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Quote: "The 3 solutions were randomly assigned 4-digit numbers from a random number table. Each subject was randomly assigned to the right or left side for the set of injections. The order of the anaesthetic solutions was also randomly assigned to determine which solutions were to be administered at each appointment" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The 3 solutions were randomly assigned 4-digit numbers from a random number table" "An opaque tape was placed on each syringe, and the corresponding 4-digit code number was written on the tape" Comment: The identity of 3.6 mL of 2% lidocaine with 1:50,000 epinephrine solution would be clear to the patient and clinician, as it would require the injection rate to be twice as fast (all injections were given over 2 minutes). However, these data were not used in this review. Participants and personnel would not be able to identify the other local anaesthetics used
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the random numbers were recorded on the data collection and post-injection survey sheets to help blind the experiment" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Low risk	Comment: Onset of pulpal anaesthesia was tested on 48 occasions for molar teeth, excluding 3.6 mL of 2% lidocaine, 1:50,000 epinephrine (for those not experiencing anaesthetic failure = 24 in each group). Because the reduction in numbers across groups was equal and the reasons identical, risk of attrition bias was rated as low
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: no patients excluded; outcome data complete
Other bias	Low risk	Comment: no other bias present

Weil 1961

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (United States of America) **Participants:** 592 enrolled, 592 completing the study (252, excluding those not commercially available). Mean age and range and male:female ratio not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Mandibular and maxillary injections (1 cartridge or more if required) of: • 3% mepivacaine, no vasoconstrictor (181) • 2% mepivacaine, 1:20,000 levonordefrin (71) Not commercially available: • 2% mepivacaine, no vasoconstrictor • 2% mepivacaine, 1:40,000 levonordefrin • 0.5% propoxycaine + 2% procaine, 1:20,000 levonordefrin
Outcomes	**Clinical anaesthesia** during operative dentistry procedures • Success: grade of anaesthesia: A - complete elimination of pain at the site of operation; B - some discomfort but in the opinion of the operator, another injection was not required; C – anaesthesia was unsatisfactory and reinjection was necessary (252/252) • Duration of operating anaesthesia (28/252 - only those with pain during the procedure reported this; remaining participants who did not experience pain had the assessment period terminated on completion of the procedure. Therefore, data were not used) **Soft tissue anaesthesia** • Onset: Patient reported onset (249/252) • Duration: Patient was given a postcard to record duration (210/252) Soft tissues tested: relevant soft tissues, depending on injection and jaw Teeth tested: not stated **Adverse events** reported (252/252)
Notes	Industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Solutions.....were supplied in identical dental cartridges marked only by a control number printed on each cartridge. At least three different code numbers were assigned to each local anaesthetic solution. All the cartridges under test were mixed indiscriminately with cartridges of the control solution, in cans of 50" Comment: exact method of generation of randomized sequence not reported (probably drawing from the can). There was a large difference in group size (71 vs 181); this may indicate a problem with the randomization process. Therefore, risk of bias was rated as unclear

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "Solutions.....were supplied in identical dental cartridges marked only by a control number printed on each cartridge. At least three different code numbers were assigned to each local anaesthetic solution. All the cartridges under test were mixed indiscriminately with cartridges of the control solution, in cans of 50" "The key to the code of control numbers was kept by the administrator in a sealed envelope until the data from the cards were tabulated and analysed" Comment: exact method of concealment not stated
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Solutions.....were supplied in identical dental cartridges marked only by a control number printed on each cartridge. At least three different code numbers were assigned to each local anaesthetic solution. All the cartridges under test were mixed indiscriminately with cartridges of the control solution, in cans of 50" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore, risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Solutions.....were supplied on identical dental cartridges marked only by a control number printed on each cartridge. At least three different code numbers were assigned to each local anaesthetic solution. All the cartridges under test were mixed indiscriminately with cartridges of the control solution, in cans of 50" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Low risk	Comment: Of the total number of participants tested, some did not have onset of soft tissue anaesthesia measured **Mandibular injection:** • 3% mepivacaine, no vasoconstrictor: 1/91; 2% mepivacaine, 1:20,000 levonordefrin: 0/31 (N/A) **Infiltration:** • 3% mepivacaine, no vasoconstrictor: 2/88; 2% mepivacaine, 1:20,000 levonordefrin: 0/40 (N/A) For onset of soft tissue anaesthesia, values of zero or only small numbers were obtained for dropouts. However, the dropout rate if present could be calculated only if those having soft tissue success were known. Soft tissue anaesthesia may have been present in those who had failure of anaesthesia or may have been absent, meaning that it was not measured. However, as the number measured is very similar to the total number enrolled, and any dropouts in both groups would be due to failure of local anaesthetic, risk of bias has been graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	High risk	Comment: Of the total number of participants recruited who had onset of soft tissue anaesthesia measured, some did not have duration of soft tissue anaesthesia measured **Mandibular injection:** • 3% mepivacaine, no vasoconstrictor: 8/90 (9%); 2% mepivacaine, 1:20,000 levonordefrin: 1/31 (3%) **Infiltration:** • 3% mepivacaine, no vasoconstrictor: 27/86 (31%); 2% mepivacaine, 1:20,000 levonordefrin: 2/40 (5%) For duration of soft tissue anaesthesia, no dropouts would occur if the numbers of participants having duration measured were equal to the numbers having soft tissue onset measured. However, dropout rates of up to 31% were seen and were based on those who had onset of soft tissue anaesthesia measured. Therefore risk of bias has been graded as high because if dropout rates were based on soft tissue success, they might be higher still. Data were not used for meta-analysis
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	Supported by a grant from Cook-Waite

Yadav 2015

Methods	Randomized controlled clinical trial, parallel study design
Participants	**Location:** university (India) **Participants:** 150 enrolled, 150 completing the study. Age ranging from 20 to 35 years. 78 male, 72 female **Inclusion criteria** • Active pain in a mandibular first and/or second molar • Prolonged response to cold testing with Endo-Frost (Roeko, Langenau, Germany) • Absence of any periapical radiolucency on periapical radiographs • Vital coronal pulp on access opening **Exclusion criteria** • Previous history of allergy to any kind of local anaesthesia, sulphites, or other drugs • Taking any medication that would alter pain perception
Interventions	Inferior alveolar nerve block (1.8 mL) followed by buccal (0.9 mL) and lingual (0.9 mL) infiltrations using the following: • 2% lidocaine, 1:80,000 epinephrine (25) • 4% articaine, 1:100,000 epinephrine (25) Other participants (100) had oral ketorolac (10 mg) with and without buccal and lingual infiltrations
Outcomes	**Clinical anaesthesia** during access cavity preparation and instrumentation in teeth with irreversible pulpitis • Success of pulpal anaesthesia: ability to access and instrument the tooth without pain (VAS score of zero or weak/mild pain ≤ 54 mm) on a Heft-Parker visual analogue scale (50/50) Teeth tested: mandibular first and second molars
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All patients were randomly divided into 2 major groups" Comment: detailed method not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "All patients were randomly divided into 2 major groups" Comment: detailed method not reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The labels of the solutions were removed, and unique 3-digit numeric values were coded on them; the results were recorded according to those values only" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low

Bias	Authors' judgement	Support for judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The labels of the solutions were removed, and unique 3-digit numeric values were coded on them; the results were recorded according to those values only" Comment: The outcome is a patient-reported outcome (outcome assessor is the patient). Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Yared 1997

Methods	Randomized controlled simulated scenario trial, cross-over study design
Participants	**Location:** university (Lebanon) **Participants:** 30 enrolled, 30 completing the study. Mean age 32 years, ranging from 22 to 50 years. 22 male, 8 female **Inclusion criteria:** in good health and not taking any medications that would alter pain perception **Exclusion criteria:** none reported
Interventions	Inferior alveolar nerve blocks (3.6 mL) of: • 2% lidocaine, 1:50,000 epinephrine (30) • 2% lidocaine, 1:80,000 epinephrine (30) • 2% lidocaine, 1:100,000 epinephrine (30)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 80 reading was achieved within 16 minutes and was sustained for the remainder of the 50-minute test period (90/90) • Failure: Patient never achieved 2 consecutive 80 readings during the 50 minutes • Non-continuous anaesthesia: Patient achieved 2 consecutive 80 readings, lost the 80 readings, and then regained the 80 readings during the 50 minutes • Anaesthesia of slow onset: 2 consecutive 80 readings after 16 minutes • Anaesthesia of short duration: 2 consecutive 80 readings, lost 80 readings, and 80 readings never regained within the 50-minute period • Incidence: percentage of maximum pulp tester readings (80) over time Teeth tested: mandibular first molars, first premolars, lateral incisors **Soft tissue anaesthesia** • Success: subjective lip and tongue numbness/sticking the alveolar mucosa with a sharp explorer (90/90) Soft tissues tested: labial and lingual to the premolar and buccal to the first molar
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each subject randomly received each anaesthetic solution on three successive appointments at least 1 week apart" "The sequence of solution administration was determined randomly" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Each subject randomly received each anaesthetic solution on three successive appointments at least 1 week apart" "The sequence of solution administration was determined randomly" Comment: exact method of concealment not stated

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "These solutions were designated by D, E, and F, respectively. The sequence of solution administration was determined randomly, and all the injections were given blindly by one operator" Comment: Disguising the cartridges of each formulation with the same code (D, E, and F) could allow identification of a solution by personnel administering injections in a cross-over study if the properties of the solutions were markedly different. Patients may comment about long duration, poor anaesthesia, etc., at their second visit. However, the properties of the 3 solutions are unlikely to allow identification, and a pre-determined method of administration was used by personnel to minimize variation. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All preinjection and post-injection tests were done by a trained person who was blinded to the solutions injected" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Yilmaz 2011

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Turkey) **Participants:** 162 enrolled, 157 completing the study. Mean age 7.2 years, standard deviation = 0.6 years. 81 male, 81 female **Inclusion criteria** • No history of allergy to drugs or local anaesthetics • No evidence of systemic illnesses • No soft tissue infection near the proposed injection site • None had used aspirin, paracetamol, or another analgesic 24 hours before the procedure and administration of the local anaesthetic agent • Scored between 3 and 4 on the Frankl Behaviour Rating Scale at the first visit, when a decayed tooth was treated **Exclusion criteria:** not reported
Interventions	Inferior alveolar nerve block and maxillary buccal infiltration (1.0 mL) of: • 4% articaine, 100,000 epinephrine (79) • 3% prilocaine, 1.08 µg (0.03 IU/mL) felypressin (78)
Outcomes	**Clinical anaesthesia** during pulpotomy • Success: signs of discomfort measured as a surrogate marker for the presence or absence of pain: facial expressions, hand movements, torso movements, leg movements, crying (157/162) Teeth tested: maxillary and mandibular deciduous posterior teeth **Soft tissue anaesthesia** • Success: probing buccal and lingual to the tooth in question (157/162) Soft tissues tested: relevant soft tissues, depending on tooth and jaw **Adverse events** reported (157/162)
Notes	No funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 162 children were randomly divided into two equal groups" Comment: exact method of generation of randomized sequence not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The 162 children were randomly divided into two equal groups" Comment: exact method of generation of concealment not reported

Bias	Authors' judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both local anaesthetic agents were administered either as a maxillary infiltration or a mandibular block by a paediatric dentist who was blinded to the type of local anaesthetic that was injected" Comment: Detailed methods were not reported. Despite no details of the blinding method, identification of the local anaesthetic by participants is unlikely. A pre-determined method of administration was used by personnel to minimize variation. Therefore, risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Both local anaesthetic agents were administered either as a maxillary infiltration or a mandibular block by a paediatric dentist who was blinded to the type of local anaesthetic that was injected" Comment: Outcomes are patient-reported outcomes (outcome assessor is the patient) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore, risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Low risk	Comment: A small number (5) were excluded from the study for the same reason: discomfort following maxillary injection (4 with articaine and 1 with prilocaine). However the groups were still well balanced; therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: A small number (5) were excluded from the study for the same reason: discomfort following maxillary injection (4 with articaine and 1 with prilocaine). However the groups were still well balanced; therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Low risk	Comment: A small number (5) were excluded from the study for the same reason: discomfort following maxillary injection (4 with articaine and 1 with prilocaine). However the groups were still well balanced; therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Yonchak 2001

Methods	Randomized controlled simulated scenario trial, parallel and cross-over study design
Participants	**Location:** university (United States of America) **Participants** Cross-over: 40 enrolled, 40 completed the study. Mean age 26 years, ranging from 21 to 34 years. 30 male, 10 female Parallel: 40 enrolled, 40 completing the study. Mean age 26 years, ranging from 20 to 34 years. 30 male, 10 female **Inclusion criteria:** in good health and not taking any medications that would alter pain perception **Exclusion criteria:** none reported
Interventions	Cross-over: mandibular labial infiltration (1.8 mL) of: • 2% lidocaine, 1:50,000 epinephrine (40) • 2% lidocaine, 1:100,000 epinephrine (40) Parallel: mandibular lingual infiltration (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine (40 - data not used)
Outcomes	**Pulpal anaesthesia** tested with an electric pulp tester • Success: 2 consecutive 80 readings were obtained (80/80) • Incidence Teeth tested: mandibular lateral incisors, central incisors, and canines **Soft tissue anaesthesia** • Success: asked if the lip was numb (80/80) Soft tissues tested: lip (cross-over study only)
Notes	Non-industry funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the experiment, the 2 anaesthetic solutions were randomly assigned 5-digit numbers from a random number table. Each subject was randomly assigned to 1 of the 2 solutions to determine the sequence of the injections" Quote (from correspondence): "Each solution had a five-digit random number for each subject and for each solution, and for each side. This was generated by a computer program"
Allocation concealment (selection bias)	Low risk	Quote: "Before the experiment, the 2 anaesthetic solutions were randomly assigned 5-digit numbers from a random number table. Each subject was randomly assigned to 1 of the 2 solutions to determine the sequence of the injections" Quote (from correspondence): "Concealment was achieved by having an experimenter label the cartridges with the random number so neither the operator, patient, or pulp tester knew which of the anaesthetic solutions were used. The cartridges with the random numbers were placed in an envelope for Subject 1, 2, 3, etc. and which random number was to be used for the first appointment was written on the outside. The master code list was not available to the investigator. The coding was broken at the end of the study by our statistician"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Each anaesthetic cartridge (1:100,000 or 1:50,000) was masked with a white opaque label and numbered to determine the order of anaesthetic administration. The random numbers were recorded on the cartridges and the data collection sheets to blind the experiment" Comment: Participants and personnel would not be able to identify the local anaesthetic used. Therefore risk of bias was graded as low
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Each anaesthetic cartridge (1:100,000 or 1:50,000) was masked with a white opaque label and numbered to determine the order of anaesthetic administration. The random numbers were recorded on the cartridges and the data collection sheets to blind the experiment" Comment: Outcomes are participant-reported outcomes (outcome assessor is the participant) and were recorded by a different person than the local anaesthetic administrator. Identification of the local anaesthetic by participants and personnel recording outcomes was not possible. Therefore risk of bias was graded as low
Incomplete outcome data (attrition bias) Clinical success	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) success	Low risk	Comment: no patients excluded; outcome data complete
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) onset	Unclear risk	

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Soft tissue anaesthesia (simulated scenario) duration	Unclear risk	
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) onset	Unclear risk	
Incomplete outcome data (attrition bias) Anaesthesia (clinical) duration	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) onset (2)	Unclear risk	
Incomplete outcome data (attrition bias) Pulpal anaesthesia (simulated scenario) duration (2)	Unclear risk	
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported
Other bias	Low risk	Comment: no other bias present

Footnotes

We suspected that two studies may be from the same clinical trial (Malamed 2000a; Malamed 2000b), but we were unable to contact the study author to confirm this. Until we receive clarification from the study author that they are, we have assumed for the review that they are different trials. Neither was used in the meta-analysis.

In the Characteristics of included studies, the number of participants tested is included in brackets after each local anaesthetic in the Interventions section and after each outcome in the Outcomes section. This latter figure is the ratio of those actually tested against the original number eligible for testing.

AE = articaine; AR = articaine; ASA= American Society of Anaesthesiologists; Aw/o = articaine with no vasoconstrictor; BI = buccal infiltration; bpm = beats per minute; CNPQ-PIBIC = Conselho Nacional de Desenvolvimento Científico e Tecnológico - Programa Institucional de Bolsas de Iniciação Científica; EPT = electric pulp tester; FLACC = Face, Legs, Activity, Cry, Consolability Scale; FPS-R = Faces Pain Scale - Revised; HCl = hydrochloride; Hg = mercury; HP VAS = Heft-Parker visual analogue scale; IAN = inferior alveolar nerve; IANB = inferior alveolar nerve block; IU = international units; JADA = Journal of the American Dental Association; LA = local anaesthetic; LE = lidocaine; ME = mepivacaine; N/A = not applicable; PDL = periodontal ligament; SD = standard deviation; SEM = standard error of the mean; V = volt.

Characteristics of excluded studies

Adler 1969

Reason for exclusion	Although a randomized trial, only optical isomers of mepivacaine were compared

Caruso 1989

Reason for exclusion	Some of the participants were sedated.

Cowan 1964

Reason for exclusion	This study compared procaine, lidocaine, mepivacaine, and prilocaine but was not a randomized controlled trial. This study is referenced in Cowan 1968 as a double-blind randomized study. However, there was no mention of this in the 1964 paper. The summary describes the study as a series of injections

Cowan 1968

Reason for exclusion	The study was not a randomized controlled study

Hassan 2011

Reason for exclusion	The study was not randomized

Kanaa 2009

Reason for exclusion	Although both groups of participants had an identical inferior alveolar nerve block initially, an additional buccal infiltration of 4% articaine, 1:100,000 epinephrine was compared with a dummy buccal infiltration

Raab 1990

Reason for exclusion	The study was double-blind but was not randomized

Shruthi 2013

Reason for exclusion	The study was referred to as a randomized clinical trial by the study authors. However, the abstract states, "This study was done on 50 subjects; 25 of them received 4% articaine HCl with 1:100,000 epinephrine, and the next 25 received 2% lignocaine HCl with 1:100,000 epinephrine", which implies that randomization of participants into each local anaesthetic group did not occur. The study fails to mention that participants, personnel, and assessors were blinded and does not describe the method of injection used, although this is likely to be IANB and BI. The author of the study was emailed for clarification, but no contact could be made

Footnotes

BI = buccal infiltration; IANB = inferior alveolar nerve block.

Characteristics of studies awaiting classification

Chen 2004

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

da Silva-Junior 2017

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Dong 2010

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Ge 2005

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Guo 2014

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

He 2010

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Huang 2011

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Im 2010

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Jin 2005

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Lee 2004

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Li 2005

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Liang 2001

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Liao 2004

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Liu 2010

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Luo 2009

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Manabe 2005

Methods	Randomized controlled simulated scenario trial
Participants	**Location:** university (Japan) **Participants:** 194 fifth grade students who had been recorded from 2002 to 2003
Interventions	Inferior alveolar nerve blocks (1.35 m) of 1 of the following: • 3% mepivacaine, no epinephrine • 2% lidocaine, 1:80,000 epinephrine
Outcomes	Soft tissue anaesthesia: • Success (numbness within 30 minutes) • Onset • Duration Soft tissues tested: tongue, lower lip, and gingiva Post-anaesthetic complications such as pain at the injection site and/or difficulty opening the mouth
Notes	Not yet assessed

Oka 1990

Methods	Randomized controlled clinical and simulated scenario trial, parallel study design
Participants	**Location:** university (Japan) **Participants:** not yet assessed
Interventions	Injections of 1 of the following: • 2% lidocaine plain • 2% lidocaine, 1:80,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine • 2% lidocaine, 1:300,000 epinephrine • 3% propitocaine, 0.03 IU felypressin
Outcomes	Adequacy of anaesthesia during tooth extraction: • Success • Duration (visual analogue scale and somatosensory evoked potentials) Teeth tested: not stated Influence of each local anaesthetic on haemodynamics, local ischaemias, bleeding was measured
Notes	Not yet assessed

Ouchi 2008

Methods	Randomized controlled simulated scenario trial, parallel study design
Participants	**Location:** university (Japan) **Participants:** 19 healthy volunteers
Interventions	Inferior alveolar nerve blocks (1.6 mL) of 1 of the following: • Prilocaine (concentration?) • Mepivacaine with felypressin (concentration?)
Outcomes	Pulpal anaesthesia (tested using an electric pulp tester): • Success • Onset • Duration Teeth tested: lateral incisors, premolars, and molars Soft tissue anaesthesia • Success (anaesthesia in less than 20 minutes) Soft tissues tested: lower lip Adverse events • Degree of discomfort associated with inferior alveolar nerve blocks
Notes	Not yet assessed

Qiu 2007

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Qiu 2011

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Shi 2002

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Shimada 2002

Methods	Randomized controlled simulated scenario trial, parallel study design, carried out at 7 sites
Participants	**Location:** university (Japan) **Participants:** 231
Interventions	Infiltration and block anaesthesia of 1 of the following: • 3% mepivacaine plain, no epinephrine • 2% lidocaine, 1:80,000 epinephrine
Outcomes	Outcomes reported: • Success • "Clinical availability" (combination of success rate and safety rate including duration of numbness) Teeth tested: not stated Soft tissue anaesthesia • Duration. Soft tissues tested: not stated Local and systemic adverse reactions were measured
Notes	Not yet assessed

Wang 2009

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Wu 2005

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Xie 2008

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Xing 2005

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Xu 1991

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Xu 2008

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Xu 2013

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Xuan 2007

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Zhang 2005

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Zhang 2009

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Zhou 2011

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Zhou 2013

Methods	Not yet assessed
Participants	Not yet assessed
Interventions	Not yet assessed
Outcomes	Not yet assessed
Notes	Not yet assessed

Footnotes

Characteristics of ongoing studies

Caicedo 1996

Study name	Evaluation of Three Anesthetic Solutions Using Two Local Anesthesia Techniques
Methods	Randomized controlled double-blind simulated scenario cross-over study?
Participants	30
Interventions	Akinosi and alveolar mandibular conventional blockade technique (AMCB) of 1 of the following: • 2% mepivacaine, 1:20,000 levonordefrin • 4% prilocaine, 1:200,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine
Outcomes	• Success (efficacy)? • Duration? Soft tissue anaesthesia • Onset (subjective sensation of numbness) Soft tissues tested: lip and tongue Pulpal anaesthesia • Onset (tested with ethyl chloride) Teeth tested: not determined
Starting date	Not determined
Contact information	Ricardo Caicedo (ri.caicedo@louisville.edu)
Notes	Available only as an abstract; unpublished as a full paper. Study author has been contacted for details of the trial

Iqbal 2009

Study name	Comparison of Anaesthetic Efficacy of Articaine and Lidocaine for Inferior Alveolar Nerve Blocks With Buccal Infiltration in Patients With Irreversible Pulpitis
Methods	Randomized double-blinded parallel clinical study
Participants	31 emergency patients
Interventions	1.8 mL of 4% articaine, 1:100,000 epinephrine and 1.8 mL of 2% lidocaine, 1:100,000 epinephrine were given in 1 of the following combinations: • Articaine inferior alveolar nerve block and articaine infiltration • Lidocaine inferior alveolar nerve block and lidocaine infiltration • Lidocaine inferior alveolar nerve block and articaine infiltration
Outcomes	Anaesthetic success (ability to access and instrument the root canal without pain - VAS score of zero) Patients who reported inadequate lip and tongue numbness and/or painful response to Endo Ice were excluded from the study Teeth tested: mandibular molars with irreversible pulpitis
Starting date	Not determined
Contact information	First study author deceased
Notes	An attempt will be made to contact one of the other study authors

Sheikh 2014

Study name	Preliminary Comparison of Missed Blocks With 4% Articaine and 2% Lidocaine Both With 1:100,000 Epinephrine on Inferior Alveolar Nerve Block Injections
Methods	Double-blind randomized controlled clinical trial
Participants	Not reported
Interventions	Inferior alveolar nerve blocks using a conventional approach of: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine
Outcomes	Soft tissue anaesthetic success • Subjective anaesthesia: participants were asked if their lower lip feels swollen • No pain from a 25-gauge needle inserted into the alveolar mucosa just inferior to the gingiva and anterior to the cuspid region puncturing periosteum Soft tissues tested: lower lip and alveolar mucosa
Starting date	Not determined
Contact information	Not determined
Notes	An attempt will be made to contact study authors

Footnotes

AMCB = alveolar mandibular conventional blockade; VAS = visual analogue scale.

Summary of findings tables

1 4% articaine, 1:100,000 epinephrine compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia

4% articaine, 1:100,000 epinephrine compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia

Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested
Settings: university departments in Brazil (n = 2), India (n = 1), and USA (n = 4)
Intervention: 4% articaine, 1:100,000 epinephrine
Comparison: 2% lidocaine, 1:100,000 epinephrine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	2% lidocaine, 1:100,000 epinephrine	4% articaine, 1:100,000 epinephrine				
Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of diseased pulps with irreversible pulpitis) Absence of pain ('0' on a visual or verbal analogue scale. Scales of 0-3, 0-4, 0-10, and Heft-Parker VAS) Follow-up: from 10 minutes post injection to end of the clinical procedure	**Moderate** [a] **309 per 1000**	**494 per 1000** (340 to 717)	**RR 1.6** (1.1 to 2.32)	203 participants, 203 interventions (4 studies)	⊕⊕⊖⊖ **low** [b,c]	Duration of follow-up not reported (estimated to be < 1 hour)
Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) Heft-Parker VAS (0-170 millimetres) Follow-up: 0-1 minute following needle insertion	Mean pain on injection in the lidocaine group was **34.92 mm**	Mean pain on injection in the articaine group was **4.74 mm higher** (1.98 mm lower to 11.46 mm higher)		157 participants, 314 interventions (3 studies)	⊕⊕⊕⊖ **moderate** [c]	
Adverse effects: pain following injection Heft-Parker VAS (0-170 millimetres) Follow-up: measured at the time anaesthesia wore off	Mean pain following injection in the lidocaine group was **18.54 mm**	Mean pain following injection in the articaine group was **6.41 mm higher** (1.01 mm to 11.8 mm higher).		156 participants, 309 interventions (3 studies)	⊕⊕⊕⊖ **moderate** [c]	Exact times of follow-up not reported
Adverse effects: paraesthesia following injection Number of participants Follow-up: not applicable	Not measured					

Adverse effects: allergy to local anaesthetic Number of participants Follow-up: not applicable	Not measured

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI = confidence interval; RR = risk ratio; VAS = visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to study limitations (unclear risks of selection and detection bias).
[c]Downgraded one level owing to imprecision (small total sample size).

2 3% prilocaine, 0.03 IU felypressin compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia

3% prilocaine, 0.03 IU felypressin compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia

Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested
Settings: university departments in Germany
Intervention: 3% prilocaine, 0.03 IU felypressin
Comparison: 2% lidocaine, 1:100,000 epinephrine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	2% lidocaine, 1:100,000 epinephrine	3% prilocaine, 0.03 IU felypressin				
Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues) Absence of pain Follow-up: not reported	**Moderate** [a]		**RR 0.86** (0.79 to 0.95)	907 participants, 907 interventions (2 studies)	⊕⊕⊕⊖ **moderate** [b]	Duration of follow-up not reported (estimated to be < 2 hours)
	763 per 1000	**656 per 1000** (603 to 725)				
Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) VAS Follow-up: not applicable	Not measured					

Adverse effects: pain following injection VAS Follow-up: not applicable	Not measured
Adverse effects: paraesthesia following injection Number of participants Follow-up: not applicable	Not measured
Adverse effects: allergy to local anaesthetic Number of participants Follow-up: not applicable	Not measured
*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI) CI = confidence interval; RR = risk ratio; VAS = visual analogue scale	
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate	

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to study limitations (unclear risk of attrition bias in one study, and both trials have unclear methods of randomization sequence generation and allocation concealment).

3 4% articaine, 1:200,000 epinephrine compared with 4% articaine, 1:100,000 epinephrine for dental anaesthesia

4% articaine, 1:200,000 epinephrine compared with 4% articaine, 1:100,000 epinephrine for dental anaesthesia						
Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested **Settings:** university departments in Brazil (n = 1), Germany (n = 2), and USA (n = 2; pain on injection/pain following injection and allergy) **Intervention:** 4% articaine, 1:200,000 epinephrine **Comparison:** 4% articaine, 1:100,000 epinephrine						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	4% articaine, 1:100,000 epinephrine	**4% articaine, 1:200,000 epinephrine**				
Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues) Absence of pain Follow-up: from 5 minutes post injection to end of the clinical procedure	**Moderate** [a] **940 per 1000**	**799 per 1000** (667 to 959)	**RR 0.85** (0.71 to 1.02)	930 participants, 930 interventions (3 studies)	⊕⊖⊖⊖ **very low** [b,c,d]	Duration of follow-up not reported (estimated to be < 1 hour)

Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) Heft-Parker VAS (0-170 millimetres) Follow-up: 0-1 minute following needle insertion	See comment	See comment		86 participants, 172 interventions (1 study)	See comment	Orphan study
Adverse effects: pain following injection Heft-Parker VAS (0-170 millimetres) Follow-up: measured at the time anaesthesia wore off	See comment	See comment		86 participants, 172 interventions (1 study)	See comment	Orphan study. Exact time of follow-up not reported
Adverse effects: paraesthesia following injection Number of participants Follow-up: not applicable	Not measured					
Adverse effects: allergy to local anaesthetic Number of participants Follow-up: 0-24 hours	See comment	See comment	Not estimable	63 participants, 187 interventions (1 study)	See comment	1 case of urticaria occurred - unclear which local anaesthetic this occurred with
*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI) CI = confidence interval; RR = risk ratio; VAS = visual analogue scale						
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate						

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to study limitations (unclear risk of attrition bias in one trial; unclear risks of selection bias in two trials).
[c]Downgraded one level owing to inconsistency (substantial, unexplained heterogeneity).
[d]Downgraded one level owing to imprecision (95% CI includes no effect and an appreciable benefit for 4% articaine, 1:100,000 epinephrine)

4 4% prilocaine plain compared with 2% lidocaine 1:100, 000 epinephrine for dental anaesthesia

4% prilocaine plain compared with 2% lidocaine 1:100, 000 epinephrine for dental anaesthesia
Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested **Settings:** private practice and a hospital setting in USA **Intervention:** 4% prilocaine plain **Comparison:** 2% lidocaine 1:100, 000 epinephrine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	2% lidocaine 1:100, 000 epinephrine	4% prilocaine plain				
Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues) Absence of pain ("complete anaesthesia") Follow-up: 5-30 minutes	**Moderate** [a]		**RR 0.86** (0.75 to 0.99)	228 participants, 228 interventions (2 studies)	⊕⊕⊖⊖ **low** [b,c]	Duration of follow-up reported only for bone study
	828 per 1000	**712 per 1000** (621 to 820)				
Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) VAS Follow-up: See comment	Not measured					
Adverse effects: pain following injection VAS Follow-up: not applicable	Not measured					
Adverse effects: paraesthesia following injection Number of participants Follow-up: See comment	See comment	1 case of prolonged anaesthesia recorded	Not estimable	0 participants (0 studies)	See comment	No clinical studies met outcome definition Unable to confirm if prolonged anaesthesia = paraesthesia and how long this lasted
Adverse effects: allergy to local anaesthetic Number of participants Follow-up: not applicable	Not measured					

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI = confidence interval; RR = risk ratio; VAS = visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to study limitations (unclear methods of randomization sequence generation and allocation concealment).
[c]Downgraded one level owing to imprecision (small total sample size).

5 4% articaine, 1:200,000 epinephrine compared with 0.5% bupivacaine, 1:200,000 epinephrine for dental anaesthesia

4% articaine, 1:200,000 epinephrine compared with 0.5% bupivacaine, 1:200,000 epinephrine for dental anaesthesia

Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies where dental local anaesthesia was tested
Settings: university departments in Spain (n = 2) and USA (n = 1; pain on injection)
Intervention: 4% articaine, 1:200,000 epinephrine
Comparison: 0.5% bupivacaine, 1:200,000 epinephrine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	0.5% bupivacaine, 1:200,000 epinephrine	4% articaine, 1:200,000 epinephrine				
Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues) Absence of pain Follow-up: from 10 minutes post injection to the end of the clinical procedure	Moderate [a]		**OR 0.87** (0.27 to 2.83)	37 participants, 74 interventions (2 studies)	⊕⊕⊖⊖ **low** [b,c]	Duration of follow-up not reported for both studies (estimated to be < 1 hour)
	481 per 1000	**446 per 1000** (200 to 724)				
Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) VAS. scale of 0-100 Follow-up: 0-30 seconds following needle insertion	See comment	See comment		18 participants, 36 interventions (1 study)	See comment	Orphan study. Unclear whether data relate to just solution deposition. Standand deviations not reported

Adverse effects: pain following injection VAS Follow-up: not applicable	Not measured
Adverse effects: paraesthesia following injection Number of participants Follow-up: not applicable	Not measured
Adverse effects: allergy to local anaesthetic Number of participants Follow-up: not applicable	Not measured
*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI) CI = confidence interval; OR = odds ratio; VAS = visual analogue scale	
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate	

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to study limitations (trials had unclear or high risk of bias related to methods of randomization sequence generation and allocation concealment, and one study had high risk of bias for blinding of participants and personnel and incomplete outcome data (high attrition rate of 46%)).
[c]Downgraded one level owing to imprecision (small total sample size, and 95% confidence interval includes no effect and an appreciable benefit for both solutions).

6 0.5% bupivacaine, 1:200,000 epinephrine compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia

0.5% bupivacaine, 1:200,000 epinephrine compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia						
Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested **Settings:** university departments in Australia (n = 1) and USA (n = 3, including speed of onset (1) and pain on injection (1)) **Intervention:** 0.5% bupivacaine, 1:200,000 epinephrine **Comparison:** 2% lidocaine, 1:100,000 epinephrine						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	2% lidocaine, 1:100,000 epinephrine	**0.5% bupivacaine, 1:200,000 epinephrine**				

Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (clinical testing of healthy pulps, hard and soft tissues) Absence of pain Follow-up: from 10 minutes post injection to the end of the clinical procedure	**Moderate** [a] **611 per 1000**	**477 per 1000** (99 to 889)	**OR 0.58** (0.07 to 5.12)	31 participants, 62 interventions (2 studies)	⊕⊕⊖⊖ **low** [b,c]	Duration of follow-up not reported for both studies (estimated to be < 1 hour)
Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: See comment	See comment	See comment	Not estimable	100 participants, 100 interventions (1 study)	See comment	Orphan study. Duration of follow-up not reported
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) VAS. scale of 0-100 Follow-up: 0-30 seconds following needle insertion	See comment	See comment		18 participants, 36 interventions (1 studies)	See comment	Orphan study. Unclear whether data relate to just solution deposition. Standand deviations not reported
Adverse effects: pain following injection VAS Follow-up: not applicable	Not measured					
Adverse effects: paraesthesia following injection Number of participants Follow-up: not applicable	Not measured					
Adverse effects: allergy to local anaesthetic Number of participants Follow-up: not applicable	Not measured					

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI = confidence interval; OR = odds ratio; VAS = visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to study limitations (unclear methods of randomization sequence generation).
[c]Downgraded one level owing to imprecision (small total sample size, and 95% confidence interval includes no effect and an appreciable benefit for both solutions).

7 4% articaine, 1:100,000 epinephrine compared with 2% mepivacaine, 1:100,000 epinephrine for dental

anaesthesia

4% articaine, 1:100,000 epinephrine compared with 2% mepivacaine, 1:100,000 epinephrine for dental anaesthesia

Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested
Settings: university departments in Brazil (n = 1), Saudi Arabia (n = 1), and Thailand (n = 1)
Intervention: 4% articaine, 1:100,000 epinephrine
Comparison: 2% mepivacaine, 1:100,000 epinephrine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	2% mepivacaine, 1:100,000 epinephrine	4% articaine, 1:100,000 epinephrine				
Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues) Absence of pain Follow-up: 10-20 minutes	**Moderate** [a]		**OR 3.82** (0.61 to 23.82)	110 participants, 130 interventions (2 studies)	⊕⊕⊖⊖ **low** [b,c]	
	931 per 1000	**996 per 1000** (912 to 1000)				
Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) VAS. scale of 0-100 Follow-up: 0-40 seconds and 0-60 seconds following needle insertion	See comment	See comment		147 participants, 147 interventions (2 studies)	See comment	Unclear whether data relate to just solution deposition in both studies
Adverse effects: pain following injection VAS Follow-up: not applicable	Not measured					
Adverse effects: paraesthesia following injection Number of participants Follow-up: not applicable	Not measured					
Adverse effects: allergy to local anaesthetic Number of participants Follow-up: not applicable	Not measured					

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI = confidence interval; RR = risk ratio; VAS = visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to study limitations (unclear risks of bias (methods of randomization sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors)).
[c]Downgraded one level owing to imprecision (small total sample size).

8 2% mepivacaine, 1:100,000 epinephrine compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia

2% mepivacaine, 1:100,000 epinephrine compared with 2% lidocaine, 1:100,000 epinephrine for dental anaesthesia

Patient or population: participants regardless of age and gender who were undergoing dental procedures and volunteers who took part in simulated scenario studies in which dental local anaesthesia was tested
Settings: university departments in Brazil (n = 2) and Saudi Arabia (n = 1)
Intervention: 2% mepivacaine, 1:100,000 epinephrine
Comparison: 2% lidocaine, 1:100,000 epinephrine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	2% lidocaine, 1:100,000 epinephrine	2% mepivacaine, 1:100,000 epinephrine				
Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of diseased pulps with irreversible pulpitis) Absence of pain Follow-up: from 10 minutes or 14 minutes post injection to the end of the clinical procedure	**Moderate** [a] **231 per 1000**	**268 per 1000** (58 to 1000)	**RR 1.16** (0.25 to 5.45)	68 participants, 68 interventions (2 studies)	⊕⊕⊖⊖ **low** [b,c]	Duration of follow-up not reported (estimated to be < 1 hour)
Speed of onset of anaesthesia Time from injection to complete anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Duration of anaesthesia Time from onset of anaesthesia to loss of anaesthesia, measured in minutes Follow-up: not applicable	Not measured					
Adverse effects: pain on injection (solution deposition) VAS. scale of 0-100 Follow-up: 0-1 minute following needle insertion	See comment	See comment		48 participants, 48 interventions (1 study)	See comment	Orphan study. Unclear whether data relate to just solution deposition
Adverse effects: pain following injection VAS Follow-up: not applicable	Not measured					

Adverse effects: paraesthesia following injection Number of participants Follow-up: not applicable	Not measured
Adverse effects: allergy to local anaesthetic Number of participants Follow-up: not applicable	Not measured
*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI) CI = confidence interval; RR = risk ratio; VAS = visual analogue scale	
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low quality:** We are very uncertain about the estimate	

Footnotes

[a]Little variation in baseline risks across studies.
[b]Downgraded one level owing to inconsistency (wide variation in point estimates and substantial unexplained heterogeneity).
[c]Downgraded one level owing to imprecision (small total sample size, and 95% CI includes no effect and an appreciable benefit for both solutions).

Additional tables

1 Pulp anaesthesia onset (time in minutes)

Study	Local anaesthetic solution	Jaw/Tooth	Onset	Standard deviation
Abdulwahab 2009	BI (0.9 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 4% prilocaine, 1:200,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 0.5% bupivacaine, 1:200,000 epinephrine	Mandibular first molars	8 10 14 12 11 9	*
Batista da Silva 2010	Mental/incisive nerve block (0.6 mL) of: • 2% lidocaine, 1:100,000 adrenaline • 4% articaine, 1:100,000 epinephrine	Mandibular canines Mandibular first premolars Mandibular second premolars	8** 5** 4** 4** 3** 2**	5-9*** 4-6*** 2-6*** 2-4*** 2-4.5*** 2-4***

Burns 2004	Palatal-anterior superior alveolar injection (1.4 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Maxillary central incisors, lateral incisors, and canines	Insufficient numbers for matched pair comparison. Onset for central incisors was within 4-8 minutes for both anaesthetic solutions	*
Caldas 2015	Maxillary BI (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Right maxillary canines	1.29 1.10	± 1.90## ± 1.47##
Costa 2005	Maxillary BI (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Maxillary posterior teeth	2.8 1.4 1.6	*
Donaldson 1987	Standard IANB (1.8 mL) or maxillary BI (0.6 mL) of: • 4% articaine, 1:200,000 epinephrine • 4% prilocaine, 1:200,000 epinephrine	Not stated	Inf' = 1.49 IANB = 1.37 Inf' = 1.35 IANB = 1.66	± 0.83 ± 0.80 ± 0.82 ± 1.13
Forloine 2010	High-tuberosity maxillary second division nerve blocks (4.0 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Mandibular first molars	2.5 2.3	*
Gazal 2015	IANB (1.8 mL) of 2% mepivacaine, 1:100,000 epinephrine, followed by BI (1.8 mL) of 1 of the following solutions: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Mandibular first molars	4.26 2.78	± 1.94 ± 1.00
Gazal 2017	Maxillary BI (1.4 mL) and PI (0.4 mL) using the following: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Various maxillary teeth	3.37 1.96	± 3.05 ± 1.93
Hinkley 1991	IANB (1.8 mL) of: • 4% prilocaine with 1:200,000 epinephrine • 2% mepivacaine with 1:20,000 levonordefrin • 2% lidocaine with 1:100,000 epinephrine	Lateral incisors First premolars Mandibular first molars	16.3 11.0 12.3 10.1 11.7 10.6 10 9.6 8.8	± 3.2† ± 2.0† ± 1.9† ± 1.7† ± 2.3† ± 1.6† ± 2.2† ± 1.9† ± 1.8†

Jaber 2010	BI (0.9 mL) of: • 4% articaine with 1:100,000 epinephrine • 2% lidocaine with 1:100,000 epinephrine	Mandibular central incisors	3.3 3.4	2-14††† 2-6†††
Kammerer 2014	BI (1.7 mL) of: • 4% articaine with no vasoconstrictor • 4% articaine with 1:100,000 epinephrine • 4% articaine with 1:200,000 epinephrine • 4% articaine with 1:400,000 epinephrine	Maxillary central incisors	6.5 5.0 4.7 5.3	± 1.5 ± 3.2 ± 2.6 ± 2.3
Kanaa 2012;	BI (2.0 mL) of: • 4% articaine with 1:100,000 epinephrine • 2% lidocaine with 1:80,000 epinephrine	Maxillary teeth	4.9 5.1	± 2.7 ± 2.4
Katz 2010;	BI (1.8 mL) of: • 4% prilocaine, 1:200,000 epinephrine • 4% prilocaine, no vasoconstrictor	Maxillary lateral incisors Maxillary first molars	2.3 1.8 3.5 3.9	± 2.9 ± 1.5 ± 2.2 ± 2.3
Knoll-Kohler 1992a;	BI (0.5 mL) of: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Right maxillary incisors	3.5 3.9 5.1	± 2.37† ± 2.23† ± 1.95†
Kramer 1958	Maxillary and mandibular injections of 1 or more cartridges of: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Not stated	Mand' < 5 minutes = 57.3% > 5 minutes = 42.7% Max' < 5 minutes = 60% > 5 minutes = 40% Mand' < 5 minutes = 36% > 5 minutes = 64% Max' < 5 minutes = 49.2% > 5 minutes = 50.8%	*
Maruthingal 2015	Mandibular BI (1.7 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Mandibular first molars	10.352 6.928	± 4.54 ± 3.463

McEntire 2011	Mandibular BI (1.8 mL) of: • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Mandibular first molars	4.7 4.6	± 3.3# ± 3.3#
McLean 1993	IANB (1.8 mL) of: • 4% prilocaine, no vasoconstrictor • 3% mepivacaine, no vasoconstrictor	Mandibular lateral incisors Mandibular first premolars Mandibular first molars	12.3 14.6 13.7 10.0 11.0 8.2	± 2.4† ± 3.3† ± 2.2† ± 1.7† ± 2.2† ± 2.0†
Mumford 1961	Infiltration (1.0 mL) and regional injection (1.5 mL) of: • 2% lidocaine with 1:80,000 epinephrine • 3% mepivacaine with no epinephrine • 2% mepivacaine with 1:80,000 epinephrine	Various teeth	Inf' 2.75†† Regional 3.5†† Inf' 3.00†† Regional 3.25†† Inf' 2.75†† Regional 4.25††	*
Nordenram 1990;	BI (0.6 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor; 3% prilocaine, 0.03 IU/mL felypressin	Maxillary anterior teeth	(Young and elderly combined) < 2 minutes = 23/38 > 2 minutes = 15/38 < 2 minutes = 21/34 > 2 minutes = 13/34 < 2 minutes = 25/34 >2 minutes = 9/34	*
Oliveira 2004;	Maxillary infiltration, buccally (1.8 mL) and palatally (0.35 mL) of: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Right maxillary canines	1.0** 3.0**	1.0–13.0††† 1.0–7.0†††
Vahatalo 1993;	BI (0.6 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Maxillary lateral incisors	3.35 3.12	± 1.47 ± 1.1
Vreeland 1989;	IANBs of: • 2% lidocaine, 1:100,000 epinephrine (1.8 mL) • 2% lidocaine, 1:200,000 epinephrine (3.6 mL)	Mandibular lateral incisors Mandibular canines Mandibular first molars	13.20 8.63 13.60 7.43 8.44 7.12	± 2.35# ± 2.25# ± 2.79# ± 1.05# ± 1.85# ± 1.87#

Footnotes

* Not available; ** median; *** lower-upper quartiles; † standard error; †† clinical anaesthesia (no pain at start of procedure (onset) or throughout the procedure); ††† range; # author unsure whether measurement is standard error or standard deviation; ## unsure whether measurement is standard error or standard deviation.

BI = buccal infiltration; IANB = Inferior alveolar nerve block; Inf' = infiltration injection; Mand' = mandibular; Max' = maxillary; PI = palatal infiltration.

2 Soft tissue anaesthesia onset (time in minutes)

Study	Local anaesthetic solution	Soft tissues tested	Onset (mean)	Standard deviation
Abdulwahab 2009	BI (0.9 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 4% prilocaine, 1:200,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 0.5% bupivacaine, 1:200,000 epinephrine	Soft tissues adjacent to mandibular first molars	Occurred between 7 and 15 minutes after injection for the 6 formulations (individual data not available)	*
Albertson 1963	Injections (type and volume not specified) of: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin	Method not stated	1.25 0.97	2.48 1.58
Batista da Silva 2010	Mental/incisive nerve blocks (0.6 mL) of: • 2% lidocaine, 1:100,000 adrenaline • 4% articaine, 1:100,000 epinephrine	Lower lip	2** 2**	*
Bradley 1969	Infiltration and “mandibular” injection (0.8-3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Tissues of upper and lower jaws (exact tissues and method of measurement not stated)	Inf' = 0.83** Mand' = 0.67** Inf' = 1.08** Mand' = 0.75**	0.17-3.83 †††† 0.17-3.00†††† 0.25-4 †††† 0.083-4.17 ††††
Chapman 1988;	IANB (2.0 mL) and BI (1.0 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Lower lip	2 2	*
Chilton 1971;	IANB (1.8 mL) and infiltration (1.5 mL) of: • 4% prilocaine, 1:200,000 epinephrine • 4% prilocaine, with no epinephrine	Maxillary and mandibular soft tissues	Inf' = 0.9 IANB = 1.4 Inf' = 0.9 IANB = 1.8	± 0.6 ± 0.9 ± 0.5 ± 1.8
Colombini 2006	IANB (1.8 mL) and BI (0.9 mL) of: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lower lip, tongue, and mucosa	2.50 2.50	± 0.13† ± 0.24†

Gazal 2017	Maxillary BI (1.4 mL) and PI (0.4 mL) using the following: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Soft tissues adjacent to various maxillary teeth	Buccal 1.74 1.05 Palatal 0.90 minutes 0.52 minutes	 ± 2.14 ± 1.68 ± 0.96 ± 0.20
Gangarosa 1967	Mandibular block and infiltration (volume not stated) of: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine plain	Not stated	Within 2 minutes = 38/100†† 5 or more minutes = 62/100†† Within 2 minutes = 50/100†† 5 or more minutes = 50/100††	*
Hersh 1995	IANB (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor • 3% mepivacaine, no vasoconstrictor	Lower lip and tongue	Within 5 minutes Within 5 minutes Within 5 minutes	*
Hinkley 1991	IANB (1.8 mL) of: • 4% prilocaine, 1:200,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin • 2% lidocaine, 1:100,000 epinephrine	Lower lip, tongue, and mucosa Mucosal probing	6.3 5.3 6.1 10.8 9.1 10.6	± 1.1† ± 0.8† ± 0.8† ± 1.8† ± 1.6† ± 1.9†
Jain 2016	IANB and BI (1.7 mL in total) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Inferior lip, corresponding half of the tongue, and buccal mucosa Measured subjectively and objectively (methods not detailed) but only 1 outcome presented in the journal article	1.47 0.94	± 0.22 ± 0.16
Kammerer 2012	IANB and BI (up to 2.2 mL) of: • 4% articaine, 1:100,000 epinephrine • 4% articaine, no vasoconstrictor	Vestibular mucosa and oral gingivae	7.2 9.2	± 2.97 ± 2.7
Karm 2017	IANB and BI (1.8 mL in total) of: • 2% lidocaine, 1:80,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Lower lip, corresponding half of tongue and mucosa	4.9 5.2	± 4.1 ± 4.1
Lasemi 2015	IANB (volume not stated) of: • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Lower lip	1.4 2.0	± 0.42## ± 0.45##

Maruthingal 2015	Mandibular BI (1.7 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lip and lingual mucosa	4.937 3.562	± 1.366 ± 1.664
McLean 1993	IANB (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor • 3% mepivacaine, no vasoconstrictor	Lower lip, tongue, and adjacent soft tissues Mucosal sticks	5.0 5.0 4.5 7.8 10.7 8.4	± 0.65† ± 0.55† ± 0.61† ± 1.49† ± 1.52† ± 1.92†
Nespeca 1976	Various types of injections (1.5-2.0 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Various soft tissues	2.40†† 4.48††	± 0.16† ± 0.28†
Odabas 2012	Maxillary BI (1.8 mL) of: • 4% articaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine	Upper lip	1 1	± 0.00 ± 0.15
Pellicer-Chover 2013	IANB (1.8 mL) and BI (1.8 mL) of: • 0.5% bupivacaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lower lip and tongue	3.1 2	± 1.5 ± 1.4
Ram 2006	IANB and maxillary infiltration (up to 1 cartridge) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Maxillary and mandibular soft tissues	Immediate (< 2 minutes) in > 80% of cases with either solution	*
Sadove 1962	Various types of dental blocks and infiltrations (volume not stated) of: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin	Various soft tissues	2.03 1.79	0.13† 0.09†
Sancho-Puchades 2012	IANB (1.8 mL) of: • 4% articaine with 1:200,000 epinephrine • 0.5% bupivacaine with 1:200,000 epinephrine	Lower lip and tongue	1.9 1.8	±1.2 ±1.2
Santos 2007	IANB (1.8 mL) and BI (0.9 mL) of: • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Lower lip, tongue, and mucosa	1.64 1.58	± 0.08† ± 0.08†

Sherman 1954	Mandibular and maxillary injections (1.1-2.2 mL) of: • 2% lidocaine, 1:50,000 adrenaline • 2% lidocaine, 1:100,000 adrenaline	Maxillary and mandibular soft tissues	Inf' = 1** Block = 2** Inf' = 1** Block = 2**	*
Sierra Rebolledo 2007	IANB (1.8 mL) and BI (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lower lip	1.25 0.93	± 0.23 ± 0.16
Stibbs 1964	"Mandibular" injection and "infiltration" (varying volumes) of: • 2% lidocaine, 1:50,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin	Maxillary and mandibular soft tissues	Mand' 1.74 Inf' 1.23 Other 1.51 Mand' 1.86 Inf' 1.25 Other 1.48	± 0.15† ± 0.13† ± 0.17† ± 0.15† ± 0.16† ± 0.24†
Thakare 2014	BI (1.4 mL) of: • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Maxillary soft tissues?	0.71 1.0	± 0.28 ± 0.44
Trieger 1979	IANB and BI (varying volumes) of: • 0.5% bupivacaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine	Tissues adjacent to extraction site	8.1 6.5	< 5-15††† < 5-10†††
Vilchez-Perez 2012	BI (0.9 mL) of: • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Upper lip	85 before withdrawal of the needle 10% < 0.5 5% > 0.5 80% volunteers before withdrawal of the needle 10% < 30 seconds 10% > 30 seconds	*
Vreeland 1989	IANB of: • 2% lidocaine with 1:100,000 epinephrine (1.8 mL) • 2% lidocaine with 1:200,000 epinephrine (3.6 mL)	Lower lip and tongue (subjective) Labial and lingual to the test canine and buccal to the test molar (alveolar mucosal sticks)	8.80 6.70 6.23 4.47	± 1.290# ± 0.757# ± 0.748# ± 0.722#
Wali 2010	IANB (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:50,000 epinephrine	Lower lip	4.4 5.9	± 0.4† ± 0.5†

Weil 1961	Infiltration and "mandibular" injection (1 or more cartridges) of: • 3% mepivacaine, no vasoconstrictor • 2% mepivacaine, 1:20,000 levonordefrin	Maxillary and mandibular soft tissues	Inf' 0.83 Mand' 1.4 Inf' 0.7 Mand' 1.07	± 0.06 ± 0.12 ± 0.09 ± 0.15

Footnotes

* Not available; ** median; † standard error; †† clinical anaesthesia (no pain at start of procedure (onset) or throughout the procedure); ††† range; †††† 90% range; # author unsure whether measurement is standard error or standard deviation; ## unsure whether measurement is standard error or standard deviation.

BI = buccal infiltration; IANB = inferior alveolar nerve block; Inf' = infiltration injection; Mand' = mandibular injection; PI = palatal infiltration.

3 Pulp anaesthesia duration (time in minutes)

Study	Local anaesthetic solution	Jaw/Tooth	Duration	Standard deviation
Batista da Silva 2010	Incisive/mental nerve block (0.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Mandibular canines Mandibular first premolars Mandibular second premolars	10** 10** 10** 20** 10** 20**	10 - 20*** 10 - 20*** 10 - 20*** 10 - 30*** 10 - 20*** 10 - 32.5***
Caldas 2015	Maxillary BI (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Right maxillary canines	41.61 41.03	± 14.16## ± 17.79##
Costa 2005	Maxillary BI (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Maxillary posterior teeth	39.2 66.3 56.7	*
Donaldson 1987	IANB (1.8 mL) or maxillary BI (0.6 mL) of: • 4% articaine, 1:200,000 epinephrine • 4% prilocaine, 1:200,000 epinephrine	Not stated	Data presented in life tables; therefore cannot be used	*
Fernandez 2005	IANB (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Lateral incisors First premolars Second premolars First molars Second molars	127 244 154 256 152 258 138 232 148 232	± 8.1† ± 18† ± 5.9† ± 15.8† ± 6.0† ± 15.5† ± 8.1† ± 16.6† ± 6.4† ± 16.3†
Gazal 2015	IANB (1.8 mL) of 2% mepivacaine, 1:100,000 epinephrine, followed by BI (1.8 mL) of 1 of the following solutions: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Mandibular first molars	40.74 42.22	± 1.94 ± 1.00

Kammerer 2014	BI (1.7 mL) of: • 4% articaine, no vasoconstrictor • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:400,000 epinephrine	Maxillary central incisors	14.75 77.6 54.8 35.9	± 5.8 ± 30.1 ± 17.5 ± 15.1
Knoll-Kohler 1992a;	BI (0.5 mL) of: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Right maxillary incisors	78.6 61.7 26.5	± 24.95† ± 15.72† ± 18.31†
Mumford 1961;	Infiltration (1.0 mL) and regional injection (1.5 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no epinephrine • 2% mepivacaine, 1:80,000 epinephrine	Various teeth	Inf' 31†† Regional 34†† Inf' 20†† Regional 33†† Inf' 32†† Regional 40††	*
Nordenram 1990;	BI (0.6 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 3% prilocaine, 0.03 IU/ml felypressin	Maxillary anterior teeth	Elderly = 59.3 Young = 44.8 Elderly = 26.6 Young = 17.5 Elderly = 43.2 Young = 24.8	± 34.3 ± 18.7 ± 13.3 ± 6.1 ± 29.2 ± 11.8
Oliveira 2004;	BI (1.8 mL) and PI (0.35) of: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Right maxillary canines	67.0** 46.5**	27.0–117.0††† 25.0–107.0†††
Vahatalo 1993;	BI (0.6 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Maxillary lateral incisors	23.8 24.5	± 8.6 ± 10.0
Weil 1961	Infiltration and mandibular injection (1 or more cartridges) of: • 3% mepivacaine, no vasoconstrictor • 2% mepivacaine, 1:20,000 levonordefrin	Various teeth	Inf ' 41.71†† Mand' 40.00†† Inf' 76.33†† Mand' 45.00††	± 4.11 ± 7.45 ± 6.77 ± 12.22

Footnotes

* Not available; ** median; *** lower-upper quartiles; † standard error; †† clinical anaesthesia (no pain at start of procedure (onset) or throughout procedure); ††† range.

BI = buccal infiltration; IANB = inferior alveolar nerve block; Inf' = infiltration injection; Mand' = mandibular; PI = palatal infiltration.

4 Soft tissue anaesthesia duration (time in minutes)

Study	Local anaesthetic solution	Jaw/Tooth	Duration	Standard deviation
Batista da Silva 2010	Mental/Incisive nerve block (0.6 mL) of: • 2% lidocaine, 1:100,000 adrenaline • 4% articaine, 1:100,000 epinephrine	Lower lip	156** 165**	135.5-184.25*** 145.75-198.5***

Bortoluzzi 2009	BI (0.18 mL) of: • 4% articaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine	Lower lip	111.3 104.5	± 26 ± 26.7
Bradley 1969	Infiltration and “mandibular” injection (0.8-3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Upper and lower jaws (1.8 mL)	Inf' = 139** IANB = 178** Inf' = 96** IANB = 182**	37-254††† 64-294††† 23-238††† 127-277†††
Caldas 2015	Maxillary BI (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Vestibular mucosa	148.06 137.93	± 58.10# ± 70.67#
Chapman 1988;	IANB (2.0 mL) and BI (1.0 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Mental region	216 510	± 36 ± 150
Elbay 2016	IANB (0.9 mL) of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Lower lip and adjacent soft tissues	149.10 139.68	49.08 45.76
Fertig 1968	IANB (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor • 4% prilocaine, 1:200,000 epinephrine	Lower lip	191.5 189.38 206.25	*
Gangarosa 1967	IANB and infiltration (volume not stated) of: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine plain	Maxillary and mandibular soft tissues	169 144	*
Hellden 1974	IANB (1.8 mL) and local infiltration (1.8 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 3.0% mepivacaine, no vasoconstrictor	Lower lip and adjacent soft tissues	185 152	± 3.5† ± 5.3†
Hersh 1995	IANB (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor • 3% mepivacaine, no vasoconstrictor	Lower lip and tongue	Exact figures not given	*

Jain 2016	IANB and BI (1.7 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Inferior lip, corresponding half of the tongue, and buccal mucosa Only postoperative duration measured	174.80 231	± 37.62 ± 57.15
Kalia 2011	IANB, IANB and BI, IONB and greater palatine nerve block (volume not stated) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lip, buccal mucosa, tongue, and palate Only postoperative duration measured	161.13 232.99	± 27.03 ± 32.44
Kambalimath 2013	IANB and BI (volume not stated) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lower lip and adjacent soft tissues Duration measured only up to when local anaesthetic effect began to fade	175.9 196.8	± 51.7 ± 57.3
Kammerer 2012	IANB and mandibular BI (up to 2.2 mL) of: • 4% articaine with 1:100,000 epinephrine • 4% articaine with no vasoconstrictor	Lower lip, tongue, and mucosa Figures for duration of soft tissue anaesthesia in the journal article are for all participants who may have had 1 or 2 sets of injections. Following communication, study author provided data for participants (70) who had only 1 injection (original data for 1 and 2 injections are given in brackets)	216 (228) 138 (150)	24 (34.2) 44.4 (58.2)
Kammerer 2014	BI (1.7 mL) of: • 4% articaine, no vasoconstrictor • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:400,000 epinephrine	Adjacent soft tissues	60.3 151.7 129.3 104.0	± 24.2 ± 27.6 ± 19.2 ± 22.5
Karm 2017	IANB and BI (1.8 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Lower lip, corresponding half of tongue, and mucosa	183.5 182.2	± 5.0 ± 5.4
Kramer 1958	Mandibular and maxillary injections (1 or more cartridges) of: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Mandibular and maxillary soft tissues	Mand' = 178** Max' = 157** Mand' = 185** Max' = 153**	*
Lasemi 2015	IANB (volume not stated) of: • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Lower lip	235.5 230	± 13.32# ± 14.10#
Maniglia-Ferreira 2009	IANB (1 cartridge) of: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Tissues not stated (possibly lower lip)	> 90 > 90	*

Mumford 1961	"Regional" (1.5 mL) and infiltration (1.0 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no epinephrine • 2% mepivacaine, 1:80,000 epinephrine	Maxillary and mandibular soft tissues	Inf' 172.2 Regional 188.4 Inf' 101.4 Regional 156.6 Inf' 116.4 Regional 187.8	*
Naik 2017	IANB (2.0 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lip and associated tissues	184.7 357.8	± 39.10 ± 58.8
Nordenram 1990	Maxillary BI (0.6 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 3% prilocaine, 0.03 IU/mL felypressin	Maxillary soft tissues	Elderly = 168.0 Young = 174.2 Elderly = 102.2 Young = 97.3 Elderly = 167.4 Young = 171.0	± 42.8 ± 53.9 ± 48.9 ± 56.8 ± 77.0 ± 53.7
Odabas 2012	Maxillary BI (1.8 mL) of: • 4% articaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine	Upper lip	140.69 117.52	± 49.76 ± 42.99
Oliveira 2004	BI (1.8 mL) and PI (0.35 mL) of: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Upper lip	238.5** 227.5**	168.0-308.0†† 159.0-273.0††
Pellicer-Chover 2013	IANB (1.8 mL) and BI (1.8 mL) of: • 0.5% bupivacaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lower lip and tongue	316.5 250.3	± 30.1 ± 48.3
Porto 2007	IANB and BI (minimum of 3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine	Lower lip	208.2 222	53.4 57.6

Ram 2006	IANB and maxillary BI (up to 1 cartridge) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Maxillary and mandibular soft tissues	180 206	± 49.2 ± 44.4
Sancho-Puchades 2012	IANB and BI (1.8 mL) of: • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine with 1:200,000 epinephrine	Lower lip and tongue	Lip 289.6 621.2 Tongue 238.1 512.1	± 82.0 ± 148.4 ± 67.9 ± 127.3
Sherman 1954	Mandibular and maxillary injections (1.1-2.2 mL) of: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 adrenaline	Maxillary and mandibular soft tissues	Inf' = 150** Conduction = 195** Inf' = 165** Conduction = 195**	*
Sierra Rebolledo 2007	IANB (1.8 mL) and BI (1.8 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Lower lip	168.20 220.8	± 10.77 ± 13.81
Stibbs 1964	"Mandibular" injection and maxillary/mandibular infiltration (varying volumes) of: • 2% lidocaine, 1:50,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin	Maxillary and mandibular soft tissues	Mand' 205.50 Inf' 177.83 Other 168.21 Mand' 224.48 Inf' 191.79 Other 180.64	Mand' ± 5.08† Inf' ± 7.32† Other ± 7.86† Mand' ± 5.74† Inf' ± 6.31 Other ± 9.27†
Tofoli 2003	IANB (1.8 mL) of: • 4% articaine with 1:100,000 epinephrine • 4% articaine with 1:200,000 epinephrine	Lower lip	264 260	± 37† ± 45†
Weil 1961	Infiltration and mandibular injections (1 or more cartridges) of: • 3% mepivacaine, no vasoconstrictor • 2% mepivacaine, 1:20,000 levonordefrin	Maxillary and mandibular soft tissues	Inf' 132.56 Mand' 193.11 Inf' 184.03 Mand' 255.50	± 10.69 ± 9.14 ± 10.37 ± 9.66

Footnotes

* Not available; ** median; *** lower-upper quartiles; † standard error; †† range; ††† 90% range; # unsure if measurement is standard error or standard deviation.

BI = buccal infiltration; IANB = inferior alveolar nerve block; Inf' = infiltration injection; Mand' = mandibular; Max' = maxillary; PI = palatal infiltration.

5 Orphan studies (success)

Study	Comparison	Outcome	Data
Abdulwahab 2009	Mandibular BI (0.9 mL) of 1 of the following solutions: • 2% lidocaine, 1:100,000 epinephrine vs 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine vs 4% prilocaine, 1:200,000 epinephrine • 4% articaine, 1:200,000 epinephrine vs 3% mepivacaine, no vasoconstrictor • 4% articaine, 1:100,000 epinephrine vs 3% mepivacaine, no vasoconstrictor • 4% articaine, 1:100,000 epinephrine vs 0.5% bupivacaine, 1:200,000 epinephrine • 4% articaine, 1:200,000 epinephrine vs 0.5% bupivacaine, 1:200,000 epinephrine • 4% prilocaine, 1:200,000 epinephrine vs 3% mepivacaine, no vasoconstrictor • 4% prilocaine, 1:200,000 epinephrine vs 0.5% bupivacaine, 1:200,000 epinephrine • 3% mepivacaine, no vasoconstrictor vs 0.5% bupivacaine, 1:200,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	Pulp anaesthesia success (EPT) **4% articaine, 1:100,000 epinephrine** BIs = 7/18 **4% articaine, 1:200,000 epinephrine** BIs = 6/18 **4% prilocaine, 1:200,000 epinephrine** BIs = 4/18 **3% mepivacaine, no vasoconstrictor** BIs = 6/18 **0.5% bupivacaine, 1:200,000 epinephrine** BIs = 2/18
Aggarwal 2009	IANB of 1.8 mL of 2% lidocaine, 1:200,000 epinephrine, followed by 1 of the following: • BI and LI (1.8 mL each) of 4% articaine, 1:200,000 epinephrine • BI and LI (1.8 mL each) of 2% lidocaine, 1:200,000 epinephrine	Success of subjective soft tissue anaesthesia Success of anaesthesia during endodontic access cavity preparation and instrumentation in teeth with irreversible pulpitis	Soft tissue anaesthesia success **4% articaine, 1:200,000 epinephrine** IANB/BI/LIs = 30/31 **2% lidocaine, 1:200,000 epinephrine** IANB/BI/LIs = 30/31 Clinical anaesthetic success **4% articaine, 1:200,000 epinephrine** IANB/BI/LIs = 14/30 **2% lidocaine, 1:200,000 epinephrine** IANB/BI/LIs = 7/30

Aggarwal 2014	IANB using 1.8 mL of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Success of soft tissue anaesthesia Success of pulpal anaesthesia during endodontic access cavity preparation and instrumentation in teeth with irreversible pulpitis	**Soft tissue anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANBs = 30/31 **2% lidocaine, 1:200,000 epinephrine** IANBs = 32/32 **Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANBs = 3/30 **2% lidocaine, 1:200,000 epinephrine** IANBs = 5/32
Aggarwal 2017	IANB using 1.8 mL of 1 of the following: • 2% lidocaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of subjective soft tissue anaesthesia Success of pulpal anaesthesia during endodontic access cavity preparation and instrumentation in teeth with irreversible pulpitis	**Soft tissue anaesthesia success** **2% lidocaine, 1:200,000 epinephrine** IANBs = 31/32 **4% articaine, 1:100,000 epinephrine** IANBs = 30/31 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 30/34 **Clinical anaesthesia success** **2% lidocaine, 1:200,000 epinephrine** IANBs = 3/32 **4% articaine, 1:100,000 epinephrine** IANBs = 2/31 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 2/34

Albertson 1963	Injections (not specified) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin	Success of anaesthesia during various dental procedures (not stated)	**Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** Injections = 64/110 **2% mepivacaine, 1:20,000 levonordefrin** Injections = 99/113
Allegretti 2016	IANB using 3.6 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine	Success of subjective soft tissue anaesthesia Success of anaesthesia during pulpectomy in mandibular first and second molars with irreversible pulpitis	**Soft tissue anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs = 22/22 **4% articaine, 1:100,000 epinephrine** IANBs = 22/22 **2% mepivacaine, 1:100,000 epinephrine** IANBs = 22/22 **Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs = 7/22 **4% articaine, 1:100,000 epinephrine** IANBs = 11/22 **2% mepivacaine, 1:100,000 epinephrine** IANBs = 4/22
Arrow 2012	IANB or mandibular BI (up to 2.2 mL) using 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during paediatric restorative procedures	**Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANBs = 17/29 BIs = 5/27 **4% articaine, 1:100,000 epinephrine** IANBs = 19/27 BIs = 7/28

Atasoy Ulusoy 2014	Maxillary BI of 1.5 mL of 1 of the following: • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine bitartrate	Success of anaesthesia during endodontic access cavity preparation and instrumentation in teeth with irreversible pulpitis	**Clinical anaesthesia success** **4% articaine, 1:100,000 epinephrine** BIs = 8/25 **4% articaine 1:100,000 epinephrine bitartrate** BIs = 9/25
Berberich 2009	Intraoral, IONBs of 1.8 mL of 1 of the following: • 2% lidocaine, 1:50,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Success of subjective soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:50,000 epinephrine** IONBs = 40/40 **3% mepivacaine, no vasoconstrictor** IONBs = 40/40
Bouloux 1999	Patients received the following injections: • Mandibular third molar: IANB (3.4 mL), lingual nerve block (0.5 mL), BI for the long buccal nerve (0.5 mL) • Maxillary third molar: BI (2.0 mL), greater palatine nerve block (0.2 mL) with either: • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of soft tissue anaesthesia using a probe	**Soft tissue anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 20/23 **0.5% bupivacaine, 1:200,000 epinephrine** IANB/BIs = 18/23
Bradley 1969	Infiltration or "mandibular" injection (1.8 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Success of anaesthesia during various dental procedures including restorative, surgical, root extirpation, and miscellaneous procedures (data for those injections of 1.8 mL presented)	**Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** Infiltrations = 40/53 Mandibular = 31/42 **3% mepivacaine, no vasoconstrictor** Infiltrations = 27/36 Mandibular = 33/39

Chilton 1971	Infiltration (of at least 1.5 mL) and IANB (of at least 1.8 mL), which may include supplemental injections of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, 1:200,000 epinephrine • 4% prilocaine, no epinephrine	Success of anaesthesia during endodontic and periodontal procedures	**Clinical anaesthesia success (periodontal)** **2% lidocaine, 1:100,000 epinephrine** Infiltrations = 57/61 IANBs = 31/43 **4% prilocaine, 1:200,000 epinephrine** Infiltrations = 61/69 IANBs = 28/35 **4% prilocaine, no epinephrine** Infiltrations = 50/66 IANBs = 26/40 **Clinical anaesthesia success (endodontic)** **2% lidocaine, 100,000 epinephrine** Infiltrations = 61/69 IANBs = 21/31 **4% prilocaine, 1:200,000 epinephrine** Infiltrations = 52/65 IANBs = 24/33 **4% prilocaine, no epinephrine** Infiltrations = 45/65 IANBs = 23/34
Cohen 1993	IANB using 1.8 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Success of pulpal anaesthesia tested with DDM Success of anaesthesia during pulpotomy in teeth with irreversible pulpitis	**Pulp anaesthesia success (DDM)** **2% lidocaine, 1:100,000 epinephrine** IANBs = 17/27 **3% mepivacaine, no vasoconstrictor** IANBs 21/34 **Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs 15/27 **3% mepivacaine, no vasoconstrictor** IANBs 19/34

Elbay 2016	IANB using 0.9 mL of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Success of anaesthesia during pulpotomy in mandibular primary molars with irreversible pulpitis Success of soft tissue anaesthesia using a probe	Clinical anaesthesia success **2% lidocaine, 1:80,000 epinephrine** IANBs = 17/30 **3% mepivacaine, no vasoconstrictor** IANBs = 15/30 Soft tissue anaesthesia success **2% lidocaine, 1:80,000 epinephrine** IANBs = 28/30 **3% mepivacaine, no vasoconstrictor** IANBs = 24/30
Epstein 1965	Maxillary BI (1.2 mL) and IANB (1.5 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor	Success of anaesthesia during restorative dentistry or "other" procedures	Clinical anaesthesia success (restorative) **2% lidocaine, 1:100,000 epinephrine** BIs = 59/63 IANBs = 49/57 **4% prilocaine, no vasoconstrictor** BIs = 71/73 IANBs = 52/53 Clinical anaesthesia success (other procedures) **2% lidocaine, 1:100,000 epinephrine** BIs = 2/2 IANBs = 2/2 **4% prilocaine, no vasoconstrictor** BIs= 8/8 IANBs = 1/1

Epstein 1969	Maxillary BI (average = 1.2 mL) and IANB (average = 1.4 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, 1:200,000 epinephrine • 4% prilocaine, no vasoconstrictor	Success of anaesthesia during extraction or restorative dentistry procedures	Clinical anaesthesia success **2% lidocaine, 1:100,000 epinephrine** BIs = 108/115 IANBs = 65/82 **4% prilocaine, 1:200,000 epinephrine** BIs = 125/135 IANBs = 62/74 **4% prilocaine, no vasoconstrictor** BIs = 119/128 IANBs = 67/76
Haase 2008	IANB (1.8 mL) of 4% articaine, 1:100,000 epinephrine followed by additional BI (1.8 mL) of either: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	Pulp anaesthesia success (EPT) **4% articaine, 1:100,000 epinephrine** IANB/BIs = 64/73 **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 52/73
Hellden 1974	IANB (1.8 mL) and local infiltration (1.8 mL) of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 3.0% mepivacaine, no vasoconstrictor	Success of anaesthesia during surgical removal of lower third molar teeth	Clinical anaesthesia success **2% lidocaine, 1:80,000 epinephrine** IANB/BIs = 123/140 **3% mepivacaine plain** IANB/BIs = 106/140
Kammerer 2012	IANB and an additional buccal nerve block using up to 2.2 mL of 1 of the following: • 4% articaine, 1:100,000 epinephrine • 4% articaine, no vasoconstrictor	Success of anaesthesia during extraction of posterior, mandibular teeth	Clinical anaesthesia success **4% articaine, 1:100,000 epinephrine** IANB/BIs = 32/41 **4% articaine, no vasoconstrictor** IANB/BIs = 27/47

Kammerer 2014	BI of: • 4% articaine, no vasoconstrictor • 4% articaine, 1:400,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **4% articaine, no vasoconstrictor** BIs = 4/10 **4% articaine, 1:400,000 epinephrine** BIs = 10/10
Kanaa 2012	Maxillary BI (2.0 mL) of the following: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:80,000 epinephrine Patients for extraction received a supplementary palatal injection of 0.2 mL 2% lidocaine, 1:80,000 epinephrine	Success of anaesthesia during extraction or pulp extirpation in teeth with irreversible pulpitis	**Clinical anaesthesia success** **4% articaine, 1:100,000 epinephrine** BIs = 33/50 **2% lidocaine, 1:80,000 epinephrine** BIs = 29/50
Katz 2010	Maxillary BI using 1.8 mL of 1 of the following: • 4% prilocaine, 1:200,000 epinephrine • 4% prilocaine, no vasoconstrictor	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **4% prilocaine, 1:200,000 epinephrine** BIs = 28/30 **4% prilocaine, no vasoconstrictor** BIs = 24/30
Khoury 1991	Various types of injections, using varying volumes (most were 2.0 mL with a range of 0.8 mL-5.0 mL - further injections of 0.5 mL-2.0 mL were injected if required) of 1 of the following: • 3% prilocaine, 0.03 IU/mL felypressin • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of anaesthesia during surgical procedures	**Clinical anaesthesia success** **3% prilocaine, 0.03IU felypressin** Injections = 207/364 **4% articaine, 1:100,000 epinephrine** Injections = 298/408 **4% articaine, 1:200,000 epinephrine** Injections = 269/382 **2% lidocaine, 1:100,000 epinephrine** Injections = 242/363

Knoll-Kohler 1992a	Maxillary BI using 0.5 mL of 1 of the following: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **2% lidocaine, 1:50,000 epinephrine** BIs = 10/10 **2% lidocaine, 1:200,000 epinephrine** BIs = 6/10
Lawaty 2010	Maxillary BI using 1.8 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **2% lidocaine, 1:100,000 epinephrine** BIs = 26/30 **2% mepivacaine, 1:20,000 levonordefrin** BIs = 27/30
McLean 1993	IANB of 1.8 mL of 1 of the following: • 4% prilocaine, no vasoconstrictor • 3% mepivacaine, no vasoconstrictor • 2% lidocaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester Subjective success of soft tissue anaesthesia	**Pulp anaesthesia success (EPT)** **4% prilocaine, no vasoconstrictor** IANBs = 17/30 **3% mepivacaine, no vasoconstrictor** IANBs = 13/30 **Soft tissue anaesthesia success** **4% prilocaine, no vasoconstrictor** IANBs = 30/30 **3% mepivacaine, no vasoconstrictor** IANBs = 30/30 **2% lidocaine, 1:100,000 epinephrine** IANBs = 30/30

Mittal 2015	Maxillary BI of 1 of the following: • 1.8 mL of 2% lidocaine, 1:80,000 epinephrine • 1.7 mL of 4% articaine, 1:100,000 epinephrine	Soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** BIs = = 0/52 **4% articaine, 1:100,000 epinephrine** BIs = 1/52
Moore 1983	Maxillary and mandibular dental block and infiltration using 2 cartridges (2 × 1.8 mL) for each procedure using 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of anaesthesia during non-surgical and surgical endodontic treatment	**Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** Injections = 8/16 **0.5% bupivacaine, 1:200,000 epinephrine** Injections = 12/16
Mumford 1961	"Regional" and infiltration injections (1.5 and 1.0 mL, respectively) of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no epinephrine	Success of anaesthesia during routine tooth cavity preparation	**Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** Infiltrations = 40/50 Regional = 43/50 **3% mepivacaine, no epinephrine** Infiltrations = 42/50 Regional = 42/50
Nordenram 1990	Maxillary BI of 0.6 mL of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 3% prilocaine, 0.03 IU/mL felypressin	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **2% lidocaine, 1:80,000 epinephrine** BIs = 38/40 **3% mepivacaine, no vasoconstrictor** BIs = 34/40 **3% prilocaine, 0.03 IU/mL felypressin** BIs = 34/40

Odabas 2012	Maxillary BI using 1.8 mL of 1 of the following: • 4% articaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine	Success of pulpal anaesthesia during operative dentistry procedures in deciduous teeth	**Clinical anaesthesia success** **4% articaine, 1:200,000 epinephrine** BIs = 50/50 **3% mepivacaine, no epinephrine** BIs = 50/50
Parirokh 2015	IANB (1.8 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of soft tissue anaesthesia (subjectively measured)	**Soft tissue anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANBs = 29/29 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 30/30
Porto 2007	IANB and BI (a minimum of 3.6 mL in total) using 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine	Success of pulpal anaesthesia (Endofrost) Success of anaesthesia during extraction of lower third molars (tested by recording teeth requiring re-anaesthesia)	**Pulp anaesthesia success (Endofrost)** **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 28/35 **2% mepivacaine, 1:100,000 epinephrine** IANB/BIs = 29/35 **Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 32/25 **2% mepivacaine, 1:100,000 epinephrine** IANB/BIs = 33/25
Ram 2006	IANB and maxillary BI (up to 1 cartridge) using the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Success of anaesthesia during paediatric dental procedures	**Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 53/62 **4% articaine, 1:200,000 epinephrine** IANB/BIs = 54/62

Sadove 1962	Various types of dental block and infiltration, using varying volumes of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin	Success of pulpal anaesthesia during restorative and surgical procedures	**Clinical anaesthesia success (surgery)** **2% lidocaine, 1:100,000 epinephrine** Injections = 119/148 **2% mepivacaine, 1:20,000 levonordefrin** Injections = 102/130 **Clinical anaesthesia success (restorative)** **2% lidocaine, 1:100,000 epinephrine** Injections = 23/26 **2% mepivacaine, 1:20,000 levo-nordefrin** Injections = 39/39
Sampaio 2012	IANB using 3.6 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of pulpal anaesthesia during access cavity preparation and instrumentation Success of pulpal anaesthesia tested with an electric pulp tester	**Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs = 14/35 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 8/35 **Pulp anaesthesia success (EPT)** **2% lidocaine, 1:100,000 epinephrine** IANBs = 15/35 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 7/35
Sherman 1954	Mandibular and maxillary injections using 1.1 mL-2.2 mL of 1 of the following: • 2% lidocaine, 1:50,000 adrenaline • 2% lidocaine, 1:100,000 adrenaline	Pulpal anaesthesia during operative dentistry procedures	**Clinical anaesthesia success** **2% lidocaine, 1:50,000 adrenaline** BIs = 84/100 **2% lidocaine, 1:100,000 adrenaline** BIs = 88/100

Sherman 2008	Gow-Gates IANB and maxillary BI of 1 of the following: • 4% articaine, 1:100,000 epinephrine (1.7 mL) • 2% lidocaine, 1:100,000 epinephrine (1.8 mL)	Success of pulpal anaesthesia tested with Endo-Ice	**Pulp anaesthesia success (Endo-Ice)** **4% articaine with 1:100,000 epinephrine** IANB/BIs = 19/20 **2% lidocaine with 1:100,000 epinephrine** IANB/BIs = 19/20
Sood 2014	IANB (1.8 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of subjective soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANBs = 50/50 **4% articaine, 1:100,000 epinephrine** IANBs = 50/50
Srisurang 2011	Maxillary BI (0.9 mL) and PI (0.3 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **2% lidocaine, 1:100,000 epinephrine** BI/PIs = 15/16 **4% articaine, 1:100,000 epinephrine** BI/PIs = 16/16 **2% mepivacaine, 1:100,000 epinephrine** BI/PIs = 16/16
Stibbs 1964	Various mandibular and maxillary injections and varying volumes of 1 of the following: • 2% mepivacaine, 1:20,000 levonordefrin (Neo-Cobefrin) • 2% lidocaine, 1 50,000 epinephrine	Success of pulpal anaesthesia during "restorative operations"	**Clinical anaesthesia success** **2% mepivacaine, 1:20,000 levonordefrin** Infiltrations = 90/99 Mandibular = 97/107 **2% lidocaine, 1:50,000 epinephrine** Infiltrations = 90/102 Mandibular = 96/114

Vahatalo 1993	Maxillary BI 0.6 mL of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **2% lidocaine, 1:80,000 epinephrine** BIs = 20/20 **4% articaine, 1:200,000 epinephrine** BIs = 20/20
Vilchez-Perez 2012	BI (0.9 mL) of 1 of the following: • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of subjective soft tissue anaesthesia Success of pulpal anaesthesia tested with an electric pulp tester	**Soft tissue anaesthesia success** **4% articaine, 1:200,000 epinephrine** BIs = 16/20 **0.5% bupivacaine, 1:200,000 epinephrine** BIs = 16/20 **Pulp anaesthesia success (EPT)** **4% articaine, 1:200,000 epinephrine** BIs = 20/20 **0.5% bupivacaine, 1:200,000 epinephrine** BIs = 18/20
Vreeland 1989	IANB of 1 of the following: • 1.8 mL 2% lidocaine, 1:100,000 epinephrine • 3.6 mL 2% lidocaine, 1:200,000 epinephrine	Success of subjective soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine 1:100,000 epinephrine** IANBs = 30/30 **2% lidocaine, 1:200,000 epinephrine** IANBs = 30/30

Weil 1961	Mandibular and maxillary injections using 1 or more cartridges, if required, of 1 of the following: • 3% mepivacaine, no vasoconstrictor • 2% mepivacaine, 1:20,000 levonordefrin	Success of anaesthesia during operative dentistry procedures	Clinical anaesthesia success **3% mepivacaine, no vasoconstrictor** Mandibular = 89/91 Infiltration = 77/88 **2% mepivacaine, 1:20,000 levo-nordefrin** Mandibular = 30/31 Infiltration = 39/40
Yilmaz 2011	IANB and maxillary BI (1.0 mL) of 1 of the following: • 4% articaine, 100,000 epinephrine • 3% prilocaine, 0.03 IU/mL felypressin	Success of soft tissue anaesthesia (probing buccal and lingual to the tooth in question)	Soft tissue anaesthesia success **4% articaine, 100,000 epinephrine** IANBs = 46/47 BIs = 32/32 **3% prilocaine, 0.03 IU/mL felypressin** IANBs = 42/42 BIs = 36/36

Footnotes

BI = buccal infiltration; DDM = dichlorodifluoromethane; EPT = electric pulp tester; Gow-Gates = Gow-Gates injection (Gow-Gates 1973); IANB = inferior alveolar nerve block; IONB = infraorbital nerve block; LI = lingual infiltration; PI = palatal infiltration.

6 Cross-over and parallel studies (success: raw data not available/not usable)

Study	Comparison	Outcome	Data
Allegretti 2016	IANB of 3.6 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis, tested with an electric pulp tester	Pulp anaesthesia success (EPT) **2% lidocaine, 1:100,000 epinephrine** IANBs = 14/22 **4% articaine, 1:100,000 epinephrine** IANBs = 14/22 **2% mepivacaine, 1:100,000 epinephrine** IANBs = 15/22
Atasoy Ulusoy 2014	Maxillary BI of 1.5 mL of 1 of the following: • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine bitartrate	Success of pulpal anaesthesia tested with Endo-Ice in teeth with irreversible pulpitis	Pulp anaesthesia success (EPT) **4% articaine, 1:100,000 epinephrine** BIs = 25/25 **4% articaine, 1:100,000 epinephrine bitartrate** BIs = 25/25

Berberich 2009	Intraoral, IONB of 1.8 mL of 1 of the following: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Success of subjective soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:50,000 epinephrine** IONBs = 40/40 **2% lidocaine, 1:100,000 epinephrine** IONBs = 40/40 **3% mepivacaine, no vasoconstrictor** IONBs = 40/40
Bhagat 2014	IANB using (volume not stated) 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during surgical extraction of mandibular third molars 1. VAS (0-10) 2. Faces Pain Scale (Wong 1988)	**Clinical anaesthesia success (VAS)** **2% lidocaine, 1:100,000 epinephrine** IANBs = 3.16 ± 2.053* **4% articaine, 1:100,000 epinephrine** IANBs = 2.19 ± 1.543* **Clinical anaesthesia success (Faces Pain Scale)** **2% lidocaine, 1:100,000 epinephrine** IANBs = 3.10 ± 1.750* **4% articaine, 1:100,000 epinephrine** IANBs = 2.32 ± 1.351*
Chapman 1988	IANB (2.0 mL) and BI (1.0 mL) of either: • 2% lidocaine, 1:80,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of anaesthesia during surgical extraction of mandibular third molars	**Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANB/BIs = 20/20 **0.5% bupivacaine, 1:200,000 epinephrine** IANB/BIs = 20/20
Cohen 1993	IANB using 1.8 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Success of subjective soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs = 27/27 **3% mepivacaine, no vasoconstrictor** IANBs = 34/34

Dagher 1997	IANB using 1.8 mL of 1 of the following: • 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:80,000 epinephrine • 2% lidocaine, 1:80,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine	Success of subjective soft tissue anaesthesia	Soft tissue anaesthesia success **2% lidocaine, 1:50,000 epinephrine** IANBs = 30/30 **2% lidocaine, 1:80,000 epinephrine** IANBs = 30/30 **2% lidocaine, 1:100,000 epinephrine** IANBs = 30/30
Elbay 2016	IANB using 0.9 mL of 1 of the following: • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor	Success of clinical anaesthesia during extraction of mandibular primary molars	Clinical anaesthetic success **2% lidocaine, 1:80,000 epinephrine** IANBs = 10/30 **3% mepivacaine, no vasoconstrictor** IANBs = 10/30
Fernandez 2005	IANB (1.8 mL) of each of the following: • 2% lidocaine with 1:100,000 epinephrine • 0.5% bupivacaine with 1:200,000 epinephrine	Success of soft tissue anaesthesia	Soft tissue anaesthesia success **2% lidocaine, 1:100,000 epinephrine** IANBs = 39/39 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 39/39
Gazal 2015	IANB (1.8 mL) of 2% mepivacaine, 1:100,000 epinephrine, followed by a BI (1.8 mL) of 1 of the following solutions: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	Pulp anaesthesia success (EPT) **2% mepivacaine, 1:100,000 epinephrine** IANB/BIs = 23/23 **4% articaine, 1:100,000 epinephrine** IANB/BIs = 23/23
Gregorio 2008	Mandibular block (1.8 mL) and local infiltration (0.9 mL) of 1 of the following: • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of clinical anaesthesia during surgical removal of mandibular third molars	Clinical anaesthesia success **4% articaine, 1:200,000 epinephrine** IANB/BIs = 49/50 **0.5% bupivacaine, 1:200,000 epinephrine** IANB/BIs = 43/50

Hersh 1995	IANB (1.8 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor • 3% mepivacaine, no vasoconstrictor	Success of subjective soft tissue anaesthesia	Soft tissue anaesthesia success **2% lidocaine, 1:100,000 epinephrine** IANBs = 14/20 **4% prilocaine, no vasoconstrictor** IANBs = 14/19 **3% mepivacaine, no vasoconstrictor** IANBs = 17/21
Hinkley 1991	IANB (1.8 mL) of 1 of the following: • 4% prilocaine, 1:200,000 epinephrine • 2% mepivacaine, 1:20,000 levonordefrin • 2% lidocaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	Pulp anaesthesia success (EPT) **4% prilocaine, 1:200,000 epinephrine** IANBs = 13/28 **2% mepivacaine, 1:20,000 levonordefrin** IANBs = 16/28 **2% lidocaine, with 1:100,000 epinephrine** IANBs = 15/28
Hosseini 2016	Maxillary BI (1.8 mL) of the following: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis	Clinical anaesthesia success **2% lidocaine, 1:80,000 epinephrine** BIs = 13/23 **4% articaine, 1:100,000 epinephrine** BIs = 16/24
Jain 2016	IANB and BI (1.7 mL) of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during surgical extraction of mandibular third molars (VAS 0-10)	Clinical anaesthesia success **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 2.6 ± 1.06* **4% articaine, 1:100,000 epinephrine** IANB/BIs = 1.31 ± 0.87*
Kambalimath 2013	IANB and BI (volume not stated) of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during surgical extraction of mandibular third molars	Clinical anaesthesia success **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 26/30 **4% articaine, 1:100,000 epinephrine** IANB/BIs = 29/30

Kammerer 2014	BI (1.7 mL) of: • 4% articaine, no vasoconstrictor • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:400,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester Success of soft tissue anaesthesia (VAS = 0-10)	**Pulp anaesthesia success (EPT)** **4% articaine, 1:100,000 epinephrine** BIs = 10/10 **4% articaine, 1:200,000 epinephrine** BIs = 10/10 **4% articaine, 1:400,000 epinephrine** BIs = 10/10 **Soft tissue anaesthesia success** **4% articaine, no vasoconstrictor** BIs = 1.4 ± 0.9* **4% articaine, 1:100,000 epinephrine** BIs = 6.2 ± 3* **4% articaine, 1:200,000 epinephrine** BIs = 6.4 ± 1.9* **4% articaine, 1:400,000 epinephrine** BIs = 6.8 ± 2*
Kanaa 2012	BI (2.0 mL) of: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine,1:80,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis, tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **4% articaine, 1:100,000 epinephrine** BIs = 38/50 **2% lidocaine,1:80,000 epinephrine** BIs = 35/50

Karm 2017	IANB and BI (1.8 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Success of anaesthesia during impacted, mandibular, third molar removal (0-100 mm VAS) Total volume of anaesthetic solution used (mL) Operator's overall satisfaction (Likert scale: 1-5) Participant's overall satisfaction (Likert scale: 1-5)	**Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANB/BIs = 13.7 ± 1.9 mm* **2% lidocaine, 1:200,000 epinephrine** IANB/BIs = 20.0 ± 2.5 mm* **Total volume of anaesthetic solution used** **2% lidocaine, 1:80,000 epinephrine** IANB/BIs = 3.6 ± 0.1* **2% lidocaine, 1:200,000 epinephrine** IANB/BIs = 3.6 ± 0.2* **Operator's overall satisfaction** **2% lidocaine, 1:80,000 epinephrine** IANB/BIs = 3.9 ± 0.9* **2% lidocaine, 1:200,000 epinephrine** IANB/BIs = 3.8 ± 1.0* **Participant's overall satisfaction** **2% lidocaine, 1:80,000 epinephrine** IANB/BIs = 3.6 ± 0.1* **2% lidocaine, 1:200,000 epinephrine** IANB/BIs = 3.7 ± 0.1*
Keskitalo 1975	IANB and BI (3.6 mL initially) of 1 of the following: • 2% lidocaine, 12.5 µg/mL (1:80,000) epinephrine • 3% prilocaine, 0.03 IU/mL felypressin	Success of anaesthesia during impacted, mandibular, third molar removal	**Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANB/BIs = 163/188 **3% prilocaine, 0.03 IU/mL felypressin** IANB/BIs = 138/191
Knoll-Kohler 1992b	Maxillary BI using 0.5 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **2% lidocaine, 1:100,000 epinephrine** BIs = 12/12 **4% articaine, 1:100,000 epinephrine** BIs = 12/12

Kolli 2017	Maxillary BI (1.7 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine (epinephrine concentrations assumed) Maxillary BI/PI (1.7 mL in total) of: • 2% lidocaine, 1:80,000 epinephrine	Success of anaesthesia during extraction of primary maxillary molars 1. Faces Pain Scale - Revised 2. Face, Legs, Activity, Cry, Consolability (FLACC) Behavioural Pain Assessment Scale	**Faces Pain Scale - Revised** **2% lidocaine, 1:80,000 epinephrine** BIs = 2.67 ± 1.91* **4% articaine, 1:100,000 epinephrine** BIs = 1.20 ± 1.34* **2% lidocaine, 1:80,000 epinephrine** BI/PIs = 0.73 ± 1.11* **FLACC Scale** **2% lidocaine, 1:80,000 epinephrine** BIs = 2.17 ± 1.46* **4% articaine, 1:100,000 epinephrine** BIs = 1.27 ± 1.28* **2% lidocaine, 1:80,000 epinephrine** BI/PIs = 0.80 ± 0.84*
Kramer 1958	Mandibular and maxillary injections using 1 cartridge, or more if required, of 1 of the following: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of pulpal anaesthesia during operative dentistry procedures	**Clinical anaesthesia success** **2% lidocaine, 1:50,000 epinephrine** Maxillary = 86% Mandibular = 82.5% **2% lidocaine, 1:100,000 epinephrine** Maxillary = 80.2% Mandibular = 76%
Malamed 2000a	Standard infiltration or nerve block of the following mean volumes: Simple procedures: • 2.5 mL ± 0.07 SEM of 4% articaine, 1:100,000 epinephrine • 2.6 mL ± 0.09 SEM of 2% lidocaine, 1:100,000 epinephrine Complex procedures: • 4.2 mL ± 0.15 SEM of 4% articaine, 1:100,000 epinephrine • 4.5 mL ± 0.21 SEM of 2% lidocaine, 1:100,000 epinephrine	Success of anaesthesia during various dental procedures	**Clinical anaesthesia success** **4% articaine, 1:100,000 epinephrine** Simple procedures = 0.4 cm (range 0-8 cm) Complex procedures = 0.6 cm (range 0-8.7 cm) **2% lidocaine, 1:100,000 epinephrine** Simple procedures = 0.6 cm (range 0-9.8 cm) Complex procedures = 0.7 cm (range 0-7.7 cm)

Malamed 2000b	Standard infiltration or nerve block of the following mean volumes: Simple procedures: • 1.9 mL ± 0.10 SEM of 4% articaine, 1:100,000 epinephrine • 1.9 mL ± 0.23 SEM of 2% lidocaine, 1:100,000 epinephrine Complex procedures: • 2.5 mL ± 0.43 SEM of 4% articaine, 1:100,000 epinephrine • 2.6 mL ± 0.00 SEM of 2% lidocaine, 1:100,000 epinephrine	Success of anaesthesia during various dental procedures	Clinical anaesthesia success **4% articaine, 1:100,000 epinephrine** Simple procedures = 0.5 cm (range 0-5.5 cm) Complex procedures = 1.1 cm (range 0-0.25 cm) **2% lidocaine, 1:100,000 epinephrine** Simple procedures = 0.7 cm (range 0-3.0 cm) Complex procedures = 2.3 cm (range 0-4.5 cm)
Maniglia-Ferreira 2009	IANB (1 cartridge) of 1 of the following: • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis	Clinical anaesthesia success **2% mepivacaine, 1:100,000 epinephrine** IANBs = 2.8 cartridges **4% articaine, 1:100,000 epinephrine** IANBs = 2.6 cartridges
Maruthingal 2015	Mandibular BI (1.7 mL) of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester Success of soft tissue anaesthesia	Pulp anaesthesia success (EPT) **2% lidocaine, 1:100,000 epinephrine** BIs = 17/32 **4% articaine, 1:100,000 epinephrine** BIs = 28/32 Soft tissue anaesthesia success **2% lidocaine, 1:100,000 epinephrine** BIs = 32/32 **4% articaine, 1:100,000 epinephrine** BIs = 32/32
McLean 1993	IANB of 1.8 mL of 1 of the following: • 3% mepivacaine, no vasoconstrictor • 2% lidocaine, 1:100,000 epinephrine	Success of soft tissue anaesthesia	Soft tissue anaesthesia success **3% mepivacaine, no vasoconstrictor** IANBs = 30/30 **2% lidocaine, 1:100,000 epinephrine** IANBs = 30/30

Mittal 2015	Maxillary BI of 1 of the following: • 1.8 mL of 2% lidocaine, 1:80,000 epinephrine • 1.7 mL of 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during extraction of primary maxillary molars 1. Wong-Baker FACES Pain Rating Scale 2. Modified Behaviour Pain Scale (Taddio 1994) • Facial expressions • Hand movements • Torso movements • Leg movements • Crying	**Clinical anaesthesia success (Wong-Baker FACES pain rating scale)** **2% lidocaine, 1:80,000 epinephrine** BIs = 1.88 ± 1.688* **4% articaine, 1:100,000 epinephrine** BIs = 1.31 ± 1.13* **Modified Behaviour Pain Scale** **2% lidocaine, 1:80,000 epinephrine** BIs: • facial expressions: 34/52 • hand movements: 19/52 • torso movements: 6/52 • leg movements: 21/52 • crying: 2/52 **4% articaine, 1:100,000 epinephrine** BIs: • facial expressions: 22/52 • hand movements: 6/52 • torso movements: 2/52 • leg movements: 12/52 • crying: 0/52
Moore 2007	Maxillary BI (buccal and palatal if required) using 1 of the following: • 4% articaine, 1:200,000 epinephrine (4.1 ± 1.3 mL) • 4% articaine, 1:100,000 epinephrine (4.1 ±1.2 mL)	Success of anaesthesia during periodontal surgery	**Clinical anaesthesia success** **4% articaine, 1:200,000 epinephrine** BIs = 42/42 **4% articaine, 1:100,000 epinephrine** BIs = 42/42
Nabeel 2014	Maxillary BI (1.7 mL) using the following: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis	**Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** BIs = 33/38 **4% articaine, 1:100,000 epinephrine** BIs = 35/38

Naik 2017	IANB (2 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during surgical extraction of mandibular third molars (volume of solution in mL)	Clinical anaesthesia success **2% lidocaine, 1:80,000 epinephrine** IANBs = 2.2 ± 0.56 mL* **4% articaine, 1:100,000 epinephrine** IANBs = 2.0 ± 0.14 mL*
Ozec 2010	Maxillary BI (1.7 mL) using 1 of the following: • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of soft tissue anaesthesia (Heft-Parker VAS)	Soft tissue anaesthesia success **4% articaine, 1:200,000 epinephrine** BIs = 75.53 ± 49.78 mm*** **4% articaine, 1:100,000 epinephrine** BIs = 57.20 ± 46.69 mm***
Parirokh 2015	IANB (1.8 mL) using the following: • 2% lidocaine, 1:80,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis (VAS score of zero or mild pain ≤ 54 mm on a Heft-Parker visual analogue scale)	Clinical anaesthesia success **2% lidocaine, 1:80,000 epinephrine** IANBs = 7/29 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 6/30
Pellicer-Chover 2013	IANB (1.8 mL) and BI (1.8 mL) using the following: • 0.5% bupivacaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during impacted, mandibular, third molar removal (no discomfort, or slight discomfort but not requiring additional anaesthesia)	Clinical anaesthetic success **0.5% bupivacaine, 1:200,000 epinephrine** IANB/BIs = 20/36 **4% articaine, 1:100,000 epinephrine** IANB/BIs = 30/36
Poorni 2011	IANB (1.8 mL) using 1 of the following: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine or a BI (1.8 mL) using: • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis	Clinical anaesthetic success **4% articaine 1:100,000 epinephrine** IANBs = 39/52 **2% lidocaine, 1:100,000 epinephrine** IANBs = 36/52 **4% articaine, 1:100,000 epinephrine** BIs = 36/52

Ruprecht 1991	Maxillary BI (0.5 mL) of 1 of the following: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success** **4% articaine, 1:100,000 epinephrine** BIs = 10/10 **2% lidocaine, 1:100,000 epinephrine** BIs = 10/10
Sampaio 2012	IANB using 3.6 mL of 1 of the following: • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine	Success of subjective soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs = 35/35 **0.5% bupivacaine, 1:200,000 epinephrine** IANBs = 35/35
Santos 2007	IANB (1.8 mL) and mandibular BI (0.9 mL) of 1 of the following: • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine	Success of anaesthesia during extraction (3-point scale: 1-3)	**Clinical anaesthesia success** **4% articaine, 1:100,000 epinephrine** IANB/BIs (with osteotomy) = 1.04 ± 0.04** IANB/BIs (without osteotomy) = 1.00 ± 0.00** **4% articaine, 1:200,000 epinephrine** IANB/BIs (with osteotomy) = 1.17 ± 0.08** IANB/BIs (without osteotomy) = 1.11 ± 0.08**
Sherman 2008	Gow-Gates IANB and maxillary BI of 1 of the following: • 4% articaine, 1:100,000 epinephrine (1.7 mL) • 2% lidocaine, 1:100,000 epinephrine (1.8 mL)	Success of pulpal anaesthesia during pulpotomy	**Clinical anaesthesia success** **4% articaine, 1:100,000 epinephrine** Gow-Gates = 9/10 Max' infiltration = 10/10 **2% lidocaine, 1:100,000 epinephrine** Gow-Gates = 8/11 Max' infiltration = 8/9

Sierra Rebolledo 2007	IANB (1.8 mL) and BI (1.8 mL) of 1 of the following: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of anaesthesia during tooth removal (visual analogue scale from 0-100 mm)	**Clinical anaesthetic success (means and standard deviations)** **4% articaine, 1:100,000 epinephrine** IANB/BIs = 13.81 mm ± 3.012 mm* **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 12.83 mm ± 3.186 mm*
Silva 2012	IANB (3.6 mL) and mandibular BI (0.9 mL) of 1 of the following: • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of anaesthesia during tooth extraction (volume of local anaesthetic solution)	**Clinical anaesthesia success (means and standard deviations)** **4% articaine, 1:100,000 epinephrine** IANB/BIs = 5.76 ± 1.09 mL* **2% lidocaine, 1:100,000 epinephrine** IANB/BIs = 6.12 ± 0.96 mL*
Sood 2014	IANB (1.8 mL) of: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of anaesthesia during pulp extirpation Success of pulpal anaesthesia in teeth with irreversible pulpitis, tested with an electric pulp tester	**Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANBs = 41/50 **4% articaine, 1:100,000 epinephrine** IANBs = 44/50 **Pulp anaesthesia success (EPT)** **2% lidocaine, 1:80,000 epinephrine** IANBs = 29/50 **4% articaine, 1:100,000 epinephrine** IANBs = 38/50
Tortamano 2009	IANB (3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia tested with an electric pulp tester	**Pulp anaesthesia success (EPT)** **2% lidocaine, 1:100,000 epinephrine** IANBs = 14/20 **4% articaine, 1:100,000 epinephrine** IANBs = 13/20

Trieger 1979	IANB and infiltration anaesthesia, using variable volumes of: • 0.5% bupivacaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine Note - some patients received a general anaesthetic, and injections were given at the end of surgery.	Success of anaesthesia during tooth extraction (dose/quadrant)	**Clinical anaesthesia success** **0.5% bupivacaine, 1:200,000 epinephrine** IANB/BIs = 11.95 mg **3% mepivacaine, no epinephrine** IANB/BIs = 68.18 mg
Visconti 2016	IANB (1.8 mL or 3.6 mL) of: • 2% lidocaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis (4-point scale: 0-4) Success of pulpal anaesthesia in teeth with irreversible pulpitis, tested with an electric pulp tester Success of soft tissue anaesthesia	**Clinical anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs (1.8 mL) = 0/21 **2% mepivacaine, 1:100,000 epinephrine** IANBs (1.8 mL) = 6/21 **Pulp anaesthesia success (EPT)** **2% lidocaine, 1:100,000 epinephrine** IANBs (1.8 mL) = 7/21 IANBs (3.6 mL) = 7/14 **2% mepivacaine, 1:100,000 epinephrine** IANBs (1.8 mL) = 11/21 IANBs (3.6 mL) = 7/10 **Soft tissue anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs = 21/21 **2% mepivacaine, 1:100,000 epinephrine** IANBs = 21/21
Wali 2010;	IANB of 1 of the following: • 1.8 ml of 2% lidocaine, 1:100,000 epinephrine • 1.8 ml of 2% lidocaine, 1:50,000 epinephrine	Success of soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:100,000 epinephrine** IANBs = 30/30 **2% lidocaine, 1:50,000 epinephrine** IANBs = 30/30

Yadav 2015	IANB (1.8 mL) followed by BI (0.9 mL) and LI (0.9 mL) of the following: • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine	Success of pulpal anaesthesia in teeth with irreversible pulpitis (VAS score of zero or mild pain ≤ 54 mm on a Heft-Parker visual analogue scale)	**Clinical anaesthesia success** **2% lidocaine, 1:80,000 epinephrine** IANB/BI/LIs = 8/25 **4% articaine, 1:100,000 epinephrine** IANB/BI/LIs = 16/25
Yared 1997	IANB (3.6 mL) of 1 of the following: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:80,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of subjective soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:50,000 epinephrine** IANBs = 30/30 **2% lidocaine, 1:80,000 epinephrine** IANBs = 30/30 **2% lidocaine, 1:100,000 epinephrine** IANBs = 30/30
Yilmaz 2011	IANB and maxillary BI of 1.0 mL of the following: • 4% articaine, 1:100,000 epinephrine • 3% prilocaine, 0.03 IU/mL felypressin	Success of anaesthesia during pulpotomy	**Clinical anaesthesia success** **4% articaine, 1:100,000 epinephrine** IANBs = 44/47 BIs = 9/32 **3% prilocaine, 0.03 IU/mL felypressin** IANBs = 39/42 BIs = 31/36
Yonchak 2001	Mandibular BI (1.8 mL) of 1 of the following: • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine	Success of soft tissue anaesthesia	**Soft tissue anaesthesia success** **2% lidocaine, 1:50,000 epinephrine** BIs = 40/40 **2% lidocaine, 1:100,000 epinephrine** BIs = 40/40

Footnotes

* = mean ± standard deviation (SD); ** = mean ± standard error of the mean (SEM); ** = unsure if SD or SEM.

BI = buccal infiltration; EPT = electric pulp tester; IANB = inferior alveolar nerve block; IONB = infraorbital nerve block; VAS = visual analogue scale; Faces Pain Scale - Revised = a modified version of the Faces Pain Scale (Hicks 2001); PI = palatal infiltration.

7 Adverse events

Adverse event	Method of measurement	Results	Statistical tests if reported
Pain on injection			

Abdulwahab 2009	0–100 mm VAS (0 = no pain, 100 = worst pain ever)	**BI (0.9 mL) of:** • 2% lidocaine, 1:100,000 epinephrine = 27.6 mm • 4% articaine, 1:200,000 epinephrine = 24.1 mm • 4% articaine, 1:100,000 epinephrine = 26.2 mm • 4% prilocaine, 1:200,000 epinephrine = 21.0 mm • 3% mepivacaine, no vasoconstrictor = 22.9 mm • 0.5% bupivacaine, 1:200,000 epinephrine = 32.2 mm	Pain ratings were similar for all test anaesthetic formulations as compared with those for 2% lidocaine with 1:100,000 epinephrine (ANOVA, P = 0.19)
Aggarwal 2014	170 mm Heft-Parker VAS: • 'No pain' corresponded to 0 mm • 'Faint, weak or mild' pain corresponded to 1–54 mm • 'Moderate' pain corresponded to 55–114 mm • 'Severe pain' corresponded above 114 mm and included 'strong, intense and maximum possible' pain	**IANB (1.8 mL) of:** 2% lidocaine 1:80,000 epinephrine • Mean ± SD = 55 ± 19 mm 2% lidocaine 1:200,000 epinephrine • Mean ± SD = 47 ± 21 mm	There was no significant difference in injection pain of 2% lidocaine, 1:80,000 and 2% lidocaine, 1:200,000 solutions (P > 0.05)
Arrow 2012	Faces Pain Scale - Revised, dichotomized into 'no or mild pain' = 0 and 'moderate to severe pain' = 1	**IANB or BI (up to 2.2 mL) of:** 2% lidocaine, 1:80,000 epinephrine • No/mild pain = 44/56 • Moderate/severe pain = 12/56 4% articaine, 1:100,000 epinephrine • No/mild pain = 42/56 • Moderate/severe pain = 14/56	There were no statistically significant differences between formulations with the test carried out (Faces: P = 0.65)
Batista da Silva 2010	100 mm VAS ranging from 0 = "no pain" to 100 = "unbearable pain"	**Mental nerve blocks (0.6 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Between 1 and 71 mm 4% articaine, 1:100,000 epinephrine • Between 1 and 70 mm	There was no significant difference (P > 0.05) between solutions regarding injection pain
Berberich 2009	Pain scale: • 0 = no pain • 1 = mild pain that was recognizable but was not discomforting • 2 = moderate pain that was discomforting but bearable • 3 = severe pain that caused considerable discomfort and was difficult to bear	**Intraoral IONB (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine • None = 28% (11/40) • Mild = 40% (16/40) • Moderate = 32% (13/40) • Severe = 0% (0/40) • Mean ± SD = 1.05 ± 0.78 2% lidocaine, 1:50,000 epinephrine • None= 20% (8/40) • Mild = 58% (23/40) • Moderate = 20% (8/40) • Severe = 2% (1/40) • Mean ± SD = 1.05 ± 0.71 3% mepivacaine, no vasoconstrictor • None = 20% (8/40) • Mild = 38% (15/40) • Moderate = 40% (16/50) • Severe = 2% (1/40) • Mean ± SD = 1.25 ± 0.81	There were no significant differences (P > 0.05) among the 3 anaesthetic formulations

Caldas 2015	10 cm VAS (0 = no pain, and 10 = the most severe pain)	**BI (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine • 29.03 ± 22.01 mm[##] 2% lidocaine, 1:200,000 epinephrine • 19.24 ± 17.83 mm[##]	There was no difference between formulations for pain during anaesthetic injection (P > 0.05)
Chilton 1971	Numbers of adverse events listed (pooled - exact type not stated)	**Infiltration (1.5 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Local events = 2/130 4% prilocaine, 1:200,000 epinephrine • Local events = 1/134 4% prilocaine, no epinephrine • Local events = 4/131 **IANB (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Local events = 3/74 4% prilocaine, 1:200,000 epinephrine • Local events = 0/68 4% prilocaine, no epinephrine • Local events = 2/74	No statistical significance between solutions, although slightly more occurred with lidocaine
Elbay 2016	The Face, Legs, Activity, Cry, Consolability (FLACC) Behavioural Pain Assessment Scale, each given a pain score of 0–2, for a total behavioural pain score in the range of 0–10, as follows: • 0 = relaxed and comfortable (no pain) • 1–3 = mild discomfort • 4–6 = moderate pain • 7–10 = severe discomfort and/or pain	**IANB (0.9 mL) of:** 2% lidocaine, 1:80,000 epinephrine • No pain = 30/60 • Mild pain = 28/60 • Moderate pain = 2/60 3% mepivacaine, no vasoconstrictor • No pain = 19/60 • Mild pain = 34/60 • Moderate pain = 7/60	Pain-related behaviour differed significantly as 2% lidocaine with 1:80,000 epinephrine produced less pain during injection than plain mepivacaine (P = 0.015) There was no statistically significant difference between solutions in pain scores during injection for ‘mild’ or ‘moderate’ pain (P = 0.275, P = 0.084, respectively)
Epstein 1969	Numbers of local adverse events listed (pooled - unclear about exact types of adverse effects)	**BI (1.2 mL) and IANB (1.4 mL) of:** Local side effects 2% lidocaine, 100,000 epinephrine • BI = 0/110 • IANB = 2/81 4% prilocaine, 1:200,000 epinephrine • BI = 0/134 • IANB = 0/71 4% prilocaine, no epinephrine • BI = 0/127 • IANB = 0/76	Not reported

Evans 2008	Heft-Parker VAS (170 mm line with various descriptive terms) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 11 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**Maxillary BI (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Needle insertion (mean ± SD)* • Lateral incisor = 23 ± 24 mm • First molar = 20 ± 16 mm *Needle placement (mean ± SD)* • Lateral incisor = 25 ± 23 mm • First molar = 19 ± 16 mm *Solution deposition (mean ± SD)* • Lateral incisor = 51 ± 33 mm • First molar = 36 ± 26 mm 4% articaine, 1:100,000 epinephrine *Needle insertion (mean ± SD)* • Lateral incisor = 24 ± 29 mm • First molar = 17 ± 14 mm *Needle placement (mean ± SD)* • Lateral incisor = 26 ± 22 mm • First molar = 22 ± 21 mm *Solution deposition (mean ± SD)* • Lateral incisor = 59 ± 33 mm • First molar = 44 ± 29 mm	There were no significant differences (P > 0.05) between the 2 anaesthetic solutions for any phases of the injection *Needle insertion* Lateral incisor: P = 0.9934 First molar: P = 0.9555 *Needle placement* Lateral incisor: P = 0.9943 First molar: P = 0.8731 *Solution deposition* Lateral incisor: P = 0.5378 First molar: P = 0.4405

Forloine 2010	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**High-tuberosity maxillary second division nerve blocks (4.0 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Needle insertion* • None = 8% (4/50) • Mild = 78% (39/50) • Moderate = 14% (7/50) • Severe = 0% (0/50) • Mean ± SD = 29 ± 20 mm *Needle placement* • None = 2% (1/50) • Mild = 42% (21/50) • Moderate = 52% (26/50) • Severe = 4% (2/50) • Mean ± SD = 57 ± 30 mm *Solution deposition* • None = 12% (6/50) • Mild = 60% (30/50) • Moderate = 26% (13/50) • Severe = 2% (1/50) • Mean ± SD = 34 ± 28 mm 3% mepivacaine, no vasoconstrictor *Needle insertion* • None = 2% (1/50) • Mild = 74% (37/50) • Moderate = 24% (12/50) • Severe = 0% (0/50) • Mean ± SD = 35 ± 21 mm *Needle placement* • None = 2% (1/50) • Mild = 52% (26/50) • Moderate = 42% (21/50) • Severe = 4% (2/50) • Mean ± SD = 51 ± 28 mm *Solution deposition* • None = 18% (9/50) • Mild = 52% (26/50) • Moderate = 28% (14/50) • Severe = 2% (1/50) • Mean ± SD = 33 ± 27 mm	There was no significant difference (P > 0.05) between the 2 solutions
Gangarosa 1967	Numbers of adverse events listed	**Mandibular block and infiltration (volume not stated) of each of the following:** • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor No adverse events were reported	Not applicable

Gazal 2017	0–100 mm VAS (0 = no pain and 100 = unbearable pain)	**Maxillary BI (1.4 mL) and PI (0.4 mL) of:** Post-buccal infiltration 2% mepivacaine, 1:100,000 epinephrine • Mean ± SD = 35 ± 18.23 mm 4% articaine, 1:100,000 epinephrine • Mean ± SD = 52 ± 21.23 mm Post-palatal infiltration 2% mepivacaine, 1:100,000 epinephrine • Mean ± SD = 51 ± 17.48 mm 4% articaine, 1:100,000 epinephrine • Mean ± SD = 46 ± 22.1 mm	Post-buccal infiltration: P < 0.001 Post-palatal infiltration: P = 0.19
Gregorio 2008	Numbers of adverse events listed	**IANB (1.8 mL) and local infiltration (0.9 mL) of:** • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine No adverse events were reported	Not applicable
Haase 2008	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**IANB of 4% articaine, 1:100,000 epinephrine (1.8 mL), followed by additional BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine (mean ± SD) • Needle insertion = 20 ± 25 mm • Needle placement = 17 ± 24 mm • Solution deposition = 23 ± 27 mm 2% lidocaine, 1:100,000 epinephrine (mean ± SD) • Needle insertion = 17 ± 20 mm • Needle placement = 20 ± 27 mm • Solution deposition = 22 ± 26 mm	There were no significant differences (P > 0.05) between the 2 anaesthetic solutions for any phases of the injection Needle insertion: P = 0.95 Needle placement: P = 0.99 Solution deposition: P > 0.99
Hellden 1974	Numbers of adverse events listed	**IANB (1.8 mL) and local infiltration (1.8 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3.0% mepivacaine, no vasoconstrictor No adverse events were reported	Not applicable
Hosseini 2016	Adverse events	**Maxillary BI (1.8 mL) of the following:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine There were no adverse events	Not applicable

Jaber 2010	100 mm visual analogue scale with endpoints marked 'no pain' (0 mm) and 'unbearable pain' (100 mm)	**BI (0.9 mL) of:** 4% articaine, 1:100,000 epinephrine • Mean ± SD = 33.5 ± 21.4 mm 2% lidocaine, 1:100,000 epinephrine • Mean ± SD = 34.7 ± 22 mm **LIs (0.9 mL) of:** 4% articaine, 1:100,000 epinephrine • Mean ± SD = 24.9 ± 20.9 mm 2% lidocaine, 1:100,000 epinephrine • Mean ± SD = 23.3 ± 17.2 mm **1 BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine • Mean ± SD = 36.8 ± 22.8 mm 2% lidocaine, 1:100,000 epinephrine • Mean ± SD = 32.9 ± 19.1 mm **Dummy LI of:** • Mean ± SD = 12.5 ± 13.9 mm	No significant differences were noted between drugs and methods of administration Lingual penetration (dummy LI) was more comfortable than lingual infiltration (student's paired t–test P < 0.01)
Jain 2016	VAS from 0 (no pain) to 10 (worst pain imaginable)	**IANB and BI (1.7 mL in total) of:** 2% lidocaine, 1:100,000 epinephrine • Mean ± SD = 1.26 ± 1.74 4% articaine, 1:100,000 epinephrine • Mean ± SD = 0.97 ± 0.92	The difference was not significant (P = 0.393)
Kammerer 2012	VAS from 0 (no pain) to 10 (worst pain)	**IANB and buccal nerve block (up to 2.2 mL) of:** 4% articaine, 1:100,000 epinephrine • Mean ± SD = 2.56 ± 1.41 4% articaine, no vasoconstrictor • Mean ± SD = 2.72 ± 1.84	The difference was not significant (P = 0.647)
Kanaa 2006	100 mm VAS with endpoints tagged no pain (0 mm) and unbearable pain (100 mm)	**Mandibular BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine • Mean ± SD = 20.9 ± 17.9 mm 2% lidocaine, 1:100,000 epinephrine • Mean ± SD = 17.8 ± 14.9 mm	There was no significant difference in injection discomfort between treatments (P = 0.320)
Kanaa 2012	100 mm VAS with endpoints tagged no pain (0 mm) and unbearable pain (100 mm)	**Maxillary BI (2.0 mL) of:** 4% articaine, 1:100,000 epinephrine • Ranged from 0 to 53 mm, mean ± SD = 10.8 ± 11.7 mm 2% lidocaine, 1:80,000 epinephrine • Ranged from 0 to 71 mm, mean ± SD = 17.5 ± 17.6 mm Patients for extraction received a supplementary palatal injection of 0.2 mL 2% lidocaine, 1:80,000 epinephrine	Articaine buccal infiltrations were more comfortable than lidocaine buccal infiltrations (P = .026)

Kolli 2017	Adverse events	**Maxillary BI (1.7 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine (epinephrine concentrations assumed) There were no adverse events	Not applicable
Kramer 1958	Numbers of adverse events listed (pooled)	**Mandibular and maxillary injections (1 or more cartridges) of:** 2% lidocaine, 1:50,000 epinephrine • Mandibular = 1.16% • Maxillary = 0.7% 2% lidocaine, 1:100,000 epinephrine • Mandibular = 2.0% • Maxillary = 0%	Not reported
McEntire 2011	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**Mandibular BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine *Needle insertion* • None = 2% (2/86) • Mild = 83% (71/86) • Moderate = 15% (13/86) • Severe = 0% (0/86) • Mean ± SD = 37 ± 22 mm *Needle placement* • None = 6% (5/86) • Mild = 76% (65/86) • Moderate = 19% (16/86) • Severe = 0% (0/86) • Mean ± SD = 37 ± 25 mm *Solution deposition* • None = 11% (9/86) • Mild = 76% (65/86) • Moderate = 14% (12/86) • Severe = 0% (0/86) • Mean ± SD = 30 ± 27 mm 4% articaine, 1:200,000 epinephrine *Needle insertion* • None = 4% (3/86) • Mild = 74% (64/86) • Moderate = 21% (18/86) • Severe = 1% (1/86) • Mean ± SD = 37 ± 24 mm *Needle placement* • None = 6% (5/86) • Mild = 74% (64/86) • Moderate =19% (16/86) • Severe = 1% (1/86) • Mean ± SD = 40 ± 26 mm *Solution deposition* • None = 12% (10/86) • Mild = 76% (65/86) • Moderate = 12% (10/86) • Severe = 1% (1/86) • Mean ± SD = 30 ± 27 mm	There was no significant difference (P > 0.05) between the 2 solutions for pain of injection

Mikesell 2005	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**IANB (1.8 mL) of:** 2% lidocaine with 1:100,000 epinephrine *Solution deposition* • None = 9% (5/57) • Mild = 72% (41/57) • Moderate = 18% (10/57) • Severe = 2% (1/57) • Mean ± SD = 32 ± 27 mm 4% articaine with 1:100,000 epinephrine *Solution deposition* • None = 12% (7/57) • Mild = 54% (31/57) • Moderate = 30% (17/57) • Severe = 4% (2/57) • Mean ± SD = 39 ± 33 mm	There was no significant difference (P > 0.05) between the 2 solutions
Moore 2006	Numbers of local adverse events (sharp injection pain) listed	**IANB (1.7 mL) or BI (1.0 mL) of:** • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 4% articaine, no vasoconstrictor Events that did occur were as follows: *IANB* • Sharp injection pain = 2/62 *Infiltration* • Sharp injection pain = 1/62	No statistically significant differences occurred between solutions in terms of numbers of adverse events
Moore 2007	Numbers of participants experiencing pain on injection were listed	**Maxillary BI (buccal and palatal if required, and variable volumes) of:** 4% articaine, 1:200,000 epinephrine • Burning injection pain = 0/42 4% articaine, 1:100,000 epinephrine • Burning injection pain = 0/42	No statistically significant differences occurred between solutions in terms of numbers of adverse events
Mumford 1961	Numbers of adverse events listed	**"Regional" (1.5 mL) and infiltration injections (1.0 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no epinephrine No adverse events reported	Not applicable
Nordenram 1990	Numbers of adverse events listed	**Maxillary BI (0.6 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 3% prilocaine, 0.03 IU/mL felypressin No adverse events occurred	Not applicable

Nydegger 2014	Heft-Parker VAS (170 mm line) • No pain = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors strong, intense, and maximum possible)	**Mandibular BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine *Needle insertion* • None = 3% (2/60) • Mild = 82% (49/60) • Moderate = 15% (9/60) • Severe = 0% (0/60) • Mean ± SD = 32 ± 22 mm *Needle placement* • None = 12% (7/60) • Mild = 70% (42/60) • Moderate = 17% (10/60) • Severe = 2% (1/60) • Mean ± SD = 33 ± 28 mm *Solution deposition* • None = 3% (2/60) • Mild = 60% (36/60) • Moderate = 35% (21/60) • Severe = 2% (1/60) • Mean ± SD = 52 ± 30 mm 4% prilocaine, 1:200,000 epinephrine *Needle insertion* • None = 10% (6/60) • Mild = 75% (45/60) • Moderate = 15% (9/60) • Severe = 0% (0/60) • Mean ± SD = 32 ± 21 mm *Needle placement* • None = 13% (8/60) • Mild = 68% (41/60) • Moderate = 15% (9/60) • Severe = 3% (2/60) • Mean ± SD = 34 ± 30 mm *Solution deposition* • None = 8% (5/60) • Mild = 67% (40/60) • Moderate = 25% (15/60) • Severe = 0% (0/60) • Mean ± SD = 41 ± 25 mm	There were no significant differences (P > .05) among the anaesthetic formulations within each injection phase
Odabas 2012	Taddio's Scale was used for objective evaluation of children: • Facial display • Arm/Leg movements • Torso movements • Crying Wong–Baker FACES Pain Rating Scale	**Maxillary BI (1.8 mL) of:** 4% articaine, 1:200,000 epinephrine • Mean ± SD = 2.32 ± 2.04 3% mepivacaine, no epinephrine • Mean ± SD = 1.90 ± 2.24	No significant difference was found between objective evaluations (Taddio's Scale) during injection or between first and second evaluation periods Wong-Baker FACES Pain Rating Scale showed children reacted positively to injections of both solutions immediately after receiving anaesthetic solutions. No significant difference was found between solutions (P = 0.07)

Oliveira 2004	VAS ranging measured in cm, from 0 = 'no pain' to 10 = 'worst pain imaginable' following injection of the palate .	**Maxillary BI (1.8 mL) and PI (0.35 mL) of:** 4% articaine, 1:100,000 epinephrine • Median = 1.57 cm (range = 0–10.0) 2% lidocaine, 1:100,000 epinephrine • Median = 1.86 cm (range = 0–10.0)	There was no difference between articaine and lidocaine (P = 0.45)
Ram 2006	Taddio's Scale was used for objective evaluation of children: • Facial display • Arm/Leg movements • Torso movements • Crying Wong-Baker FACES Pain Rating Scale	**IANB and BI (up to 1 cartridge) of:** 2% lidocaine, 1:100,000 epinephrine • Mean = 1.06 ± 0.73# (Wong–Baker FPS) 4% articaine, 1:200,000 epinephrine • Mean = 1.08 ± 0.79# (Wong–Baker FPS)	There was no difference in subjective evaluation (Wong–Baker FPS) of pain reaction between lidocaine and articaine between boys and girls when maxillary infiltration or mandibular block techniques were used. Ninety-eight per cent of scores ≤ 3 were recorded when either method was used and for either solution No significant difference was found between solutions in the objective evaluation (according to Taddio's Scale) during injection or between maxillary infiltrations or mandibular blocks
Robertson 2007	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**Mandibular BI (1.8 mL) of:** 4% articaine with 1:100,000 epinephrine (mean ± SD) • Needle insertion = 24 ± 25 mm • Needle placement = 33 ± 29 mm • Solution deposition = 36 ± 30 mm 2% lidocaine with 1:100,000 epinephrine (mean ± SD) • Needle insertion = 27 ± 26 mm • Needle placement = 32 ± 25 mm • Solution deposition = 37 ± 36 mm	There were no significant differences between the 2 anaesthetic formulations in terms of this variable Needle insertion P = 0.9795 Needle placement P = 1.0 Solution deposition P = 0.9999
Santos 2007	Numbers of adverse events listed	**IANB (1.8 mL) and mandibular BI (0.9 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine No adverse reactions occurred with each local anaesthetic solution intraoperatively	Not applicable
Sherman 1954	Numbers of adverse events listed	**Mandibular and maxillary injections (1.1-2.2 mL) of:** • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine There were no adverse events	Not applicable

Srisurang 2011	100 mm VAS (no pain = 0 mm, worst pain imaginable = 100 mm)	**Maxillary BI (0.9 mL) and PI (0.3 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Buccal mean ± SD = 19.8 ± 21.3 mm • Palatal mean ± SD = 38.1 ± 23.5 mm 4% articaine, 1:100,000 epinephrine • Buccal mean ± SD = 18.5 ± 12.5 mm • Palatal mean ± SD = 34.7 ± 17.1 mm 2% mepivacaine, 1:100,000 epinephrine • Buccal mean ± SD = 19.8 ± 17.1 mm • Palatal mean ± SD = 30.3 ±19.7 mm	There was no statistically significant difference between the 3 local anaesthetic solutions for buccal or palatal injection
Yilmaz 2011	Signs of discomfort measured as a surrogate marker for the presence or absence of pain: • Facial expressions • Hand movements • Torso movements • Leg movements • Crying	**IANB and BI (1.0 mL) of:** 4% articaine, 100,000 epinephrine *Maxilla* • Facial expressions = 8/32 • Hand movements = 10/32 • Torso movements = 11/32 • Leg movements = 3/32 • Crying = 8/32 *Mandible* • Facial expressions = 10/47 • Hand movements = 4/47 • Torso movements = 10/47 • Leg movements = 1/47 • Crying = 4/47 3% prilocaine, 0.03 IU/mL felypressin *Maxilla* • Facial expressions = 22/36 • Hand movements = 10/36 • Torso movements = 10/36 • Leg movements = 8/28 • Crying = 16/36 *Mandible* • Facial expressions = 10/42 • Hand movements = 3/42 • Torso movements = 2/42 • Leg movements = 2/42 • Crying = 7/42	More pain was present with maxillary infiltration than with inferior alveolar nerve blocks Pain following injections of both solutions was also statistically significant (P < 0.05) – twice as many responses to maxillary prilocaine than articaine. There were no pain-related behaviours among inferior alveolar nerve block patients
Postoperative injection pain, swelling, and bruising			
Abdulwahab 2009	Numbers of adverse events listed	**Mandibular BI (0.9 mL) of:** *During testing session* • Pain/soreness = 1/108 *Follow-up (24 hours after testing)* • Pain/soreness at injection site = 6/108 • Swelling = 2/108	"Minor in number and not dependent on local anesthetic formulation"

Albertson 1963	Numbers of adverse events listed	**Injections (unspecified in terms of technique and volume) of:** 2% mepivacaine, 1:20,000 levonordefrin • Oedema = 28/113 • Swelling at site = 1/113 • Irritation = 0/113 • Soreness = 3/113 2% lidocaine, 1:100,000 epinephrine • Oedema = 29/110 • Swelling at site = 2/110 • Irritation = 3/110 • Soreness = 4/110 Total numbers of participants assessed were not clear (dropouts, etc). Totals are based on those whose success was measured	None reported
Arrow 2012	Numbers of adverse events listed	**BI (up to 2.2 mL) of:** 4% articaine, 1:100,000 epinephrine • Pain at injection site = 1/56 Other solutions and injections produced no pain at injection sites	Tests of association between postoperative complications and local anaesthetic technique and local anaesthetic type were not statistically significant
Batista da Silva 2010	Postoperative pain: 100 mm VAS ranging from 0 = "no pain" to 100 = "unbearable pain"	**Mental nerve blocks (0.6 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Range = 0-25 mm 4% articaine, 1:100,000 epinephrine • Range = 0-34 mm	There was no significant difference (P > 0.05) between solutions regarding injection pain and postoperative pain
		IONBs (1.8 mL) of: 2% lidocaine, 1:100,000 epinephrine *Day 0 (day of injection)* • None = 80% (32/40) • Mild = 18% (7/40) • Moderate = 2% (1/40) • Severe = 0% (0/40) • Mean ± SD = 0.23 ± 0.48 *Day 1* • None = 82% (33/40) • Mild = 15% (6/40) • Moderate = 2% (1/40) • Severe = 0% (0/40) • Mean ± SD = 0.20 ± 0.46 *Day 2* • None = 90% (36/40) • Mild = 8% (3/40) • Moderate = 2% (1/40) • Severe = 0% (0/40) • Mean ± SD = 0.13 ± 0.40 *Day 3* • None = 92% (37/40) • Mild = 5% (2/40) • Moderate = 2% (1/40) • Severe = 0% (0/40) • Mean ± SD = 0.10 ± 0.39 2% lidocaine, 1:50,000 epinephrine *Day 0 (day of injection)*	

Berberich 2009	Pain following injection (after numbness wore off and each morning on arising for 3 days): • 0 = no pain • 1 = mild pain that was recognizable but not discomforting • 2 = moderate pain that was discomforting but bearable • 3 = severe pain that caused considerable discomfort and was difficult to bear Facial bruising: numbers of adverse events, pooled for all 3 solutions	• None = 85% (34/40) • Mild = 15% (6/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.15 ± 0.36 *Day 1* • None = 82% (33/40) • Mild = 18% (7/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.18 ± 0.38 *Day 2* • None = 90% (36/40) • Mild = 10% (4/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.10 ± 0.30 *Day 3* • None = 95% (38/40) • Mild = 5% (2/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.05 ± 0.22 3% mepivacaine, no vasoconstrictor *Day 0 (day of injection)* • None = 82% (33/40) • Mild = 18% (7/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.20 ± 0.41 *Day 1* • None = 90% (36/40) • Mild = 10% (4/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.10 ± 0.30 *Day 2* • None = 95% (38/40) • Mild = 5% (2/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.05 ± 0.22 *Day 3* • None = 95% (38/40) • Mild = 5% (2/40) • Moderate = 0% (0/40) • Severe = 0% (0/40) • Mean ± SD = 0.05 ± 0.22 Facial bruising = 2/120 total injections	There were no significant differences (P > .05) among the 3 anaesthetic formulations Moderate pain was reported by only 1 patient when the anaesthesia wore off, which decreased during the next 3 days

Bradley 1969	Numbers of adverse events listed	**Infiltration or "mandibular" injection (0.8-3.6 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Infiltration* • Soreness = 1/82 • Swelling = 0/82 *Mandibular* • Soreness = 0/56 • Swelling = 0/56 3% mepivacaine, no vasoconstrictor *Infiltration* • Soreness = 1/66 • Swelling = 3/66 *Mandibular* • Soreness = 2/50 • Swelling = 0/50	None reported
Caldas 2015	10 cm VAS (0 = no pain, and 10 = the most severe pain)	**BI (1.8 mL) of:** • 2% lidocaine, 1:100,000 epinephrine = 2.58 ± 7.28 mm## • 2% lidocaine, 1:200,000 epinephrine = 0.00 ± 0.00mm##	For pain after injection, there was a difference between 2% lidocaine with 1:200,000 epinephrine and 2% lidocaine and 1:100,000 epinephrine 24 hours later (P = 0.001)
Chilton 1971	Numbers of adverse events listed (pooled - exact type not stated)	**Infiltration (1.5 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Local events = 2/130 4% prilocaine, 1:200,000 epinephrine • Local events = 1/134 4% prilocaine, no epinephrine • Local events = 4/131 **IANB (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Local events = 3/74 4% prilocaine, 1:200,000 epinephrine • Local events = 0/68 4% prilocaine,no epinephrine • Local events = 2/74	No statistical significance between solutions, although slightly more occurred with lidocaine

Elbay 2016	Numbers of adverse events listed	**IANB (0.9 mL) of:** 2% lidocaine, 1:80,000 epinephrine *Pulpotomy* • Mild pain = 3/30 • Moderate pain = 0/30 *Extraction* • Mild pain = 7/30 • Moderate pain = 0/30 3% mepivacaine, no vasoconstrictor *Pulpotomy* • Mild pain = 4/30 • Moderate pain = 1/30 *Extraction* • Mild pain = 9/30 • Moderate pain = 4/30	There was no statistically significant difference in postoperative pain between the 2 local anaesthetics (P = 0.130)
Epstein 1965	Numbers of adverse events listed	**BI (1.2 mL) and IANB (1.5 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Pain = 0/133 4% prilocaine, no vasoconstrictor • Pain = 1/145	Not reported
Epstein 1969	Numbers of local adverse events listed (pooled - unclear of exact types of adverse effects)	**BI (1.2 mL) and IANB (1.4 mL) of:** Local side effects 2% lidocaine, 1:100,000 epinephrine • BI = 0/110 • IANB = 2/81 4% prilocaine, 1:200,000 epinephrine • BI = 0/134 • IANB = 0/71 4% prilocaine, no epinephrine • BI = 0/127 • IANB = 0/76	Not reported

Evans 2008	Heft-Parker VAS (170 mm line with various descriptive terms) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**Maxillary BI (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Day 0 (day of injection: mean ± SD)* • Lateral incisor = 15 ± 18 mm • First molar = 13 ± 15 mm *Day 1 (mean ± SD)* • Lateral incisor = 6 ± 9 mm • First molar = 4 ± 12 mm *Day 2 (mean ± SD)* • Lateral incisor = 5 ± 11 mm • First molar = 2 ± 7 mm *Day 3 (mean ± SD)* • Lateral incisor = 3 ± 10 mm • First molar = 0 ± 1 mm Swelling = 2/80 (1 lateral incisor and 1 molar) Bruising = 0/80 4% articaine, 1:100,000 epinephrine *Day 0 (day of injection: mean ± SD)* • Lateral incisor = 29 ± 27 mm • First molar = 26 ± 27 mm *Day 1 (mean ± SD)* • Lateral incisor = 15 ±18 mm • First molar = 13 ± 20 mm *Day 2 (mean ± SD)* • Lateral incisor = 11 ± 17 mm • First molar = 4 ± 8 mm *Day 3 (mean ± SD)* • Lateral incisor = 6 ± 15 mm • First molar = 1 ± 3 mm Swelling = 1/80 (1 molar) Bruising = 1/80 (lateral incisor)	P values for lidocaine vs articaine comparisons: *Day 0* Lateral incisor = 0.0049‡ First molar = 0.0035‡ *Day 1* Lateral incisor = 0.2888§ First molar = 0.2506§ *Day 2* Lateral incisor = 0.0617§ First molar = 1.0000§ *Day 3* Lateral incisor = 0.3432§ First molar = 1.0000§ ‡There was a significant difference (P < 0.05) between anaesthetic solutions §There was no significant difference (P > 0.05) between solutions

Forloine 2010	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**High-tuberosity maxillary second division nerve blocks (4.0 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Day 0 (day of injection)* • None = 24% (12/50) • Mild = 48% (24/50) • Moderate = 28% (14/50) • Severe = 0% (0/50) • Mean ± SD = 30 ± 29 mm *Day 1* • None = 30% (15/50) • Mild = 48% (24/50) • Moderate = 22% (11/50) • Severe = 0% (0/50) • Mean ± SD = 26 ± 30 mm *Day 2* • None = 60% (30/50) • Mild = 30% (15/50) • Moderate = 10% (5/50) • Severe = 0% (0/50) • Mean ± SD = 12 ± 21 mm *Day 3* • None = 84% (42/50) • Mild = 14% (7/50) • Moderate = 2% (1/50) • Severe = 0% (0/50) • Mean ± SD = 4 ± 13 mm 3% mepivacaine, no vasoconstrictor *Day 0 (day of injection)* • None = 8% (4/50) • Mild = 62% (31/50) • Moderate = 30% (15/50) • Severe = 0% (0/50) • Mean ± SD = 41 ± 29 mm *Day 1* • None = 24% (12/50) • Mild = 50% (25/50) • Moderate = 26% (13/50) • Severe = 0% (0/50) • Mean ± SD = 30 ± 26 mm *Day 2* • None = 46% (23/50) • Mild = 48% (24/50) • Moderate = 6% (3/50) • Severe = 0% (0/50) • Mean ± SD = 16 ± 19 mm *Day 3* • None = 68% (34/50) • Mild = 30% (15/50) • Moderate = 2% (1/50) • Severe = 0% (0/50) • Mean ± SD = 7 ± 13 mm	There was no significant difference between the 2 anaesthetic formulations

Gangarosa 1967	Numbers of adverse events listed	**Mandibular block and infiltration (volume not stated) of each of the following:** • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor No adverse events reported	Not applicable
Gregorio 2008	Numbers of adverse events listed	**IANB (1.8 mL) and local infiltration (0.9 mL) of:** • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine No adverse events reported	Not applicable
Haase 2008	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**IANB of 4% articaine, 1:100,000 epinephrine (1.8 mL) and an additional BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine (mean pain ± SD) • Day 0 (day of injection) = 28 ± 28 mm • Day 1 = 16 ± 20 mm • Day 2 = 9 ± 15 mm • Day 3 = 4 ± 13 mm Swelling = 4/73 Bruising = 2/73 2% lidocaine, 1:100,000 epinephrine (mean pain ± SD) • Day 0 (day of injection) = 26 ± 26 mm • Day 1 = 16 ± 23 mm • Day 2 = 9 ± 17 mm • Day 3 = 5 ± 14 mm Swelling = 3/73 Bruising = 2/73	Results showed no significant differences (P > 0.05) between anaesthetic formulations. Day 0: P > 0.99 Day 1: P > 0.99 Day 2: P > 0.99 Day 3: P > 0.99
Hellden 1974	Numbers of adverse events listed	**IANB (1.8 mL) and local infiltration (1.8 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3.0% mepivacaine, no vasoconstrictor No adverse events reported	Not applicable
Hosseini 2016	Adverse events.	**Maxillary BI (1.8 mL) of the following:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine There were no adverse events	Not applicable
Jain 2016	VAS from 0 (no pain) to 10 (worst pain imaginable)	**IANB and BI (1.7 mL in total) of:** 2% lidocaine, 1:100,000 epinephrine • Mean ± SD = 1.31 ± 1.05 4% articaine, 1:100,000 epinephrine • Mean ± SD = 0.89 ± 0.58	The difference was significant (P = 0.039)
Kammerer 2012	Adverse events	**IANB and buccal nerve block (up to 2.2 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, no vasoconstrictor No adverse events reported	Not applicable

Karm 2017	100 mm VAS from “minimum” = no pain at all (left end) to “maximum” = maximum imaginable pain (right end)	**IANB and BI (1.8 mL in total) of:** *2 hours post injection* 2% lidocaine, 1:80,000 epinephrine • Mean ± SD = 17.2 ± 2.3 mm 2% lidocaine, 1:200,000 epinephrine • Mean ± SD = 21.04 ± 2.2 mm *4 hours post injection* 2% lidocaine, 1:80,000 epinephrine • Mean ± SD = 38.8 ± 2.5 mm 2% lidocaine, 1:200,000 epinephrine • Mean ± SD = 35.7 ± 2.3 mm *6 hours post injection* 2% lidocaine, 1:80,000 epinephrine • Mean ± SD = 34.8 ± 2.6 mm 2% lidocaine, 1:200,000 epinephrine • Mean ± SD = 38.0 ± 2.7 mm	P = 0.405 P = 0.433 P = 0.267
Kolli 2017	Adverse events	**Maxillary BI (1.7 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine (epinephrine concentrations assumed) There were no adverse events	Not applicable
Kramer 1958	Numbers of adverse events listed (pooled)	**Mandibular and maxillary injections (1 or more cartridges) of:** 2% lidocaine, 1:50,000 epinephrine • Mandibular = 1.16% • Maxillary = 0.7% 2% lidocaine, 1:100,000 epinephrine • Mandibular = 2.0% • Maxillary = 0%	Not reported
Malamed 2000b	Numbers of local adverse events listed	**Infiltration or nerve block (1.9-2.6 mL depending on solution and complexity of procedure) of:** 4% articaine, 1:100,000 epinephrine • Injection site pain = 1/50 2% lidocaine, 1:100,000 epinephrine • Injection site pain = 0/20	Not reported

McEntire 2011	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**Mandibular BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine *Day 0 (day of injection)* • None = 27% (23/86) • Mild = 67% (57/86) • Moderate = 6% (5/86) • Severe = 0% (0/86) • Mean ± SD = 20 ± 22 mm *Day 1* • None = 42% (36/86) • Mild = 54% (46/86) • Moderate = 4% (3/86) • Severe = 0% (0/86) • Mean ± SD = 13 ± 19 mm *Day 2* • None = 56% (48/86) • Mild = 42% (36/86) • Moderate = 1% (1/86) • Severe = 0% (0/86) • Mean ± SD = 8 ± 14 mm *Day 3* • None = 69% (59/86) • Mild = 29% (25/86) • Moderate = 1% (1/86) • Severe = 0% (0/86) • Mean ± SD = 5 ± 13 mm 4% articaine, 1:200,000 epinephrine *Day 0 (day of injection)* • None = 28% (24/86) • Mild = 59% (50/86) • Moderate = 13% (11/86) • Severe = 0% (0/86) • Mean ± SD = 23 ± 26 mm *Day 1* • None = 40% (34/86) • Mild = 54% (46/86) • Moderate = 6% (5/86) • Severe = 0% (0/86) • Mean ± SD = 15 ± 21 mm *Day 2* • None = 53% (45/86) • Mild = 44% (37/86) • Moderate = 4% (3/86) • Severe = 0% (0/86) • Mean ± SD = 10 ± 19 mm *Day 3* • None = 61% (52/86) • Mild = 37% (31/86) • Moderate = 2% (2/86) • Severe = 0% (0/86) • Mean ± SD = 6 ± 16 mm For both solutions • Initial tenderness = 5%–7% • Intraoral bruising = 1%–4% • Slight subjective swelling in the area of the injection = 1%–2%	There was no significant difference (P > 0.05) between the 2 solutions

Mikesell 2005	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible) Episodes of soreness and swelling	**IANB (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Day 0 (day of injection)* • None = 30% (17/57) • Mild = 54% (31/57) • Moderate = 16% (9/57) • Severe = 0% (0/57) • Mean ± SD = 23 ± 24 mm • Soreness = 5% (3/5) • Swelling = 0% (0/57) *Day 1* • None = 47% (27/57) • Mild = 49% (28/57) • Moderate = 4% (2/57) • Severe = 0% (0/57) • Mean ± SD = 14 ± 19 mm • Soreness = 2% (1/57) • Swelling = 0% (0/57) *Day 2* • None = 61% (35/57) • Mild = 35% (20/57) • Moderate =4% (2/57) • Severe = 0% (0/57) • Mean ± SD = 4 ± 12 mm • Soreness = 0% (0/57) • Swelling = 0% (0/57) *Day 3* • None = 70% (40/57) • Mild = 30% (17/57) • Moderate = 0% (0/57) • Severe = 0% (0/57) • Mean ± SD = 2 ± 7mm • Soreness = 0% (0/57) • Swelling = 0% (0/57) 4% articaine, 1:100,000 epinephrine *Day 0 (day of injection)* • None = 28% (16/57) • Mild = 51% (29/57) • Moderate = 21% (12/57) • Severe = 0% (0/57) • Mean ± SD = 28 ± 29 mm • Soreness = 4% (2/57) • Swelling = 2% (1/57) *Day 1* • None = 39% (22/57) • Mild = 51% (29/57) • Moderate = 11% (6/57) • Severe = 0% (0/57) • Mean ± SD = 17 ± 23 mm • Soreness = 5% (3/57) • Swelling = 2% (1/57) *Day 2* • None = 54% (31/57) • Mild = 44% (25/57) • Moderate = 2% (1/57) • Severe = 0% (0/57)	P values for lidocaine vs articaine comparison: Day 0: P = 0.1746 Day 1: P = 0.2756 Day 2: P = 0.0236 Day 3: P = 0.0458 There was no significant difference between the 2 formulations for the day of injection and the first post-injection day. Articaine had statistically higher pain ratings for days 2 and 3 There was no significant difference (P < 0.05) between the 2 formulations (soreness and swelling, on each day)

		• Mean ± SD = 10 ± 16 mm • Soreness = 2% (1/57) • Swelling = 0% (0/57) *Day 3* • None = 67% (38/57) • Mild = 33% (19/57) • Moderate = 2% (1/57) • Severe = 0% (0/57) • Mean ± SD = 4 ± 9 mm • Soreness = 2% (1/57) • Swelling = 0% (0/57)	
Moore 2006	Numbers of local adverse events (pain following injection) listed	**IANB (1.7 mL) or BI (1.0 mL) of:** • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 4% articaine, no vasoconstrictor Events that did occur were as follows: *IANB* • Soreness at injection site = 15/62 *Infiltration* • Soreness at injection site = 3/62	No statistically significant differences occurred between solutions in terms of numbers of adverse events
Moore 2007	Numbers of participants experiencing pain on injection, swelling, and bruising	**Maxillary BI (buccal and palatal if required, and variable volumes) of:** 4% articaine, 1:200,000 epinephrine • Pain/soreness = 6/42 • Swelling = 3/42 4% articaine, 1:100,000 epinephrine • Pain/soreness = 3/42 • Swelling = 5/42	No statistically significant differences occurred between solutions in terms of numbers of adverse events
Mumford 1961	Numbers of adverse events listed	**"Regional" (1.5 mL) and infiltration injections (1.0 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no epinephrine No adverse events reported	Not applicable
Nordenram 1990	Numbers of adverse events listed	**Maxillary BI (0.6 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 3% prilocaine, 0.03 IU/ml felypressin No adverse events occurred	Not applicable

Nydegger 2014	Pain following injection, tested after numbness wore off and each morning, on rising, for 3 days Heft-Parker VAS (170 mm line) • No pain = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors strong, intense, and maximum possible)	**Mandibular BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine *Day 0* • None = 10% (6/60) • Mild = 68% (41/60) • Moderate = 22% (13/60) • Severe = 0% (0/60) • Mean ± SD = 37 ± 27 mm *Day 1* • None = 27% (16/60) • Mild = 65% (39/60) • Moderate = 8% (5/60) • Severe = 0% (0/60) • Mean ± SD = 27 ± 24 mm *Day 2* • None = 40% (24/60) • Mild = 55% (33/60) • Moderate = 5% (3/60) • Severe = 0% (0/60) • Mean ± SD = 18 ± 20 mm *Day 3* • None = 52% (31/60) • Mild = 43% (26/60) • Moderate = 5% (3/60) • Severe = 0% (0/60) • Mean ± SD = 10 ± 16 mm 4% prilocaine, 1:200,000 epinephrine *Day 0* • None = 25% (15/60) • Mild = 72% (43/60) • Moderate = 3% (2/60) • Severe = 0% (0/60) • Mean ± SD = 22 ± 20 mm *Day 1* • None = 37% (22/60) • Mild = 57% (34/60) • Moderate = 7% (4/60) • Severe = 0% (0/60) • Mean ± SD = 18 ± 21 mm *Day 2* • None = 52% (32/60) • Mild = 42% (25/60) • Moderate = 5% (3/60) • Severe = 0% (0/60) • Mean ± SD = 12 ± 19 mm *Day 3* • None = 55% (33/60) • Mild = 43% (26/60) • Moderate = 2% (1/60) • Severe = 0% (0/60) • Mean ± SD = 8 ± 14 mm	Articaine was significantly more painful than prilocaine (P = 0.0014) on day 1

Odabas 2012	Taddio's Scale was used for objective evaluation of children: • Facial display • Arm/Leg movements • Torso movements • Crying Wong-Baker FACES Pain Rating Scale	**BI (1.8 mL) of:** 4% articaine, 1:200,000 epinephrine *Pain after 1 hour* • Mean ± SD = 0.51 ± 1.14 *Pain after 2 hours* • Mean ± SD = 0.13 ± 0.46 3% mepivacaine, no epinephrine *Pain after 1 hour* • Mean ± SD = 0.45 ± 0.94 *Pain after 2 hours* • Mean ± SD = 0.16 ± 0.53	No significant difference was found between objective evaluation (Taddio's Scale) during injection and first and second evaluation periods Wong-Baker FACES Pain Rating Scale showed children reacted positively to injections of both solutions by phone 1 hour (P = 0.89) and 2 hours after (P = 0.77) injection
Ram 2006	Taddio's Scale was used for objective evaluation of children: • Facial display • Arm/Leg movements • Torso movements • Crying Wong-Baker FACES Pain Rating Scale	**IANB and BI (up to 1 cartridge) of:** 2% lidocaine, 1:100,000 epinephrine (Wong–Baker FPS) *Pain after 1 hour* • Mean = 1.03 ± 0.63# *Pain after 2 hours* • Mean = 1.03 ± 0.81# 4% articaine, 1:200,000 epinephrine (Wong–Baker FPS) *Pain after 1 hour* • Mean = 0.95 ± 0.65# *Pain after 2 hours* • Mean = 0.90 ± 0.68#	There was no difference in subjective evaluation (Wong–Baker FPS) of pain reaction between lidocaine and articaine between boys and girls when maxillary infiltration or mandibular block techniques were used No significant difference was found between solutions in objective evaluation (according to Taddio's Scale) during injection or between maxillary infiltrations or mandibular blocks
Robertson 2007	Heft-Parker VAS (170 mm line) • None = 0 mm • Mild pain > 0 mm ≤ 54 mm (included descriptors of faint, weak, and mild pain) • Moderate pain > 54 mm < 114 mm (included descriptor of moderate pain) • Severe pain ≥ 114 mm (included descriptors of strong, intense, and maximum possible)	**Mandibular BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine (mean ± SD) • Day 0 (day of injection) = 20 ± 23 mm • Day 1 = 15 ± 24 mm • Day 2 = 11 ± 22 mm • Day 3 = 6 ± 18 mm Swelling = 2/56 Bruising = 0/56 2% lidocaine, 1:100,000 epinephrine (mean ± SD) • Day 0 (day of injection) = 18 ± 25 mm • Day 1 = 12 ± 24 mm • Day 2 = 9 ± 20 mm • Day 3 = 5 ± 15 mm Swelling = 3/59 Bruising = 1/59	There were no significant differences (P > 0.05) between anaesthetic formulations for post-injection pain: Day 0: P = .9976 Day 1: P = .9841 Day 2: P = .9957 Day 3: P = 1.0000
Santos 2007	Numbers of adverse events listed	**IANB (1.8 mL) and mandibular BI (0.9 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine No adverse reactions occurred with each local anaesthetic solution intraoperatively or postoperatively	Not applicable

Sherman 1954	Numbers of adverse events listed	**Mandibular and maxillary injections (1.1-2.2 mL) of:** 2% lidocaine, 1:50,000 epinephrine • "Blebs" at site of injection = 0/100 2% lidocaine, 1:100,000 epinephrine • "Blebs" at site of injection = 1/100	Not reported
Stibbs 1964	Numbers of adverse events listed (pooled)	**"Mandibular" injections and infiltrations (varying volumes) of:** 2% mepivacaine, 1:20,000 levonordefrin • Tissue irritation (oedema, swelling, postoperative soreness at injection site) = 3/248 2% lidocaine, 1:50,000 epinephrine • Tissue irritation (oedema, swelling, postoperative soreness at injection site) = 11/264	Not reported
Trullenque-Eriksson 2011	Numbers of local adverse events	**IANB and mandibular BI (1.8 mL) of:** 0.5% bupivacaine, 1:200,000 epinephrine • Postoperative swelling, infection and bleeding, pain at injection site (exact numbers not stated) 4% articaine, 1:200,000 epinephrine • Postoperative swelling, infection, and bleeding (exact numbers not stated) 42.1% had ≥ 1 adverse event (figure includes both local anaesthetics)	Not reported
Yilmaz 2011	Adverse event frequency was measured at 24 hours and 7 days after the procedure	**IANB and maxillary infiltration (1.0 mL) of:** 4% articaine, 1:100,000 epinephrine • IANB pain = 2/47 • Maxillary infiltration pain = 1/32 3% prilocaine, 0.03 IU/mL felypressin • IANB pain = 0/42 • Maxillary infiltration pain = 0/36	Not reported
Other local adverse events.			
Abdulwahab 2009	Numbers of adverse events (results for each solution were pooled)	**Mandibular BI (0.9 mL) of:** *Follow-up (24 hours after testing)* • Tooth sensitivity = 1/108 • Fissure at corner of the lip = 1/108	"Minor in number and not dependent on local anaesthetic formulation"
Allegretti 2016	Adverse effects were recorded if present	**IANB (3.6 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine No local adverse events reported	Not applicable

Arrow 2012	Numbers of adverse events listed	**IANB (up to 2.2 mL) of:** 2% lidocaine, 1:80,000 epinephrine • Cheek-bite = 1/29 **BI of:** 2% lidocaine, 1:80,000 epinephrine • Postoperative lip-bite = 1/28 **IANB of:** 4% articaine, 1:100,000 epinephrine • Tender tooth = 1/28 Episodes of aching jaw occurred in 2 participants = (2 articaine and 2 lidocaine)	Tests of association between postoperative complications and different formulations were not statistically significant
Atasoy Ulusoy 2014	Numbers of adverse events listed	**Maxillary BI (1.5 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine bitartrate No local adverse events were reported during the investigation	Not reported
Batista da Silva 2010	Postoperative complications (24 hours later)	**Mental nerve block (0.6 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine No local adverse effect other than pain was reported by any participants	Not applicable
Chilton 1971	Numbers of adverse events listed (pooled - exact type not stated)	**Infiltration (1.5 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Local events = 2/130 4% prilocaine, 1:200,000 epinephrine • Local events = 1/134 4% prilocaine, no epinephrine • Local events = 4/131 **IANB (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Local events = 3/74 4% prilocaine, 1:200,000 epinephrine • Local events = 0/68 4% prilocaine,no epinephrine • Local events = 2/74	No statistical significance between solutions, although slightly more occurred with lidocaine

Colombini 2006	Assessment of mouth opening at suture removal (5 days postoperatively), measured as a percentage of preoperative mouth opening Total amount of rescue medication taken Numbers of local adverse events listed	**IANB (1.8 mL) and local infiltration (0.9 mL) of:** 2% mepivacaine, 1:100,000 epinephrine (mean ± SEM) • Mouth opening = 93.87% ± 4.72% • Rescue medication = 1162.50 ± 405.25 mg 4% articaine, 1:100,000 epinephrine (mean ± SEM) • Mouth opening = 83.20% ± 3.82% • Rescue medication = 975.00 ± 361.33 mg No adverse reactions were reported during surgery and during the first postoperative hour	There was no significant difference in mouth opening at suture removal compared with preoperative measures for both treatment groups (P > 0.05) There was no statistically significant difference concerning the total amount of rescue analgesic medication (paracetamol) ingested by patients (P > 0.05) Not applicable
Elbay 2016	Numbers of adverse events listed	**IANB (0.9 mL) of:** 2% lidocaine, 1:80,000 epinephrine • Bleeding following extraction (requiring a change in sponge) = 5/30 • Lip biting (extraction + pulpectomy) = 1/60 • Haematoma, swelling and infection = 0/60 3% mepivacaine, no vasoconstrictor • Bleeding following extraction (requiring a change in sponge) = 8/30 • Lip biting (extraction + pulpotomy) = 1/60 • Haematoma, swelling and infection = 0/60	There was no statistically significant difference in bleeding following extraction between the 2 anaesthetic solutions (P = 0.102)
Epstein 1965	Numbers of local adverse events listed	**BI (1.2 mL) and IANB (1.5 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Excessive bleeding = 1/133 • Prolonged anaesthesia = 0/133 4% prilocaine, no vasoconstrictor • Excessive bleeding = 0/145 • Prolonged anaesthesia = 1/145	Not reported
Epstein 1969	Numbers of local adverse events listed (pooled - unclear of exact types of adverse effects)	**BI (1.2 mL) and IANB (1.4 mL) of:** Local side effects 2% lidocaine, 1:100,000 epinephrine • BI = 0/110 • IANB = 2/81 4% prilocaine, 1:200,000 epinephrine • BI = 0/134 • IANB = 0/71 4% prilocaine, no epinephrine • BI = 0/127 • IANB = 0/76	Not reported

Forloine 2010	Numbers of adverse events listed	**High-tuberosity maxillary second division nerve blocks (4.0 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Diplopia = 6/50 • Mandibuar lip numbness = 16/50 3% mepivacaine, no vasoconstrictor • Diplopia = 8/50 • Mandibuar lip numbness = 13/50	Not reported
Gangarosa 1967	Amount of bleeding (surgical cases only) • None • Slight • Moderate • Severe	**Mandibular block and infiltration (volume not stated) of each of the following:** • 2% lidocaine, 1:100,000 epinephrine • 4% prilocaine, no vasoconstrictor Exact data for each solution not reported	Not applicable
Gregorio 2008	Assessment of mouth opening at suture removal (7 days postoperatively), measured as a percentage of preoperative mouth opening Surgeon's assessment of quality of wound healing at suture removal (7 days postoperatively). Three-point scale: 1 = normal healing 2 = delayed healing 3 = complicated healing due to alveolitis	**IANB and local infiltration of:** 4% articaine, 1:200,000 epinephrine *Mouth opening* Without osteotomy • Mean ± SEM = 97.72% ± 2.68% With osteotomy • Mean ± SEM = 91.90% ± 3.00% *Wound healing* Without osteotomy • Mean ± SEM = 1.05 ± 0.05 With osteotomy • Mean ± SEM = 1.25 ± 0.09 0.5% bupivacaine, 1:200,000 epinephrine *Mouth opening* Without osteotomy • Mean ± SEM = 100.80% ± 2.55% With osteotomy • Mean ± SEM = 88.57% ± 2.38% *Wound healing* Without osteotomy • Mean ± SEM = 1.14 ± 0.08 With osteotomy • Mean ± SEM = 1.39 ± 0.11	Mouth opening at suture removal for patients with surgery not requiring osteotomy was not significant (P > .05), whereas with those requiring osteotomy it was significant (P < .05) The quality of wound healing was similar for both local anaesthetics, with or without osteotomy (P > .05)
Hellden 1974	Numbers of adverse events listed	**IANB (1.8 mL) and local infiltration (1.8 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3.0% mepivacaine, no vasoconstrictor No adverse events reported	Not applicable
Hosseini 2016	Adverse events	**Maxillary BI (1.8 mL) of the following:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine There were no adverse events	Not applicable

Kammerer 2012	Postoperative pain. (VAS from 0 (no pain) to 10 (worst pain)) Bleeding complications	**IANB and buccal nerve block (up to 2.2 mL) of:** 4% articaine, 1:100,000 epinephrine • Mean ± SD = 0.4 ± 0.5 4% articaine, no vasoconstrictor • Mean ± SD = 0.3 ± 0.4 No data for bleeding complications were reported	The difference was not significant (P = 0.96)
Karm 2017	Perioperative bleeding (Likert scale: scored 1–5: 1 = “a little bleeding” and 5 = “very much bleeding”)	**IANB and BI (1.8 mL in total) of:** *Perioperative bleeding* 2% lidocaine, 1:80,000 epinephrine • Mean ± SD = 2.0 ± 0.1 2% lidocaine, 1:200,000 epinephrine • Mean ± SD = 2.2 ± 0.1 *Alveolar osteitis* • 2% lidocaine, 1:80,000 epinephrine = 2/51 • 2% lidocaine, 1:200,000 epinephrine = 2/51 *Inflammation at injection site* • 2% lidocaine, 1:80,000 epinephrine = 0/51 • 2% lidocaine, 1:200,000 epinephrine = 1/51	No significant differences between groups (P = .206) There was no statistically significant difference between groups in frequency of these adverse events (P = 1.000) There was no statistically significant difference between groups in frequency of these adverse events (P = 1.000)
Keskitalo 1975	Numbers of adverse events listed	**IANB and BI (3.6 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% prilocaine, 0.03 IU/mL felypressin No differences between solutions in terms of ability to open mouth, as well as swelling, dry socket, and postoperative bleeding	Not reported
Khoury 1991	Numbers of adverse events listed (pooled)	**"Conduction" and infiltration injections (varying volumes) of:** • 3% prilocaine, 0.03 IU felypressin • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine Uncomplicated wound healing was observed In > 91% of cases in both upper and lower jaw in all groups. There were no differences in occurrence of dry socket between all groups	Not reported
Kolli 2017	Adverse events	**Maxillary BI (1.7 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine (epinephrine concentrations assumed) There were no adverse events	Not applicable

Kramer 1958	Numbers of adverse events listed (pooled)	**Mandibular and maxillary injections (1 or more cartridges) of:** 2% lidocaine, 1:50,000 epinephrine • Mandibular = 1.16% • Maxillary = 0.7% 2% lidocaine, 1:100,000 epinephrine • Mandibular = 2.0% • Maxillary = 0%	Not reported
Laskin 1977	Not reported	**IANB and BI (1.8 mL) of:** • 0.5% bupivacaine, epinephrine 1:200,000 • 2% lidocaine 2%, epinephrine 1:100,000 No side effects were reported	Not applicable
Linden 1986	Numbers of local adverse events listed	**In the mandible, IANB (2.7 mL), lingual and long buccal injections, while in the maxilla, posterior superior alveolar nerve block, local and palatal infiltration (1.8 mL)** • 0.5% bupivacaine, epinephrine 1:200,000 • 2% lidocaine 2%, epinephrine 1:100,000 The bupivacaine group demonstrated more bleeding during surgery in 11 of 20 patients	Not reported
Malamed 2000a	Numbers of local adverse events listed	**Infiltration or nerve block (2.5-4.5 mL depending on solution and complexity of procedure) of:** • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine No serious adverse events occurred. Minor events included postprocedural pain, facial oedema, infection, gingivitis, and transient paraesthesia They occurred in low numbers in both groups	Not reported
Malamed 2000b	Numbers of local adverse events listed	**Infiltration or nerve block (1.9-2.6 mL depending on solution and complexity of procedure) of:** 4% articaine, 1:100,000 epinephrine • Accidental lip injury = 1/50 • Pain = 1/50 2% lidocaine, 1:100,000 epinephrine • Accidental lip injury = 0/20 • Pain = 2/20	Not reported

Mikesell 2005	Numbers of other local adverse events listed	**IANB (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Day 0 (day of injection)* • Trismus = 9% (5/57) *Day 1* • Trismus = 7% (4/57) *Day 2* • Trismus = 0% (0/57) *Day 3* • Trismus = 0% (0/57) 4% articaine, 1:100,000 epinephrine *Day 0 (day of injection)* • Trismus = 9% (5/57) *Day 1* • Trismus = 9% (5/57) *Day 2* • Trismus = 5% (3/57) *Day 3* • Trismus = 2% (1/57)	There was no significant difference ($P < 0.05$) between the 2 formulations on each day
Moore 2006	Numbers of local adverse events listed	**IANB (1.7 mL) or maxillary BI (1.0 mL) of:** • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 4% articaine, no vasoconstrictor *Adverse events* No serious adverse events occurred. Events that did occur were as follows: IANB • Positive aspiration = 9/62 • Trismus = 2/62 • Numbness and tingling = 1/62 • Sensitive teeth = 1/62 • Sinus congestion/pain = 0/62 • Itchy throat = 0/62 • Oral lesion = 0/62 Infiltration • Positive aspiration = 1/62 • Trismus = 0/62 • Numbness and tingling = 1/62 • Sensitive teeth = 0/62 • Sinus congestion/pain = 2/62 • Itchy throat = 1/62 • Oral lesion = 1/62	No statistically significant differences occurred between solutions in terms of numbers of adverse events

Moore 2007	Numbers of adverse events listed	**Maxillary BI (buccal and palatal if required, and variable volumes) of:** • 4% articaine, 1:200,000 epinephrine (A200) = 3 events • 4% articaine, 1:100,000 epinephrine (A100) = 3 events (possibly related to the solutions used. These were not specifically detailed in the results) Events that did occur were as follows: 4% articaine, 1:100,000 epinephrine • Loose tooth/filling = 1/42 • Numbness and tingling = 1/42 • Sensitive teeth = 1/42 • Angular cheilitis = 0/42 4% articaine, 1:200,000 epinephrine • Loose tooth/filling = 1/42 • Numbness and tingling = 0/42 • Sensitive teeth = 0/42 • Angular cheilitis = 1/42	No statistically significant differences occurred between solutions in terms of numbers of adverse events
Mumford 1961	Numbers of adverse events listed	**"Regional" (1.5 mL) and infiltration injections (1.0 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no epinephrine No local adverse events were reported	Not applicable
Naik 2017	Analgesic medication consumed	**IANB (2 mL) of:** 2% lidocaine, 1:80,000 epinephrine • Mean ± SD = 3.2 ± 0.40 tablets 4% articaine, 1:100,000 epinephrine • Mean ± SD = 2.0 ± 0.14 tablets	The difference was statistically significant (P < 0.001)
Nespeca 1976	Numbers of adverse events listed	**IANB and infiltration injection (1.5-2.0 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine There were no local adverse events with either solution	Not applicable
Nordenram 1990	Numbers of adverse events listed	**BI (0.6 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 3% prilocaine, 0.03 IU/mL felypressin There were no adverse events with any solution	Not applicable

Nydegger 2014	Numbers of adverse events listed	**Mandibular BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine *Tenderness* • Day 0 = 12% (7/60) • Day 1 = 17% (10/60) • Day 2 = 5% (3/60) • Day 3 = 0% (0/60) *Subjective swelling* • Day 0 = 10% (6/60) • Day 1 = 3% (2/60) • Day 2 = 3% (2/60) • Day 3 = 0% (0/60) 4% prilocaine, 1:200,000 epinephrine *Tenderness* • Day 0 = 3% (2/60) • Day 1 = 10% (6/60) • Day 2 = 10% (6/60) • Day 3 = 8% (5/60) *Subjective swelling* • Day 0 = 2% (1/60) • Day 1 = 2% (1/60) • Day 2 = 0% (0/60) • Day 3 = 0% (0/60)	Not reported
Odabas 2012	Numbers of adverse events listed	**Maxillary injections (1.8 mL) of:** • 4% articaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine Similar for both solutions: • Accidental lip and/or cheek injury = 2/50 • Post-procedural pain = 2/50	No statistically significant differences between solutions
Pässler 1996	Numbers of adverse events listed	**Injections (2.0-4.0 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Blood filling of tooth socket after extraction* • Low = 40/65 • Moderate = 25/65 • Strongly = 0/65 *Haemorrhage during apicectomy* • Low = 12/28 • Moderate = 12/28 • Strongly = 4/28 3% prilocaine, felypressin (0.03 IU) *Blood filling of tooth socket after extraction* • Low = 23/63 • Moderate = 30/63 • Strongly = 10/63 *Haemorrhage following apicectomy* • Low = 8/24 • Moderate = 4/24 • Strongly = 12/24	Not reported

Pellicer-Chover 2013	Bleeding during the procedure Postoperative pain, VAS 0-10 (means) Postoperative analgesia duration (means and SDs) Postoperative analgesia (number needing rescue medication)	**IANB (1.8 mL) and BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine • Bleeding (abundant) = 1/36 • Postoperative pain = 5.1 • Postoperative analgesia = 203.2 ± 20.5 minutes • Postoperative analgesia = 15/36 0.5% bupivacaine, 1:200,000 epinephrine • Bleeding (abundant) = 11/36 • Postoperative pain = 4.4 • Postoperative analgesia = 215.8 ± 15.4 minutes • Postoperative analgesia = 19/36	Bleeding during the procedure: P = 0.000 Postoperative pain: P = 0.072 Postoperative analgesia duration: P = 0.363 Postoperative analgesia (number needing rescue medication): P = 0.836
Porto 2007	Postoperative pain (100 mm VAS)	**IANB and BI (3.6 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Mean ± SD = 4.10 ± 2.45 2% mepivacaine, 1:100,000 epinephrine • Mean ± SD = 4.14 ± 2.82	P = 0.4607
Ram 2006	Numbers of adverse events listed	**IANB and BI (up to 1 cartridge) of:** 2% lidocaine, 1:100,000 epinephrine • Accidental lip and/or cheek injury = 2/62 • Post-procedural pain = 1/62 • Haematoma = 1/62 4% articaine, 1:200,000 epinephrine • Accidental lip and/or cheek injury = 1/62 • Post-procedural pain = 3/62 • Haematoma = 1/62	No statistically significant differences between solutions
Sancho-Puchades 2012	Postoperative pain (100 mm VAS) Amount of rescue analgesic medication needed during first 4 postoperative days	**IANB and BI (1.8 mL) of:** 4% articaine, 1:200,000 epinephrine *Postoperative pain* • Results presented only graphically *Mean number of rescue analgesic tablets* • Day 1 = 0.17 • Day 2 = 0.24 • Day 3 = 0 • Day 4 = 0.32 0.5% bupivacaine, 1:200,000 epinephrine *Postoperative pain* • Results presented only graphically. *Mean number of rescue analgesic tablets* • Day 1 = 0.55 • Day 2 = 0 • Day 3 = 0 • Day 4 = 0	Postoperative VAS of pain varied significantly across time (P = 0.017). The bupivacaine group had lower pain scores during day 1, being statistically significant at 2:00 PM (P = 0.011) and 4:00 PM (P = 0.007) There were no statistically significant differences between total intake of rescue analgesics during the first 4 postoperative days (P > 0.05)

Santos 2007	Numbers of adverse events listed	**IANB (1.8 mL) and mandibular BI (0.9 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine No adverse reactions occurred with each local anaesthetic solution intraoperatively or postoperatively	Not applicable
Sherman 1954	Numbers of adverse events listed	**Mandibular and maxillary injections (1.1-2.2 mL) of:** • 2% lidocaine, 1:50,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine No adverse reactions were observed	Not applicable
Thakare 2014	Time to first rescue analgesic medication	**Maxillary BI (1.4 mL) of:** 4% articaine, 1:200,000 epinephrine • Mean ± SD = 131.38 ± 43.74 minutes 0.5% bupivacaine, 1:200,000 epinephrine • Mean ± SD = 288.38 ± 91.25 minutes	P < 0.0001
Trieger 1979	Numbers of adverse events listed	**IANB and infiltration (varying volumes) of:** • 0.5% bupivacaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine There were no side effects or complications with either solution	Not applicable
Trullenque-Eriksson 2011	Numbers of local adverse events	**IANB and mandibular BI (1.8 mL) of:** 0.5% bupivacaine, 1:200,000 epinephrine • Cramps in the hemi-mandible, where the surgical procedure was performed (exact numbers not stated) 4% articaine, 1:200,000 epinephrine • Postoperative ulcers, heat sensation, temporomandibular joint pain, lip droop (exact numbers not stated) 42.1% of patients had at least one adverse event (figure includes both local anaesthetics).	Not applicable
Weil 1961	Numbers of adverse events listed	**Mandibular and maxillary injections (1 cartridge or more) of:** • 3% mepivacaine, no vasoconstrictor • 2% mepivacaine, 1:20,000 levonordefrin Local postoperative side effects were few in number (exact number not stated) and were possibly due to needle trauma	Not reported

Yilmaz 2011	Adverse event frequency was measured at 24 hours and 7 days after the procedure	**IANB (1.0 mL) and maxillary infiltration (1.0 mL) of:** 4% articaine, 100,000 epinephrine *Self-inflicted soft tissue injury* • IANB = 0/47 • Maxillary infiltration = 0/32 3% prilocaine, 0.03 IU/mL felypressin *Self-inflicted soft tissue injury* • IANB = 1/42 • Maxillary infiltration = 0/36	Not reported
Systemic adverse events			
Abdulwahab 2009	Numbers of systemic adverse events (results for each solution were pooled)	**Mandibular BI (0.9 mL)** *Follow-up (24 hours after testing)* • Headache = 1/108	"Minor in number and not dependent on local anaesthetic formulation"
Albertson 1963	Numbers of adverse events listed	**Injections (unspecified in terms of technique and volume) of:** 2% mepivacaine, 1:20,000 levonordefrin • Tremor = 1/113 • Palpitation = 1/113 • Perspiration = 3/113 • Nausea = 3/113 • Faintness = 3/113 • Weakness = 2/113 2% lidocaine, 1:100,000 epinephrine • Tremor = 1/113 • Palpitation = 3/113 • Perspiration = 10/113 • Nausea = 4/113 • Faintness = 7/113 • Weakness = 0/113 Total number of participants assessed is not clear (dropouts, etc.). Totals are based on those for whom success was measured	None reported
Allegretti 2016	Adverse effects were recorded if present	**IANB (3.6 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine No systemic adverse effects reported	Not applicable
Atasoy Ulusoy 2014	Heart rates of patients were measured with a pulse oximeter during root canal procedures	**Maxillary BI (1.5 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine bitartrate No systemic adverse events were reported during the investigation	There was no significant difference between solutions regarding heart rate measurements during root canal treatment (P > 0.05) Heart rates during treatment of palatal root canals were significantly higher than during treatment of mesiobuccal and distobuccal canals with both solutions (P < 0.0001)
Batista da Silva 2010	Postoperative complications (24 hours later)	**Mental nerve block (0.6 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine No systemic adverse effect other than pain was reported by any participants	Not applicable

Bortoluzzi 2009	Blood pressure and heart rate were measured at 0, 3, and 15 minutes after injection	**Mandibular BI (0.18 mL) of:** • 4% articaine, 1:100,000 epinephrine • 2% mepivacaine, 1:100,000 epinephrine No differences were found between solutions	When solutions were compared, no differences were found at the times measured
Bouloux 1999	Cardiovascular responses as well as systemic adverse effects were assessed	**IANB and infiltration (4.4 mL), or BI and greater palatine nerve block (2.2 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine No signs or symptoms of central nervous system or cardiovascular toxicity were seen	There were no differences in cardiovascular responses between solutions; a statistically significant decrease in mean heart rate occurred between 15 and 30 minutes with bupivacaine (P = 0.002) and lidocaine (P = 0.007)
Bradley 1969	Numbers of adverse events listed	**Infiltration or "mandibular" injection (0.8-3.6 mL) of:** 2% lidocaine, 1:100,000 epinephrine *Infiltration* • Nausea = 2/82 • Faintness = 2/82 • Palpitations = 0/82 • Perspiration = 0/82 • Irritation = 0/82 *"Mandibular" injections* • Nausea = 1/56 • Faintness = 1/56 • Palpitations = 0/56 • Perspiration = 0/56 • Irritation = 0/56 3% mepivacaine, no vasoconstrictor *Infiltration* • Nausea = 2/66 • Faintness = 2/66 • Palpitations = 0/66 • Perspiration = 1/66 • Irritation = 1/66 *"Mandibular" injections* • Nausea = 1/50 • Faintness = 0/50 • Palpitations = 1/50 • Perspiration = 1/50 • Irritation = 0/50 Unclear whether these symptoms were related to the injection, the local anaesthetic used, or the anxiety of patients: "the systemic and local postoperative reactions recorded could be attributed (respectively) to the high proportion of emotionally nervous subjects"	Not applicable

Caldas 2015	Blood pressure, partial oxygen concentration, and heart rate were measured at each of 3 sessions in 3 periods: 5 minutes before anaesthetic administration, during anaesthetic injection, and immediately after injection	**BI (1.8 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 2% lidocaine, 1:200,000 epinephrine	Oxygen saturation: no variation in initial observed levels, which remained at around 96% of saturation Heart rate: no significant variations that could interfere with study results There were no statistically significant differences in systolic blood pressure (Friedman, P = 0.33), diastolic blood pressure (Friedman, P = 0.1505), heart rate (Friedman, P = 0.9464), and oxygen saturation (Friedman, P = 0.9297) with each local anaesthetic during and after local anaesthesia
Chilton 1971	Numbers of systemic adverse events listed (pooled)	**BI (1.5 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Systemic events = 5/130 4% prilocaine, 1:200,000 epinephrine • Systemic events = 1/134 4% prilocaine, no epinephrine • Systemic events = 1/131 **IANB (1.8 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Systemic events = 0/74 4% prilocaine, 1:200,000 epinephrine • Systemic events = 3/68 4% prilocaine, no epinephrine • Systemic events = 1/74 Most were syncope reactions	There was no statistical significance between solutions, although slightly more occurred with lidocaine
Colombini 2006	Numbers of systemic adverse events listed	**IANB (1.8 mL) and local infiltration (0.9 mL) of:** • 2% mepivacaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine No adverse reactions were reported during surgery and during the first postoperative hour	No statistically significant difference in blood pressure, heart rate, or oxygen saturation was seen before and during surgery, and after suture, for both groups (P > 0.05). Data were presented only in graphs
Epstein 1965	Numbers of systemic adverse events listed	**Maxillary BI (1.2 mL) and IANB (1.5 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Systemic adverse reactions = 2/133 4% prilocaine, no vasoconstrictor • Systemic adverse reactions = 1/145	Not reported

Epstein 1969	Numbers of systemic adverse events listed	**Maxillary BI (1.2 mL) and IANB (1.5 mL) of:** Systemic side effects 2% lidocaine, 1:100,000 epinephrine • BI = 0/110 • IANB = 0/81 4% prilocaine, 1:200,000 epinephrine • BI = 0/134 • IANB = 0/71 4% prilocaine, no epinephrine • BI = 0/127 • IANB = 0/76	Not reported
Forloine 2010	Numbers of systemic adverse events listed	**High-tuberosity maxillary second division nerve block (4.0 mL) of:** 2% lidocaine, 1:100,000 epinephrine • Subjective increase in heart rate = 15/50 3% mepivacaine, no vasoconstrictor • Subjective increase in heart rate = 0/50	Not reported
Gangarosa 1967	Numbers of systemic adverse events listed	**Mandibular block and infiltration (volume not stated) of each of the following:** 2% lidocaine, 1:100,000 epinephrine • Syncope = 1/118 • Anxiety = 3/118 • Local pallor = 1/118 • General pallor = 1/118 • Other = 0/118 4% prilocaine, no vasoconstrictor • Syncope = 0/56 • Anxiety = 0/56 • Local pallor = 0/56 • General pallor = 0/56 • Other = 1/56	Not reported
Gregorio 2008	Numbers of systemic adverse events listed, as well as assessments of systolic, diastolic, mean arterial pressure, heart rate, and oxygen saturation	**IANB (1.8 mL) and local infiltration (0.9 mL) of:** 4% articaine, 1:200,000 epinephrine • Vomiting = 1/50 0.5% bupivacaine, 1:200,000 epinephrine • Dizziness = 2/50 There were no differences measured for the following parameters between solutions: • Systolic, diastolic, and mean arterial pressure • Heart rate • Oxygen saturation apart from diastolic and mean arterial pressures for surgery with osteotomy	No significant differences between systolic, diastolic, and mean arterial pressure during surgery without osteotomy (P > 0.05) For surgery with osteotomy, there were statistically significant differences in diastolic (64 mmHg and 68 mmHg, respectively, P = 0.001) and mean arterial pressures (86 mmHg and 89 mmHg, respectively; P = 0.031) for pooled data from all surgical phases Heart rate was not influenced by the local anaesthetic used (P > 0.05) No statistically significant difference was seen between solutions for oxygen saturation during surgery with or without osteotomy (P > 0.05). The solution used did not influence the results of oximetry (P > 0.05)

Hellden 1974	Numbers of systemic adverse events listed	**IANB (1.8 mL) and local infiltration (1.8 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3.0% mepivacaine, no vasoconstrictor No adverse events were reported	Not applicable
Hosseini 2016	Adverse events	**Maxillary BI (1.8 mL) of the following:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine There were no adverse events	Not applicable
Kammerer 2012	Adverse events	**IANB and buccal nerve block (up to 2.2 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, no vasoconstrictor No adverse events reported	Not applicable
Kammerer 2014	Heart rate, systolic and diastolic blood pressures, and oxygen saturation measured	**Maxillary BI (1.7 mL) of:** • 4% articaine plain • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 4% articaine, 1:400,000 epinephrine No systemic side effects or complications were detected in any groups. Heart rate, blood pressure, and oxygen saturation were not affected	Not applicable
Karm 2017	Numbers of systemic adverse events listed Vital signs	**IANB and BI (1.8 mL in total) of:** 2% lidocaine, 1:80,000 epinephrine • Diarrhoea = 1/51 • Headache = 1/51 2% lidocaine, 1:200,000 epinephrine • Lower abdominal pain = 1/51 • Myalgia = 1/51 • Temporomandibular joint syndrome = 1/51 2% lidocaine, 1:80,000 epinephrine • Change in systolic blood pressure = 14.1 ± 10.2 mmHg (mean ± SD) • Change in diastolic blood pressure = –10.8 ± 12.9 mmHg (mean ± SD) • Change in heart rate = 14.8 ± 11.1 (mean ± SD) 2% lidocaine, 1:200,000 epinephrine • Change in systolic blood pressure = 9.3 ± 7.3 mmHg (mean ± SD) • Change in diastolic blood pressure = –8.4 ± 6.6 mmHg (mean ± SD) • Change in heart rate = 10.5 ± 12.5 (mean ± SD)	There was no statistically significant difference between groups in terms of the frequency of these adverse events (P = 1.0) *Systolic blood pressure* P < 0.002 *Diastolic blood pressure* P < 0.205 *Heart rate* P < 0.010

Khoury 1991	Blood pressure and heart rate measured	**"Conduction" and infiltration anaesthesia (varying volumes) of:** • 3% prilocaine, 0.03 IU felypressin • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine No differences were measured between solutions	Not reported
Kolli 2017	Heart rate	**Maxillary BI (1.7 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 4% articaine, 1:100,000 epinephrine (epinephrine concentrations assumed) **Maxillary BI/PI (1.7 mL in total) of:** Heart rate (means ± SD) *Baseline* • 2% lidocaine, 1:80,000 epinephrine BI = 89.20 ± 11.14 • 4% articaine, 1:100,000 epinephrine BI = 93.80 ± 13.08 • 2% lidocaine, 1:80,000 epinephrine BI/PI = 89.43 ± 12.17 *During* • 2% lidocaine, 1:80,000 epinephrine BI = 93.57 ± 14.20 • 4% articaine, 1:100,000 epinephrine BI = 100.93 ± 14.58 • 2% lidocaine, 1:80,000 epinephrine BI/PI = 94.47 ± 12.743 *After* • 2% lidocaine, 1:80,000 epinephrine BI = 100.3 ± 7.99 • 4% articaine, 1:100,000 epinephrine BI = 102.47 ± 12.80 • 2% lidocaine, 1:80,000 epinephrine BI/PI = 99.77 ± 9.804 There were no adverse events	P = 0.26 P = 0.08 P = 0.56
Kramer 1958	Numbers of adverse events listed (pooled)	**Mandibular and maxillary injections (1 or more cartridges) of:** 2% lidocaine, 1:50,000 epinephrine • Mandibular = 1.16% • Maxillary = 0.7% 2% lidocaine, 1:100,000 epinephrine • Mandibular = 2.0% • Maxillary = 0%	Not reported

Lasemi 2015	Heart rate Systolic blood pressure Diastolic blood pressure	**IANB (volume not stated) of:** 4% articaine, 1:100,000 epinephrine Heart rate (beats per minute): • during treatment = 2.35 ± 7.76# • post injection (5 minutes) = 1.75 ± 7.46# Systolic blood pressure (mm of mercury): • during treatment = -1.9 ± 8.21# • post injection (5 minutes) = -2.75 ± 9.08# Diastolic blood pressure (mm of mercury): • during treatment = 0.25 ± 4.75# • post injection (5 minutes) = -1.2 ± 5.14# 4% articaine, 1:200,000 epinephrine Heart rate (beats per minute): • during treatment = -0.7 ± 9.40# • post injection (5 minutes) = -1.5 ± 5.59# Systolic blood pressure (mm of mercury): • during treatment = -1.2 ± 6.33# • post injection (5 minutes) = -0.45 ± 8.40# Diastolic blood pressure (mm of mercury): • during treatment = -0.35 ± 5.63# • post injection (5 minutes) = -1.35 ± 5.91#	For both local anaesthetics: Heart rate during treatment: P = 0.6 Heart rate after 5 minutes: P = 0.8 Systolic blood pressure during treatment: P = 0.9 Systolic blood pressure after 5 minutes: P = 0.4 Diastolic blood pressure during treatment: P = 0.9 Diastolic blood pressure after 5 minutes: P = 0.8
Laskin 1977	Numbers of systemic adverse events listed	**IANB and BI (1.8 mL) of:** • 0.5% bupivacaine, 1:200,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine No adverse events were seen	Not applicable
Malamed 2000a	Numbers of systemic adverse events listed	**Infiltration or nerve block (2.5-4.5 mL depending on solution and complexity of procedure) of:** • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine No serious systemic adverse events occurred	Not reported

Malamed 2000b	Numbers of systemic adverse events listed	**Infiltration or nerve block (1.9-2.6 mL depending on solution and complexity of procedure) of:** 4% articaine, 1:100,000 epinephrine • Headache = 1/50 2% lidocaine, 1:100,000 epinephrine • Headache = 0/20 Vital signs: Slight increases were seen in supine blood pressure with articaine, as compared with a slight decrease overall. These changes were not clinically significant and produced no adverse effects	Not reported
Martinez-Rodriguez 2012	Numbers of systemic adverse events listed	**IANB (1.8 mL) and mandibular BI (0.9 mL) of:** 4% articaine, 1:100,000 epinephrine • Tachycardia = 1/48 • Vagal syncope = 1/48 2% lidocaine, 1:100,000 epinephrine • Tachycardia = 0/48 • Vagal syncope = 0/48	Not reported
Mikesell 2005	Numbers of adverse events listed	**IANB (1.8 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:100,000 epinephrine No systemic adverse events occurred	Not applicable

Mittal 2015	Blood pressure and heart rate were measured Stage 1: before injection (average of 4 readings taken at 2-minute intervals for 8 minutes before administration of anaesthetic injection) Stage 2: taken 5 minutes after injection, before the start of extraction (average of readings taken at 15-second intervals) Stage 3: taken during extraction (average of readings taken at 15-second intervals)	**Maxillary BI (1.8 mL lidocaine, 1.7 mL lidocaine) of:** 2% lidocaine, 1:80,000 epinephrine *Heart rate (mean beats per minute ± SD)* • Pre injection = 94.23 ± 14.64 • Post injection (5 minutes) = 99.51 ± 14.86 • During treatment = 105.92 ± 14.32 *Systolic blood pressure (mean mm of mercury ± SD)* • Pre injection = 106.5 ± 8.45 • Post injection (5 minutes) = 107.06 + 8.12 • During treatment = 110.27 + 13.08 *Diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection = 65.08 ± 6.97 • Post injection (5 minutes) = 64.88 ± 5.73 • During treatment = 64.67 ± 6.94 4% articaine, 1:100,000 epinephrine *Heart rate (mean beats per minute ± SD)* • Pre injection = 97.13 ± 14.65 • Post injection (5 minutes) = 100.64 ± 13.11 • During treatment = 105.13 ± 16.20 *Systolic blood pressure (mean mm of mercury ± SD)* • Pre injection = 108.29 ± 7.91 • Post injection (5 minutes) = 109.67 ± 7.02 • During treatment = 110.57 ± 10.12 *Diastolic blood pressure (mean mm of mercury ± SD)* • *Pre injection =* 64.56 ± 5.18 • *Post injection (5 minutes) =* 64.52 ± 4.13 • *During treatment =* 64.48 ± 5.92	*Heart rate* Student t-test found no statistically significant difference in mean heart rate values with either local anaesthetic (P > 0.05) *Systolic blood pressure* Student t-test found no statistically significant difference between the 2 local anaesthetics (P > 0.05) *Diastolic blood pressure* There was no statistically significant difference between local anaesthetics (P > 0.05)
		IANB (1.7 mL) or maxillary BI (1.0 mL) of: 4% articaine, 1:200,000 epinephrine (A200) *IANB heart rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 74.9 ± 12.1 • Post injection (5 or 10 minutes) = 77.5 ± 11.6¶# • Completion (180 minutes) = 72.5 ± 11.8†† *Infiltration heart rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 74.4 ± 10.5	

		• Post injection (5 or 10 minutes) = 73.0 ± 11.5 • Completion (180 minutes) = 70.9 ± 12.4¶ *IANB systolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 123.6 ± 11.1 • Post injection (5 or 10 minutes) = 123.4 ± 13.9 • Completion (180 minutes) = 122.4 ± 11.7 *Infiltration systolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 122.5 ± 11.5 • Post injection (5 or 10 minutes) = 117.9 ± 10.4¶ • Completion (180 minutes) = 119.3 ± 10.4†† *IANB diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 75.0 ± 8.2 • Post injection (5 or 10 minutes) = 72.1 ± 8.7¶ • Completion (180 minutes) = 71.7 ± 8.9¶ *Infiltration diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 71.9 ± 8.6 • Post injection (5 or 10 minutes) = 67.6 ± 8.4¶ • Completion (180 minutes) = 71.1 ± 8.4 Mean values for vital signs were similar for all solutions and were not clinically significant. *Adverse events* 4% articaine, 1:100,000 epinephrine (A100) *IANB heart rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 73.8 ± 10.5 • Post injection (5 or 10 minutes) = 77.3 ± 11.3¶# • Completion (180 minutes) = 72.3 ± 10.8 *Infiltration heart rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 73.9 ± 11.6 • Post injection (5 or 10 minutes) = 73.8 ± 11.8** • Completion (180 minutes) = 70.1 ± 11.9¶ *IANB systolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 124.3 ±	¶ P < 0.01 compared with pre injection (t = 0 minutes) # P < 0.01 compared with Aw/O at the same time ** P < 0.05 compared with Aw/O at the same time †† P < 0.05 compared with pre injection (t = 0 minutes) *Inferior alveolar nerve block* A100 and A200 groups' heart rate increased 5 minutes post injection (A100 increased 3.5 beats/min, P = 0.0051; A200 increased 2.6 beats/min, P = 0.0064). The A200 treatment group showed a decrease in heart rate at completion (A200 decreased 2.4 beats/min, P = 0.0421) No difference was seen for the pairwise treatment comparison of A100 and A200 groups' heart rates from baseline to post injection; There was a difference when A100 and Aw/O groups were compared (P = 0.0005) and when A200 and Aw/O

Moore 2006	Numbers of systemic adverse events were listed and blood pressure and heart rate were measured 5 minutes before injection, immediately after injection, and on completion of treatment	11.1 • Post injection (5 or 10 minutes) = 124.3 ± 12.5 • Completion (180 minutes) = 121.7 ± 10.5†† *Infiltration systolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 122.5 ± 11.9 • Post injection (5 or 10 minutes) = 119.0 ± 13.3¶ • Completion (180 minutes) = 119.8 ± 11.4†† *IANB diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 73.4 ± 8.4 • Post injection (5 or 10 minutes) = 70.2 ± 7.8¶ • Completion (180 minutes) = 70.8 ± 8.6¶ *Infiltration diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 72.1 ± 9.1 • Post injection (5 or 10 minutes) = 67.4 ± 8.5¶ • Completion (180 minutes) = 71.2 ± 10.3 Mean values for vital signs were similar for all solutions and were not clinically significant *Adverse events* No serious adverse events occurred 4% articaine, no vasoconstrictor (Aw/O) *IANB heart rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 75.2 ± 11.2 • Post injection (5 or 10 minutes) = 73.3 ± 12.0†† • Completion (180 minutes) = 74.6 ± 11.6 *Infiltration heart rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 73.4 ± 11.8 • Post injection (5 or 10 minutes) = 69.8 ± 11.9¶ • Completion (180 minutes) = 70.5 ± 10.5¶ *IANB systolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 123.7 ± 10.8 • Post injection (5 or 10 minutes) = 123.1 ± 11.5 • Completion (180 minutes) = 122.5 ± 11.6 *Infiltration systolic blood pressure (mean mm of mercury ± SD)*	groups (P = 0.0016) were compared post injection The A100 treatment group was the only one that showed a statistically significant decrease in systolic blood pressure at completion (A100 decreased 2.6 mmHg, P = 0.0153) Both A100 and A200 treatment groups showed small (2-4 mmHg) but statistically significant decreases in diastolic blood pressure at 5 minutes post injection (P = 0.0002 and 0.0062, respectively), but with diastolic blood pressure, all 3 solutions showed a significant decrease at completion *Maxillary infiltration* The Aw/O treatment group's heart rate decreased significantly (3.6 beats/min) compared with the preinjection heart rate immediately post injection (P = 0.0013) There was a significant increase in heart rate when A100 was compared with Aw/O at post-injection dose (P = 0.0150) There was a significant decrease in pulse rate for all solutions at completion of the study (P = 0.0034 for Aw/O, P = 0.0025 for A100, P = 0.0009 for A200) There was a significant decrease in diastolic blood pressure for all 3 groups 10 minutes post injection (P = 0.0079 for Aw/O, P < 0.0001 for A100, P < 0.0001 for A200) There was a significant decrease in diastolic blood pressure from baseline to completion for the Aw/O treatment group (P = 0.0046) A significant decrease in systolic blood pressure occurred with all 3 groups 10 minutes post injection (P = 0.0041 for Aw/O, P = 0.0065 for A100, P = 0.0003 for A200). A significant decrease in systolic blood pressure at completion of the testing occurred with 2 solutions (P = 0.0487 for A100, P = 0.0333 for A200) *Adverse events* No statistically significant differences occurred between solutions in terms of numbers of adverse events

		• Pre injection (0 minutes) = 121.7 ± 11.8 • Post injection (5 or 10 minutes) = 118.8 ± 11.5¶ • Completion (180 minutes) = 120.1 ± 10.7 *IANB diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 75.0 ± 8.2 • Post injection (5 or 10 minutes) = 73.5 ± 8.4 • Completion (180 minutes) = 73.0 ± 8.0¶ *Infiltration diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 72.9 ± 7.6 • Post injection (5 or 10 minutes) = 70.3 ± 7.8¶ • Completion (180 minutes) = 69.6 ± 8.8¶ Mean values for vital signs were similar for all solutions and were not clinically significant *Adverse events* No serious adverse events occurred. Events that did occur were as follows: IANB • Headache = 7/62 • Shoulder/neck/ear pain = 3/62 • Elevated blood pressure = 2/62 • Heartburn = 2/62 • Nausea = 1/62 • Urticaria = 1/62 • Syncope =1/62 • Anemia = 0/62 Infiltrations • Headache = 6/62 • Shoulder/neck/ear pain = 0/62 • Elevated blood pressure = 1/62 • Heartburn = 0/62 • Nausea = 1/62 • Urticaria = 0/62 • Syncope = 0/62 • Anaemia = 1/62	
		Maxillary BI (buccal and palatal if required, and variable volumes) of: 4% articaine, 1:200,000 epinephrine (A200) *Heart rate (mean beats/min ± SD)* • Pre injection (0 minutes) = 73.7 ± 10.0 • Post injection (10 minutes) = 75.4 ± 12.0 • Completion = 70.0 ± 9.7* *Systolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 126.5 ± 9.6	

[Moore 2007](#)	Vital signs (blood pressure, pulse, and respiratory rate) measured: • before injection • 10 minutes after anesthetic administration • at the conclusion of the session Adverse events	• Post injection (10 minutes) = 125.1 ± 13.6 • Completion = 129.8 ± 12.8† *Diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 77.3 ± 6.9 • Post injection (10 minutes) = 75.2 ± 9.7* • Completion = 80.0 ± 9.6† *Respiratory rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 15.2 ± 2.0 • Post injection (10 minutes) = 15.2 ± 2.0 • Completion = 15.2 ± 2.1 *Adverse events* Events that did occur were as follows: • Headache = 0/42 • Ear pain = 0/42 • Nausea/vomiting = 1/42 • Sinus congestion = 0/42 • Fractured toe = 0/42 4% articaine, 1:100,000 epinephrine (A100) *Heart rate (mean beats/min ± SD)* • Pre injection (0 minutes) = 76.1 ± 10.4 • Post injection (10 minutes) = 76.6 ± 9.8 • Completion = 69.3 ± 9.8* *Systolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 127.1 ± 10.9 • Post injection (10 minutes) = 127.5 ± 11.6 • Completion = 131.3 ± 10.8† *Diastolic blood pressure (mean mm of mercury ± SD)* • Pre injection (0 minutes) = 78.4 ± 6.4 • Post injection (10 minutes) = 75.0 ± 6.9* • Completion = 81.4 ± 8.1† *Respiratory rate (mean beats per minute ± SD)* • Pre injection (0 minutes) = 15.0 ± 2.2 • Post injection (10 minutes) = 15.1 ± 2.3 • Completion = 15.1 ± 2.3 *Adverse events* Events that did occur were as follows: • Headache = 1/42 • Ear pain = 1/42 • Nausea/vomiting = 0/42 • Sinus congestion = 1/42 • Fractured toe = 1/42	* P < 0.01 compared with pre injection † P < 0.05 compared with pre injection There were only 2 statistically significant differences in cardiovascular and respiratory functions following local anaesthetic administration: • A100: 6.8 beats/min • A200: 3.7 beats/min for the decrease in pulse rate from pre to post treatment (6.8 beats/min and 3.7 beats/min (P = 0.0433). In each surgical session, statistically significant findings were found *Heart rate:* pre injection to completion showed a decrease for: A200: P = 0.0013 A100: P < 0.0001 *Diastolic blood pressure:* A100: decreased from pre to post injection (P = 0.0003) A200 and A100: increased from pre injection to completion of surgery (P = 0.0303 and P = 0.0162, respectively) *Systolic blood pressure:* An increase was seen from pre injection to completion of surgery for A200 (P = 0.0220) and A100 (P = 0.0118) *Adverse events:* No statistically significant differences occurred between solutions in terms of numbers of adverse events

Mumford 1961	Numbers of systemic adverse events listed	**"Regional" (1.5 mL) and infiltration injections (1.0 mL) of:** 2% lidocaine, 1:80,000 epinephrine • Patient collapse ("adrenaline shock") = 1/100 3% mepivacaine, no epinephrine • Patient collapse ("adrenaline shock") = 1/100	Not reported
Nespeca 1976	Numbers of systemic adverse events listed	**IANB and infiltration injection (1.5-2.0 mL) of:** • 2% lidocaine, 1:100,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine No systemic adverse events occurred	Not applicable
Nordenram 1990	Numbers of systemic adverse events listed	**Maxillary BI (0.6 mL) of:** • 2% lidocaine, 1:80,000 epinephrine • 3% mepivacaine, no vasoconstrictor • 3% prilocaine, 0.03 IU/mL felypressin No systemic adverse events occurred	Not applicable
Odabas 2012	Measurements of blood pressure, heart rate, and oxygen saturation	**Maxillary injection (1.8 mL) of:** • 4% articaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine Similar measurements for both solutions (results presented graphically)	No statistically significant differences between solutions (P = 0.72)
Pellicer-Chover 2013	Systolic blood pressure Diastolic blood pressure Cardiac rate	**IANB (1.8 mL) and BI (1.8 mL) of:** 4% articaine, 1:100,000 epinephrine • Systolic blood pressure (mean mm of mercury) = 124.7 • Diastolic blood pressure (mean mm of mercury) = 72.6 • Heart rate (mean beats/min) = 81.5 0.5% bupivacaine, 1:200,000 epinephrine • Systolic blood pressure (mean mm of mercury) = 124.1 • Diastolic blood pressure (mean mm of mercury) = 74.3 • Heart rate (mean beats per minute) = 80.7	No statistically significant differences between solutions: • Systolic blood pressure: P = 0.449 • Diastolic blood pressure: P = 0.414 • Heart rate: P = 0.409
Ram 2006	Numbers of systemic adverse events listed	**IANB and maxillary BI (up to 1 cartridge) of:** • 2% lidocaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine No systemic adverse effects occurred	Not applicable
Robertson 2007	Numbers of systemic adverse events listed	**Mandibular BI (1.8 mL) of:** • 4% articaine, 1:100,000 epinephrine • 2% lidocaine, 1:100,000 epinephrine No systemic adverse effects occurred	Not applicable

Sancho-Puchades 2012	Systolic and diastolic arterial pressure, heart rate, and oxygen saturation Adverse reactions during surgery or during first postoperative week	**IANB and BI (1.8 mL in total) of:** 4% articaine, 1:200,000 epinephrine • Systolic and diastolic blood pressure, oxygen saturation, and heart rate were presented only graphically • No adverse reactions occurred during surgery or were reported postoperatively 0.5% bupivacaine, 1:200,000 epinephrine • Systolic and diastolic blood pressure, oxygen saturation, and heart rate were presented only graphically • No adverse reactions occurred during surgery or were reported postoperatively	Statistically significant higher levels of systolic blood pressure were seen in the articaine group (P = 0.013), which varied significantly across time (P = 0.024) Diastolic blood pressure was similar between groups (P = 0.320), with no significant changes over time (P = 0.090) Oxygen saturation did not differ significantly between groups (P = 0.194) with no significant changes over time (P = 0.199) Heart rate varied significantly between groups over time (P = 0.036) and was higher in the articaine group at tissue incision and bone removal
Santos 2007	Numbers of systemic adverse events listed as well as measurements of systolic, diastolic, and mean arterial pressures and heart rate	**IANB (1.8 mL) and mandibular BI (0.9 mL) of:** • 4% articaine, 1:100,000 epinephrine • 4% articaine, 1:200,000 epinephrine No adverse reactions occurred with each local anaesthetic solution intraoperatively and postoperatively. For systolic, diastolic, and mean arterial pressures, no hypertensive peak was observed during all steps of treatment	There were no significant differences between solutions when measuring: • Arterial pressure: P > 0.05 • Heart rate: P > 0.05 • Oxygen saturation: P > 0.05 Oxygen saturation increased immediately after first cartridge of articaine (P < 0.05) was given. This remained until the end with surgery without osteotomy (data not shown), although it was not dependent on the local anaesthetic used (P > 0.05) Data were presented on graphs
Sherman 1954	Numbers of systemic adverse events listed.	**Mandibular and maxillary injections (1.1-2.2 mL) of:** 2% lidocaine, 1:50,000 epinephrine • Tremors = 2/100 2% lidocaine, 1:100,000 epinephrine • Tremors with palpitations = 1/100 • Fainting = 2/100	Not reported
Stibbs 1964	Numbers of systemic adverse events listed	**Various mandibular and BI (varying volumes) of:** 2% mepivacaine, 1:20,000 levonordefrin • Tremors, palpitation, perspiration, nausea, faintness, headache, drowsiness, or feeling of weakness = 6/248 2% lidocaine, 1:50,000 epinephrine • Tremors, palpitation, perspiration, nausea, faintness, headache, drowsiness, or feeling of weakness = 12/264	Not reported
Trieger 1979	Numbers of systemic adverse events listed	**IANB and BI (varying volumes) of:** • 0.5% bupivacaine, 1:200,000 epinephrine • 3% mepivacaine, no epinephrine No systemic adverse effects occurred	Not applicable

Trullenque-Eriksson 2011	Number of systemic adverse events and measurement of patients' vital signs with a blood pressure monitor, and pulse and oxygen saturation with a pulse oximeter	**IANB and mandibular BI (1.8 mL) of:** 0.5% bupivacaine, 1:200,000 epinephrine • Postoperative headache (exact numbers not stated) 4% articaine, 1:200,000 epinephrine • Postoperative sleepiness (exact numbers not stated) 42.1% of patients had at least 1 adverse event (figure includes both local anaesthetics)	No statistically significant differences were found for blood pressure, pulse, or bleeding during surgery The only significant differences for oxygen saturation were found at initial and final measurements, but not between measurements after administration of anaesthesia or changes in oxygen saturation
Vilchez-Perez 2012	Numbers of systemic adverse events including haemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation) were recorded	**BI (0.9 mL) of:** • 4% articaine, 1:200,000 epinephrine • 0.5% bupivacaine, 1:200,000 epinephrine No complications were reported with either solution	No statistically significant differences were found for either anaesthetic solution during the intervals under study (ANOVA test P > 0.05)
Weil 1961	Numbers of systemic adverse events listed	**Mandibular and maxillary injections (1 cartridge or more) of:** • 3% mepivacaine, no vasoconstrictor • 2% mepivacaine, 1:20,000 levonordefrin Few systemic adverse reactions. Most were attributed to apprehension rather than toxicity. Average incidence of lack of systemic reactions for each formulation ranged from 96.92 ± 1.52 to 100%	No significant differences in local or systemic tolerance were found between solutions

Yilmaz 2011	Adverse event frequency was measured at 24 hours and 7 days after the procedure	**IANB and BI (1.0 mL) of:** 4% articaine, 100,000 epinephrine *IANB* • Infection = 0/47 • Headache = 0/47 • Accidental injury = 3/47 • Vomiting = 0/47 • Diarrhoea = 0/47 • Pruritus = 1/47 *Maxillary infiltration* • Infection = 0/32 • Headache = 0/32 • Accidental injury = 0/32 • Vomiting = 0/32 • Diarrhoea = 0/32 • Pruritus = 0/32 3% prilocaine, 0.03 IU/mL felypressin *IANB* • Infection = 0/42 • Headache = 0/42 • Accidental injury = 2/42 • Vomiting = 0/42 • Diarrhoea = 0/42 • Pruritus = 0/42 *Maxillary infiltration* • Infection = 0/36 • Headache = 0/36 • Accidental injury = 0/36 • Vomiting = 0/36 • Diarrhoea = 0/36 • Pruritus = 0/36	Not reported

Footnotes

A100 = 4% articaine, 1:100,000 epinephrine ; A200 = 4% articaine, 1:200,000 epinephrine; ANOVA = analysis of variance; Aw/O = 4% articaine with no vasoconstrictor; BI = buccal infiltration; Faces Pain Scale Revised = a modified version of the Faces Pain Scale (Hicks 2001); Heft-Parker VAS = Heft-Parker visual analogue scale (Heft 1984); Hg = mercury; IANB = inferior alveolar nerve block; IONB = infraorbital nerve block; L80 = 2% lidocaine, 1:80,000 epinephrine; LA = local anaesthetic; LI = lingual infiltration; PI = palatal infiltration; SD = standard deviation; T = Taddio's Scale (Taddio 1994); VAS = visual analogue scale; Wong–Baker FPS = Wong-Baker FACES Pain Rating Scale (Wong 1988).

unsure if measurement is standard error or standard deviation; ## unsure if measurements are means and standard errors, or standard deviations.

8 Definitions of success, if changed, for each study and data used

Abdulwahab 2009	Soft tissue data (success and onset) requested, but not possible to obtain from first study author. Available data for success using pulp testing, when additional studies were not available to perform meta-analysis, are included in the table of orphan studies, Table 5. For comparisons of different solutions when meta-analysis was possible, we requested paired data, but it was not possible to obtain them. Therefore, study data were treated as parallel study data. Mandibular first molar data were used for pulpal anaesthetic success and are presented in Analysis 1.2, Analysis 3.2, Analysis 6.2, Analysis 13.1, Analysis 16.1, Analysis 19.1, and Analysis 18.1

Aggarwal 2009	Three participants (1 from each group) were eliminated owing to lack of soft tissue anaesthesia. These were excluded from the study's results but have been included in our calculation of success of soft tissue anaesthesia Pulpal anaesthesia success was defined as "no pain" and "faint, weak, or mild pain", but we classed only "no pain" as successful (raw data obtained from study authors) Quote (from correspondence): "Three out of 24 patients (12%) in control IANB group, 7 out of 30 patients (23%) in IANB and lidocaine infiltration group and 14 out of 30 patients (47%) in IANB and articaine infiltration group had no pain (HP-VAS '0 mm')" Only data for additional lidocaine or articaine injections have been used (placebo excluded). Available data are included in the table of orphan studies, Table 5
Aggarwal 2014	Pulpal anaesthesia success was defined as "no pain" and "faint, weak, or mild pain", but we classed only "no pain" as successful (raw data obtained from study authors) Quote (from correspondence): "Out of 30 patients receiving lidocaine, 1:80,000 epinephrine, 3 patients had no pain (HP VAS score of 0), whereas in patients receiving lidocaine, 1:200,000 epinephrine 5 patients (out of 32) had no pain" Of the original 63 patients, 1 patient receiving 2% lidocaine, 1:80,000 epinephrine did not have profound lip numbness at 15 minutes and was excluded from the study. For the review, this patient was included as a failure in the 2% lidocaine, 1:80,000 epinephrine group, when failure of pulpal and soft tissue anaesthesia was calculated (i.e. group size was still 31 participants. Available data are included in the table of orphan studies, Table 5
Aggarwal 2017	In this study, success during access cavity preparation and instrumentation in teeth with irreversible pulpitis was defined as no pain or mild pain (0 or ≤ 54 mm on a VAS, respectively). Only patients with a VAS of 0 were classed as successful for this systematic review. Also, participants excluded owing to absence of lip numbness were classed as failures. Pulpal and soft tissue success data are included in the table of orphan studies, Table 5
Albertson 1963	Only grade A anaesthesia (complete absence of pain) was classed as successful anaesthesia. Grade B and grade C were classed as failure. Available data are included in the table of orphan studies, Table 5
Allegretti 2016	In this study, success for pulpectomy included patients who had no pain (0) or mild, bearable pain (1). Only patients with scores of 0 were classed as successful anaesthesia in the review. Data for success of clinical pulpal anaesthesia for 2% lidocaine, 1:100,000 epinephrine vs 4% articaine, 1:100,000 epinephrine were used for meta-analysis and are presented in Analysis 1.1. Data for 2% mepivacaine, 1:100,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine are presented in Analysis 8.1. Data for 2% mepivacaine, 1:100,000 epinephrine vs 4% articaine, 1:100,000 epinephrine are presented in Table 5 Subjective soft tissue success data are presented in Analysis 1.3 and Analysis 7.2, apart from the data for 2% lidocaine, 1:100,000 epinephrine vs 2% mepivacaine, 1:100,000 epinephrine, which are presented in Table 6 (local anaesthetics have 100% success in all studies in that analysis) Simulated scenario pulpal anaesthesia success data are included in Table 6, as a negative response to electric pulp testing is not a reliable indicator of pulpal anaesthesia
Arrow 2012	Available data are included in the table of orphan studies (Table 5) and were obtained from the study author. Data for IANBs and mandibular infiltrations are presented. One hundred fourteen outcomes were scheduled to be recorded, but because of failure of 1 visit, only 113 were recorded. Of these interventions, 111 recorded children's response to treatment (confirmed by the study author)
Ashraf 2013	Although the study looked at the success of supplemental injections following initial anaesthetic failure, success data for the initial IANB for each solution could be used in this review. The exact numbers of successful injections for pulpal and soft tissue anaesthesia for each local anaesthetic were not given. Attempts were made to get both pulpal and soft tissue anaesthesia data, but we were unable to contact the study author; therefore no data could be used
Atasoy Ulusoy 2014	Clinical, pulpal anaesthetic success was defined as "no pain" or "weak/mild" at various stages of treatment including endodontic access and instrumentation of each root canal in the paper. It was defined as "no pain" during access cavity preparation for this review Pulpal anaesthetic success, when measured by simulated scenario testing, was defined as no response to cold stimuli (Endo-Ice), 10 minutes after local anaesthetic administration. Available data for clinical, pulpal anaesthetic success are included in the table of orphan studies, Table 5, and data for simulated scenario testing of pulps are included in Table 6
Batista da Silva 2010	Pulpal anaesthetic success values were shown only graphically in the original research paper, but the study author supplied actual numerical values for success via email correspondence,.as well as paired data. Mandibular second premolar data are included in Analysis 1.2

Berberich 2009	Definitions of success from the study were used. Paired data for comparisons in this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Maxillary canine data were used for pulpal anaesthetic success and are presented in Analysis 10.1, Analysis 14.1, and Analysis 13.1. Soft tissue anaesthesia success data are presented in the table of orphan studies, Table 5 (2% lidocaine, 1:50,000 epinephrine vs 3% mepivacaine plain), and in Table 6 (local anaesthetics have 100% success in all studies in that analysis)
Bhagat 2014	Success for each local anaesthetic group was presented as mean VAS scores in the study. Also, only IANBs appear to have been used for extractions, as there was no mention of buccal infiltrations administered. An attempt to obtain VAS = 0 data and to clarify the injections given were unsuccessful, as no contact could be made with the study author. Data are presented in Table 6
Bortoluzzi 2009	Tests for soft tissue success (VAS = 0) were done at 3 minutes and at 15 minutes and are presented as such. However local anaesthetic could have been successful at 3 minutes, at 15 minutes, at both times, or at neither time. Therefore data were requested from the study author to allow soft tissue success at any time during the first 15 minutes. Test 1 (a little scrub over the anaesthetized area with a standardized piece of cotton) data were used, as they are similar to patients' self-reported anaesthesia of the lip. Available data are presented in Analysis 7.2
Bouloux 1999	No pain on the global pain scale was classed as anaesthetic success (a little, some, a lot, and worst possible were classed as failure) and used in this review after raw data were obtained from the study author. Success defined as 0 on a VAS (0–100 mm scale) was not used, as success for each solution was less than success on the global pain scale, which suggested that some patients with single-figure VAS scores said they had no pain on the global pain scale. Success was measured in terms of patients, not teeth, as each patient needed either 2 or 4 teeth extracted (i.e.data were pooled for both jaws) Although paired data for this cross-over study were available for meta-analysis, paired data from the other study it could be combined with - Laskin 1977 - were not available. Therefore, study data from this latter study were treated as if they were parallel study data and were combined with paired data from this study, as detailed in Unit of analysis issues, allowing Laskin 1977 to be removed in a sensitivity analysis. The data are presented in Analysis 6.1. Data for soft tissue anaesthetic success, tested with a probe, are presented in the table of orphan studies, Table 5
Bradley 1969	A variety of treatments were carried out, and their results were pooled. Injections were described as infiltrations and "mandibular" injections. It was assumed that infiltration data could reflect injections into the maxilla and mandible, while with "mandibular injections", it was assumed that these were IANBs Only combined data for 1.8 mL injections were used, as 1.8 mL is a standard volume of anaesthetic to inject, while the 0.8–3.6 mL data contain much greater variation in volume. Success was classed as grade A only. Grade B and grade C were classed as failure. Available data are included in the table of orphan studies, Table 5
Burns 2004	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Right maxillary central incisor data were used for pulpal anaesthetic success and are presented in Analysis 13.1
Caldas 2015	Paired data for this cross-over study were not available for meta-analysis, although success for each formulation was 100%. Therefore, study data were treated as parallel study data. Right maxillary canine data are presented in Analysis 12.1
Chapman 1988	The method of success measurement was not stated Quote: "Satisfactory depth of anaesthesia was established within a further five minutes with both agents" Data are not usable and are presented in Table 6
Chilton 1971	Only those injections graded as "complete" were classed as successful (complete but wore off, partial no reinjection, partial reinjection were excluded). Injections were classed as infiltrations and IANBs rather than mandibular/maxillary (i.e. some infiltrations may have been mandibular injections). Available data for periodontal and endodontic treatment are included in the table of orphan studies, Table 5, apart from periodontal treatment using inferior alveolar nerve blocks and infiltrations, comparing 2% lidocaine, 1:100,000 epinephrine vs 4% prilocaine, no vasoconstrictor, when meta-analysis was possible (Analysis 4.1)
Claffey 2004	In this study, success was defined as the ability to access and instrument the teeth with no pain or mild pain (0 or ≤ 54 mm on a VAS, respectively). Only patients with VAS of 0 were classed as successful for the systematic review 5 patients were excluded from the lidocaine group and 2 from the articaine group, as they failed to achieve lip anaesthesia. These were also counted as failures when overall success was calculated. Data are presented in Analysis 1.1. The final figures for soft tissue anaesthesia success are therefore based on 79 rather than 72 patients (confirmed by the study author). Soft tissue data are presented in Analysis 1.3

Cohen 1993	Definition of success and data from the study were used. Data for mandibular molars for simulated scenario pulp anaesthesia and anaesthesia during pulpotomy are included in the table of orphan studies, Table 5. Data for simulated scenario soft tissue anaesthesia are included in Table 6 (local anaesthetics have 100% success in all studies in that analysis)
Colombini 2006	Success was classed as "no perceived pain during the surgical procedures". Data for extraction of mandibular third molar teeth are presented in Analysis 7.1
Costa 2005	Anaesthetic success was not measured - only onset and duration of pulpal anaesthesia
Dagher 1997	Success of pulpal anaesthesia: Only mandibular, first molar data were used for the review. Soft tissue anaesthesia: Subjective feeling of soft tissue numbness was used for the review. Definitions of success from the study were used. Paired data for were not available for meta-analysis. Therefore, study data were treated as parallel study data and are presented in Analysis 9.1, Analysis 10.1, and Analysis 11.1. The data for soft tissue anaesthetic success are presented in Table 6 (local anaesthetics have 100% success in all studies in that analysis)
Donaldson 1987	Anaesthetic success was not measured - only onset and duration of pulpal anaesthesia
Elbay 2016	For clinical anaesthesia, success was classed as no pain (mild discomfort, moderate pain, and severe discomfort and/or pain were classed as failure). For extractions, the data for success during extraction were used (data for probing were used for soft tissue success, and data for gingival elevation were not used). Only an inferior alveolar nerve block was used; therefore the long buccal nerve may not have been anaesthetized. This may have reduced any differences between the 2 solutions tested rather than show their true differences. Study data could not be combined with the data from Hellden 1974 for this reason. For pulpotomies, participants who had no pain during every part of the procedure were classed as successful; these data were requested from the study author but were not obtained. Paired data for this cross-over study were not available for meta-analysis Data for success of clinical anaesthesia during pulpotomies (removal of coronal pulp) and for soft tissue anaesthesia are presented in Table 5, and data for success during extractions are presented in Table 6
Epstein 1965	Complete anaesthesia was classed as successful (complete but wore off; partial or failure was classed as failure). Overall impression was also recorded, but this looked at other factors such as haemostasis and side effects and did not specifically look at anaesthetic success. Available data for restorative treatment and "other" procedures (endodontic and periodontal) are included in the table of orphan studies, Table 5, apart from extractions using inferior alveolar nerve blocks and infiltrations comparing 2% lidocaine, 1:100,000 epinephrine vs 4% prilocaine, no vasoconstrictor when meta-analysis was possible. Data are presented in Analysis 4.1
Epstein 1969	Complete anaesthesia was classed as successful (complete but wore off; partial or failure was classed as failure) General impression was also recorded, but this looked at other factors such as haemostasis and side effects and did not specifically look at anaesthetic success. Available data for combined restorative treatment and extractions are included in the table of orphan studies, Table 5
Evans 2008	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 1.2
Fernandez 2005	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Data for first molar teeth simulated scenario pulpal anaesthetic success were used and are presented in Analysis 6.2. Data for simulated scenario soft tissue anaesthetic success are presented in Table 6 (both local anaesthetics have 100% success in all studies in that analysis)
Fertig 1968	Anaesthetic success was not measured - only duration of soft tissue anaesthesia
Forloine 2010	Success of soft tissue anaesthesia could not be presented, as it was not known which local anaesthetic groups those participants who were re-appointed following initial soft tissue anaesthesia failure and then went on to have success a second time belonged to. Overall success for pulpal anaesthesia could not be re-calculated for the same reason; therefore the pulpal anaesthetic success quoted in the original journal article for first molar is presented in Analysis 13.1. Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data
Gangarosa 1967	Unable to use anaesthetic success data for each solution, as available data were difficult to interpret. The total number of participants in each group was not the same as the figures attached to the graphs in the results section. Therefore no data were used
Gazal 2015	Pulpal anaesthetic success data are presented in Table 6, as data were not usable

Gazal 2017	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Data for extraction of various maxillary teeth are presented in Analysis 7.1
Gregorio 2008	Quote: "the percentage of people who required complementary anaesthetic infiltration was significantly higher (P < .05) for B200 (14%) than for A200 (2%)" This allowed anaesthetic success to be calculated but calculations may have included those participants who required no additional local anaesthetic to complete treatment, but still felt pain. As we could not make contact with the study author to obtain paired data for this cross-over study, we were not able to use the study for meta-analysis. Data for anaesthetic success are therefore presented in Table 6
Gross 2007	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 6.2
Haas 1990	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Data for pulpal anaesthetic success are presented in Analysis 18.1. Data for soft tissue anaesthetic success were excluded, as testing was carried out with an electric pulp tester
Haas 1991	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Data for pulpal anaesthetic success are presented in Analysis 18.1. Data for soft tissue anaesthetic success were excluded, as testing was carried out with an electric pulp tester
Haase 2008	Paired data for this cross-over study were not available for meta-analysis. The study involved both test groups receiving 4% articaine with 1:100,000 epinephrine IANB, followed by a buccal infiltration of 4% articaine, 1:100,000 epinephrine or 2% lidocaine, 1:100,000 epinephrine. First molar data were used for pulpal anaesthetic success and are included in the table of orphan studies, Table 5
Hellden 1974	"Good" anaesthesia was classed as success (when treatment could be carried out without any additional injection and no pain was felt). "Acceptable" or "poor" anaesthesia was classed as failure. Available data are included in the table of orphan studies, Table 5
Hersh 1995	For soft tissue anaesthetic success, participants who did not rate numbness at 50 mm or greater on the 1-100 mm scale (1 = "not numb" and 100 = "completely numb") by 45 minutes after the injection were considered as "injection technique failures". Success was graded as < 50 on the 1-100 mm scale; therefore available data are included in Table 6
Hinkley 1991	Two of 30 patients achieved lip numbness after 20 minutes and were excluded from the data analysis, although the study author was unsure which solution this occurred with. Therefore data for soft tissue anaesthesia could not be calculated. Overall success for pulpal anaesthesia could not be re-calculated for the same reason, and paired data were not available for meta-analysis. Pulpal anaesthetic success as quoted in the original journal article for the first molar is presented in Table 6
Hosseini 2016	In this study, success was defined as the ability to access and instrument the teeth with no pain or mild pain (0 or < 54 mm on a VAS, respectively). We attempted to contact the study author for the numbers of participants with a VAS of zero, but we were unsuccessful. Data are presented in Table 6
Jaber 2010	Data for the right mandibular incisor and 1.8 mL buccal injection were used, as this is where the injection was given. After communication with the study author, success was defined as 2 successive 80 readings on the electric pulp tester and no sustained anaesthesia, as reported in the study. Paired data for pulpal anaesthetic success were obtained from the study author and are presented in Analysis 1.2
Jain 2016	Success for each local anaesthetic group was presented as a mean VAS score in the study. An attempt to obtain zero VAS data was unsuccessful, as no contact could be made with the study author. Data are presented in Table 6
Kambalimath 2013	Success for each local anaesthetic group was defined as no pain during surgery or a short duration of pain sensation when a tooth was sectioned. An attempt to obtain data for participants who had no pain was unsuccessful, as no contact could be made with the study author. Paired data for this cross-over study were not available for meta-analysis. Data are presented in Table 6
Kammerer 2012	The study author was contacted to obtain the numbers of patients who had a VAS of 0, which was the criterion chosen for success. This differed slightly from those who did not need an additional injection, as reported in the study (some of these patients may have had the procedure completed with a small amount of discomfort, despite receiving no extra injection). Available data are included in the table of orphan studies, Table 5

Kammerer 2014	Definition of success and data from the study were used. Soft tissue anaesthetic success was measured on a VAS (0-10) and was reported as mean values. Data for patients with a VAS of 0 were not available from the study author Data for pulpal anaesthetic success for 4% articaine, 1:100,000 epinephrine vs 4% articaine; 1:200,000 epinephrine 4% articaine, 1:100,000 epinephrine vs 4% articaine plain; and 4% articaine, 1:200,000 epinephrine vs 4% articaine plain, when meta-analyses were possible, are presented in Analysis 3.2, Analysis 20.1, and Analysis 21.1, respectively. Data for pulpal anaesthetic success for 4% articaine plain vs 4% articaine, 1:400,000 are included in the table of orphan studies, Table 5. Other comparisons, including continuous data for soft tissue success, are included in Table 6
Kanaa 2006	The definition of success and data from the study were used. For soft tissue success, lip anaesthesia data were chosen and are presented in Analysis 1.3. Paired data for pulpal anaesthetic success were obtained from the study author and are presented in Analysis 1.2
Kanaa 2012	Only teeth deemed successfully anaesthetized after pulp testing were included in the clinical portion (extraction/pulp extirpation) of the study. For the review, overall success was calculated as the proportion of anaesthetized teeth from the total number of study participants entering each study group - not from only those who tested negatively with the electric pulp tester. Extraction and pulp extirpation success data were combined. Available data are included in the table of orphan studies, Table 5. Simulated scenario pulpal anaesthesia success data are included in Table 6, as a negative response to electric pulp testing is not a reliable indicator of pulpal anaesthesia
Karm 2017	Success for each local anaesthetic group was presented as a mean VAS score in the study. An attempt to obtain zero VAS data was unsuccessful, as no contact could be made with the study author. Data are presented in Table 6
Katz 2010	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Data for pulpal anaesthetic success for first molar teeth are presented in Analysis 4.2 and Analysis 19.1. First molar data for pulpal anaesthetic success for 4% prilocaine with no vasoconstrictor vs 4% prilocaine, 1:200,000 epinephrine are presented in the table of orphan studies, Table 5
Keskitalo 1975	The study looked at extraction of wisdom teeth including for patients who received 1 local anaesthetic or another (parallel comparison), while some patients had bilateral extractions when a different local anaesthetic was used for each side. Therefore, the study was a mixture of parallel and cross-over comparisons. The original data could not be obtained; therefore the study data could not be used for meta-analysis and are included in Table 6
Khoury 1991	The definition of success and data from the study were used. Available data are included in the table of orphan studies, Table 5, apart from data comparing 2% lidocaine, 1:100,000 epinephrine vs 3% prilocaine, 0.03 IU felypressin and 4% articaine, 1:100,000 epinephrine vs 4% articaine, 1:200,000 epinephrine, when meta-analyses are possible. Data for these are presented in Analysis 2.1 and Analysis 3.1, respectively
Knoll-Kohler 1992a	Definitions of success for the right maxillary incisor from the study were used. Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Data for pulpal anaesthetic success for 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine and for 2% lidocaine, 1:100,000 epinephrine vs 2% lidocaine, 1:200,000 epinephrine and 1:100,000 epinephrine are presented in Analysis 10.1 and Analysis 12.1, respectively. Data for 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:200,000 epinephrine are included in the table of orphan studies, Table 5
Knoll-Kohler 1992b	Data for pulpal anaesthetic success were not usable (100% success for local anaesthetics for all studies; data could not be added to Analysis 1.2, because the data could not be entered as logs of the OR and associated SE using the 'inverse variance' method) and are presented in Table 6
Kolli 2017	Success for each local anaesthetic group was presented in the study as a mean score from the Faces Pain Scale - Revised. An attempt to obtain "no pain" data was unsuccessful, as no contact could be made with the study author. Data are presented in Table 6
Kramer 1958	Figure 1 and Figure 2 in the study gave graphical representation of success in terms of percentages only, but the number of successful injections and the totals from which the percentages were calculated were not stated. These could be calculated from the induction time data in Table 1 (number of injections), which should represent induction times for patients who had grade A potency (success). However the total number of injections calculated from this (2163) for maxillary injections was different from the 2128 figure stated in Figure 1. The same applies for mandibular injections (1670 vs 1575, stated in Figure 2). Therefore success data were presented in Table 6 as percentages

Laskin 1977	For this systematic review, success was classed as no additional local anaesthetic required after mandibular nerve block and long buccal nerve injection (the further dose of 1.8 mL was deemed failure if used). The paper states that the procedure was painless if no additional local anaesthetic was used Paired data for this cross-over study were not available for meta-analysis. Therefore, data from this study were treated as if they were parallel study data and were combined with the paired data from Bouloux 1999, as detailed in Unit of analysis issues, allowing this study to be removed from a sensitivity analysis. Data for success of anaesthesia during extraction are presented in Analysis 6.1
Lawaty 2010	Paired data for this cross-over study were not available for meta-analysis. First molar pulpal anaesthetic success data are presented in the table of orphan studies, Table 5
Lima 2009	Teeth extracted with no pain was the criterion chosen for anaesthetic success. Success was tested after 5 minutes and 10 minutes. The data for 10 minutes were used, as they yielded the maximum success rate, allowing maximum diffusion of local anaesthetic (only 1 buccal injection was given, no palatal). Data are presented in Analysis 3.1
Linden 1986	Success was not measured
Malamed 2000a	The results section combines different procedures requiring anaesthesia of different tissues and different injections. Raw data would be needed to calculate success (scores of 0), but attempts to contact the study author were unsuccessful. Available data (patient VAS scores in cm, on a scale of 0-10) are included in Table 6
Malamed 2000b	The data from this study were possibly derived from the Malamed 2000a study. Attempts to contact the study author to confirm this were unsuccessful. Available data (patient VAS scores in cm, on a scale of 0-10) are included in Table 6
Maniglia-Ferreira 2009	Data for success in the study were presented as the average number of cartridges of local anaesthetic required to obtain anaesthesia, or were rated as excellent (although a VAS was used). Attempts to contact the study author for those patients who had a VAS score of 0 during treatment were unsuccessful. Data (average number of cartridges used) are included in Table 6
Martinez-Rodriguez 2012	Success was not measured
Maruthingal 2015	Although the study was described as a prospective randomized double-blind cross-over trial, the order of local anaesthetic administration appeared to be pre-determined for every participant. Clarification was sought from the study author, but contact by email could not be made. Paired data for this cross-over study were not available for meta-analysis. Data are presented in Table 6
Mason 2009	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data for pulpal anaesthetic success were used for pulpal anaesthetic success and are presented in Analysis 10.1, Analysis 13.1, and Analysis 14.1
McEntire 2011	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 3.2
McLean 1993	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 4.2 and Analysis 13.1. First molar data are presented for 4% prilocaine with no vasoconstrictor vs 3% mepivacaine, no vasoconstrictor in the table of orphan studies, Table 5 Subjective soft tissue anaesthesia success data are presented in Table 6 for 2% lidocaine, 1:100,000 epinephrine vs 3% mepivacaine plain (local anaesthetics have 100% success in all studies in that analysis) and in the table of orphan studies, Table 5, for the other comparisons (orphan study)
Mikesell 2005	Success of soft tissue and pulpal anaesthesia was based on the original number of participants in each group (57). Some of the participants who failed to develop soft tissue anaesthesia initially were re-appointed and successfully achieved anaesthesia at the second visit. Therefore they were classed as overall failures and were deducted from the totals of success for pulpal anaesthesia. Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Subjective soft tissue and first molar pulpal anaesthetic success data are presented in Analysis 1.2 and Analysis 1.3
Mittal 2015	Success of anaesthesia during extraction of primary maxillary molars was not usable, and data are presented in Table 6. Success of soft tissue anaesthesia following probing is included in the table of orphan studies, Table 5

Moore 1983	Success of anaesthesia was pooled for both dental arches and procedures (access/instrumentation, canal obturation, apicoectomy + retrofilling). The study author was asked for individual data, but these were not available. Satisfactory and unsatisfactory anaesthesia were classed as failure. Only excellent anaesthesia was classed as successful and was judged by "Clinician decisions for lack or near lack of response to treatment", which may not necessarily mean pain-free treatment. Available data are included in the table of orphan studies, Table 5
Moore 2006	One patient withdrew consent after the first drug treatment session, following testing with 4% articaine, 1:100,000 epinephrine. Sixty-two patients completed all sessions of the study protocol; therefore success was re-calculated after communication with the study author. Paired data were not available for meta-analysis for IANBs and infiltrations. Therefore, study data were treated as parallel study data. Data for pulpal anaesthetic success are presented in Analysis 3.2, Analysis 20.1, and Analysis 21.1
Moore 2007	Failure was defined as the need to administer an alternative anaesthetic agent for pain control or visualization of the surgical field, which may mean that a minor degree of pain was present during the procedure. Data for meta-analysis were not usable. Therefore data for success of anaesthesia during periodontal surgery are presented in Table 6
Mumford 1961	Injections were described as infiltrations and regional injections. It was assumed that infiltration data could be obtained from injections into the maxilla and mandible; for regional injections, it was assumed that these were IANBs. Pulpal anaesthesia success data for male and female patients were combined. Data are included in the table of orphan studies, Table 5
Nabeel 2014	Success was defined in the study as no pain or mild pain (0 to 3 on the VAS). However, despite emailing the study author for numbers of participants with scores of only zero on the VAS, it was not possible to make contact. Data for maxillary first premolars are presented in Table 6
Naik 2017	The volume of anaesthetic solution used during surgery for each local anaesthetic group was used to demonstrate success. Data are presented in Table 6
Nespeca 1976	Success was not measured
Nordenram 1990	Data for elderly patients and young patients were combined. Paired data were not available for meta-analysis. Data for success of pulpal anaesthesia (tested with an electric pulp tester) are presented in the table of orphan studies, Table 5
Nydegger 2014	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Mandibular first molar data for pulpal anaesthetic success are presented in Analysis 23.1
Odabas 2012	Success was defined by the study author, following correspondence, as follows: "No pain and feeling numbness. During dental treatment, when children did not feel pain from their treated teeth and told us of feeling numbness of their lip, we considered anaesthesia complete" Data are presented in the table of orphan studies, Table 5
Oliveira 2004	Success was not measured
Ozec 2010	Results were represented graphically rather than as numbers, and it was not possible to contact the study author to confirm figures. Paired data for this cross-over study were not available for meta-analysis. Soft tissue success data (average VAS scores) are presented in Table 6
Parirokh 2015	Success during access cavity preparation and instrumentation in teeth with irreversible pulpitis was defined as ability to access and instrument teeth without pain or with mild pain. The contact author was emailed for raw data (patients who experienced no pain), but it was not possible to make contact. Data for this outcome and for success of soft tissue anaesthesia are presented in Table 6 and Table 5, respectively
Pässler 1996	Success was estimated from graphs, as numerical data were not available. Part 1 success data were not used, as 1 of the local anaesthetic formulations contained norepinephrine (not commercially available). Part 2 success – criterion for success was not stated but was likely to be absence of pain, which was the criterion chosen for success. Data for extraction and apicectomy were pooled. Part 3 success – criterion chosen for success was no pain (both partial success (additional LA given and then no pain) and failure (unable to anaesthetize) were classed as failure) Data for part 2 and part 3 are presented in Analysis 2.1 and Analysis 3.1, respectively
Pellicer-Chover 2013	Success was graded as no discomfort and as slight discomfort but not requiring additional anaesthesia. The contact author was emailed for raw data (patients who experienced no discomfort), but it was not possible to make contact. Paired data for this cross-over study were not available for meta-analysis. Data are presented in Table 6

Poorni 2011	The study author was emailed for data regarding success of pulpal anaesthesia, as the study classes success as < mild pain, rather than no pain, on the Heft-Parker VAS. After making contact with the study author, I was unable to make email contact again to obtain the data. Therefore data are included in Table 6. Soft tissue data are presented in Analysis 1.3
Porto 2007	Clinical success was determined by the number of re-anaesthesia cases for each solution; patients not needing re-anaesthesia may have felt pain but may not have received further local anaesthetic. Paired data for this cross-over study were not available for meta-analysis. Data for success of pulpal anaesthesia (cold test) and anaesthesia during extraction of lower third molars are included in the table of orphan studies, Table 5
Ram 2006	"No pain during drilling" (communication with study author) was the criterion for success. Available data are included in the table of orphan studies, Table 5
Robertson 2007	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 1.2
Ruprecht 1991	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. The data for 4% articaine with 1:100,000 epinephrine vs 4% articaine with 1:200,000 epinephrine are presented in Analysis 3.2, and for 2% lidocaine with 1:100,000 epinephrine vs 4% articaine with 1:200,000 epinephrine in Analysis 16.1. Data for pulpal anaesthetic success for 2% lidocaine with 1:100,000 epinephrine vs 4% articaine with 1:100,000 epinephrine were not usable (100% success for local anaesthetics for all studies; data could not be added to Analysis 1.2 because the data could not be entered as logs of the OR and associated SE using the 'inverse variance' method) and are presented in Table 6
Sadove 1962	"Grade A: profound anaesthesia" was classed as success (patient did not experience any discomfort). "Grade B: adequate anaesthesia" and "grade C: inadequate anaesthesia" were classed as failure. Only data for 2% lidocaine with 1:100,000 epinephrine and 2% mepivacaine with 1:20,000 levonordefrin were used, as 2% mepivacaine, no vasoconstrictor and 2% lidocaine, no vasoconstrictor are not commercially available. Available data are included in the table of orphan studies, Table 5
Sampaio 2012	In the study, clinical anaesthesia was considered successful when the dentist accessed the pulp chamber without the patient reporting pain (pain score of 0 or 1). For the systematic review, only a score of 0 was classed as success. Data for this were obtained from the study author: "Eight (8) patients from the bupivacaine group did not report any pain (score of zero), while twenty (20) reported mild pain (score of 1). Fourteen (14) patients from the lidocaine group did not report any pain (score of zero), while eight (8) reported mild pain (score of 1)" Available data for pulpal anaesthesia during access cavity preparation and instrumentation and pulp testing using an electric pulp tester are included in the table of orphan studies, Table 5. Data for soft tissue anaesthesia are included in Table 6 (both local anaesthetics have 100% success in all studies in that analysis)
Sancho-Puchades 2012	Anaesthetic success was classified as no pain during extraction. Only success for anaesthesia during extraction was entered, as the data for overall success for testing with tetrafluoroethane were not provided in the journal article. Only failure data at each stage of the extraction, when re-injection was required, were given. The contact author was emailed, but it was not possible to make contact. Paired data for clinical anaesthetic success (global pain judged by the patient) are presented in Analysis 5.1
Santos 2007	As paired data were not available for meta-analysis, means of anaesthetic success measured on a 3-point scale (continuous data) are presented in Table 6. The study author was emailed, but it was not possible to make contact
Sherman 1954	Only grade A anaesthesia was classed as success. Grade B and grade C were classed as failure. Mandibular and maxillary injections for both operators were combined. Data (VAS) are included in the table of orphan studies, Table 5
Sherman 2008	Data for success during pulpotomy included cases for which pain on the VAS was mild. Despite making contact with the study author, individual success data (VAS scores of 0) for each local anaesthetic solution were not available. Data for success during pulpotomy are included in Table 6. Data for success when testing with Endo-Ice are included in the table of orphan studies, Table 5, because it became an orphan study, and the other study that measured success, Tortamano 2009, used an electric pulp tester
Sierra Rebolledo 2007	Success of anaesthesia was presented as average VAS values or need for re-injection. The contact author was emailed for data on those with no pain during extraction and for clarification of patient numbers, but it was not possible to make contact. Paired data were not available for meta-analysis. Available data (VAS) are included in Table 6

Silva 2012	Total volume of anaesthetic solution used during surgery was used to demonstrate success. The contact author was emailed for raw data, but it was not possible to make contact; therefore data were entered into Table 6
Sood 2014	Success during pulp extirpation was defined as when the pulp chamber was accessed with no pain or mild, bearable pain reported by the patient (pain score of 0 or 1). The contact author was emailed for raw data (patient scoring just 0; no pain), but it was not possible to make contact; therefore data were entered into Table 6, while data for success of soft tissue anaesthesia were entered into Table 5. Simulated scenario pulpal anaesthesia success data are included in Table 6, as a negative response to electric pulp testing is not a reliable indicator of pulpal anaesthesia
Srinivasan 2009	Success defined as no pain or mild pain. However data in the study allowed re-calculation of success using the criterion of no pain as success. Combined maxillary first premolar and first molar data are presented in Analysis 1.1
Srisurang 2011	Paired data for this cross-over study were not available for meta-analysis. Data for pulpal anaesthetic success are presented in the table of orphan studies, Table 5, apart from the data for 2% lidocaine, 1:100,000 epinephrine vs 4% articaine, 1:100,000 epinephrine, which are presented in Analysis 1.2
Stibbs 1964	Success was classed as grade A anaesthesia only. Grade B and grade C were classed as failure. It was assumed that "mandibular" injections were IANBs, and that "infiltrations" could be injections in the maxilla and mandible. It is not clear whether "other" injections included supplemental injections; therefore the data were excluded Data for 2% lidocaine, 1:50,000 epinephrine vs 2% mepivacaine, 1:20,000 levonordefrin (Neo-Cobefrin) are included in the table of orphan studies, Table 5 (2% procaine/1.5% tetracaine, 1:20,000 levonordefrin is not commercially available)
Thakare 2014	Although intraoperative and postoperative pain were measured, it is not clear whether results presented (VAS) pertain to intraoperative or postoperative pain. The study author was emailed, but we were unable to maintain contact, although we were initially successful. Data have not been used
Tofoli 2003	Success was not measured
Tortamano 2009	In the study, success for pulpectomy included patients who had no pain (0) or mild, bearable pain (1). Only patients with a score of 0 were classed as successful anaesthesia in the review. Data for this were obtained from the study author: "Ten patients from the articaine group did not report any pain (score of zero), while three reported mild pain (score of 1). Six patients from the lidocaine group did not report any pain (score of zero), while three reported mild pain (score of 1)." Data for success of clinical pulpal anaesthesia were used for meta-analysis and are presented in Analysis 1.1. Subjective soft tissue success data are presented in Analysis 1.3. Simulated scenario pulpal anaesthesia success is included in Table 6, as a negative response to electric pulp testing is not a reliable indicator of pulpal anaesthesia
Tortamano 2013	Success was not measured
Trieger 1979	Although the study looked at postoperative analgesia, anaesthetic success measured in terms of the volume injected per quadrant to obtain local anaesthesia was presented in Figure 1 in the study. From this, the success rate for a specific volume could be calculated. It was not possible to determine if success was based on no pain. Some patients were given a general anaesthetic and received injections at the end of surgery. Data for anaesthetic success are presented in Table 6
Trullenque-Eriksson 2011	Success was classed as no need for local anaesthetic reinforcement. The study author was contacted to determine whether patients who had no reinforcement had any pain Quote: "Surgery was only carried out if the anaesthesia had been successful. Some of them may have felt discomfort due to the force applied in more complicated extractions but not pain as such" Paired data were provided for meta-analysis and are presented in Analysis 5.1
Vahatalo 1993	Definitions of success from the study were used. Pulpal anaesthesia data could not be entered and are included in the table of orphan studies, Table 5
Vilchez-Perez 2012	Raw data obtained from the study author. For pulpal anaesthesia, peak rate of anaesthetic success was chosen, which occurred for articaine and bupivacaine at 10 and 15 minutes, respectively. For soft tissue anaesthesia, peak rate of anaesthetic success was chosen for the lip mucosa. After making contact with the study author, I was unable to make email contact again to obtain paired data. Available data are included in the table of orphan studies, Table 5

Visconti 2016	Clinical success of pulpal anaesthesia included teeth for which pain was rated as 0 = no pain and 1 = mild pain, on a 4-point scale. The study author was emailed for details of those participants who had scores of only zero. Data for success using 3.6 mL of solution (the same volume used in the study by Allegretti 2016) are presented in Analysis 8.1 Success of pulpal anaesthesia upon testing with an electric pulp tester is unreliable in teeth with irreversible pulpitis. Therefore, the data are presented in Table 6, along with subjective soft tissue success data (local anaesthetics have 100% success in all studies in that analysis)
Vreeland 1989	Only first molar data for 2% lidocaine, 1:100,000 epinephrine vs 2% lidocaine, 1:200,000 epinephrine were used, as 4% lidocaine, 1:100,000 epinephrine is not commercially available. Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 12.1. Subjective soft tissue data are included in the table of orphan studies, Table 5
Wali 2010	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 10.1. Subjective soft tissue data are presented in Table 6 (local anaesthetics have 100% success in all studies in that analysis). Only data for solutions administered as 1.8 mL were used (2% lidocaine, 1:100,000 epinephrine and 2% lidocaine, 1:50,000 epinephrine)
Weil 1961	Injections were described as infiltrations and mandibular injections. It was assumed that infiltration data could be obtained from injections in the maxilla and the mandible, while with mandibular injections, it was assumed that these were inferior alveolar blocks. Only grade A anaesthesia was classed as success. Grade B and grade C were classed as failure. Available data (VAS) are included in the table of orphan studies, Table 5
Yadav 2015	In this study, success was defined as the ability to access and instrument the teeth with no pain or mild pain (0 or ≤ 54 mm on a VAS, respectively). Only patients with a VAS of zero were classed as successful for this systematic review. The contact author was emailed for data for those participants with a VAS of zero, but it was not possible to make contact. Paired data were not available for meta-analysis. Data are presented in Table 6
Yared 1997	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. First molar data were used for pulpal anaesthetic success and are presented in Analysis 9.1, Analysis 10.1, and Analysis 11.1. Subjective soft tissue success data are presented in Table 6 (local anaesthetics have 100% success in all studies in that analysis)
Yilmaz 2011	For pulpal anaesthesia, the clinical procedures performed were divided up into individual stages: use of a high-speed handpiece, use of a low-speed handpiece, removal of coronal pulp, restoration of the tooth. Pain (failure) could have occurred at any stage in different patients or at more than 1 stage. The first major pain event would have occurred at entry to the pulp with a high-speed handpiece; therefore this stage was used to determine success/failure. Original data would be needed to determine overall success for the whole clinical intervention, as failure may have occurred at any stage of the procedure, but we were unable to contact the study author. Available data (VAS) are therefore included in Table 6. Subjective soft tissue success data are included in the table of orphan studies, Table 5
Yonchak 2001	Paired data for this cross-over study were not available for meta-analysis. Therefore, study data were treated as parallel study data. Lateral incisor data were used for pulpal anaesthetic success and are presented in Analysis 10.1. Subjective soft tissue success data are presented in Table 6 (local anaesthetics have 100% success in all studies in that analysis)

Footnotes

Faces Pain Scale - Revised = a modified version of the Faces Pain Scale (Hicks 2001); HP-VAS = Heft-Parker visual analogue scale; IANB = inferior alveolar nerve block; LA = local anaesthetic; VAS = visual analogue scale.

9 Sensitivity analysis (local anaesthetic success, with and without cross-over studies with no paired data, and with and without studies with high risk of bias)

Outcomes following removal of cross-over studies without paired data								
Outcome	With all studies included				With cross-over studies removed			
	Studies	Participants (events)	Effect estimate	Heterogeneity	Studies	Participants	Effect estimate	Heterogeneity

Analysis 1.2	Abdulwahab 2009; Batista da Silva 2010; Evans 2008; Jaber 2010; Kanaa 2006; Mikesell 2005; Robertson 2007; Srisurang 2011	309 (586)	OR 2.71, 95% CI 1.74 to 4.22	P = 0.45, I² = 0%	Batista da Silva 2010; Jaber 2010; Kanaa 2006; Srisurang 2011	134 (236)	OR 3.28, 95% CI 1.23 to 8.80	P = 0.46, I² = 0%
Analysis 1.3	Allegretti 2016; Claffey 2004; Kanaa 2006; Mikesell 2005; Poorni 2011; Tortamano 2009	355 (443)	RR 1.03, 95% CI 0.99 to 1.07	P = 0.3, I² = 17%	Allegretti 2016; Claffey 2004; Poorni 2011; Tortamano 2009	179 (267)	RR 1.02, 95% CI 0.98 to 1.07	P = 0.47, I² = 0%
Analysis 1.6	Bhagat 2014; Kalia 2011; Kambalimath 2013; Kanaa 2006; Martinez-Rodriguez 2012; Silva 2012	637 (818)	(MD -0.23 minutes, 95% CI -0.45 to -0.01 minutes)	P = 0.00001, I² = 87%	Bhagat 2014; Martinez-Rodriguez 2012	456 (456)	MD -0.18 minutes, 95% CI -0.30 to -0.07 minutes	P = 0.23, I² = 29%
Analysis 4.4	Chilton 1971; McLean 1993	406 (436)	MD 0.02 minutes, 95% CI -0.10 to 0.14 minutes	P = 0.51, I² = 0%	Chilton 1971 (orphan)	376 (376)	MD 0.02 minutes, 95% CI -0.10 to 0.14 minutes	Not applicable
Analysis 6.1	Bouloux 1999; Laskin 1977	31 (62)	OR 0.58, 95% CI 0.07 to 5.12	P = 0.17, I² = 47%	Bouloux 1999 (orphan)	23 (46)	OR 0.14, 95% CI 0.01 to 2.77	Not applicable
Analysis 6.4	Fernandez 2005; Laskin 1977; Moore 1983	79 (126)	MD 0.02 minutes, 95% CI -1.07 to 1.10 minutes	P = 0.06, I² = 64%	Moore 1983 (orphan)	32 (32)	MD -0.90 minutes, 95% CI -1.96 to 0.16 minutes	Not applicable
Analysis 6.5	Fernandez 2005; Gross 2007; Laskin 1977; Linden 1986; Moore 1983; Nespeca 1976	232 (332)	MD 222.88 minutes, 95% CI 135.99 to 309.76 minutes	P < 0.00001, I² = 92%	Moore 1983; Nespeca 1976	132 (132)	MD 261.07 minutes, 95% CI 195.96 to 326.18 minutes	P = 0.12, I² = 53%
Analysis 7.2	Allegretti 2016; Bortoluzzi 2009	68 (92)	RR 1.07, 95% CI 0.73 to 1.59	P = 0.06, I² = 72%	Allegretti 2016 (orphan)	44 (44)	RR 1.00, 95% CI 0.92 to 1.09	Not applicable
Analysis 19.3	Chilton 1971; Hinkley 1991	421 (449)	MD -0.01 minutes, 95% CI -0.14 to 0.11 minutes	P = 0.86, I² = 0%	Chilton 1971 (orphan)	393 (393)	MD -0.01 minutes, 95% CI -0.14 to 0.11 minutes	Not applicable
Outcomes following removal of studies with high risk of bias								
Outcome	With all studies included				With high risk of bias studies removed			
	Studies	Participants (events)	Effect estimate	Heterogeneity	Number of studies	Participants (events)	Effect estimate	Heterogeneity

Analysis 5.1	Sancho-Puchades 2012; Trullenque-Eriksson 2011	37 (74)	OR 0.87, 95% CI 0.27 to 2.83	P = 0.18, I² = 44%	Sancho-Puchades 2012 (orphan)	18 (36)	OR 2.00, 95% CI 0.37 to 10.92	Not applicable
Analysis 5.2	Gregorio 2008; Trullenque-Eriksson 2011	69 (138)	MD -0.85 minutes, 95% CI -1.26 to -0.44 minutes	P = 0.98, I² = 0%	Gregorio 2008 (orphan)	50 (100)	MD -0.85 minutes, 95% CI -1.27 to -0.43 minutes	Not applicable
Analysis 5.3	Trullenque-Eriksson 2011; Vilchez-Perez 2012	39 (78)	MD -172.61 minutes, 95% CI -239.69 to -105.53 minutes	P = 1.0, I² = 0%	Vilchez-Perez 2012 (orphan)	20 (40)	MD -172.55 minutes, 95% CI -249.73 to -95.37 minutes	Not applicable
Outcomes following removal of studies in which topical anaesthetic was not used before injection								
Analysis 1.8	Evans 2008; Mikesell 2005; Robertson 2007	157 (314)	MD 4.74 mm, 95% CI -1.98 to 11.46 mm	P = 0.51 I² = 0%	Evans 2008; Mikesell 2005	97 (194)	MD 7.46 mm, 95% CI -0.70 to 15.61 mm)	P = 0.90 I² = 0%

Footnotes

10 Studies showing success grouped according to local anaesthetic used, testing method, and subgroup

Comparison: lidocaine vs lidocaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)		**2% lid' 1:80,000 vs 2% lid' 1:200,000** Karm 2017	
Healthy pulps (clinical testing)	**2% lid' 1:50,000 vs 2% lid' 1:100,000** Kramer 1958	**2% lid' 1:50,000 vs 2% lid' 1:100,000** Kramer 1958	**2% lid' 1:50,000 vs 2% lid' 1:100,000** Sherman 1954
Diseased pulps with irreversible pulpitis (clinical testing)		**2% lid' 1:80,000 vs 2% lid' 1:200,000** Aggarwal 2014	
Healthy pulps (simulated scenario testing)	**2% lid' 1:50,000 vs 2% lid' 1:100,000** Berberich 2009; Knoll-Kohler 1992a; Mason 2009 **2% lid' 1:50,000 vs 2% lid' 1:200,000** Knoll-Kohler 1992a **2% lid' 1:100,000 vs lid' 1:200,000** Caldas 2015; Knoll-Kohler 1992a	**2% lid' 1:50,000 vs 2% lid' 1:80,000** Dagher 1997; Yared 1997 **2% lid' 1:50,000 vs 2% lid' 1:100,000** Dagher 1997; Wali 2010; Yared 1997; Yonchak 2001 **2% lid' 1:80,000 vs 2% lid' 1:100,000** Dagher 1997; Yared 1997 **2% lid' 1:100,000 vs 2% lid' 1:200,000** Vreeland 1989	

Soft tissues (simulated scenario testing)	2% lid' 1:50,000 vs 2% lid' 1:100,000 Berberich 2009	2% lid' 1:50,000 vs 2% lid' 1:80,000 Dagher 1997; Yared 1997 2% lid' 1:80,000 vs 2% lid' 1:100,000 Dagher 1997; Yared 1997 2% lid' 1:50,000 vs 2% lid' 1:100,000 Dagher 1997; Wali 2010; Yared 1997; Yonchak 2001 2% lid' 1:100,000 vs 2% lid' 1:200,000 Vreeland 1989 2% lid' 1:80,000 vs 2% lid' 1:200,000 Aggarwal 2014	
Comparison: lidocaine vs mepivacaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)		2% lid' 1:80,000 vs 3% mep' plain Elbay 2016; Hellden 1974 2% lid' 1:100,000 vs 2% mep' 1:100,000 Porto 2007	2% lid' 1:100,000 vs 2% mep' 1:20,000 Sadove 1962
Healthy pulps (clinical testing)		2% lid' 1:50,000 vs 2% mep' 1:20,000 Stibbs 1964 2% lid' 1:80,000 vs 3% mep' plain Mumford 1961	2% lid' 1:50,000 vs 2% mep' 1:20,000 Stibbs 1964 2% lid' 1:80,000 vs 3% mep' plain Mumford 1961 2% lid' 1:100,000 vs 2% mep' 1:20,000 Sadove 1962
Diseased pulps with irreversible pulpitis (clinical testing)		2% lid' 1:100,000 vs 2% mep' 1:100,000 Allegretti 2016; Visconti 2016 2% lid' 1:100,000 vs 3% mep' plain Cohen 1993 2% lid' 1:80,000 vs 3% mep' plain Elbay 2016	
Different tissues pooled (clinical testing)		2% lid' 1:100,000 vs 3% mep' plain Bradley 1969	2% lid' 1:100,000 vs 3% mep' plain Bradley 1969

Tissues, when tissues tested were unclear (clinical testing)			**2% lid' 1:100,000 vs 3% mep' plain** Albertson 1963 **2% lid' 1:100,000 vs 2% mep' 1:20,000** Albertson 1963
Healthy pulps (simulated scenario testing)	**2% lid 1:100,000 vs 3% mep' plain** Berberich 2009; Burns 2004; Forloine 2010; Mason 2009 **2% lid' 1:50,000 vs 3% mep' plain** Berberich 2009; Mason 2009 **2% lid' 1:80,000 vs 3% mep' plain** Nordenram 1990 **2% lid' 1:100,000 vs 2% mep' plain 1:20,000** Lawaty 2010 **2% lid' 1:100,000 vs 2% mep' 1:100,000** Srisurang 2011	**2% lid' 1:100,000 vs 3% mep' plain** Abdulwahab 2009; Cohen 1993; McLean 1993 **2% lid' 1:100,000 vs 2% mep' 1:20,000** Hinkley 1991 **2% lid' 1:100,000 vs 2% mep' 1:100,000** Porto 2007	
Diseased pulps with irreversible pulpitis (simulated scenario testing)		**2% lid' 1:100,000 vs 2% mep' 1:100,000** Allegretti 2016; Visconti 2016	
Soft tissues (simulated scenario testing)	**2% lid' 1:50,000 vs 3% mep' plain** Berberich 2009 **2% lid 1:100,000 vs 3% mep' plain** Berberich 2009; Forloine 2010	**2% lid' 1:100,000 vs 2% mep' 1:100,000** Allegretti 2016; Visconti 2016 **2% lid' 1:100,000 vs 3% mep' plain** Abdulwahab 2009; Cohen 1993; Hersh 1995; McLean 1993 **2% lid' 1:100,000 vs 2% mep' 1:20,000** Hersh 1995; Hinkley 1991 **2% lid' 1:80,000 vs 3% mep' plain** Elbay 2016	
Comparison: lidocaine vs articaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**

Healthy pulps, hard and soft tissues (clinical testing)	**2% lid' 1:80,000 vs 4% art' 1:100,000** Kolli 2017	**2% lid' 1:100,000 vs 4% art' 1:100,000** Bhagat 2014; Jain 2016; Kambalimath 2013; Sierra Rebolledo 2007; Silva 2012 **2% lid' 1:80,000 vs 4% art' 1:100,000** Naik 2017	**2% lid' 1:100,000 vs 4% art' 1:100,000** Khoury 1991 **2% lid' 1:100,000 vs 4% art' 1:200,000** Khoury 1991
Healthy pulps (clinical testing)		**2% lid' 1:80,000 vs 4% art' 1:100,000** Arrow 2012	**2% lid' 1:100,000 vs 4% art' 1:200,000** Ram 2006
Diseased pulps with irreversible pulpitis (clinical testing)	**2% lid' 1:100,000 vs 4% art' 1:100,000** Nabeel 2014; Srinivasan 2009 **2% lid' 1:80,000 vs 4% art' 1:100,000** Hosseini 2016	**2% lid' 1:200,000 vs 4% art' 1:200,000** Aggarwal 2009 **2% lid' 1:100,000 vs 4% art' 1:100,000** Allegretti 2016; Ashraf 2013; Claffey 2004; Poorni 2011; Tortamano 2009 **2% lid' 1:200,000 vs 4% art' 1:100,000** Aggarwal 2017 **2% lid' 1:80,000 vs 4% art' 1:100,000** Sood 2014; Yadav 2015	**2% lid' 1:100,000 vs 4% art' 1:100,000** Sherman 2008
Different tissues pooled (clinical testing)	**2% lid' 1:80,000 vs 4% art' 1:100,000** Kanaa 2012		**2% lid' 1:100,000 vs 4% art' 1:100,000** Malamed 2000a; Malamed 2000b
Healthy pulps (simulated scenario testing)	**2% lid' 1:80,000 vs 4% art' 1:100,000** Kanaa 2012 **2% lid' 1:100,000 vs 4% art' 1:100,000** Evans 2008; Knoll-Kohler 1992b; Ruprecht 1991; Srisurang 2011 **2% lid' 1:100,000 vs 4% art' 1:200,000** Ruprecht 1991 **2% lid' 1:80,000 vs 4% art' 1:200,000** Vahatalo 1993	**2% lid' 1:100,000 vs 4% art' 1:100,000** Abdulwahab 2009; Batista da Silva 2010; Haase 2008; Jaber 2010; Kanaa 2006; Maruthingal 2015; Mikesell 2005; Robertson 2007 **2% lid' 1:100,000 vs 4% art' 1:200,000** Abdulwahab 2009	**2% lid' 1:100,000 vs 4% art' 1:100,000** Sherman 2008
Diseased pulps with irreversible pulpitis (simulated scenario testing)		**2% lid' 1:100,000 vs 4% art' 1:100,000** Allegretti 2016; Tortamano 2009 **2% lid' 1:80,000 vs 4% art' 1:100,000** Sood 2014;	

Soft tissues (simulated scenario testing)		**2% lid' 1:200,000 vs 4% art' 1:200,000** Aggarwal 2009; **2% lid' 1:100,000 vs 4% art' 1:100,000** Abdulwahab 2009; Allegretti 2016; Ashraf 2013; Claffey 2004; Hersh 1995; Kanaa 2006; Maruthingal 2015; Mikesell 2005; Poorni 2011; Tortamano 2009 **2% lid' 1:100,000 vs 4% art' 1:200,000** Abdulwahab 2009 **2% lid' 1:80,000 vs 4% art' 1:100,000** Sood 2014; Yadav 2015	
Comparison: lidocaine vs prilocaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)	**2% lid' 1:100,000 vs 4% pril' plain** Epstein 1965	**2% lid' 1:100,000 vs 4% pril' plain** Chilton 1971; Epstein 1965 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Chilton 1971 **2% lid' 1:80,000 vs 3% pril' 0.03IU fely'** Keskitalo 1975	**2% lid' 1:100,000 vs 3% pril' 0.03IU fely'** Khoury 1991; Pässler 1996 **2% lid' 1:100,000 vs 4% pril' plain** Chilton 1971 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Chilton 1971
Healthy pulps (clinical testing)	**2% lid' 1:100,000 vs 4% pril' plain** Epstein 1965	**2% lid' 1:100,000 vs 4% pril' plain** Epstein 1965	
Different tissues, pooled (clinical testing)	**2% lid' 1:100,000 vs 4% pril' plain** Epstein 1969 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Epstein 1969	**2% lid' 1:100,000 vs 4% pril' plain** Epstein 1969; Gangarosa 1967 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Epstein 1969	**2% lid' 1:100,000 vs 4% pril' plain** Gangarosa 1967
Tissues, when tissues tested were unclear (clinical testing)		**2% lid' 1:100,000 vs 4% pril' plain** Chilton 1971; **2% lid' 1:100,000 vs 4% pril' 1:200,000** Chilton 1971	**2% lid' 1:100,000 vs 4% pril' plain** Chilton 1971 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Chilton 1971

Healthy pulps (simulated scenario testing)	**2% lid' 1:100,000 vs 4% pril' plain** Katz 2010 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Katz 2010 **2% lid' 1:80,000 vs 3% pril' 0.03IU fely'** Nordenram 1990	**2% lid' 1:100,000 vs 4% pril' plain** McLean 1993 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Abdulwahab 2009; Hinkley 1991	
Soft tissues (simulated scenario testing)		**2% lid' 1:100,000 vs 4% pril' plain** Hersh 1995; McLean 1993 **2% lid' 1:100,000 vs 4% pril' 1:200,000** Abdulwahab 2009; Hinkley 1991	
Comparison: lidocaine vs bupivacaine			
	Maxilla	**Mandible**	**Both jaws/not stated**
Healthy pulps, hard and soft tissues (clinical testing)	**2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Bouloux 1999	**2% lid' 1:80,000 vs 0.5% bup' 1:200,000** Chapman 1988 **2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Bouloux 1999; Laskin 1977	
Diseased pulps with irreversible pulpitis (clinical testing)		**2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Sampaio 2012 **2% lid' 1:200,000 vs 0.5% bup' 1:200,000** Aggarwal 2017 **2% lid' 1:80,000 vs 0.5% bup' 1:200,000** Parirokh 2015	
Different tissues, pooled (clinical testing)			**2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Moore 1983
Healthy pulps (simulated scenario testing)	**2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Gross 2007	**2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Abdulwahab 2009; Fernandez 2005; Sampaio 2012	
Soft tissues (simulated scenario testing)		**2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Abdulwahab 2009; Fernandez 2005; Sampaio 2012 **2% lid' 1:80,000 vs 0.5% bup' 1:200,000** Parirokh 2015	**2% lid' 1:100,000 vs 0.5% bup' 1:200,000** Bouloux 1999
Comparison: articaine vs articaine			
	Maxilla	**Mandible**	**Both jaws/not stated**

Healthy pulps, hard and soft tissues (clinical testing)	**4% art' 1:100,000 vs 4% art' 1:200,000** Lima 2009; Moore 2007 **4% art' 1:100,000 vs 4% art' plain** Moore 2007 **4% art' 1:200,000 vs 4% art' 1:200,000** Moore 2007	**4% art' 1:100,000 vs 4% art' plain** Kammerer 2012 **4% art' 1:100,000 vs 4% art' 1:200,000** Pässler 1996; Santos 2007	**4% art' 1:100,000 vs 4% art' 1:200,000** Khoury 1991
Diseased pulps with irreversible pulpitis (clinical testing)		**4% art' 1:100,000 vs 4% art' 1:100,000 bitartrate** Atasoy Ulusoy 2014	
Healthy pulps (simulated scenario testing)	**4% art' 1:100,000 vs 4% art' 1:200,000** Kammerer 2014; Moore 2006; Ruprecht 1991 **4% art' 1:100,000 vs 4% art' plain** Kammerer 2014; Moore 2006 **4% art' 1:200,000 vs 4% art' plain** Kammerer 2014; Moore 2006 **4% art' 1:100,000 vs 4% art' 1:400,000** Kammerer 2014 **4% art' 1:400,000 vs 4% art' plain** Kammerer 2014 **4% art' 1:200,000 vs 4% art' 1:400,000** Kammerer 2014	**4% art' 1:100,000 vs 4% art' 1:200,000** Abdulwahab 2009; McEntire 2011; Moore 2006 **4% art' 1:100,000 vs 4% art' plain** Moore 2006 **4% art' 1:200,000 vs 4% art' plain** Moore 2006 **4% art' 1:100,000 vs 4% art' 1:100,000 bitartrate** Atasoy Ulusoy 2014	

Soft tissues (simulated scenario testing)	**4% art' 1:100,000 vs 4% art' 1:200,000** Kammerer 2014; Ozec 2010 **4% art' 1:100,000 vs 4% art' plain** Kammerer 2014; Moore 2006 **4% art' 1:200,000 vs 4% art' plain** Kammerer 2014; Moore 2006 **4% art' 1:100,000 vs 4% art' 1:400,000** Kammerer 2014 **4% art' 1:400,000 vs 4% art' plain** Kammerer 2014 **4% art' 1:200,000 vs 4% art' 1:400,000** Kammerer 2014	**4% art' 1:100,000 vs 4% art' 1:200,000** Abdulwahab 2009	
Comparison: articaine vs prilocaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)			**4% art' 1:100,000 vs 3% pril' 0.03IU fely'** Khoury 1991 **4% art' 1:200,000 vs 3% pril' 0.03IU fely'** Khoury 1991
Diseased pulps with irreversible pulpitis (clinical testing)	**4% art' 1:100,000 vs 3% pril' 0.03IU fely'** Yilmaz 2011	**4% art' 1:100,000 vs 3% pril' 0.03IU fely'** Yilmaz 2011	
Healthy pulps (simulated scenario testing)	**4% art' 1:200,000 vs 4% pril' 1:200,000** Donaldson 1987; Haas 1990; Haas 1991	**4% art' 1:200,000 vs 4% pril' 1:200,000** Donaldson 1987; Haas 1990; Haas 1991 **4% art 1:100,000 vs 4% pril 1:200,000** Abdulwahab 2009; Nydegger 2014	
Soft tissues (simulated scenario testing)	**4% art' 1:200,000 vs 4% pril' 1:200,000** Haas 1990; Haas 1991 **4% art' 1:100,000 vs 3% pril' 0.03IU fely'** Yilmaz 2011	**4% art' 1:200,000 vs 4% pril' 1:200,000** Haas 1990; Haas 1991 **4% art' 1:100,000 vs 3% pril' 0.03IU fely** Yilmaz 2011 **4% art' 1:100,000 vs 4% pril' 1:200,000** Abdulwahab 2009	

Comparison: articaine vs mepivacaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)	**4% art' 1:100,000 vs 2% mep' 1:100,000** Gazal 2017	**4% art' 1:100,000 vs 2% mep' 1:100,000** Colombini 2006	
Healthy pulps (clinical testing)	**4% art' 1:200,000 vs 3% mep' plain** Odabas 2012		
Diseased pulps with irreversible pulpitis (clinical testing)		**4% art' 1:100,000 vs 2% mep' 1:100,000** Allegretti 2016; Maniglia-Ferreira 2009	
Healthy pulps (simulated scenario testing)	**4% art' 1:100,000 vs 2% mep' 1:100,000** Srisurang 2011	**4% art' 1:100,000 vs 2% mep' 1:100,000** Gazal 2015 **4% art' 1:200,000 vs 3% mep' plain** Abdulwahab 2009 **4% art 1:100,000 vs 3% mep plain** Abdulwahab 2009	
Diseased pulps with irreversible pulpitis (simulated scenario testing)		**4% art' 1:100,000 vs 2% mep' 1:100,000** Allegretti 2016;	
Soft tissues (simulated scenario testing)		**4% art' 1:100,000 vs 2% mep' 1:100,000** Allegretti 2016; Bortoluzzi 2009 **4% art' 1:200,000 vs 3% mep' plain** Abdulwahab 2009 **4% art' 1:100,000 vs 3% mep' plain** Abdulwahab 2009	
Comparison: articaine vs bupivacaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)		**4% art' 1:200,000 vs 0.5% bup' 1:200,000** Gregorio 2008; Sancho-Puchades 2012; Trullenque-Eriksson 2011 **4% art' 1:100,000 vs 0.5% bup' 1:200,000** Pellicer-Chover 2013	
Diseased pulps with irreversible pulpitis (clinical testing)		**4% art' 1:100,000 vs 0.5% bup' 1:200,000** Aggarwal 2017	
Healthy pulps (simulated scenario testing)	**4% art' 1:200,000 vs 0.5% bup' 1:200,000** Vilchez-Perez 2012	**4% art' 1:200,000 vs 0.5% bup' 1:200,000** Abdulwahab 2009; Sancho-Puchades 2012 **4% art' 1:100,000 vs 0.5% bup' 1:200,000** Abdulwahab 2009	

Soft tissues (simulated scenario testing)	4% art' 1:200,000 vs 0.5% bup' 1:200,000 Vilchez-Perez 2012	4% art' 1:200,000 vs 0.5% bup' 1:200,000 Abdulwahab 2009 4% art' 1:100,000 vs 0.5% bup' 1:200,000 Abdulwahab 2009	
Comparison: prilocaine vs mepivacaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps (simulated scenario testing)	3% mep' plain vs 3% pril' 0.03 IU fely' Nordenram 1990	2% mep' 1:20,000 vs 4% pril' 1:200,000 Hinkley 1991 3% mep' plain vs 4% pril' plain McLean 1993 3% mep' plain vs 4% pril' 1:200,000 Abdulwahab 2009	
Soft tissues (simulated scenario testing)		3% mep' plain vs 4% pril' plain Hersh 1995; McLean 1993 2% mep' 1:20,000 vs 4% pril' 1:200,000 Hersh 1995; Hinkley 1991 3% mep' plain vs 4% pril' 1:200,000 Abdulwahab 2009	
Comparison: prilocaine vs prilocaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)		4% pril' plain vs 4% pril' 1:200,000 Chilton 1971	4% pril' plain vs 4% pril' 1:200,000 Chilton 1971
Different tissues, pooled (clinical testing)	4% pril' plain vs 4% pril' 1:200,000 Epstein 1969	4% pril' plain vs 4% pril' 1:200,000 Epstein 1969	
Tissues, where the tissues tested were unclear (clinical testing)		4% pril' plain vs 4% pril' 1:200,000 Chilton 1971	4% pril' plain vs 4% pril' 1:200,000 Chilton 1971
Healthy pulps (simulated scenario testing)	4% pril' plain vs 4% pril' 1:200,000 Katz 2010		
Comparison: prilocaine vs bupivacaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps (simulated scenario testing)		4% pril' 1:200,000 vs 0.5% bup' 1:200,000 Abdulwahab 2009	
Soft tissues (simulated scenario testing)		4% pril' 1:200,000 vs 0.5% bup' 1:200,000 Abdulwahab 2009	

Comparison: mepivacaine vs bupivacaine			
	Maxilla	**Mandible**	**Both jaws/Not stated**
Healthy pulps, hard and soft tissues (clinical testing)			**3% mep' plain vs 0.5% bup' 1:200,000** Trieger 1979
Healthy pulps (simulated scenario testing)		**3% mep' plain vs 0.5% bup' 1:200,000** Abdulwahab 2009	
Soft tissues (simulated scenario testing)		**3% mep' plain vs 0.5% bup' 1:200,000** Abdulwahab 2009	
Comparison: mepivacaine vs mepivacaine			
	Maxilla	**Mandible**	**Both jaws/not stated**
Healthy pulps (clinical testing)		**3% mep' plain vs 2% mep' 1:20,000** Weil 1961	**3% mep' plain vs 2% mep' 1:20,000** Weil 1961
Tissues, when tissues tested were unclear (clinical testing)			**3% mep' plain vs 2% mep' 1:20,000** Albertson 1963

Footnotes

art' = articaine; BI = buccal infiltration; bup' = bupivacaine; conc' = concentration; fely' = felypressin; IANB = inferior alveolar nerve block; lid' = lidocaine; mep' = mepivacaine; pril = prilocaine.

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Classification pending references

Data and analyses

1 4% articaine, 1:100,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of diseased pulps with irreversible pulpitis)	4	203	Risk Ratio(M-H, Fixed, 95% CI)	1.60 [1.10, 2.32]
1.1.1 Maxillary infiltration	1	40	Risk Ratio(M-H, Fixed, 95% CI)	2.25 [1.29, 3.92]
1.1.2 Mandibular block (IANB)	3	163	Risk Ratio(M-H, Fixed, 95% CI)	1.32 [0.81, 2.16]
1.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	8		(IV, Fixed, 95% CI)	2.71 [1.74, 4.22]
1.2.1 Maxillary infiltration	2		(IV, Fixed, 95% CI)	1.41 [0.54, 3.73]
1.2.2 Mandibular infiltration	3		(IV, Fixed, 95% CI)	4.88 [2.30, 10.37]
1.2.3 Mandibular block (mental block)	1		(IV, Fixed, 95% CI)	2.00 [0.60, 6.64]
1.2.4 Mandibular block (IANB)	1		(IV, Fixed, 95% CI)	2.19 [0.95, 5.04]
1.2.5 Mandibular infiltration (buccal and lingual)	1		(IV, Fixed, 95% CI)	11.00 [0.61, 198.97]
1.3 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of soft tissues)	6	443	Risk Ratio(M-H, Fixed, 95% CI)	1.03 [0.99, 1.07]
1.3.1 Mandibular block (IANB)	5	381	Risk Ratio(M-H, Fixed, 95% CI)	1.04 [0.99, 1.08]
1.3.2 Mandibular infiltration	1	62	Risk Ratio(M-H, Fixed, 95% CI)	1.00 [0.94, 1.06]
1.4 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	6	402	Mean Difference(IV, Random, 95% CI)	-0.63 [-1.69, 0.42]
1.4.1 Maxillary infiltration	3	104	Mean Difference(IV, Random, 95% CI)	0.45 [-1.10, 2.00]
1.4.2 Mandibular infiltration	1	66	Mean Difference(IV, Random, 95% CI)	-3.50 [-5.31, -1.69]
1.4.3 Mandibular block (IANB)	1	60	Mean Difference(IV, Random, 95% CI)	-1.30 [-2.82, 0.22]
1.4.4 Both jaws combined/Jaw not stated	1	172	Mean Difference(IV, Random, 95% CI)	-0.18 [-0.30, -0.06]
1.5 Duration of anaesthesia (simulated scenario testing of healthy pulps)	3	104	Mean Difference(IV, Random, 95% CI)	21.87 [-10.96, 54.71]
1.5.1 Maxillary infiltration	2	44	Mean Difference(IV, Random, 95% CI)	5.50 [-11.33, 22.33]
1.5.2 Mandibular block (IANB)	1	60	Mean Difference(IV, Random, 95% CI)	44.80 [33.22, 56.38]

1.6 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)	6	818	Mean Difference(IV, Random, 95% CI)	-0.23 [-0.45, -0.01]
1.6.1 Mandibular infiltration	1	62	Mean Difference(IV, Random, 95% CI)	0.07 [-0.18, 0.32]
1.6.2 Mandibular block (IANB)	1	360	Mean Difference(IV, Random, 95% CI)	-0.18 [-0.29, -0.07]
1.6.3 Mandibular block (IANB) and infiltration	3	196	Mean Difference(IV, Random, 95% CI)	-0.11 [-0.20, -0.03]
1.6.4 Both jaws combined/Jaw not stated	1	200	Mean Difference(IV, Random, 95% CI)	-0.81 [-1.03, -0.59]
1.7 Duration of anaesthesia (simulated scenario testing of soft tissues)	2	422	Mean Difference(IV, Fixed, 95% CI)	56.88 [44.08, 69.69]
1.7.1 Mandibular block (IANB) and infiltration	1	96	Mean Difference(IV, Fixed, 95% CI)	33.00 [-27.63, 93.63]
1.7.2 Mandibular block (IANB)	1	326	Mean Difference(IV, Fixed, 95% CI)	58.00 [44.90, 71.10]
1.8 Local adverse effects, pain on injection	3	314	Mean Difference(IV, Fixed, 95% CI)	4.74 [-1.98, 11.46]
1.8.1 Maxillary infiltration	1	80	Mean Difference(IV, Fixed, 95% CI)	8.00 [-4.07, 20.07]
1.8.2 Mandibular infiltration	1	120	Mean Difference(IV, Fixed, 95% CI)	-1.00 [-12.86, 10.86]
1.8.3 Mandibular block (IANB)	1	114	Mean Difference(IV, Fixed, 95% CI)	7.00 [-4.07, 18.07]
1.9 Local adverse effects, pain following injection	3	309	Mean Difference(IV, Fixed, 95% CI)	6.41 [1.01, 11.80]
1.9.1 Maxillary infiltration	1	80	Mean Difference(IV, Fixed, 95% CI)	13.00 [3.43, 22.57]
1.9.2 Mandibular infiltration	1	115	Mean Difference(IV, Fixed, 95% CI)	2.00 [-6.77, 10.77]
1.9.3 Mandibular block (IANB)	1	114	Mean Difference(IV, Fixed, 95% CI)	5.00 [-4.77, 14.77]

2 3% prilocaine, 0.03 IU felypressin vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues)	2	907	Risk Ratio(M-H, Fixed, 95% CI)	0.86 [0.79, 0.95]
2.1.1 Both jaws combined/Jaw not stated	2	907	Risk Ratio(M-H, Fixed, 95% CI)	0.86 [0.79, 0.95]

3 4% articaine, 1:200,000 epinephrine vs 4% articaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues)	3	930	Risk Ratio(M-H, Random, 95% CI)	0.85 [0.71, 1.02]
3.1.1 Maxillary infiltration	1	100	Risk Ratio(M-H, Random, 95% CI)	0.77 [0.64, 0.92]
3.1.2 Mandibular testing (injection type not stated)	1	40	Risk Ratio(M-H, Random, 95% CI)	0.77 [0.58, 1.03]
3.1.3 Both jaws combined/Jaw not stated	1	790	Risk Ratio(M-H, Random, 95% CI)	0.96 [0.88, 1.05]
3.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	5	496	Risk Ratio(M-H, Fixed, 95% CI)	0.97 [0.87, 1.08]
3.2.1 Maxillary infiltration	3	164	Risk Ratio(M-H, Fixed, 95% CI)	0.99 [0.92, 1.06]
3.2.2 Mandibular infiltration	2	208	Risk Ratio(M-H, Fixed, 95% CI)	0.88 [0.70, 1.10]
3.2.3 Mandibular block (IANB)	1	124	Risk Ratio(M-H, Fixed, 95% CI)	1.13 [0.80, 1.60]

3.3 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	5	322	Mean Difference(IV, Fixed, 95% CI)	0.15 [-0.42, 0.73]
3.3.1 Maxillary infiltration	3	158	Mean Difference(IV, Fixed, 95% CI)	0.02 [-0.69, 0.73]
3.3.2 Mandibular block (IANB)	3	164	Mean Difference(IV, Fixed, 95% CI)	0.41 [-0.58, 1.40]
3.4 Duration of anaesthesia (simulated scenario testing of healthy pulps)	5	322	Mean Difference(IV, Fixed, 95% CI)	-8.98 [-15.17, -2.79]
3.4.1 Maxillary infiltration	3	158	Mean Difference(IV, Fixed, 95% CI)	-6.62 [-13.68, 0.44]
3.4.2 Mandibular block (IANB)	3	164	Mean Difference(IV, Fixed, 95% CI)	-16.80 [-29.65, -3.95]

4 4% prilocaine plain vs 2% lidocaine 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues)	2	228	Risk Ratio(M-H, Fixed, 95% CI)	0.86 [0.75, 0.99]
4.1.1 Maxillary infiltration	1	9	Risk Ratio(M-H, Fixed, 95% CI)	0.83 [0.48, 1.44]
4.1.2 Mandibular block (IANB)	2	92	Risk Ratio(M-H, Fixed, 95% CI)	0.96 [0.73, 1.26]
4.1.3 Both jaws combined/Jaw not stated	1	127	Risk Ratio(M-H, Fixed, 95% CI)	0.81 [0.70, 0.94]
4.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	120	Risk Ratio(M-H, Fixed, 95% CI)	0.93 [0.75, 1.17]
4.2.1 Maxillary infiltration	1	60	Risk Ratio(M-H, Fixed, 95% CI)	0.96 [0.76, 1.22]
4.2.2 Mandibular block (IANB)	1	60	Risk Ratio(M-H, Fixed, 95% CI)	0.89 [0.59, 1.35]
4.3 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	2	103	Mean Difference(IV, Fixed, 95% CI)	-0.96 [-2.87, 0.95]
4.3.1 Maxillary infiltration	1	48	Mean Difference(IV, Fixed, 95% CI)	-1.10 [-3.12, 0.92]
4.3.2 Mandibular block (IANB)	1	55	Mean Difference(IV, Fixed, 95% CI)	0.20 [-5.63, 6.03]
4.4 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)	2	436	Mean Difference(IV, Fixed, 95% CI)	0.02 [-0.10, 0.14]
4.4.1 Mandibular block (IANB)	2	199	Mean Difference(IV, Fixed, 95% CI)	0.28 [-0.20, 0.75]
4.4.2 Both jaws combined/Jaw not stated	1	237	Mean Difference(IV, Fixed, 95% CI)	0.00 [-0.13, 0.13]
4.5 Duration of anaesthesia (simulated scenario testing of soft tissues)	3	698	Mean Difference(IV, Random, 95% CI)	-33.95 [-48.05, -19.84]
4.5.1 Maxillary infiltration	2	220	Mean Difference(IV, Random, 95% CI)	-47.36 [-63.24, -31.49]
4.5.2 Mandibular block (IANB)	3	300	Mean Difference(IV, Random, 95% CI)	-21.09 [-37.23, -4.94]
4.5.3 Both jaws combined/Jaw not stated	1	178	Mean Difference(IV, Random, 95% CI)	-49.40 [-71.00, -27.80]

5 0.5% bupivacaine, 1:200,000 epinephrine vs 4% articaine, 1:200,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

5.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues)	2		Odds Ratio(IV, Fixed, 95% CI)	0.87 [0.27, 2.83]
5.1.1 Mandibular block (IANB) and infiltration	2		Odds Ratio(IV, Fixed, 95% CI)	0.87 [0.27, 2.83]
5.2 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)	2	138	Mean Difference(IV, Fixed, 95% CI)	-0.85 [-1.26, -0.44]
5.2.1 Mandibular block (IANB) and infiltration	2	138	Mean Difference(IV, Fixed, 95% CI)	-0.85 [-1.26, -0.44]
5.3 Duration of anaesthesia (simulated scenario testing of soft tissues)	2	78	Mean Difference(IV, Fixed, 95% CI)	-172.61 [-239.69, -105.53]
5.3.1 Maxillary infiltration	1	40	Mean Difference(IV, Fixed, 95% CI)	-172.55 [-249.73, -95.37]
5.3.2 Mandibular block (IANB) and infiltration	1	38	Mean Difference(IV, Fixed, 95% CI)	-172.80 [-308.44, -37.16]

6 0.5% bupivacaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (clinical testing of healthy pulps, hard and soft tissues)	2		Odds Ratio(IV, Fixed, 95% CI)	0.58 [0.07, 5.12]
6.1.1 Mandibular block (IANB) and infiltration	1		Odds Ratio(IV, Fixed, 95% CI)	3.00 [0.12, 73.65]
6.1.2 Both jaws combined/Jaw not stated	1		Odds Ratio(IV, Fixed, 95% CI)	0.14 [0.01, 2.77]
6.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (simulated scenario testing of healthy pulps)	3	180	Risk Ratio(M-H, Fixed, 95% CI)	0.80 [0.62, 1.05]
6.2.1 Maxillary infiltration	1	66	Risk Ratio(M-H, Fixed, 95% CI)	0.78 [0.57, 1.05]
6.2.2 Mandibular infiltration	1	36	Risk Ratio(M-H, Fixed, 95% CI)	0.67 [0.13, 3.53]
6.2.3 Mandibular block (IANB)	1	78	Risk Ratio(M-H, Fixed, 95% CI)	0.86 [0.55, 1.34]
6.3 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	2	116	Mean Difference(IV, Fixed, 95% CI)	3.32 [0.27, 6.37]
6.3.1 Maxillary infiltration	1	48	Mean Difference(IV, Fixed, 95% CI)	3.36 [-0.12, 6.84]
6.3.2 Mandibular block (IANB)	1	68	Mean Difference(IV, Fixed, 95% CI)	3.20 [-3.16, 9.56]
6.4 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)	3	126	Mean Difference(IV, Random, 95% CI)	0.02 [-1.07, 1.10]
6.4.1 Mandibular block (IANB)	1	78	Mean Difference(IV, Random, 95% CI)	1.64 [-0.25, 3.53]
6.4.2 Mandibular block (IANB) and infiltration	1	16	Mean Difference(IV, Random, 95% CI)	0.00 [-0.73, 0.73]
6.4.3 Both jaws combined/Jaw not stated	1	32	Mean Difference(IV, Random, 95% CI)	-0.90 [-1.96, 0.16]

6.5 Duration of anaesthesia (simulated scenario testing of soft tissues)	6	332	Mean Difference(IV, Random, 95% CI)	222.88 [135.99, 309.76]
6.5.1 Maxillary infiltration	2	82	Mean Difference(IV, Random, 95% CI)	109.52 [-39.40, 258.44]
6.5.2 Mandibular infiltration	1	16	Mean Difference(IV, Random, 95% CI)	228.00 [146.69, 309.31]
6.5.3 Mandibular block (IANB)	1	78	Mean Difference(IV, Random, 95% CI)	273.00 [233.89, 312.11]
6.5.4 Mandibular block (IANB) and infiltration	1	16	Mean Difference(IV, Random, 95% CI)	374.00 [279.54, 468.46]
6.5.5 Both jaws combined/Jaw not stated	2	140	Mean Difference(IV, Random, 95% CI)	224.26 [47.01, 401.50]

7 4% articaine, 1:100,000 epinephrine vs 2% mepivacaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of healthy pulps, hard and soft tissues)	2		Odds Ratio(IV, Fixed, 95% CI)	3.82 [0.61, 23.82]
7.1.1 Maxillary infiltration (buccal and palatal)	1		Odds Ratio(IV, Fixed, 95% CI)	4.29 [0.46, 40.01]
7.1.2 Mandibular block (IANB) and infiltration	1		Odds Ratio(IV, Fixed, 95% CI)	3.00 [0.12, 73.65]
7.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of soft tissues)	2	92	Risk Ratio(M-H, Random, 95% CI)	1.07 [0.73, 1.59]
7.2.1 Mandibular block (IANB)	1	44	Risk Ratio(M-H, Random, 95% CI)	1.00 [0.92, 1.09]
7.2.2 Mandibular infiltration	1	48	Risk Ratio(M-H, Random, 95% CI)	1.21 [0.79, 1.86]

8 2% lidocaine, 1:100,000 epinephrine vs 2% mepivacaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical testing of diseased pulps with irreversible pulpitis)	2	68	Risk Ratio(M-H, Random, 95% CI)	1.16 [0.25, 5.45]
8.1.1 Mandibular block (IANB)	2	68	Risk Ratio(M-H, Random, 95% CI)	1.16 [0.25, 5.45]

9 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:80,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
9.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	120	Risk Ratio(M-H, Fixed, 95% CI)	0.81 [0.65, 1.01]
9.1.1 Mandibular infiltration	1	60	Risk Ratio(M-H, Fixed, 95% CI)	0.79 [0.50, 1.24]
9.1.2 Mandibular block (IANB)	1	60	Risk Ratio(M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]

10 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

10.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	7	420	Risk Ratio(M-H, Fixed, 95% CI)	0.99 [0.88, 1.12]
10.1.1 Maxillary infiltration	2	80	Risk Ratio(M-H, Fixed, 95% CI)	0.97 [0.88, 1.08]
10.1.2 Maxillary block (Infraorbital block)	1	80	Risk Ratio(M-H, Fixed, 95% CI)	1.09 [0.93, 1.27]
10.1.3 Mandibular infiltration	2	140	Risk Ratio(M-H, Fixed, 95% CI)	1.00 [0.70, 1.43]
10.1.4 Mandibular block (IANB)	2	120	Risk Ratio(M-H, Fixed, 95% CI)	0.92 [0.69, 1.22]
10.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	4	184	Mean Difference(IV, Fixed, 95% CI)	-0.44 [-1.66, 0.79]
10.2.1 Maxillary infiltration	2	76	Mean Difference(IV, Fixed, 95% CI)	-0.75 [-3.04, 1.54]
10.2.2 Maxillary block (Infraorbital block)	1	60	Mean Difference(IV, Fixed, 95% CI)	-0.40 [-1.87, 1.07]
10.2.3 Mandibular block (IANB)	1	48	Mean Difference(IV, Fixed, 95% CI)	2.60 [-5.91, 11.11]

11 2% lidocaine, 1:80,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
11.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	120	Risk Ratio(M-H, Fixed, 95% CI)	1.27 [1.01, 1.59]
11.1.1 Mandibular infiltration	1	60	Risk Ratio(M-H, Fixed, 95% CI)	1.36 [0.85, 2.17]
11.1.2 Mandibular block (IANB)	1	60	Risk Ratio(M-H, Fixed, 95% CI)	1.22 [0.98, 1.52]

12 2% lidocaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
12.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	3	140	Risk Ratio(M-H, Random, 95% CI)	0.89 [0.63, 1.26]
12.1.1 Maxillary infiltration	2	80	Risk Ratio(M-H, Random, 95% CI)	0.80 [0.33, 1.95]
12.1.2 Mandibular block (IANB)	1	60	Risk Ratio(M-H, Random, 95% CI)	1.00 [0.68, 1.47]

13 3% mepivacaine plain vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
13.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	6	416	Risk Ratio(M-H, Fixed, 95% CI)	0.92 [0.83, 1.02]
13.1.1 Maxillary infiltration	1	60	Risk Ratio(M-H, Fixed, 95% CI)	0.97 [0.86, 1.08]
13.1.2 Maxillary block (Infraorbital block)	1	80	Risk Ratio(M-H, Fixed, 95% CI)	1.03 [0.86, 1.23]
13.1.3 Maxillary block (palatal-anterior superior alveolar nerve block)	1	80	Risk Ratio(M-H, Fixed, 95% CI)	0.61 [0.37, 1.00]
13.1.4 Maxillary block (high-tuberosity maxillary second division nerve block)	1	100	Risk Ratio(M-H, Fixed, 95% CI)	1.00 [0.89, 1.12]
13.1.5 Mandibular infiltration	1	36	Risk Ratio(M-H, Fixed, 95% CI)	2.00 [0.59, 6.79]
13.1.6 Mandibular block (IANB)	1	60	Risk Ratio(M-H, Fixed, 95% CI)	0.68 [0.42, 1.12]

13.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	3	170	Mean Difference(IV, Fixed, 95% CI)	-1.23 [-2.31, -0.16]
13.2.1 Maxillary infiltration	1	56	Mean Difference(IV, Fixed, 95% CI)	-1.10 [-3.39, 1.19]
13.2.2 Maxillary block (Infraorbital block)	1	60	Mean Difference(IV, Fixed, 95% CI)	-1.20 [-2.45, 0.05]
13.2.3 Mandibular block (IANB)	1	54	Mean Difference(IV, Fixed, 95% CI)	-2.60 [-8.14, 2.94]

14 3% mepivacaine plain vs 2% lidocaine, 1:50,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
14.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	140	Risk Ratio(M-H, Fixed, 95% CI)	0.97 [0.88, 1.07]
14.1.1 Maxillary infiltration	1	60	Risk Ratio(M-H, Fixed, 95% CI)	1.00 [0.87, 1.14]
14.1.2 Maxillary block (infraorbital block)	1	80	Risk Ratio(M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
14.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	2	116	Mean Difference(IV, Fixed, 95% CI)	-0.56 [-1.54, 0.42]
14.2.1 Maxillary infiltration	1	56	Mean Difference(IV, Fixed, 95% CI)	-0.30 [-1.71, 1.11]
14.2.2 Maxillary block (infraorbital block)	1	60	Mean Difference(IV, Fixed, 95% CI)	-0.80 [-2.16, 0.56]

15 2% mepivacaine, 1:20,000 levonordefrin vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
15.1 Duration of anaesthesia (simulated scenario testing of soft tissues)	2	458	Mean Difference(IV, Fixed, 95% CI)	4.43 [-10.63, 19.48]
15.1.1 Both jaws combined/Jaw not stated	2	458	Mean Difference(IV, Fixed, 95% CI)	4.43 [-10.63, 19.48]

16 4% articaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
16.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	56	Risk Ratio(M-H, Random, 95% CI)	1.33 [0.33, 5.36]
16.1.1 Maxillary infiltration	1	20	Risk Ratio(M-H, Random, 95% CI)	1.00 [0.83, 1.20]
16.1.2 Mandibular infiltration	1	36	Risk Ratio(M-H, Random, 95% CI)	2.00 [0.59, 6.79]
16.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	2	80	Mean Difference(IV, Random, 95% CI)	0.19 [-2.06, 2.45]
16.2.1 Maxillary infiltration	1	20	Mean Difference(IV, Random, 95% CI)	1.30 [0.03, 2.57]
16.2.2 Mandibular block (IANB)	1	60	Mean Difference(IV, Random, 95% CI)	-1.00 [-2.54, 0.54]
16.3 Duration of anaesthesia (simulated scenario testing of healthy pulps)	2	80	Mean Difference(IV, Random, 95% CI)	10.33 [-22.08, 42.74]
16.3.1 Maxillary infiltration	1	20	Mean Difference(IV, Random, 95% CI)	-6.90 [-24.50, 10.70]
16.3.2 Mandibular block (IANB)	1	60	Mean Difference(IV, Random, 95% CI)	26.20 [14.46, 37.94]

17 4% articaine, 1:100,000 epinephrine vs 2% lidocaine, 1:80,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

17.1 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)	2	125	Mean Difference(IV, Fixed, 95% CI)	-0.78 [-1.04, -0.52]
17.1.1 Mandibular block (IANB)	2	125	Mean Difference(IV, Fixed, 95% CI)	-0.78 [-1.04, -0.52]

18 4% articaine, 1:200,000 epinephrine vs 4% prilocaine, 1:200,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
18.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	3	194	Risk Ratio(M-H, Fixed, 95% CI)	1.15 [0.93, 1.41]
18.1.1 Maxillary infiltration	2	80	Risk Ratio(M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]
18.1.2 Mandibular infiltration	3	114	Risk Ratio(M-H, Fixed, 95% CI)	1.29 [0.89, 1.87]

19 4% prilocaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
19.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	96	Risk Ratio(M-H, Fixed, 95% CI)	1.14 [0.91, 1.43]
19.1.1 Maxillary infiltration	1	60	Risk Ratio(M-H, Fixed, 95% CI)	1.12 [0.93, 1.35]
19.1.2 Mandibular infiltration	1	36	Risk Ratio(M-H, Fixed, 95% CI)	1.33 [0.35, 5.13]
19.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	2	76	Mean Difference(IV, Fixed, 95% CI)	-1.19 [-3.08, 0.70]
19.2.1 Maxillary infiltration	1	48	Mean Difference(IV, Fixed, 95% CI)	-1.50 [-3.50, 0.50]
19.2.2 Mandibular block (IANB)	1	28	Mean Difference(IV, Fixed, 95% CI)	1.20 [-4.37, 6.77]
19.3 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)	2	449	Mean Difference(IV, Fixed, 95% CI)	-0.01 [-0.14, 0.11]
19.3.1 Mandibular block (IANB)	2	191	Mean Difference(IV, Fixed, 95% CI)	-0.10 [-0.43, 0.24]
19.3.2 Both jaws combined/jaw not stated	1	258	Mean Difference(IV, Fixed, 95% CI)	0.00 [-0.13, 0.13]
19.4 Duration of anaesthesia (simulated scenario testing of soft tissues)	2	533	Mean Difference(IV, Random, 95% CI)	-11.80 [-27.76, 4.16]
19.4.1 Maxillary infiltration	1	148	Mean Difference(IV, Random, 95% CI)	-22.60 [-39.89, -5.31]
19.4.2 Mandibular block (IANB)	2	198	Mean Difference(IV, Random, 95% CI)	2.19 [-12.26, 16.65]
19.4.3 Both jaws combined/Jaw not stated	1	187	Mean Difference(IV, Random, 95% CI)	-28.00 [-49.36, -6.64]

20 4% articaine plain vs 4% articaine, 1:100,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
20.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	268	Risk Ratio(M-H, Random, 95% CI)	0.61 [0.38, 0.97]
20.1.1 Maxillary infiltration	2	144	Risk Ratio(M-H, Random, 95% CI)	0.64 [0.34, 1.19]
20.1.2 Mandibular block (IANB)	1	124	Risk Ratio(M-H, Random, 95% CI)	0.53 [0.33, 0.87]

20.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	2	167	Mean Difference(IV, Fixed, 95% CI)	0.13 [-0.54, 0.80]
20.2.1 Maxillary infiltration	2	121	Mean Difference(IV, Fixed, 95% CI)	0.14 [-0.61, 0.88]
20.2.2 Mandibular block (IANB)	1	46	Mean Difference(IV, Fixed, 95% CI)	0.10 [-1.48, 1.68]
20.3 Duration of anaesthesia (simulated scenario testing of healthy pulps)	2	167	Mean Difference(IV, Random, 95% CI)	-37.08 [-60.95, -13.21]
20.3.1 Maxillary infiltration	2	121	Mean Difference(IV, Random, 95% CI)	-45.85 [-76.25, -15.45]
20.3.2 Mandibular block (IANB)	1	46	Mean Difference(IV, Random, 95% CI)	-12.10 [-42.35, 18.15]

21 4% articaine plain vs 4% articaine, 1:200,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
21.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	268	Risk Ratio(M-H, Random, 95% CI)	0.58 [0.33, 1.01]
21.1.1 Maxillary infiltration	2	144	Risk Ratio(M-H, Random, 95% CI)	0.64 [0.34, 1.22]
21.1.2 Mandibular block (IANB)	1	124	Risk Ratio(M-H, Random, 95% CI)	0.47 [0.29, 0.76]
21.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)	2	169	Mean Difference(IV, Fixed, 95% CI)	0.03 [-0.66, 0.71]
21.2.1 Maxillary infiltration	2	119	Mean Difference(IV, Fixed, 95% CI)	0.14 [-0.63, 0.91]
21.2.2 Mandibular block (IANB)	1	50	Mean Difference(IV, Fixed, 95% CI)	-0.40 [-1.90, 1.10]
21.3 Duration of anaesthesia (simulated scenario testing of healthy pulps)	2	169	Mean Difference(IV, Random, 95% CI)	-28.36 [-42.06, -14.65]
21.3.1 Maxillary infiltration	2	119	Mean Difference(IV, Random, 95% CI)	-32.88 [-44.12, -21.65]
21.3.2 Mandibular block (IANB)	1	50	Mean Difference(IV, Random, 95% CI)	-1.50 [-30.17, 27.17]

22 4% prilocaine, 1:200,000 epinephrine vs 4% prilocaine plain

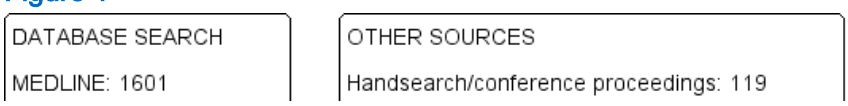
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
22.1 Duration of anaesthesia (simulated scenario testing of soft tissues)	2	506	Mean Difference(IV, Fixed, 95% CI)	18.78 [9.02, 28.54]
22.1.1 Maxillary infiltration	1	143	Mean Difference(IV, Fixed, 95% CI)	23.00 [6.36, 39.64]
22.1.2 Mandibular block (IANB)	2	194	Mean Difference(IV, Fixed, 95% CI)	14.03 [-0.85, 28.91]
22.1.3 Both jaws combined/Jaw not stated	1	169	Mean Difference(IV, Fixed, 95% CI)	21.40 [0.86, 41.94]

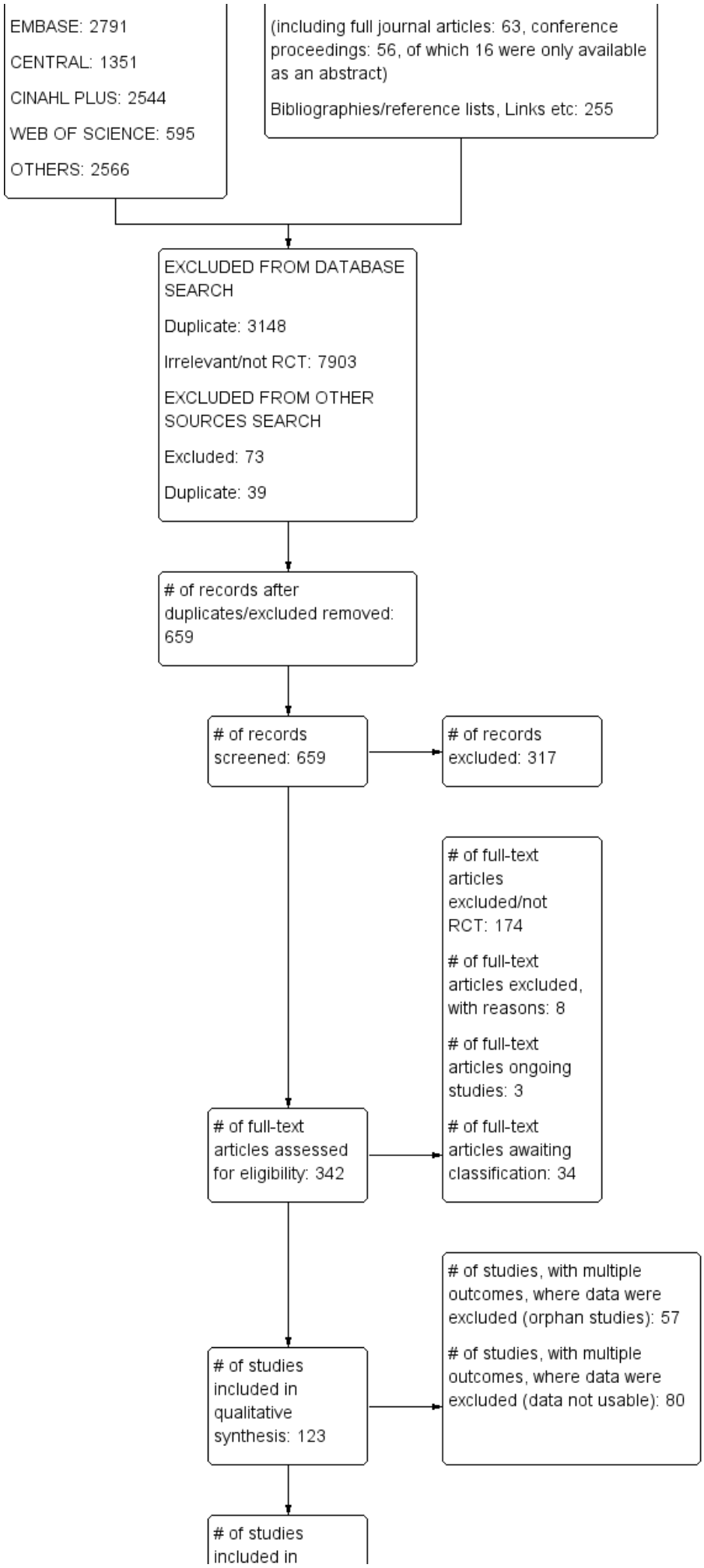
23 4% articaine, 1:100,000 epinephrine vs 4% prilocaine, 1:200,000 epinephrine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
23.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simulated scenario testing of healthy pulps)	2	156	Risk Ratio(M-H, Fixed, 95% CI)	1.74 [1.16, 2.60]
23.1.1 Mandibular infiltration	2	156	Risk Ratio(M-H, Fixed, 95% CI)	1.74 [1.16, 2.60]

Figures

Figure 1

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# of studies, with multiple outcomes, where data were excluded (orphan studies): 57
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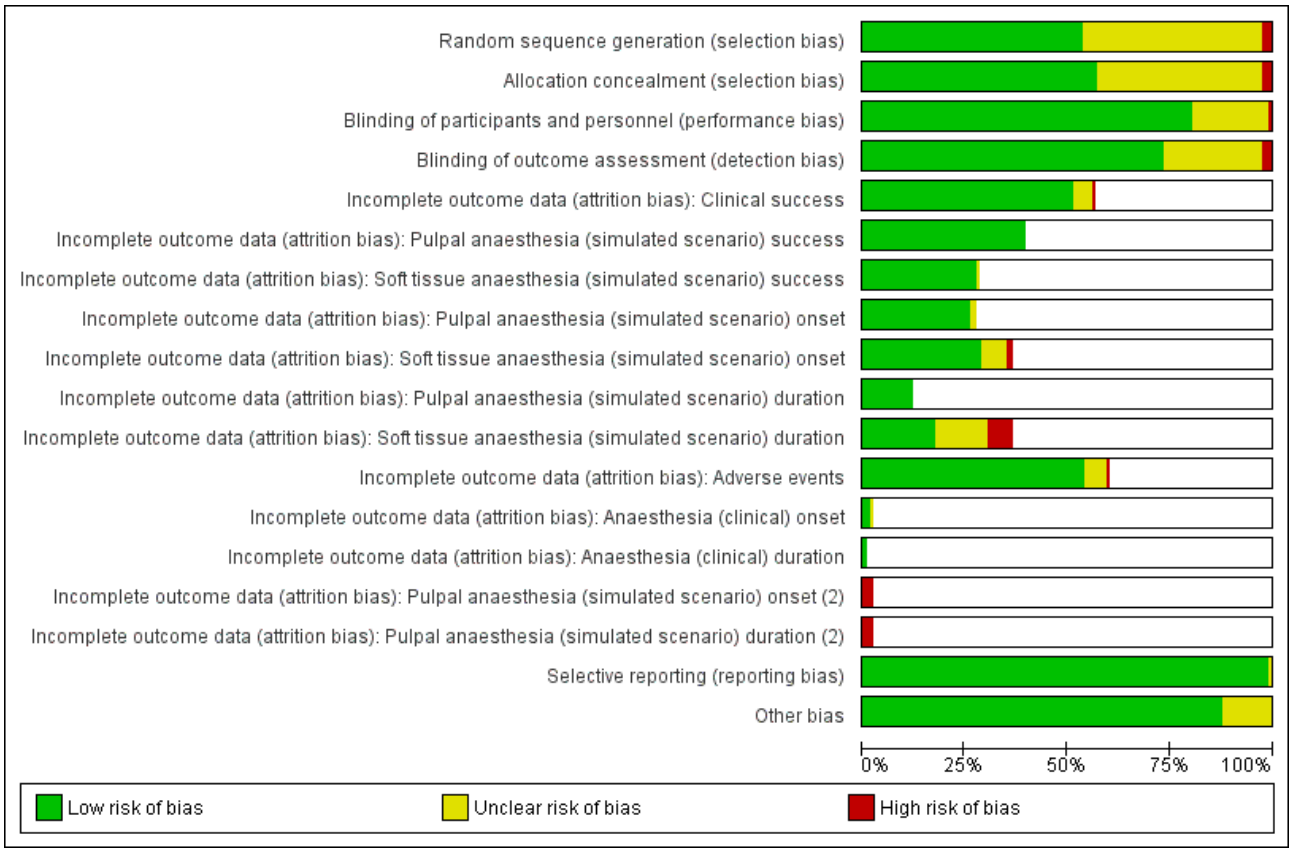
# of studies included in qualitative synthesis: 123
# of studies included in

quantitative synthesis (meta-analysis): 68

Caption

Study flow diagram.

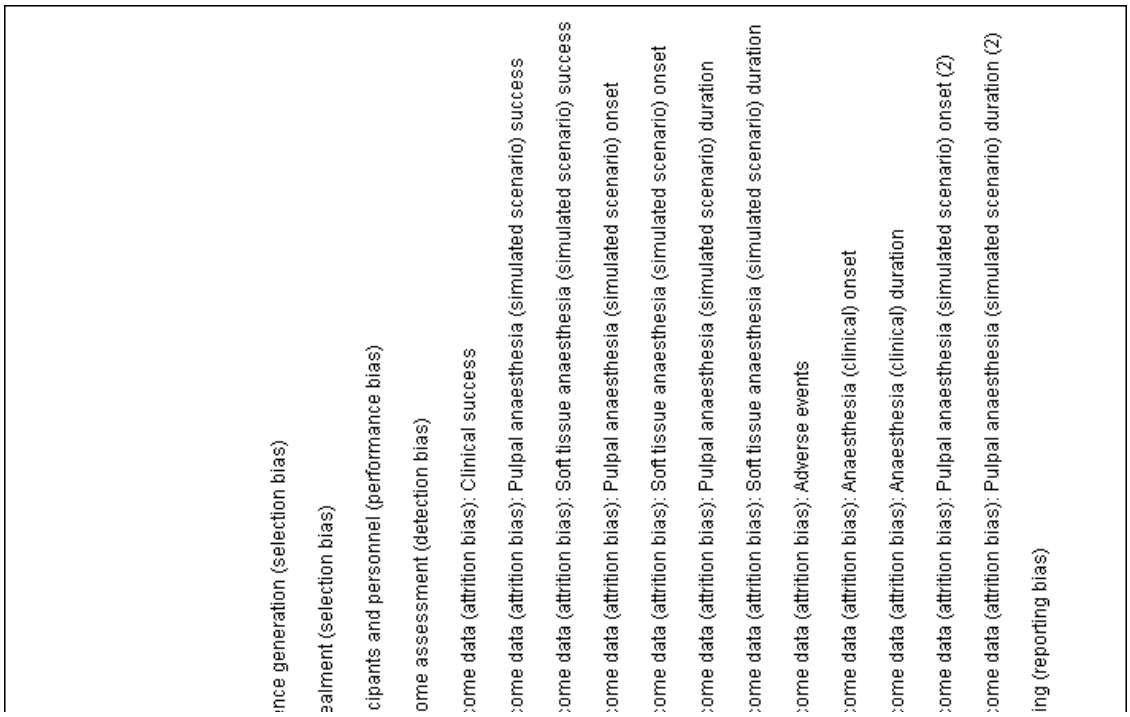
Figure 2

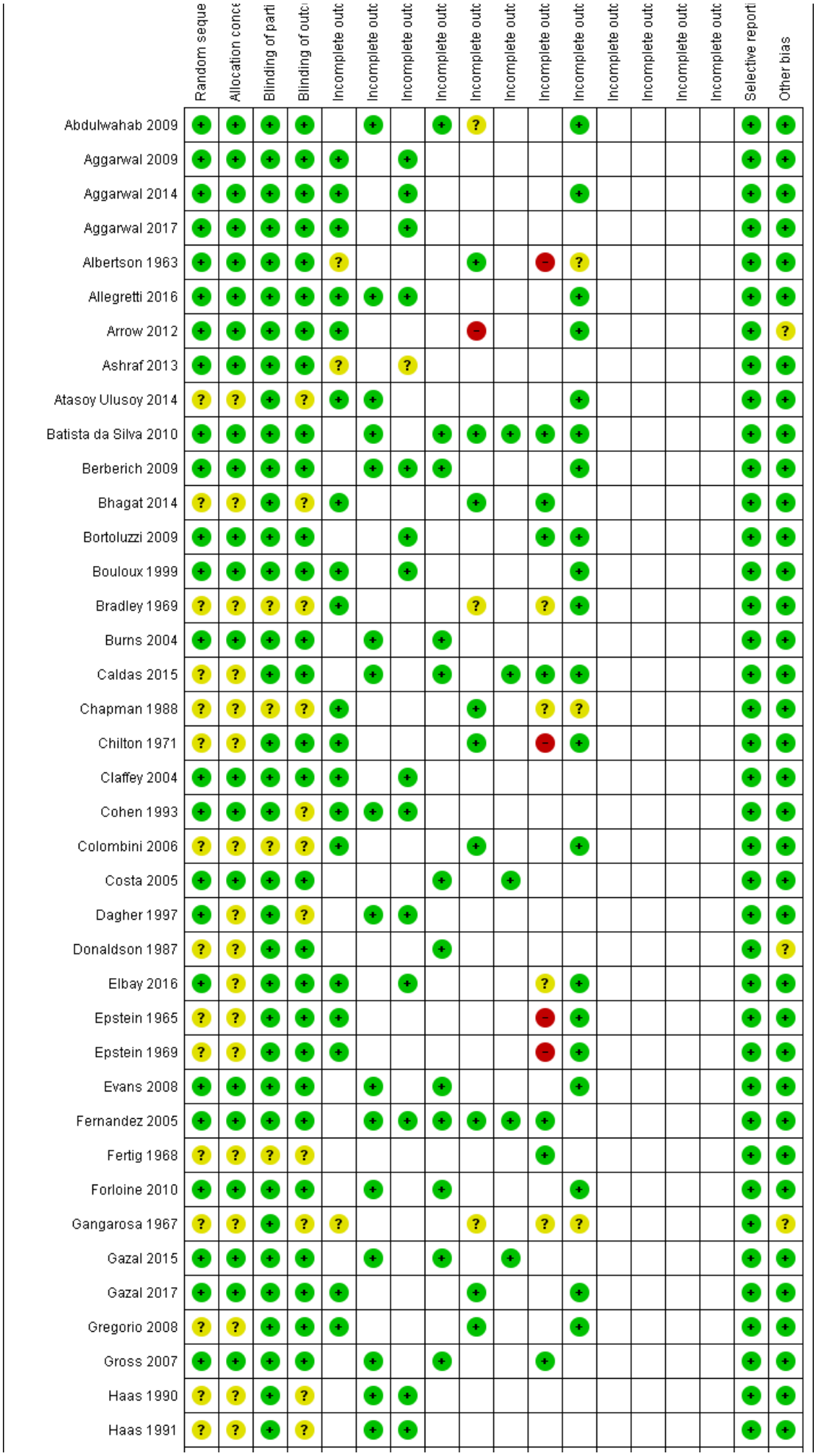


Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3

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Abdulwahab 2009
Aggarwal 2009
Aggarwal 2014
Aggarwal 2017
Albertson 1963
Allegretti 2016
Arrow 2012
Ashraf 2013
Atasoy Ulusoy 2014
Batista da Silva 2010
Berberich 2009
Bhagat 2014
Bortoluzzi 2009
Bouloux 1999
Bradley 1969
Burns 2004
Caldas 2015
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Chilton 1971
Claffey 2004
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Colombini 2006
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Dagher 1997
Donaldson 1987
Elbay 2016
Epstein 1965
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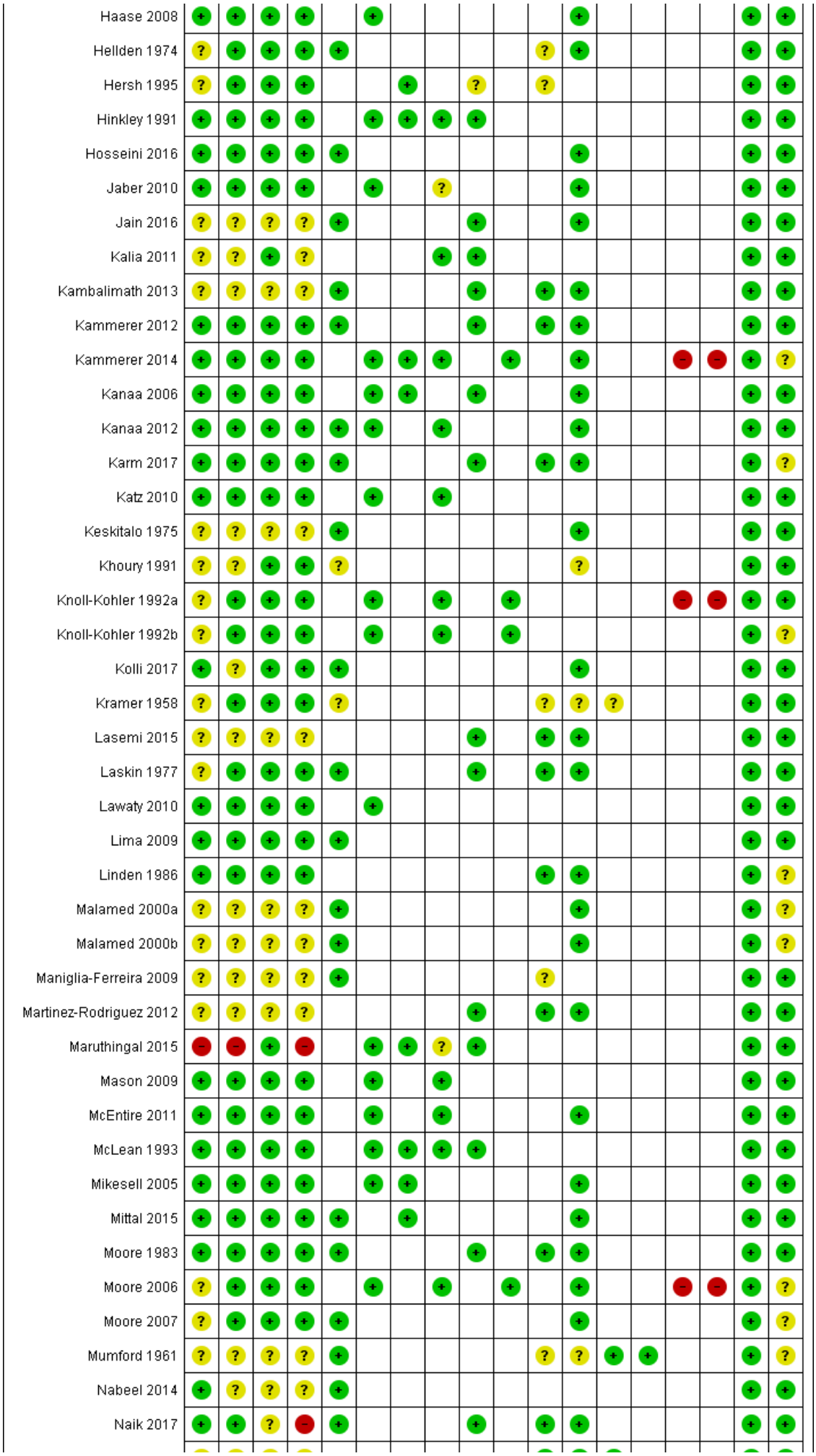
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Kalia 2011
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Kanaa 2006
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Karm 2017
Katz 2010
Keskitalo 1975
Khoury 1991
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Kolli 2017
Kramer 1958
Lasemi 2015
Laskin 1977
Lawaty 2010
Lima 2009
Linden 1986
Malamed 2000a
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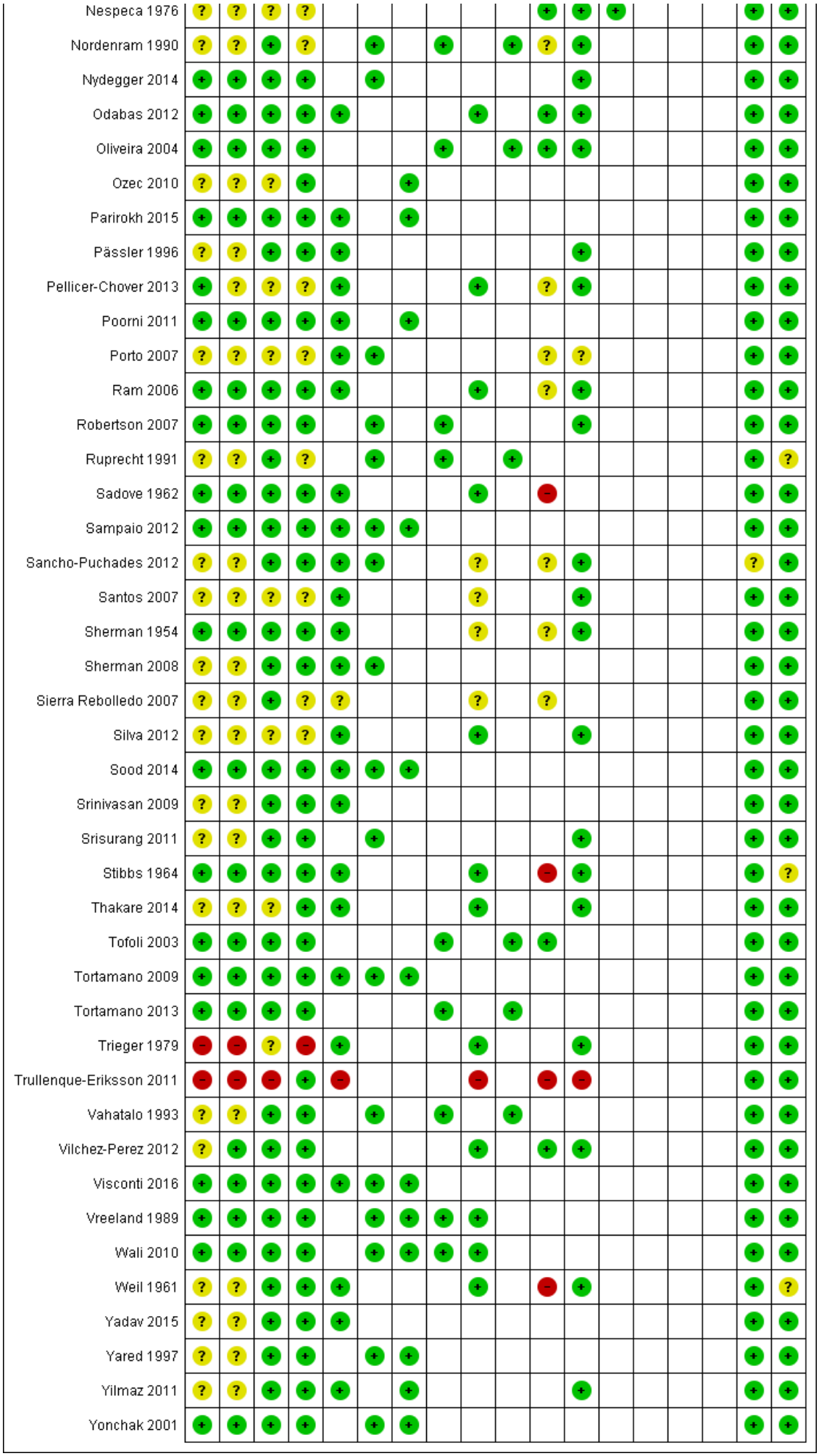
Maniglia-Ferreira 2009
Martinez-Rodriguez 2012
Maruthingal 2015
Mason 2009
McEntire 2011
McLean 1993
Mikesell 2005
Mittal 2015
Moore 1983
Moore 2006
Moore 2007
Mumford 1961
Nabeel 2014
Naik 2017


Nespeca 1976
Nordenram 1990
Nydegger 2014
Odabas 2012
Oliveira 2004
Ozec 2010
Parirokh 2015
Pässler 1996
Pellicer-Chover 2013
Poorni 2011
Porto 2007
Ram 2006
Robertson 2007
Ruprecht 1991
Sadove 1962
Sampaio 2012
Sancho-Puchades 2012
Santos 2007
Sherman 1954
Sherman 2008
Sierra Rebolledo 2007
Silva 2012
Sood 2014
Srinivasan 2009
Srisurang 2011
Stibbs 1964
Thakare 2014
Tofoli 2003
Tortamano 2009
Tortamano 2013
Trieger 1979
Trullenque-Eriksson 2011
Vahatalo 1993
Vilchez-Perez 2012
Visconti 2016
Vreeland 1989
Wali 2010
Weil 1961
Yadav 2015
Yared 1997
Yilmaz 2011
Yonchak 2001

Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Sources of support

Internal sources

- New Source of support, Other
- Eastman Dental Hospital and Institute, UK
  Library facilities, Internet access to journal databases and e-Journals

External sources

- No sources of support provided

Feedback

Appendices

1 Search strategy for CENTRAL, the Cochrane Library

#1 MeSH descriptor Anesthesia, Local explode all trees
#2 MeSH descriptor Anesthetics, Local explode all trees
#3 ((an?est* or analg*) near local)
#4 (an?est* near (solution* or agent*))
#5 (#1 OR #2 OR #3 OR #4)
#6 (dent* or pulp*):ti,ab
#7 MeSH descriptor Oral Surgical Procedures explode all trees
#8 MeSH descriptor Surgery, Oral explode all trees
#9 MeSH descriptor Dentistry explode all trees
#10 (#6 OR #7 OR #8 OR #9)
#11 (#5 AND #10)

2 Search strategy for MEDLINE (Ovid SP)

1. ((an?est* or analg*) adj3 local).mp.
2. (an?est* adj3 (solution* or agent*)).mp.
3. exp Anesthesia-Local/ or exp Anesthetics-Local/
4. 1 or 2 or 3
5. (dent* or pulp*).ti,ab.
6. exp v/ or exp Dentistry-Operative/ or Surgery-Oral/ or Dentistry/
7. 6 or 5
8. 4 and 7
9. exp Anesthesia-Dental/
10. 8 or 9
11. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
12. 11 and 10

3 Search strategy for Embase (Ovid SP)

1. exp local anesthetic agent/ or exp local anesthesia/
2. ((an?est* or analg*) adj3 local).mp.
3. (an?est* adj3 (solution* or agent*)).mp.
4. 1 or 2 or 3
5. (dent* or pulp*).ti,ab.
6. exp oral surgery/ or exp dental surgery/ or dentistry/
7. 6 or 5
8. 4 and 7
9. exp dental anesthesia/
10. 8 or 9
11. (RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLED-STUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4-CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/ or (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER* or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab.) not (animals not (humans and animals)).sh.
12. 11 and 10

4 Seartch strategy for CINAHL PLUS (EBSCOhost)

S1 (MM "Anesthesia, Local") or (MH "Anesthetics, Local+")
S2 TX ((an?est* or analg*) and local)
S3 (an?est* and (solution* or agent*))

S4 S1 or S2 or S3
S5 TX ((dent* or pulp*)) or AB ((dent* or pulp*))
S6 (MH "Surgery, Oral+") or (MH "Dentistry, Operative+")
S7 (MH "Dentistry")
S8 S5 or S6 or S7
S9 S4 and S8
S10 (MM "Anesthesia, Dental")
S11 S9 or S10
S12 (MM "Random Assignment") or (MH "Clinical Trials+")
S13 AB (random* or placebo)
S14 TI trial*
S15 (MM "Double-Blind Studies") or (MM "Single-Blind Studies") or (MM "Triple-Blind Studies")
S16 S12 or S13 or S14 or S15
S17 S11 and S16

5 Search strategy for Web of Science

#1 TS=((an?est* or analg*) SAME local) or TS=(an?est* SAME (solution* or agent*))
#2 TS=(dent* or pulp*) or TS=(Surgery SAME Oral) or TS=(Dentistry SAME Operative)
#3 #2 AND #1
#4 TS=(random* or placebo*) or TI=trial* or TS=((Doubl* or Sinlg*?or Tripl*) SAME blind)
#5 #4 AND #3

6 Data collection form

Bibliographic reference:			
Authors:			
Medline journal ID:			
Year of publication:			
Country where performed:			
Language:			
Source of funding:			
Type of study:	**RCT**	**CCT**	**Non-randomized**
Experimental trial?	**Patient treatment trial?**		
Comments on study design:			
METHOD OF RANDOMIZATION	Generation of random number sequence: Method of concealment:		
Quality of concealment of random allocation	A. Concealment was adequate B. Methods of concealment were unclear C. Allocation concealment was inadequate D. Allocation was not concealed		
Inclusion/Exclusion criteria	Inclusion and exclusion criteria were clearly defined in the text?		
	Patients taking medication that alter pain perception excluded?		
	Inclusion/Exclusion criteria: Inclusion Exclusion		
Age	Age range: (or mean age + standard deviation)		
Blinding	**Yes**	**No**	**Unclear**

Participant blinded?			
Physician blinded?			
Outcome assessor blinded?			
Were the administrator and the outcome assessor the same person?			
INTERVENTION			
	Treatment group 1	Treatment group 2	Treatment group 3
Local anaesthetic (specify type)			
Local anaesthetic (concentration)			
Dose (volume)			
Vasoconstrictor (specify type)			
Vasoconstrictor (concentration)			
No. of injections			
Technique			
Needle gauge			
Type of syringe used			
Duration of injection or rate of injection			
Topical anaesthetic used? (specify type)			
Topical anaesthetic (duration)			
Quantity of topical anaesthetic used			
Concentration of topical anaesthetic used			
Intra-individual (cross-over design) or parallel?			
If cross-over, time between injections			
COMMENT ON TREATMENT			
PARTICIPANTS			
Number of eligible participants		Number enrolled in study	
Number of males		Number of females	
Statistics			
No. of participants recruited to Group 1		No. of participants completing study in Group 1	

No. of participants recruited to Group 2		No. of participants completing study in Group 2	
No. of participants recruited to Group 3		No. of participants completing study in Group 3	
No. of participants recruited to Group 4		No. of participants completing study in Group 4	
Outcomes of patients who withdrew or were excluded after allocation were EITHER detailed separately OR included in an intention-to-treat analysis OR the text stated there were no withdrawals			
Treatment and control groups were adequately described at entry?			
SAMPLE SIZE AND STATISTICS			
Size			
Methods used to estimate sample size (statistical power)			
Statistical method used			
Unit of analysis			
Use of intention-to-treat analysis			
OUTCOMES			
Calibration of examiners?			
Number of examiners			
Pulpal anaesthesia			
Method of testing	EPT thermal other (model) (hot/cold?) (type)		
Teeth tested			
Teeth Isolated?			
Frequency of testing			
Number of repeat readings to confirm anaesthesia			
Criteria for success			
Teeth tested before local anaesthesia given? (state no. of times)			
Control teeth used during experiment?			
Control teeth tested before LA given?			
Speed of onset			

Speed of onset statistics			
Anaesthetic success			
Anaesthetic success statistics			
Duration			
Duration statistics			
Soft tissue anaesthesia			
Method of measurement			
Soft tissues tested? (state location)			
Frequency of testing			
Number of repeat readings to confirm anaesthesia			
Tissues tested before local anaesthesia given? (state no. of times)			
Control site used during experiment?			
Control site tested before LA given?			
Speed of onset			
Speed of onset statistics			
Anaesthetic success			
Anaesthetic success statistics			
Duration			
Duration statistics			
Local anaesthesia during an operative procedure			
Diagnosis	Secure?	Insecure?	Unclear?
Method of testing			
Procedure(s) carried out			
Criteria for success			
Teeth tested			
Statistics			
Onset			
Onset statistics			

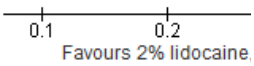
Anaesthetic success	
Anaesthetic success statistics	
Duration	
Duration statistics	
Duration of procedure (+ range)	
Adverse effects: pain on injection	
Method of measurement	
Results	
Pain on injection statistics	
Adverse effects: pain following injection	
Method of measurement	
Frequency of testing	
Results	
Pain following injection statistics	
Other adverse effects:	
CHANGES IN PROTOCOL:	
CONTACT WITH STUDY AUTHOR:	
OTHER COMMENTS ON THIS STUDY:	

Graphs

1 - 4% articaine, 1:100,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

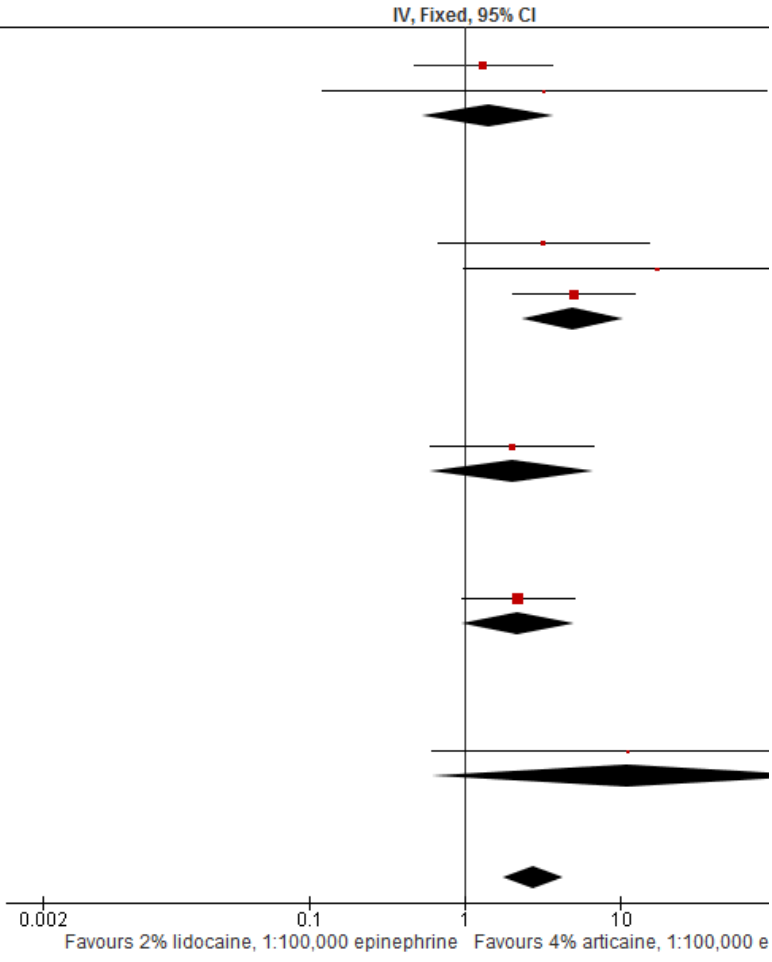
1.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical tes

Study or Subgroup	4% articaine, 1:100,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Maxillary infiltration						
Srinivasan 2009	18	20	8	20	29.7%	2.25 [1.29, 3.92]
Subtotal (95% CI)		**20**		**20**	**29.7%**	**2.25 [1.29, 3.92]**
Total events	18		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
1.1.2 Mandibular block (IANB)						
Allegretti 2016	11	22	7	22	26.0%	1.57 [0.75, 3.30]
Claffey 2004	4	39	6	40	22.0%	0.68 [0.21, 2.24]
Tortamano 2009	10	20	6	20	22.3%	1.67 [0.75, 3.71]
Subtotal (95% CI)		**81**		**82**	**70.3%**	**1.32 [0.81, 2.16]**
Total events	25		19			
Heterogeneity: Chi² = 1.72, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**101**		**102**	**100.0%**	**1.60 [1.10, 2.32]**
Total events	43		27			
Heterogeneity: Chi² = 3.43, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 2.48 (P = 0.01)						
Test for subgroup differences: Chi² = 1.96, df = 1 (P = 0.16), I² = 49.0%						



1.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simu

Study or Subgroup	log[]	SE	Weight	IV, Fixed, 95% CI
1.2.1 Maxillary infiltration				
Evans 2008	0.2674	0.5184	19.1%	1.31 [0.47, 3.61]
Srisurang 2011	1.1611	1.6709	1.8%	3.19 [0.12, 84.44]
Subtotal (95% CI)			**20.9%**	**1.41 [0.54, 3.73]**
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%				
Test for overall effect: Z = 0.70 (P = 0.48)				
1.2.2 Mandibular infiltration				
Abdulwahab 2009	1.1575	0.7961	8.1%	3.18 [0.67, 15.15]
Kanaa 2006	2.8335	1.4552	2.4%	17.00 [0.98, 294.61]
Robertson 2007	1.6035	0.4605	24.2%	4.97 [2.02, 12.26]
Subtotal (95% CI)			**34.7%**	**4.88 [2.30, 10.37]**
Heterogeneity: Chi² = 1.03, df = 2 (P = 0.60); I² = 0%				
Test for overall effect: Z = 4.12 (P < 0.0001)				
1.2.3 Mandibular block (mental block)				
Batista da Silva 2010	0.6932	0.6124	13.7%	2.00 [0.60, 6.64]
Subtotal (95% CI)			**13.7%**	**2.00 [0.60, 6.64]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.13 (P = 0.26)				
1.2.4 Mandibular block (IANB)				
Mikesell 2005	0.7828	0.4254	28.3%	2.19 [0.95, 5.04]
Subtotal (95% CI)			**28.3%**	**2.19 [0.95, 5.04]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.84 (P = 0.07)				
1.2.5 Mandibular infiltration (buccal and lingual)				
Jaber 2010	2.3981	1.4771	2.4%	11.00 [0.61, 198.97]
Subtotal (95% CI)			**2.4%**	**11.00 [0.61, 198.97]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.62 (P = 0.10)				
Total (95% CI)			**100.0%**	**2.71 [1.74, 4.22]**
Heterogeneity: Chi² = 6.76, df = 7 (P = 0.45); I² = 0%				
Test for overall effect: Z = 4.40 (P < 0.0001)				
Test for subgroup differences: Chi² = 5.47, df = 4 (P = 0.24), I² = 26.9%				



1.3 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simu

Study or Subgroup	4% articaine, 1:100,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Mandibular block (IANB)						
Allegretti 2016	22	22	22	22	10.6%	1.00 [0.92, 1.09]
Claffey 2004	37	39	35	40	16.3%	1.08 [0.94, 1.24]
Mikesell 2005	55	57	51	57	24.0%	1.08 [0.97, 1.19]
Poorni 2011	52	52	52	52	24.7%	1.00 [0.96, 1.04]
Tortamano 2009	20	20	20	20	9.6%	1.00 [0.91, 1.10]
Subtotal (95% CI)		**190**		**191**	**85.2%**	**1.04 [0.99, 1.08]**
Total events	186		180			
Heterogeneity: Chi² = 6.15, df = 4 (P = 0.19); I² = 35%						
Test for overall effect: Z = 1.68 (P = 0.09)						
1.3.2 Mandibular infiltration						
Kanaa 2006	31	31	31	31	14.8%	1.00 [0.94, 1.06]
Subtotal (95% CI)		**31**		**31**	**14.8%**	**1.00 [0.94, 1.06]**
Total events	31		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**221**		**222**	**100.0%**	**1.03 [0.99, 1.07]**
Total events	217		211			
Heterogeneity: Chi² = 6.03, df = 5 (P = 0.30); I² = 17%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 0.94, df = 1 (P = 0.33), I² = 0%						

0.85
Favours 2% lidocaine

1.4 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Maxillary infiltration								
Evans 2008	3.3	2.35	31	3.7	2.29	29	21.0%	-0.40 [-1.57, 0.77]
Ruprecht 1991	5	2.83	10	3.4	1.31	10	14.6%	1.60 [-0.33, 3.53]
Knoll-Kohler 1992b	5	9.8	12	3.4	4.54	12	2.7%	1.60 [-4.51, 7.71]
Subtotal (95% CI)			**53**			**51**	**38.3%**	**0.45 [-1.10, 2.00]**
Heterogeneity: Tau² = 0.73; Chi² = 3.22, df = 2 (P = 0.20); I² = 38%								
Test for overall effect: Z = 0.57 (P = 0.57)								
1.4.2 Mandibular infiltration								
Robertson 2007	4.2	3.1	33	7.7	4.3	33	15.5%	-3.50 [-5.31, -1.69]
Subtotal (95% CI)			**33**			**33**	**15.5%**	**-3.50 [-5.31, -1.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.79 (P = 0.0001)								
1.4.3 Mandibular block (IANB)								
Tortamano 2013	7.4	2.9	30	8.7	3.1	30	17.9%	-1.30 [-2.82, 0.22]
Subtotal (95% CI)			**30**			**30**	**17.9%**	**-1.30 [-2.82, 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								
1.4.4 Both jaws combined/Jaw not stated								
Kalia 2011	0.97	0.4	86	1.15	0.4	86	28.3%	-0.18 [-0.30, -0.06]
Subtotal (95% CI)			**86**			**86**	**28.3%**	**-0.18 [-0.30, -0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.95 (P = 0.003)								
Total (95% CI)			**202**			**200**	**100.0%**	**-0.63 [-1.69, 0.42]**
Heterogeneity: Tau² = 1.03; Chi² = 18.68, df = 5 (P = 0.002); I² = 73%								
Test for overall effect: Z = 1.17 (P = 0.24)								
Test for subgroup differences: Chi² = 15.59, df = 3 (P = 0.001), I² = 80.8%								

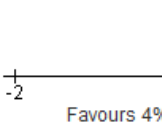
-4
Favours 4% artic

1.5 Duration of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 Maxillary infiltration								
Knoll-Kohler 1992b	66.8	78.64	12	61.3	59.62	12	19.3%	5.50 [-50.34, 61.34]
Ruprecht 1991	66.8	22.7	10	61.3	17.21	10	39.0%	5.50 [-12.16, 23.16]
Subtotal (95% CI)			**22**			**22**	**58.3%**	**5.50 [-11.33, 22.33]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 0.64 (P = 0.52)								
1.5.2 Mandibular block (IANB)								
Tortamano 2013	106.6	28.4	30	61.8	15.5	30	41.7%	44.80 [33.22, 56.38]
Subtotal (95% CI)			**30**			**30**	**41.7%**	**44.80 [33.22, 56.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.58 (P < 0.00001)								
Total (95% CI)			**52**			**52**	**100.0%**	**21.87 [-10.96, 54.71]**
Heterogeneity: Tau² = 638.62; Chi² = 14.21, df = 2 (P = 0.0008); I² = 86%								
Test for overall effect: Z = 1.31 (P = 0.19)								
Test for subgroup differences: Chi² = 14.21, df = 1 (P = 0.0002), I² = 93.0%								

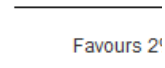
1.6 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Mandibular infiltration								
Kanaa 2006	0.85	0.44	31	0.78	0.55	31	18.2%	0.07 [-0.18, 0.32]
Subtotal (95% CI)			**31**			**31**	**18.2%**	**0.07 [-0.18, 0.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								
1.6.2 Mandibular block (IANB)								
Bhagat 2014	1.23	0.5	180	1.41	0.6	180	22.3%	-0.18 [-0.29, -0.07]
Subtotal (95% CI)			**180**			**180**	**22.3%**	**-0.18 [-0.29, -0.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.09 (P = 0.002)								
1.6.3 Mandibular block (IANB) and infiltration								
Kambalimath 2013	1.35	0.49	30	1.4	0.6	30	17.2%	-0.05 [-0.33, 0.23]
Martinez-Rodriguez 2012	1.04	0.7	48	3.75	14.71	48	0.3%	-2.71 [-6.88, 1.46]
Silva 2012	0.91	0.1	20	1.03	0.17	20	22.9%	-0.12 [-0.21, -0.03]
Subtotal (95% CI)			**98**			**98**	**40.4%**	**-0.11 [-0.20, -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 2 (P = 0.42); I² = 0%								
Test for overall effect: Z = 2.73 (P = 0.006)								
1.6.4 Both jaws combined/Jaw not stated								
Kalia 2011	1.08	0.8	100	1.89	0.81	100	19.1%	-0.81 [-1.03, -0.59]
Subtotal (95% CI)			**100**			**100**	**19.1%**	**-0.81 [-1.03, -0.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.11 (P < 0.00001)								
Total (95% CI)			**409**			**409**	**100.0%**	**-0.23 [-0.45, -0.01]**
Heterogeneity: Tau² = 0.05; Chi² = 38.63, df = 5 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 2.01 (P = 0.04)								
Test for subgroup differences: Chi² = 36.91, df = 3 (P < 0.00001), I² = 91.9%								



1.7 Duration of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Mandibular block (IANB) and infiltration								
Martinez-Rodriguez 2012	246	148	48	213	155	48	4.5%	33.00 [-27.63, 93.63]
Subtotal (95% CI)			**48**			**48**	**4.5%**	**33.00 [-27.63, 93.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.29)								
1.7.2 Mandibular block (IANB)								
Bhagat 2014	217	66	162	159	54	164	95.5%	58.00 [44.90, 71.10]
Subtotal (95% CI)			**162**			**164**	**95.5%**	**58.00 [44.90, 71.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.68 (P < 0.00001)								
Total (95% CI)			**210**			**212**	**100.0%**	**56.88 [44.08, 69.69]**
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%								
Test for overall effect: Z = 8.71 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.62, df = 1 (P = 0.43), I² = 0%								



1.8 Local adverse effects, pain on injection

Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 Maxillary infiltration								
Evans 2008	44	29	40	36	26	40	31.0%	8.00 [-4.07, 20.07]
Subtotal (95% CI)			**40**			**40**	**31.0%**	**8.00 [-4.07, 20.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
1.8.2 Mandibular infiltration								
Robertson 2007	36	30	60	37	36	60	32.1%	-1.00 [-12.86, 10.86]
Subtotal (95% CI)			**60**			**60**	**32.1%**	**-1.00 [-12.86, 10.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.87)								
1.8.3 Mandibular block (IANB)								
Mikesell 2005 (1)	39	33	57	32	27	57	36.9%	7.00 [-4.07, 18.07]
Subtotal (95% CI)			**57**			**57**	**36.9%**	**7.00 [-4.07, 18.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.24 (P = 0.22)								
Total (95% CI)			**157**			**157**	**100.0%**	**4.74 [-1.98, 11.46]**
Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.38 (P = 0.17)								
Test for subgroup differences: Chi² = 1.34, df = 2 (P = 0.51), I² = 0%								

Favours 4% arti

Footnotes

(1) Pain measured in millimetres on a Heft Parker VAS

1.9 Local adverse effects, pain following injection

Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 Maxillary infiltration								
Evans 2008	26	27	40	13	15	40	31.8%	13.00 [3.43, 22.57]
Subtotal (95% CI)			**40**			**40**	**31.8%**	**13.00 [3.43, 22.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.66 (P = 0.008)								
1.9.2 Mandibular infiltration								
Robertson 2007	20	23	56	18	25	59	37.8%	2.00 [-6.77, 10.77]
Subtotal (95% CI)			**56**			**59**	**37.8%**	**2.00 [-6.77, 10.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.45 (P = 0.66)								
1.9.3 Mandibular block (IANB)								
Mikesell 2005	28	29	57	23	24	57	30.5%	5.00 [-4.77, 14.77]
Subtotal (95% CI)			**57**			**57**	**30.5%**	**5.00 [-4.77, 14.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.00 (P = 0.32)								
Total (95% CI)			**153**			**156**	**100.0%**	**6.41 [1.01, 11.80]**
Heterogeneity: Chi² = 2.87, df = 2 (P = 0.24); I² = 30%								
Test for overall effect: Z = 2.33 (P = 0.02)								
Test for subgroup differences: Chi² = 2.87, df = 2 (P = 0.24), I² = 30.3%								

-10

Favours 4% artica

2 - 3% prilocaine, 0.03 IU felypressin vs 2% lidocaine, 1:100,000 epinephrine

2.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical tes

Study or Subgroup	3% prilocaine 0.03 IU felypressin Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Both jaws combined/Jaw not stated						
Khoury 1991	207	364	242	363	75.8%	0.85 [0.76, 0.96]
Pässler 1996	67	87	80	93	24.2%	0.90 [0.78, 1.03]
Subtotal (95% CI)		**451**		**456**	**100.0%**	**0.86 [0.79, 0.95]**
Total events	274		322			
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.08 (P = 0.002)						
Total (95% CI)		**451**		**456**	**100.0%**	**0.86 [0.79, 0.95]**
Total events	274		322			
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.08 (P = 0.002)						
Test for subgroup differences: Not applicable						

0.85

Favours 2% lidocaine, 1:10

3 - 4% articaine, 1:200,000 epinephrine vs 4% articaine, 1:100,000 epinephrine

3.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical tes

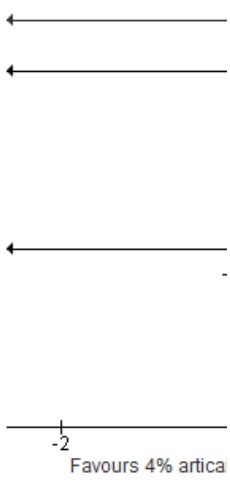
Study or Subgroup	4% articaine 1:200,000 epinephrine Events	Total	4% articaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Maxillary infiltration						
Lima 2009	36	50	47	50	32.8%	0.77 [0.64, 0.92]
Subtotal (95% CI)		**50**		**50**	**32.8%**	**0.77 [0.64, 0.92]**
Total events	36		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.80 (P = 0.005)						
3.1.2 Mandibular testing (injection type not stated)						
Pässler 1996	14	19	20	21	22.4%	0.77 [0.58, 1.03]
Subtotal (95% CI)		**19**		**21**	**22.4%**	**0.77 [0.58, 1.03]**
Total events	14		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
3.1.3 Both jaws combined/Jaw not stated						
Khoury 1991	269	382	298	408	44.9%	0.96 [0.88, 1.05]
Subtotal (95% CI)		**382**		**408**	**44.9%**	**0.96 [0.88, 1.05]**
Total events	269		298			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**451**		**479**	**100.0%**	**0.85 [0.71, 1.02]**
Total events	319		365			
Heterogeneity: Tau² = 0.02; Chi² = 6.35, df = 2 (P = 0.04); I² = 68%						
Test for overall effect: Z = 1.74 (P = 0.08)						
Test for subgroup differences: Chi² = 6.18, df = 2 (P = 0.05), I² = 67.6%						

3.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simu

Study or Subgroup	4% articaine 1:200,000 epinephrine Events	Total	4% articaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Maxillary infiltration						
Kammerer 2014	10	10	10	10	6.0%	1.00 [0.83, 1.20]
Moore 2006	58	62	59	62	33.7%	0.98 [0.90, 1.07]
Ruprecht 1991	10	10	10	10	6.0%	1.00 [0.83, 1.20]
Subtotal (95% CI)		**82**		**82**	**45.7%**	**0.99 [0.92, 1.06]**
Total events	78		79			
Heterogeneity: Chi² = 0.05, df = 2 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
3.2.2 Mandibular infiltration						
Abdulwahab 2009	6	18	7	18	4.0%	0.86 [0.36, 2.05]
McEntire 2011	51	86	58	86	33.1%	0.88 [0.70, 1.11]
Subtotal (95% CI)		**104**		**104**	**37.1%**	**0.88 [0.70, 1.10]**
Total events	57		65			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
3.2.3 Mandibular block (IANB)						
Moore 2006	34	62	30	62	17.1%	1.13 [0.80, 1.60]
Subtotal (95% CI)		**62**		**62**	**17.1%**	**1.13 [0.80, 1.60]**
Total events	34		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Total (95% CI)		**248**		**248**	**100.0%**	**0.97 [0.87, 1.08]**
Total events	169		174			
Heterogeneity: Chi² = 1.86, df = 5 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
Test for subgroup differences: Chi² = 1.67, df = 2 (P = 0.43), I² = 0%						

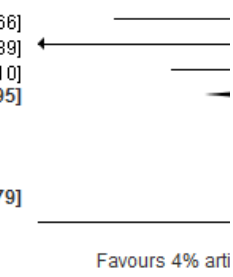
3.3 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% articaine 1:200,000 epinephrine Mean	SD	Total	4% articaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.3.1 Maxillary infiltration								
Kammerer 2014	4.7	2.6	10	5	3.2	10	5.1%	-0.30 [-2.86, 2.26]
Moore 2006	3.1	2.3	58	3	2.1	60	52.7%	0.10 [-0.70, 0.90]
Ruprecht 1991	4.7	1.58	10	5	2.83	10	8.3%	-0.30 [-2.31, 1.71]
Subtotal (95% CI)			**78**			**80**	**66.0%**	**0.02 [-0.69, 0.73]**
Heterogeneity: Chi² = 0.20, df = 2 (P = 0.91); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
3.3.2 Mandibular block (IANB)								
Moore 2006	4.7	2.6	34	4.2	2.8	30	18.9%	0.50 [-0.83, 1.83]
Tofoli 2003	8	26.83	20	7	17.89	20	0.2%	1.00 [-13.13, 15.13]
Tortamano 2013	7.7	3	30	7.4	2.9	30	14.9%	0.30 [-1.19, 1.79]
Subtotal (95% CI)			**84**			**80**	**34.0%**	**0.41 [-0.58, 1.40]**
Heterogeneity: Chi² = 0.05, df = 2 (P = 0.98); I² = 0%								
Test for overall effect: Z = 0.82 (P = 0.41)								
Total (95% CI)			**162**			**160**	**100.0%**	**0.15 [-0.42, 0.73]**
Heterogeneity: Chi² = 0.65, df = 5 (P = 0.99); I² = 0%								
Test for overall effect: Z = 0.52 (P = 0.60)								
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.52), I² = 0%								



3.4 Duration of anaesthesia (simulated scenario testing of healthy pulps)

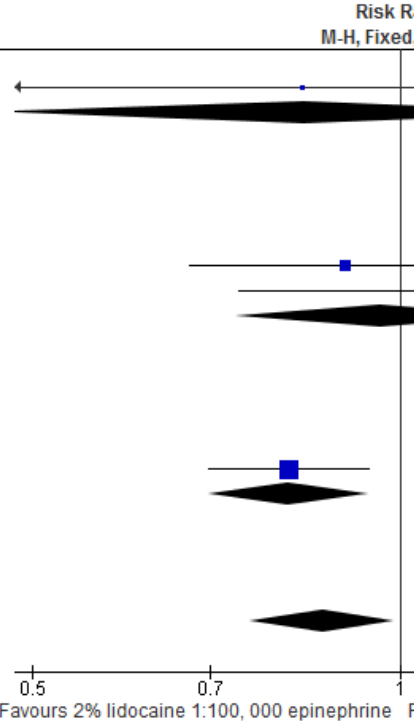
Study or Subgroup	4% articaine 1:200,000 epinephrine Mean	SD	Total	4% articaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.4.1 Maxillary infiltration								
Kammerer 2014	54.8	17.5	10	77.6	30.1	10	8.2%	-22.80 [-44.38, -1.22]
Moore 2006	41.6	21.1	58	45	23.6	60	58.8%	-3.40 [-11.47, 4.67]
Ruprecht 1991	54.4	22.58	10	66.8	22.7	10	9.7%	-12.40 [-32.24, 7.44]
Subtotal (95% CI)			**78**			**80**	**76.8%**	**-6.62 [-13.68, 0.44]**
Heterogeneity: Chi² = 3.10, df = 2 (P = 0.21); I² = 35%								
Test for overall effect: Z = 1.84 (P = 0.07)								
3.4.2 Mandibular block (IANB)								
Moore 2006	51.2	55.9	34	61.8	59	30	4.8%	-10.60 [-38.86, 17.66]
Tofoli 2003	168	223.61	20	169	232.55	20	0.2%	-1.00 [-142.39, 140.39]
Tortamano 2013	88	28.9	30	106.6	28.4	30	18.2%	-18.60 [-33.10, -4.10]
Subtotal (95% CI)			**84**			**80**	**23.2%**	**-16.80 [-29.65, -3.95]**
Heterogeneity: Chi² = 0.29, df = 2 (P = 0.86); I² = 0%								
Test for overall effect: Z = 2.56 (P = 0.01)								
Total (95% CI)			**162**			**160**	**100.0%**	**-8.98 [-15.17, -2.79]**
Heterogeneity: Chi² = 5.24, df = 5 (P = 0.39); I² = 5%								
Test for overall effect: Z = 2.84 (P = 0.004)								
Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 46.0%								



4 - 4% prilocaine plain vs 2% lidocaine 1:100,000 epinephrine

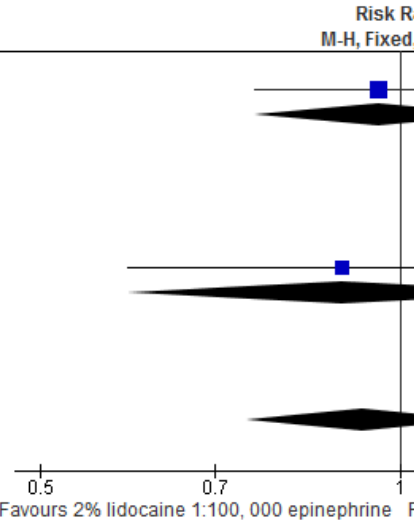
4.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical tes

Study or Subgroup	4% prilocaine plain Events	Total	2% lidocaine 1:100, 000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Maxillary infiltration						
Epstein 1965	4	5	4	4	5.0%	0.83 [0.48, 1.44]
Subtotal (95% CI)		**5**		**4**	**5.0%**	**0.83 [0.48, 1.44]**
Total events	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.51)						
4.1.2 Mandibular block (IANB)						
Chilton 1971	26	40	31	43	30.7%	0.90 [0.67, 1.21]
Epstein 1965	4	4	3	5	3.3%	1.54 [0.74, 3.22]
Subtotal (95% CI)		**44**		**48**	**34.0%**	**0.96 [0.73, 1.26]**
Total events	30		34			
Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 43%						
Test for overall effect: Z = 0.27 (P = 0.79)						
4.1.3 Both jaws combined/Jaw not stated						
Chilton 1971	50	66	57	61	60.9%	0.81 [0.70, 0.94]
Subtotal (95% CI)		**66**		**61**	**60.9%**	**0.81 [0.70, 0.94]**
Total events	50		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.71 (P = 0.007)						
Total (95% CI)		**115**		**113**	**100.0%**	**0.86 [0.75, 0.99]**
Total events	84		95			
Heterogeneity: Chi² = 3.15, df = 3 (P = 0.37); I² = 5%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Chi² = 1.18, df = 2 (P = 0.55), I² = 0%						



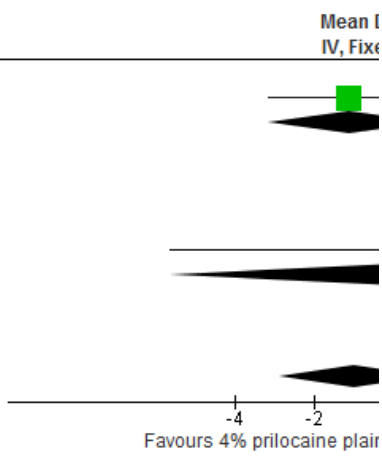
4.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simu

Study or Subgroup	4% prilocaine plain Events	Total	2% lidocaine 1:100, 000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Maxillary infiltration						
Katz 2010	24	30	25	30	56.8%	0.96 [0.76, 1.22]
Subtotal (95% CI)		**30**		**30**	**56.8%**	**0.96 [0.76, 1.22]**
Total events	24		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
4.2.2 Mandibular block (IANB)						
McLean 1993	17	30	19	30	43.2%	0.89 [0.59, 1.35]
Subtotal (95% CI)		**30**		**30**	**43.2%**	**0.89 [0.59, 1.35]**
Total events	17		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**60**		**60**	**100.0%**	**0.93 [0.75, 1.17]**
Total events	41		44			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						



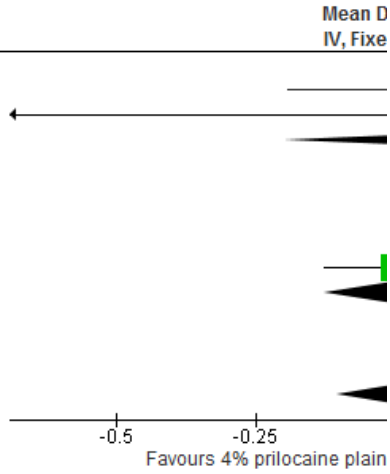
4.3 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% prilocaine plain Mean	SD	Total	2% lidocaine 1:100, 000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.3.1 Maxillary infiltration								
Katz 2010	3.9	2.3	24	5	4.5	24	89.3%	-1.10 [-3.12, 0.92]
Subtotal (95% CI)			**24**			**24**	**89.3%**	**-1.10 [-3.12, 0.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.29)								
4.3.2 Mandibular block (IANB)								
McLean 1993	11	11.64	28	10.8	10.39	27	10.7%	0.20 [-5.63, 6.03]
Subtotal (95% CI)			**28**			**27**	**10.7%**	**0.20 [-5.63, 6.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.95)								
Total (95% CI)			**52**			**51**	**100.0%**	**-0.96 [-2.87, 0.95]**
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 0.99 (P = 0.32)								
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%								



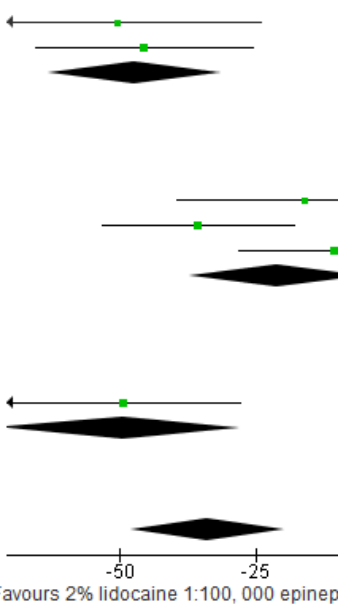
4.4 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% prilocaine plain Mean	SD	Total	2% lidocaine 1:100, 000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.4.1 Mandibular block (IANB)								
Chilton 1971	1.8	1.8	72	1.5	1.1	67	6.3%	0.30 [-0.19, 0.79]
McLean 1993	5	3.01	30	5	3.56	30	0.5%	0.00 [-1.67, 1.67]
Subtotal (95% CI)			**102**			**97**	**6.8%**	**0.28 [-0.20, 0.75]**
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%								
Test for overall effect: Z = 1.15 (P = 0.25)								
4.4.2 Both jaws combined/Jaw not stated								
Chilton 1971	0.9	0.5	113	0.9	0.5	124	93.2%	0.00 [-0.13, 0.13]
Subtotal (95% CI)			**113**			**124**	**93.2%**	**0.00 [-0.13, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**215**			**221**	**100.0%**	**0.02 [-0.10, 0.14]**
Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); I² = 0%								
Test for overall effect: Z = 0.30 (P = 0.77)								
Test for subgroup differences: Chi² = 1.22, df = 1 (P = 0.27), I² = 18.3%								



4.5 Duration of anaesthesia (simulated scenario testing of soft tissues)

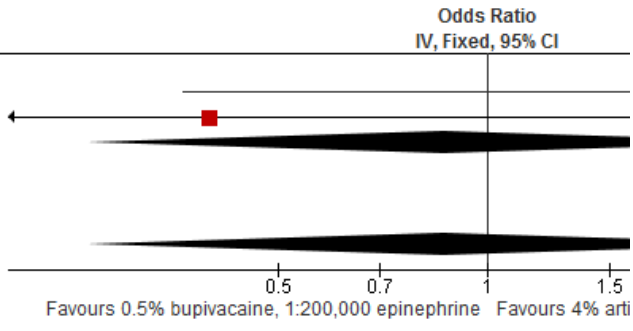
Study or Subgroup	4% prilocaine plain Mean	SD	Total	2% lidocaine 1:100, 000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.5.1 Maxillary infiltration								
Epstein 1965	98.9	57.13	51	149.3	67.67	40	13.8%	-50.40 [-76.58, -24.22]
Epstein 1969	101.7	55.12	62	147.3	60.57	67	17.3%	-45.60 [-65.56, -25.64]
Subtotal (95% CI)			**113**			**107**	**31.1%**	**-47.36 [-63.24, -31.49]**
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%								
Test for overall effect: Z = 5.85 (P < 0.00001)								
4.5.2 Mandibular block (IANB)								
Chilton 1971	181.4	64.6	47	197.4	53.5	50	15.1%	-16.00 [-39.69, 7.69]
Epstein 1965	165.7	52.5	49	201.3	36.4	51	18.6%	-35.60 [-53.37, -17.83]
Epstein 1969	179.2	41.42	51	189.7	49.04	52	18.8%	-10.50 [-28.02, 7.02]
Subtotal (95% CI)			**147**			**153**	**52.6%**	**-21.09 [-37.23, -4.94]**
Heterogeneity: Tau² = 104.97; Chi² = 4.14, df = 2 (P = 0.13); I² = 52%								
Test for overall effect: Z = 2.56 (P = 0.01)								
4.5.3 Both jaws combined/Jaw not stated								
Chilton 1971	119.9	67.1	80	169.3	79.9	98	16.3%	-49.40 [-71.00, -27.80]
Subtotal (95% CI)			**80**			**98**	**16.3%**	**-49.40 [-71.00, -27.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.48 (P < 0.00001)								
Total (95% CI)			**340**			**358**	**100.0%**	**-33.95 [-48.05, -19.84]**
Heterogeneity: Tau² = 195.85; Chi² = 13.84, df = 5 (P = 0.02); I² = 64%								
Test for overall effect: Z = 4.72 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.62, df = 2 (P = 0.04), I² = 69.8%								



5 - 0.5% bupivacaine, 1:200,000 epinephrine vs 4% articaine, 1:200,000 epinephrine

5.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical tes

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
5.1.1 Mandibular block (IANB) and infiltration				
Sancho-Puchades 2012	0.69321906	0.8660254	48.3%	2.00 [0.37, 10.92]
Trullenque-Eriksson 2011	-0.91638575	0.83666003	51.7%	0.40 [0.08, 2.06]
Subtotal (95% CI)			**100.0%**	**0.87 [0.27, 2.83]**
Heterogeneity: Chi² = 1.79, df = 1 (P = 0.18); I² = 44%				
Test for overall effect: Z = 0.23 (P = 0.82)				
Total (95% CI)			**100.0%**	**0.87 [0.27, 2.83]**
Heterogeneity: Chi² = 1.79, df = 1 (P = 0.18); I² = 44%				
Test for overall effect: Z = 0.23 (P = 0.82)				
Test for subgroup differences: Not applicable				



5.2 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% articaine, 1:200,000 epinephrine Mean	SD	Total	0.5% bupivacaine, 1:200,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.2.1 Mandibular block (IANB) and infiltration								
Gregorio 2008	1.66	0.36	50	2.51	1.48	50	93.8%	-0.85 [-1.27, -0.43]
Trullenque-Eriksson 2011	2.81	1.92	19	3.68	3.11	19	6.2%	-0.87 [-2.51, 0.77]
Subtotal (95% CI)			**69**			**69**	**100.0%**	**-0.85 [-1.26, -0.44]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 4.08 (P < 0.0001)								
Total (95% CI)			**69**			**69**	**100.0%**	**-0.85 [-1.26, -0.44]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 4.08 (P < 0.0001)								
Test for subgroup differences: Not applicable								

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5.3 Duration of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	0.5% bupivacaine, 1:200,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.3.1 Maxillary infiltration								
Vilchez-Perez 2012	163.45	57.48	20	336	166.46	20	75.5%	-172.55 [-249.73, -95.37]
Subtotal (95% CI)			**20**			**20**	**75.5%**	**-172.55 [-249.73, -95.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.38 (P < 0.0001)								
5.3.2 Mandibular block (IANB) and infiltration								
Trullenque-Eriksson 2011	319.2	129.6	19	492	272.4	19	24.5%	-172.80 [-308.44, -37.16]
Subtotal (95% CI)			**19**			**19**	**24.5%**	**-172.80 [-308.44, -37.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.50 (P = 0.01)								
Total (95% CI)			**39**			**39**	**100.0%**	**-172.61 [-239.69, -105.53]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 5.04 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%								

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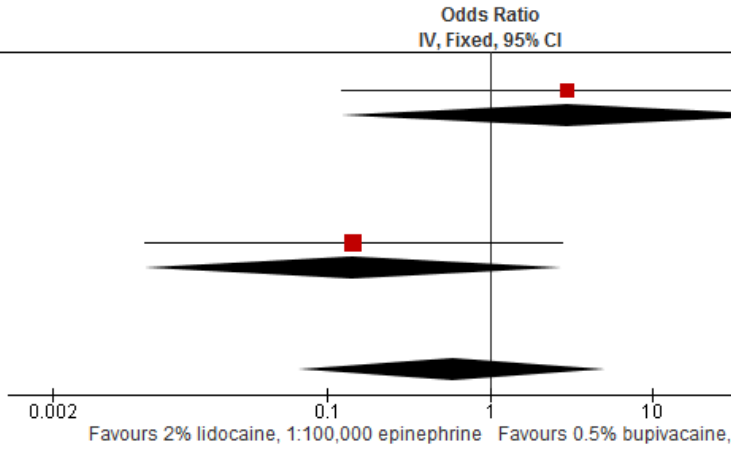
6 - 0.5% bupivacaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

6.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (clinic

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
6.1.1 Mandibular block (IANB) and infiltration				
Laskin 1977	1.0987	1.633	46.2%	3.00 [0.12, 73.65]
Subtotal (95% CI)			**46.2%**	**3.00 [0.12, 73.65]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.67 (P = 0.50)				
6.1.2 Both jaws combined/Jaw not stated				
Bouloux 1999	-1.9461	1.5119	53.8%	0.14 [0.01, 2.77]
Subtotal (95% CI)			**53.8%**	**0.14 [0.01, 2.77]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.29 (P = 0.20)				
Total (95% CI)			**100.0%**	**0.58 [0.07, 5.12]**
Heterogeneity: Chi² = 1.87, df = 1 (P = 0.17); I² = 47%				
Test for overall effect: Z = 0.49 (P = 0.63)				
Test for subgroup differences: Chi² = 1.87, df = 1 (P = 0.17), I² = 46.6%				



6.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (simulated

Study or Subgroup	0.5% bupivacaine, 1:200,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 Maxillary infiltration						
Gross 2007	21	33	27	33	52.9%	0.78 [0.57, 1.05]
Subtotal (95% CI)		**33**		**33**	**52.9%**	**0.78 [0.57, 1.05]**
Total events	21		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.11)						
6.2.2 Mandibular infiltration						
Abdulwahab 2009	2	18	3	18	5.9%	0.67 [0.13, 3.53]
Subtotal (95% CI)		**18**		**18**	**5.9%**	**0.67 [0.13, 3.53]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
6.2.3 Mandibular block (IANB)						
Fernandez 2005	18	39	21	39	41.2%	0.86 [0.55, 1.34]
Subtotal (95% CI)		**39**		**39**	**41.2%**	**0.86 [0.55, 1.34]**
Total events	18		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**90**		**90**	**100.0%**	**0.80 [0.62, 1.05]**
Total events	41		51			
Heterogeneity: Chi² = 0.17, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 0.17, df = 2 (P = 0.92), I² = 0%						

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Favours 2% li

6.3 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	0.5% bupivacaine, 1:200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
6.3.1 Maxillary infiltration								
Gross 2007	7.69	7.19	21	4.33	4.31	27	76.9%	3.36 [-0.12, 6.84]
Subtotal (95% CI)			**21**			**27**	**76.9%**	**3.36 [-0.12, 6.84]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.89 (P = 0.06)								
6.3.2 Mandibular block (IANB)								
Fernandez 2005	13.9	13.63	32	10.7	13.02	36	23.1%	3.20 [-3.16, 9.56]
Subtotal (95% CI)			**32**			**36**	**23.1%**	**3.20 [-3.16, 9.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.99 (P = 0.32)								
Total (95% CI)			**53**			**63**	**100.0%**	**3.32 [0.27, 6.37]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%								
Test for overall effect: Z = 2.13 (P = 0.03)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%								

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Favours 0.5% bu

6.4 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	0.5% bupivacaine, 1:200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
6.4.1 Mandibular block (IANB)								
Fernandez 2005	6.53	4.25	39	4.89	4.25	39	20.6%	1.64 [-0.25, 3.53]
Subtotal (95% CI)			**39**			**39**	**20.6%**	**1.64 [-0.25, 3.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.70 (P = 0.09)								
6.4.2 Mandibular block (IANB) and infiltration								
Laskin 1977	1.13	0.83	8	1.13	0.64	8	43.6%	0.00 [-0.73, 0.73]
Subtotal (95% CI)			**8**			**8**	**43.6%**	**0.00 [-0.73, 0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
6.4.3 Both jaws combined/Jaw not stated								
Moore 1983	1.9	0.8	16	2.8	2	16	35.8%	-0.90 [-1.96, 0.16]
Subtotal (95% CI)			**16**			**16**	**35.8%**	**-0.90 [-1.96, 0.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.09)								
Total (95% CI)			**63**			**63**	**100.0%**	**0.02 [-1.07, 1.10]**
Heterogeneity: Tau² = 0.57; Chi² = 5.55, df = 2 (P = 0.06); I² = 64%								
Test for overall effect: Z = 0.03 (P = 0.98)								
Test for subgroup differences: Chi² = 5.55, df = 2 (P = 0.06), I² = 63.9%								

-4
Favours 0.5%

6.5 Duration of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	0.5% bupivacaine, 1:200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
6.5.1 Maxillary infiltration								
Moore 1983	417	196.1	10	218	66.14	6	12.0%	199.00 [66.44, 331.56]
Gross 2007	213	142	33	168	63	33	15.7%	45.00 [-8.00, 98.00]
Subtotal (95% CI)			**43**			**39**	**27.7%**	**109.52 [-39.40, 258.44]**
Heterogeneity: Tau² = 9205.05; Chi² = 4.47, df = 1 (P = 0.03); I² = 78%								
Test for overall effect: Z = 1.44 (P = 0.15)								
6.5.2 Mandibular infiltration								
Moore 1983	447	97.98	6	219	34.79	10	14.5%	228.00 [146.69, 309.31]
Subtotal (95% CI)			**6**			**10**	**14.5%**	**228.00 [146.69, 309.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.50 (P < 0.00001)								
6.5.3 Mandibular block (IANB)								
Fernandez 2005	493	115.53	39	220	46.71	39	16.1%	273.00 [233.89, 312.11]
Subtotal (95% CI)			**39**			**39**	**16.1%**	**273.00 [233.89, 312.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 13.68 (P < 0.00001)								
6.5.4 Mandibular block (IANB) and infiltration								
Laskin 1977	570	134	8	196	25	8	13.9%	374.00 [279.54, 468.46]
Subtotal (95% CI)			**8**			**8**	**13.9%**	**374.00 [279.54, 468.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.76 (P < 0.00001)								
6.5.5 Both jaws combined/Jaw not stated								
Linden 1986	354	246	20	234	204	20	11.6%	120.00 [-20.06, 260.06]
Nespeca 1976	493.3	135.01	60	190.6	58.81	40	16.1%	302.70 [263.98, 341.42]
Subtotal (95% CI)			**80**			**60**	**27.7%**	**224.26 [47.01, 401.50]**
Heterogeneity: Tau² = 13941.21; Chi² = 6.07, df = 1 (P = 0.01); I² = 84%								
Test for overall effect: Z = 2.48 (P = 0.01)								
Total (95% CI)			**176**			**156**	**100.0%**	**222.88 [135.99, 309.76]**
Heterogeneity: Tau² = 11799.39; Chi² = 75.80, df = 6 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 5.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 10.41, df = 4 (P = 0.03), I² = 61.6%								

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7 - 4% articaine, 1:100,000 epinephrine vs 2% mepivacaine, 1:100,000 epinephrine

7.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical tes

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
7.1.1 Maxillary infiltration (buccal and palatal)				
Gazal 2017	1.4569	1.1389	67.3%	4.29 [0.46, 40.01]
Subtotal (95% CI)			**67.3%**	**4.29 [0.46, 40.01]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.28 (P = 0.20)				
7.1.2 Mandibular block (IANB) and infiltration				
Colombini 2006	1.0987	1.633	32.7%	3.00 [0.12, 73.65]
Subtotal (95% CI)			**32.7%**	**3.00 [0.12, 73.65]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.67 (P = 0.50)				
Total (95% CI)			**100.0%**	**3.82 [0.61, 23.82]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%				
Test for overall effect: Z = 1.43 (P = 0.15)				
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%				

Odds Ratio IV, Fixed, 95% CI

0.01 0.1 1 10

Favours 2% mepivacaine, 1:100,000 epinephrine Favours 4% articaine, 1:100

7.2 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simu

	4% articaine, 1:100,000 epinephrine		2% mepivacaine, 1:100,000 epinephrine			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
7.2.1 Mandibular block (IANB)						
Allegretti 2016	22	22	22	22	63.1%	1.00 [0.92, 1.09]
Subtotal (95% CI)		**22**		**22**	**63.1%**	**1.00 [0.92, 1.09]**
Total events	22		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
7.2.2 Mandibular infiltration						
Bortoluzzi 2009	17	24	14	24	36.9%	1.21 [0.79, 1.86]
Subtotal (95% CI)		**24**		**24**	**36.9%**	**1.21 [0.79, 1.86]**
Total events	17		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**46**		**46**	**100.0%**	**1.07 [0.73, 1.59]**
Total events	39		36			
Heterogeneity: Tau² = 0.06; Chi² = 3.51, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 0.77, df = 1 (P = 0.38), I² = 0%						

Favours 2% mep

8 - 2% lidocaine, 1:100,000 epinephrine vs 2% mepivacaine, 1:100,000 epinephrine

8.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale or other appropriate method (clinical tes

	2% mepivacaine, 1:100,000 epinephrine		2% lidocaine, 1:100,000 epinephrine			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
8.1.1 Mandibular block (IANB)						
Allegretti 2016	4	22	7	22	55.5%	0.57 [0.19, 1.68]
Visconti 2016	4	10	2	14	44.5%	2.80 [0.63, 12.43]
Subtotal (95% CI)		**32**		**36**	**100.0%**	**1.16 [0.25, 5.45]**
Total events	8		9			
Heterogeneity: Tau² = 0.82; Chi² = 2.87, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**32**		**36**	**100.0%**	**1.16 [0.25, 5.45]**
Total events	8		9			
Heterogeneity: Tau² = 0.82; Chi² = 2.87, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: Not applicable						

0.01

Favours 2%

9 - 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:80,000 epinephrine

9.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (simu

	2% lidocaine, 1:50,000 epinephrine		2% lidocaine, 1:80,000 epinephrine			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
9.1.1 Mandibular infiltration						
Dagher 1997	15	30	19	30	40.4%	0.79 [0.50, 1.24]
Subtotal (95% CI)		**30**		**30**	**40.4%**	**0.79 [0.50, 1.24]**
Total events	15		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
9.1.2 Mandibular block (IANB)						
Yared 1997	23	30	28	30	59.6%	0.82 [0.66, 1.02]
Subtotal (95% CI)		**30**		**30**	**59.6%**	**0.82 [0.66, 1.02]**
Total events	23		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
Total (95% CI)		**60**		**60**	**100.0%**	**0.81 [0.65, 1.01]**
Total events	38		47			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

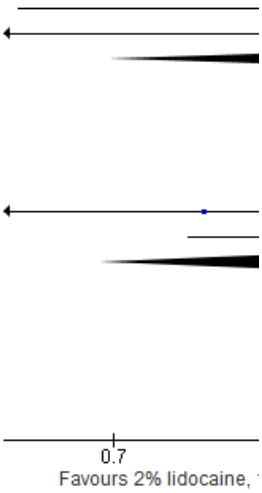
0.5 0

Favours 2% lidocaine, 1

10 - 2% lidocaine, 1:50,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

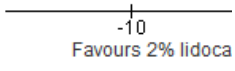
10.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	2% lidocaine, 1:50,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 Maxillary infiltration						
Knoll-Kohler 1992a	10	10	10	10	7.4%	1.00 [0.83, 1.20]
Mason 2009	28	30	29	30	20.5%	0.97 [0.86, 1.08]
Subtotal (95% CI)		**40**		**40**	**27.9%**	**0.97 [0.88, 1.08]**
Total events	38		39			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
10.1.2 Maxillary block (Infraorbital block)						
Berberich 2009	37	40	34	40	24.0%	1.09 [0.93, 1.27]
Subtotal (95% CI)		**40**		**40**	**24.0%**	**1.09 [0.93, 1.27]**
Total events	37		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
10.1.3 Mandibular infiltration						
Dagher 1997	15	30	14	30	9.9%	1.07 [0.63, 1.81]
Yonchak 2001	17	40	18	40	12.7%	0.94 [0.57, 1.55]
Subtotal (95% CI)		**70**		**70**	**22.6%**	**1.00 [0.70, 1.43]**
Total events	32		32			
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
10.1.4 Mandibular block (IANB)						
Wali 2010	10	30	13	30	9.2%	0.77 [0.40, 1.47]
Yared 1997	23	30	23	30	16.3%	1.00 [0.76, 1.32]
Subtotal (95% CI)		**60**		**60**	**25.4%**	**0.92 [0.69, 1.22]**
Total events	33		36			
Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**210**		**210**	**100.0%**	**0.99 [0.88, 1.12]**
Total events	140		141			
Heterogeneity: Chi² = 2.25, df = 6 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Chi² = 1.73, df = 3 (P = 0.63), I² = 0%						



10.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

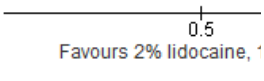
Study or Subgroup	2% lidocaine, 1:50,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
10.2.1 Maxillary infiltration								
Knoll-Kohler 1992a	3.5	7.49	10	3.9	7.05	10	3.7%	-0.40 [-6.78, 5.98]
Mason 2009	4.3	3.17	28	5.1	5.82	28	24.9%	-0.80 [-3.25, 1.65]
Subtotal (95% CI)			**38**			**38**	**28.6%**	**-0.75 [-3.04, 1.54]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%								
Test for overall effect: Z = 0.64 (P = 0.52)								
10.2.2 Maxillary block (Infraorbital block)								
Berberich 2009	3.6	3.1	30	4	2.7	30	69.3%	-0.40 [-1.87, 1.07]
Subtotal (95% CI)			**30**			**30**	**69.3%**	**-0.40 [-1.87, 1.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.59)								
10.2.3 Mandibular block (IANB)								
Wali 2010	15.9	16.66	24	13.3	13.23	24	2.1%	2.60 [-5.91, 11.11]
Subtotal (95% CI)			**24**			**24**	**2.1%**	**2.60 [-5.91, 11.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								
Total (95% CI)			**92**			**92**	**100.0%**	**-0.44 [-1.66, 0.79]**
Heterogeneity: Chi² = 0.58, df = 3 (P = 0.90); I² = 0%								
Test for overall effect: Z = 0.70 (P = 0.48)								
Test for subgroup differences: Chi² = 0.56, df = 2 (P = 0.75), I² = 0%								



11 - 2% lidocaine, 1:80,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

11.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	2% lidocaine, 1:80,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 Mandibular infiltration						
Dagher 1997	19	30	14	30	37.8%	1.36 [0.85, 2.17]
Subtotal (95% CI)		**30**		**30**	**37.8%**	**1.36 [0.85, 2.17]**
Total events	19		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						
11.1.2 Mandibular block (IANB)						
Yared 1997	28	30	23	30	62.2%	1.22 [0.98, 1.52]
Subtotal (95% CI)		**30**		**30**	**62.2%**	**1.22 [0.98, 1.52]**
Total events	28		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
Total (95% CI)		**60**		**60**	**100.0%**	**1.27 [1.01, 1.59]**
Total events	47		37			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.07 (P = 0.04)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



12 - 2% lidocaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

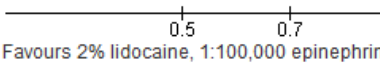
12.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	2% lidocaine, 1:200,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
12.1.1 Maxillary infiltration						
Caldas 2015	30	30	30	30	46.8%	1.00 [0.94, 1.07]
Knoll-Kohler 1992a	6	10	10	10	23.4%	0.62 [0.37, 1.03]
Subtotal (95% CI)		**40**		**40**	**70.2%**	**0.80 [0.33, 1.95]**
Total events	36		40			
Heterogeneity: Tau² = 0.38; Chi² = 12.08, df = 1 (P = 0.0005); I² = 92%						
Test for overall effect: Z = 0.49 (P = 0.63)						
12.1.2 Mandibular block (IANB)						
Vreeland 1989	19	30	19	30	29.8%	1.00 [0.68, 1.47]
Subtotal (95% CI)		**30**		**30**	**29.8%**	**1.00 [0.68, 1.47]**
Total events	19		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**70**		**70**	**100.0%**	**0.89 [0.63, 1.26]**
Total events	55		59			
Heterogeneity: Tau² = 0.06; Chi² = 7.13, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%						

13 - 3% mepivacaine plain vs 2% lidocaine, 1:100,000 epinephrine

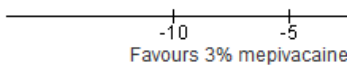
13.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	3% mepivacaine plain Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.1.1 Maxillary infiltration						
Mason 2009	28	30	29	30	18.8%	0.97 [0.86, 1.08]
Subtotal (95% CI)		**30**		**30**	**18.8%**	**0.97 [0.86, 1.08]**
Total events	28		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
13.1.2 Maxillary block (Infraorbital block)						
Berberich 2009	35	40	34	40	22.1%	1.03 [0.86, 1.23]
Subtotal (95% CI)		**40**		**40**	**22.1%**	**1.03 [0.86, 1.23]**
Total events	35		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
13.1.3 Maxillary block (palatal-anterior superior alveolar nerve block)						
Burns 2004	14	40	23	40	14.9%	0.61 [0.37, 1.00]
Subtotal (95% CI)		**40**		**40**	**14.9%**	**0.61 [0.37, 1.00]**
Total events	14		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
13.1.4 Maxillary block (high-tuberosity maxillary second division nerve block)						
Forloine 2010	46	50	46	50	29.9%	1.00 [0.89, 1.12]
Subtotal (95% CI)		**50**		**50**	**29.9%**	**1.00 [0.89, 1.12]**
Total events	46		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
13.1.5 Mandibular infiltration						
Abdulwahab 2009	6	18	3	18	1.9%	2.00 [0.59, 6.79]
Subtotal (95% CI)		**18**		**18**	**1.9%**	**2.00 [0.59, 6.79]**
Total events	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
13.1.6 Mandibular block (IANB)						
McLean 1993	13	30	19	30	12.3%	0.68 [0.42, 1.12]
Subtotal (95% CI)		**30**		**30**	**12.3%**	**0.68 [0.42, 1.12]**
Total events	13		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
Total (95% CI)		**208**		**208**	**100.0%**	**0.92 [0.83, 1.02]**
Total events	142		154			
Heterogeneity: Chi² = 9.63, df = 5 (P = 0.09); I² = 48%						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: Chi² = 7.32, df = 5 (P = 0.20), I² = 31.7%						



13.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

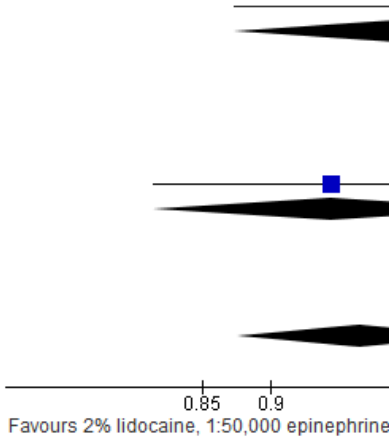
Study or Subgroup	3% mepivacaine plain Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
13.2.1 Maxillary infiltration								
Mason 2009	4	2.12	28	5.1	5.82	28	21.9%	-1.10 [-3.39, 1.19]
Subtotal (95% CI)			**28**			**28**	**21.9%**	**-1.10 [-3.39, 1.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.94 (P = 0.35)								
13.2.2 Maxillary block (Infraorbital block)								
Berberich 2009	2.8	2.2	30	4	2.7	30	74.3%	-1.20 [-2.45, 0.05]
Subtotal (95% CI)			**30**			**30**	**74.3%**	**-1.20 [-2.45, 0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.89 (P = 0.06)								
13.2.3 Mandibular block (IANB)								
McLean 1993	8.2	10.39	27	10.8	10.39	27	3.8%	-2.60 [-8.14, 2.94]
Subtotal (95% CI)			**27**			**27**	**3.8%**	**-2.60 [-8.14, 2.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.92 (P = 0.36)								
Total (95% CI)			**85**			**85**	**100.0%**	**-1.23 [-2.31, -0.16]**
Heterogeneity: Chi² = 0.25, df = 2 (P = 0.88); I² = 0%								
Test for overall effect: Z = 2.25 (P = 0.02)								
Test for subgroup differences: Chi² = 0.25, df = 2 (P = 0.88), I² = 0%								



14 - 3% mepivacaine plain vs 2% lidocaine, 1:50,000 epinephrine

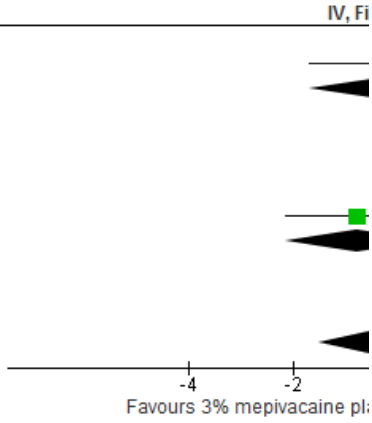
14.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	3% mepivacaine plain Events	Total	2% lidocaine, 1:50,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk M-H, Fix
14.1.1 Maxillary infiltration							
Mason 2009	28	30	28	30	43.1%	1.00 [0.87, 1.14]	
Subtotal (95% CI)		**30**		**30**	**43.1%**	**1.00 [0.87, 1.14]**	
Total events	28		28				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
14.1.2 Maxillary block (infraorbital block)							
Berberich 2009	35	40	37	40	56.9%	0.95 [0.82, 1.10]	
Subtotal (95% CI)		**40**		**40**	**56.9%**	**0.95 [0.82, 1.10]**	
Total events	35		37				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.74 (P = 0.46)							
Total (95% CI)		**70**		**70**	**100.0%**	**0.97 [0.88, 1.07]**	
Total events	63		65				
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%							
Test for overall effect: Z = 0.60 (P = 0.55)							
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%							



14.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	3% mepivacaine plain Mean	SD	Total	2% lidocaine, 1:50,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean IV, Fi
14.2.1 Maxillary infiltration									
Mason 2009	4	2.12	28	4.3	3.17	28	48.1%	-0.30 [-1.71, 1.11]	
Subtotal (95% CI)			**28**			**28**	**48.1%**	**-0.30 [-1.71, 1.11]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.42 (P = 0.68)									
14.2.2 Maxillary block (infraorbital block)									
Berberich 2009	2.8	2.2	30	3.6	3.1	30	51.9%	-0.80 [-2.16, 0.56]	
Subtotal (95% CI)			**30**			**30**	**51.9%**	**-0.80 [-2.16, 0.56]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.15 (P = 0.25)									
Total (95% CI)			**58**			**58**	**100.0%**	**-0.56 [-1.54, 0.42]**	
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%									
Test for overall effect: Z = 1.12 (P = 0.26)									
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%									



15 - 2% mepivacaine, 1:20,000 levonordefrin vs 2% lidocaine, 1:100,000 epinephrine

15.1 Duration of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	2% mepivacaine, 1:20,000 levonordefrin Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
15.1.1 Both jaws combined/Jaw not stated								
Albertson 1963	170.21	70.62	106	167	56.13	89	71.5%	3.21 [-14.59, 21.01]
Sadove 1962	216	103.78	141	208.52	126.36	122	28.5%	7.48 [-20.74, 35.70]
Subtotal (95% CI)			**247**			**211**	**100.0%**	**4.43 [-10.63, 19.48]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.58 (P = 0.56)								
Total (95% CI)			**247**			**211**	**100.0%**	**4.43 [-10.63, 19.48]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.58 (P = 0.56)								
Test for subgroup differences: Not applicable								

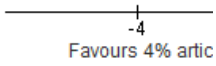
16 - 4% articaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

16.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	4% articaine, 1:200,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
16.1.1 Maxillary infiltration						
Ruprecht 1991	10	10	10	10	59.1%	1.00 [0.83, 1.20]
Subtotal (95% CI)		**10**		**10**	**59.1%**	**1.00 [0.83, 1.20]**
Total events	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
16.1.2 Mandibular infiltration						
Abdulwahab 2009	6	18	3	18	40.9%	2.00 [0.59, 6.79]
Subtotal (95% CI)		**18**		**18**	**40.9%**	**2.00 [0.59, 6.79]**
Total events	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**28**		**28**	**100.0%**	**1.33 [0.33, 5.36]**
Total events	16		13			
Heterogeneity: Tau² = 0.85; Chi² = 5.27, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.3%						

16.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% articaine, 1:200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
16.2.1 Maxillary infiltration								
Ruprecht 1991	4.7	1.58	10	3.4	1.31	10	51.9%	1.30 [0.03, 2.57]
Subtotal (95% CI)			**10**			**10**	**51.9%**	**1.30 [0.03, 2.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.00 (P = 0.05)								
16.2.2 Mandibular block (IANB)								
Tortamano 2013	7.7	3	30	8.7	3.1	30	48.1%	-1.00 [-2.54, 0.54]
Subtotal (95% CI)			**30**			**30**	**48.1%**	**-1.00 [-2.54, 0.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.20)								
Total (95% CI)			**40**			**40**	**100.0%**	**0.19 [-2.06, 2.45]**
Heterogeneity: Tau² = 2.12; Chi² = 5.08, df = 1 (P = 0.02); I² = 80%								
Test for overall effect: Z = 0.17 (P = 0.87)								
Test for subgroup differences: Chi² = 5.08, df = 1 (P = 0.02), I² = 80.3%								



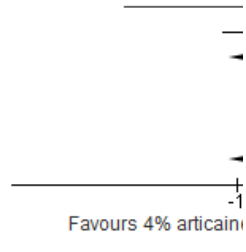
16.3 Duration of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% articaine, 1:200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
16.3.1 Maxillary infiltration								
Ruprecht 1991	54.4	22.58	10	61.3	17.21	10	48.0%	-6.90 [-24.50, 10.70]
Subtotal (95% CI)			**10**			**10**	**48.0%**	**-6.90 [-24.50, 10.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								
16.3.2 Mandibular block (IANB)								
Tortamano 2013	88	28.9	30	61.8	15.5	30	52.0%	26.20 [14.46, 37.94]
Subtotal (95% CI)			**30**			**30**	**52.0%**	**26.20 [14.46, 37.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.38 (P < 0.0001)								
Total (95% CI)			**40**			**40**	**100.0%**	**10.33 [-22.08, 42.74]**
Heterogeneity: Tau² = 489.58; Chi² = 9.41, df = 1 (P = 0.002); I² = 89%								
Test for overall effect: Z = 0.62 (P = 0.53)								
Test for subgroup differences: Chi² = 9.41, df = 1 (P = 0.002), I² = 89.4%								

17 - 4% articaine, 1:100,000 epinephrine vs 2% lidocaine, 1:80,000 epinephrine

17.1 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)

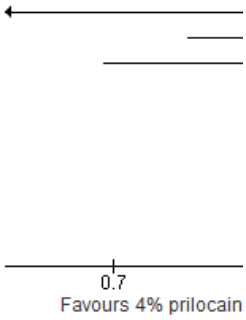
Study or Subgroup	4% articaine, 1:100,000 epinephrine Mean	SD	Total	2% lidocaine, 1:80,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
17.1.1 Mandibular block (IANB)								
Arrow 2012	2.15	2.8	16	1.98	1.45	9	2.4%	0.17 [-1.50, 1.84]
Naik 2017	2.2	0.5	50	3	0.81	50	97.6%	-0.80 [-1.06, -0.54]
Subtotal (95% CI)			**66**			**59**	**100.0%**	**-0.78 [-1.04, -0.52]**
Heterogeneity: Chi² = 1.27, df = 1 (P = 0.26); I² = 21%								
Test for overall effect: Z = 5.84 (P < 0.00001)								
Total (95% CI)			**66**			**59**	**100.0%**	**-0.78 [-1.04, -0.52]**
Heterogeneity: Chi² = 1.27, df = 1 (P = 0.26); I² = 21%								
Test for overall effect: Z = 5.84 (P < 0.00001)								
Test for subgroup differences: Not applicable								



18 - 4% articaine, 1:200,000 epinephrine vs 4% prilocaine, 1:200,000 epinephrine

18.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

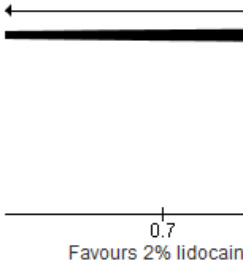
Study or Subgroup	4% articaine, 1:200,000 epinephrine Events	Total	4% prilocaine, 1;200,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
18.1.1 Maxillary infiltration						
Haas 1990	13	20	13	20	23.6%	1.00 [0.63, 1.58]
Haas 1991	19	20	18	20	32.7%	1.06 [0.88, 1.26]
Subtotal (95% CI)		**40**		**40**	**56.4%**	**1.03 [0.83, 1.28]**
Total events	32		31			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
18.1.2 Mandibular infiltration						
Abdulwahab 2009	6	18	4	18	7.3%	1.50 [0.51, 4.43]
Haas 1990	13	20	10	20	18.2%	1.30 [0.75, 2.24]
Haas 1991	12	19	10	19	18.2%	1.20 [0.69, 2.07]
Subtotal (95% CI)		**57**		**57**	**43.6%**	**1.29 [0.89, 1.87]**
Total events	31		24			
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.35 (P = 0.18)						
Total (95% CI)		**97**		**97**	**100.0%**	**1.15 [0.93, 1.41]**
Total events	63		55			
Heterogeneity: Chi² = 1.63, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.31), I² = 4.7%						



19 - 4% prilocaine, 1:200,000 epinephrine vs 2% lidocaine, 1:100,000 epinephrine

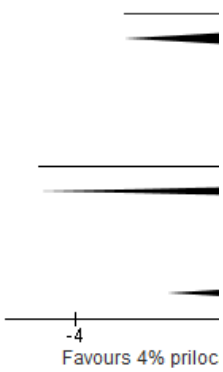
19.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	4% prilocaine, 1;200,000 epinephrine Events	Total	2% lidocaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
19.1.1 Maxillary infiltration						
Katz 2010	28	30	25	30	89.3%	1.12 [0.93, 1.35]
Subtotal (95% CI)		**30**		**30**	**89.3%**	**1.12 [0.93, 1.35]**
Total events	28		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.23)						
19.1.2 Mandibular infiltration						
Abdulwahab 2009	4	18	3	18	10.7%	1.33 [0.35, 5.13]
Subtotal (95% CI)		**18**		**18**	**10.7%**	**1.33 [0.35, 5.13]**
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						
Total (95% CI)		**48**		**48**	**100.0%**	**1.14 [0.91, 1.43]**
Total events	32		28			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%						



19.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% prilocaine, 1;200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
19.2.1 Maxillary infiltration								
Katz 2010	3.5	2.2	24	5	4.5	24	88.5%	-1.50 [-3.50, 0.50]
Subtotal (95% CI)			**24**			**24**	**88.5%**	**-1.50 [-3.50, 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.47 (P = 0.14)								
19.2.2 Mandibular block (IANB)								
Hinkley 1991	10	7.93	13	8.8	6.97	15	11.5%	1.20 [-4.37, 6.77]
Subtotal (95% CI)			**13**			**15**	**11.5%**	**1.20 [-4.37, 6.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.67)								
Total (95% CI)			**37**			**39**	**100.0%**	**-1.19 [-3.08, 0.70]**
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 1.24 (P = 0.22)								
Test for subgroup differences: Chi² = 0.80, df = 1 (P = 0.37), I² = 0%								



19.3 Speed of onset of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% prilocaine, 1;200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
19.3.1 Mandibular block (IANB)								
Hinkley 1991	6.3	5.82	28	6.1	4.23	28	0.2%	0.20 [-2.46, 2.86]
Chilton 1971	1.4	0.9	68	1.5	1.1	67	13.5%	-0.10 [-0.44, 0.24]
Subtotal (95% CI)			**96**			**95**	**13.8%**	**-0.10 [-0.43, 0.24]**
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%								
Test for overall effect: Z = 0.55 (P = 0.58)								
19.3.2 Both jaws combined/jaw not stated								
Chilton 1971	0.9	0.6	134	0.9	0.5	124	86.2%	0.00 [-0.13, 0.13]
Subtotal (95% CI)			**134**			**124**	**86.2%**	**0.00 [-0.13, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**230**			**219**	**100.0%**	**-0.01 [-0.14, 0.11]**
Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.21 (P = 0.84)								
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.61), I² = 0%								

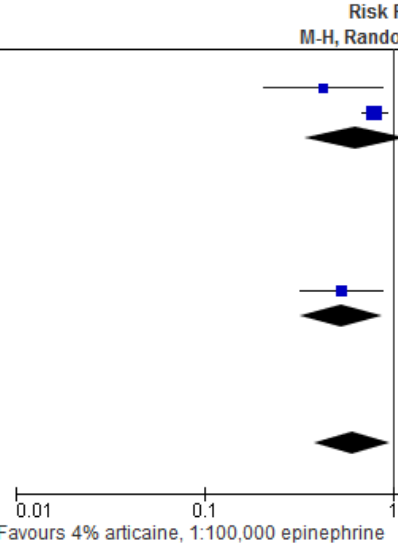
19.4 Duration of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% prilocaine, 1;200,000 epinephrine Mean	SD	Total	2% lidocaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
19.4.1 Maxillary infiltration								
Epstein 1969	124.7	43.2	81	147.3	60.57	67	27.6%	-22.60 [-39.89, -5.31]
Subtotal (95% CI)			**81**			**67**	**27.6%**	**-22.60 [-39.89, -5.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.56 (P = 0.01)								
19.4.2 Mandibular block (IANB)								
Chilton 1971	204.6	49.3	50	197.4	53.5	50	24.7%	7.20 [-12.97, 27.37]
Epstein 1969	186.6	54.94	46	189.7	49.04	52	24.2%	-3.10 [-23.83, 17.63]
Subtotal (95% CI)			**96**			**102**	**48.9%**	**2.19 [-12.26, 16.65]**
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 1 (P = 0.49); I² = 0%								
Test for overall effect: Z = 0.30 (P = 0.77)								
19.4.3 Both jaws combined/Jaw not stated								
Chilton 1971	141.3	69.1	89	169.3	79.9	98	23.6%	-28.00 [-49.36, -6.64]
Subtotal (95% CI)			**89**			**98**	**23.6%**	**-28.00 [-49.36, -6.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.57 (P = 0.01)								
Total (95% CI)			**266**			**267**	**100.0%**	**-11.80 [-27.76, 4.16]**
Heterogeneity: Tau² = 162.62; Chi² = 7.79, df = 3 (P = 0.05); I² = 61%								
Test for overall effect: Z = 1.45 (P = 0.15)								
Test for subgroup differences: Chi² = 7.30, df = 2 (P = 0.03), I² = 72.6%								

20 - 4% articaine plain vs 4% articaine, 1:100,000 epinephrine

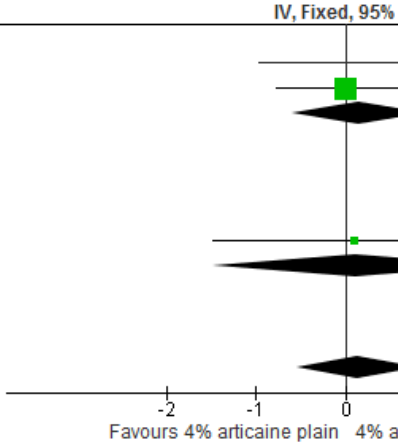
20.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	4% articaine plain Events	Total	4% articaine, 1:100,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
20.1.1 Maxillary infiltration						
Kammerer 2014	4	10	10	10	22.3%	0.43 [0.21, 0.88]
Moore 2006	47	62	59	62	46.3%	0.80 [0.68, 0.93]
Subtotal (95% CI)		**72**		**72**	**68.7%**	**0.64 [0.34, 1.19]**
Total events	51		69			
Heterogeneity: Tau² = 0.15; Chi² = 3.09, df = 1 (P = 0.08); I² = 68%						
Test for overall effect: Z = 1.41 (P = 0.16)						
20.1.2 Mandibular block (IANB)						
Moore 2006	16	62	30	62	31.3%	0.53 [0.33, 0.87]
Subtotal (95% CI)		**62**		**62**	**31.3%**	**0.53 [0.33, 0.87]**
Total events	16		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.49 (P = 0.01)						
Total (95% CI)		**134**		**134**	**100.0%**	**0.61 [0.38, 0.97]**
Total events	67		99			
Heterogeneity: Tau² = 0.11; Chi² = 6.79, df = 2 (P = 0.03); I² = 71%						
Test for overall effect: Z = 2.08 (P = 0.04)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						



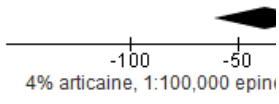
20.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% articaine plain Mean	SD	Total	4% articaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
20.2.1 Maxillary infiltration								
Kammerer 2014	6.5	1.5	4	5	3.2	10	7.4%	1.50 [-0.97, 3.97]
Moore 2006	3	2	47	3	2.1	60	74.4%	0.00 [-0.78, 0.78]
Subtotal (95% CI)			**51**			**70**	**81.9%**	**0.14 [-0.61, 0.88]**
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 22%								
Test for overall effect: Z = 0.36 (P = 0.72)								
20.2.2 Mandibular block (IANB)								
Moore 2006	4.3	2.5	16	4.2	2.8	30	18.1%	0.10 [-1.48, 1.68]
Subtotal (95% CI)			**16**			**30**	**18.1%**	**0.10 [-1.48, 1.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.12 (P = 0.90)								
Total (95% CI)			**67**			**100**	**100.0%**	**0.13 [-0.54, 0.80]**
Heterogeneity: Chi² = 1.29, df = 2 (P = 0.52); I² = 0%								
Test for overall effect: Z = 0.38 (P = 0.71)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%								



20.3 Duration of anaesthesia (simulated scenario testing of healthy pulps)

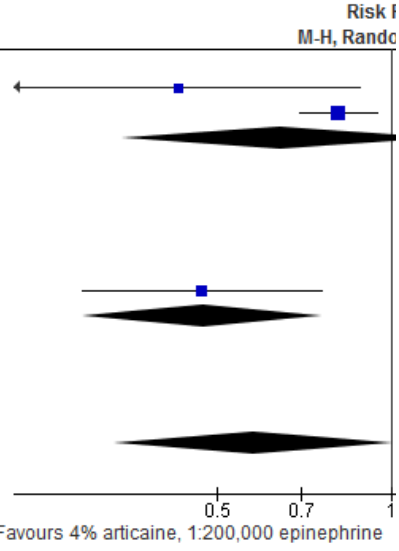
Study or Subgroup	Favours 4% articaine plain Mean	SD	Total	4% articaine, 1:100,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
20.3.1 Maxillary infiltration								
Kammerer 2014	14.75	5.8	4	77.6	30.1	10	33.2%	-62.85 [-82.35, -43.35]
Moore 2006	13.3	6.8	47	45	23.6	60	41.5%	-31.70 [-37.98, -25.42]
Subtotal (95% CI)			**51**			**70**	**74.7%**	**-45.85 [-76.25, -15.45]**
Heterogeneity: Tau² = 430.52; Chi² = 8.88, df = 1 (P = 0.003); I² = 89%								
Test for overall effect: Z = 2.96 (P = 0.003)								
20.3.2 Mandibular block (IANB)								
Moore 2006	49.7	44.2	16	61.8	59	30	25.3%	-12.10 [-42.35, 18.15]
Subtotal (95% CI)			**16**			**30**	**25.3%**	**-12.10 [-42.35, 18.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.43)								
Total (95% CI)			**67**			**100**	**100.0%**	**-37.08 [-60.95, -13.21]**
Heterogeneity: Tau² = 347.52; Chi² = 10.93, df = 2 (P = 0.004); I² = 82%								
Test for overall effect: Z = 3.04 (P = 0.002)								
Test for subgroup differences: Chi² = 2.38, df = 1 (P = 0.12), I² = 58.0%								



21 - 4% articaine plain vs 4% articaine, 1:200,000 epinephrine

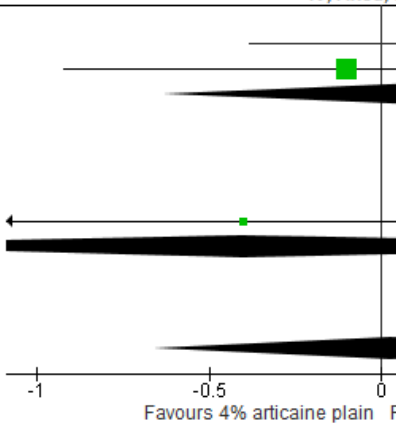
21.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	4% articaine plain Events	Total	4% articaine, 1:200,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
21.1.1 Maxillary infiltration						
Kammerer 2014	4	10	10	10	25.2%	0.43 [0.21, 0.88]
Moore 2006	47	62	58	62	41.9%	0.81 [0.69, 0.95]
Subtotal (95% CI)		**72**		**72**	**67.1%**	**0.64 [0.34, 1.22]**
Total events	51		68			
Heterogeneity: Tau² = 0.16; Chi² = 3.23, df = 1 (P = 0.07); I² = 69%						
Test for overall effect: Z = 1.35 (P = 0.18)						
21.1.2 Mandibular block (IANB)						
Moore 2006	16	62	34	62	32.9%	0.47 [0.29, 0.76]
Subtotal (95% CI)		**62**		**62**	**32.9%**	**0.47 [0.29, 0.76]**
Total events	16		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
Total (95% CI)		**134**		**134**	**100.0%**	**0.58 [0.33, 1.01]**
Total events	67		102			
Heterogeneity: Tau² = 0.19; Chi² = 10.13, df = 2 (P = 0.006); I² = 80%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%						



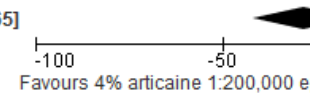
21.2 Speed of onset of anaesthesia (simulated scenario testing of healthy pulps)

Study or Subgroup	4% articaine plain Mean	SD	Total	4% articaine 1:200,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
21.2.1 Maxillary infiltration								
Kammerer 2014	6.5	1.5	4	4.7	2.6	10	9.9%	1.80 [-0.38, 3.98]
Moore 2006	3	2	47	3.1	2.3	58	69.4%	-0.10 [-0.92, 0.72]
Subtotal (95% CI)			**51**			**68**	**79.2%**	**0.14 [-0.63, 0.91]**
Heterogeneity: Chi² = 2.55, df = 1 (P = 0.11); I² = 61%								
Test for overall effect: Z = 0.35 (P = 0.73)								
21.2.2 Mandibular block (IANB)								
Moore 2006	4.3	2.5	16	4.7	2.6	34	20.8%	-0.40 [-1.90, 1.10]
Subtotal (95% CI)			**16**			**34**	**20.8%**	**-0.40 [-1.90, 1.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
Total (95% CI)			**67**			**102**	**100.0%**	**0.03 [-0.66, 0.71]**
Heterogeneity: Chi² = 2.94, df = 2 (P = 0.23); I² = 32%								
Test for overall effect: Z = 0.07 (P = 0.94)								
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%								



21.3 Duration of anaesthesia (simulated scenario testing of healthy pulps)

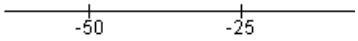
Study or Subgroup	Favours 4% articaine plain Mean	SD	Total	4% articaine 1:200,000 epinephrine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
21.3.1 Maxillary infiltration								
Kammerer 2014	14.75	5.8	4	54.8	17.5	10	36.7%	-40.05 [-52.30, -27.80]
Moore 2006	13.3	6.8	47	41.6	21.1	58	47.5%	-28.30 [-34.07, -22.53]
Subtotal (95% CI)			**51**			**68**	**84.1%**	**-32.88 [-44.12, -21.65]**
Heterogeneity: Tau² = 45.18; Chi² = 2.89, df = 1 (P = 0.09); I² = 65%								
Test for overall effect: Z = 5.74 (P < 0.00001)								
21.3.2 Mandibular block (IANB)								
Moore 2006	49.7	44.2	16	51.2	55.9	34	15.9%	-1.50 [-30.17, 27.17]
Subtotal (95% CI)			**16**			**34**	**15.9%**	**-1.50 [-30.17, 27.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
Total (95% CI)			**67**			**102**	**100.0%**	**-28.36 [-42.06, -14.65]**
Heterogeneity: Tau² = 94.31; Chi² = 6.68, df = 2 (P = 0.04); I² = 70%								
Test for overall effect: Z = 4.06 (P < 0.0001)								
Test for subgroup differences: Chi² = 3.99, df = 1 (P = 0.05), I² = 74.9%								



22 - 4% prilocaine, 1:200,000 epinephrine vs 4% prilocaine plain

22.1 Duration of anaesthesia (simulated scenario testing of soft tissues)

Study or Subgroup	4% prilocaine, 1:200,000 epinephrine Mean	SD	Total	4% prilocaine plain Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
22.1.1 Maxillary infiltration								
Epstein 1969	124.7	43.2	81	101.7	55.12	62	34.4%	23.00 [6.36, 39.64]
Subtotal (95% CI)			**81**			**62**	**34.4%**	**23.00 [6.36, 39.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.71 (P = 0.007)								
22.1.2 Mandibular block (IANB)								
Chilton 1971	204.6	49.3	50	181.4	64.6	47	18.0%	23.20 [0.23, 46.17]
Epstein 1969	186.6	54.94	46	179.2	41.42	51	25.0%	7.40 [-12.13, 26.93]
Subtotal (95% CI)			**96**			**98**	**43.0%**	**14.03 [-0.85, 28.91]**
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.30); I² = 5%								
Test for overall effect: Z = 1.85 (P = 0.06)								
22.1.3 Both jaws combined/Jaw not stated								
Chilton 1971	141.3	69	89	119.9	67.1	80	22.6%	21.40 [0.86, 41.94]
Subtotal (95% CI)			**89**			**80**	**22.6%**	**21.40 [0.86, 41.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.04 (P = 0.04)								
Total (95% CI)			**266**			**240**	**100.0%**	**18.78 [9.02, 28.54]**
Heterogeneity: Chi² = 1.76, df = 3 (P = 0.62); I² = 0%								
Test for overall effect: Z = 3.77 (P = 0.0002)								
Test for subgroup differences: Chi² = 0.70, df = 2 (P = 0.70), I² = 0%								



23 - 4% articaine, 1:100,000 epinephrine vs 4% prilocaine, 1:200,000 epinephrine

23.1 Success of local anaesthesia, measured by the absence of pain during a procedure using a visual analogue scale (VAS) or other appropriate method (sim

Study or Subgroup	4% articaine, 1:100,000 epinephrine Events	Total	4% prilocaine, 1:200,000 epinephrine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
23.1.1 Mandibular infiltration						
Abdulwahab 2009	7	18	4	18	17.4%	1.75 [0.62, 4.95]
Nydegger 2014	33	60	19	60	82.6%	1.74 [1.12, 2.69]
Subtotal (95% CI)		**78**		**78**	**100.0%**	**1.74 [1.16, 2.60]**
Total events	40		23			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Total (95% CI)		**78**		**78**	**100.0%**	**1.74 [1.16, 2.60]**
Total events	40		23			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Test for subgroup differences: Not applicable