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Topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults (Review)

Minakaran N, Ezra DG, Allan BDS

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[Intervention Review]

Topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults

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ABSTRACT

Background

Phacoemulsification cataract surgery is usually performed in adults under local anaesthesia. Topical anaesthesia, which involves instilling anaesthetic drops to the ocular surface prior to and during surgery, has found large acceptance internationally. It is safe and allows for rapid patient turnover and visual recovery. Some surgeons have supplemented topical anaesthesia with intracameral lidocaine, reasoning that this may further reduce intraoperative pain, particularly during surgical stages involving manipulation of intraocular structures and rapid changes in fluid dynamics. This review, originally published in 2006 and updated in 2020, explores the efficacy and safety of using supplementary intracameral lidocaine in phacoemulsification cataract surgery.

Objectives

To assess whether supplementing topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults reduces intraoperative and postoperative pain, and to assess differences in participant satisfaction, need for additional intraoperative anaesthesia, surgeon satisfaction, measures of intraocular toxicity, and adverse effects attributable to choice of anaesthesia.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS BIREME iAH, and six trial registries on 4 February 2020. We also searched the reference lists of identified studies. There were no language restrictions.

Selection criteria

We included only randomized controlled trials (RCTs) where participants underwent phacoemulsification for age-related cataract under topical anaesthesia with or without intracameral lidocaine either in two eyes of the same participant, or in different participants. We also included studies that used oral or intravenous sedation in addition to local anaesthesia.

Data collection and analysis

Two review authors independently extracted data and assessed trial methodological quality using standard Cochrane procedures.

Main results

We identified five new RCTs in this updated review. We included a total of 13 trials in the review, conducted in the UK, the USA, Australia, Italy, Canada, Taiwan, Singapore, India, and Pakistan, and comprising 2388 eyes of 2355 participants (one study was a paired-eye study with each participant acting as their own control). The age range of participants was 34 to 95 years. We excluded studies that only included low-

risk participants and excluded more difficult operative cases, for example hard lens nuclei or small pupils. We excluded studies assessing only participants with Fuchs' endothelial dystrophy.

We judged one study as at high risk for selection bias. We assessed five studies as having an unclear risk of bias for random sequence generation and seven studies an unclear risk of bias for allocation concealment. We judged three studies as at high risk of performance bias, as the surgeon was not blinded, and two studies as at unclear risk of bias for this domain. No studies were judged as at high risk for detection bias, but five studies were judged to have an unclear risk of bias for this domain. We judged all 13 included studies to have a low risk of attrition bias and an unclear risk of reporting bias.

Data from eight RCTs favoured topical anaesthesia plus intracameral lidocaine 0.5% to 1% over topical anaesthesia alone for reducing intraoperative pain when measured using a 10-point visual analogue scale, analysed as a continuous outcome. Mean pain score was 0.26 lower in the supplemental intracameral lidocaine group (95% confidence interval (CI) −0.39 to −0.13, 1692 eyes, moderate-quality evidence). Data from seven RCTs favoured supplemental intracameral lidocaine for reducing intraoperative pain when measured as a dichotomous outcome. The odds ratio of experiencing any pain was 0.40 versus the topical anaesthesia-only group (95% CI 0.29 to 0.57, 1268 eyes, moderate-quality evidence). Data from four RCTs did not show any additional benefit on postoperative pain when measured using a 10-point visual analogue scale (mean difference 0.12 points, 95% CI −0.29 to 0.05, 751 eyes, moderate-quality evidence).

The impact on participant satisfaction was uncertain as only one small study investigated this outcome. The study suggested no difference between groups (mean difference 0.1 points, 95% CI −0.47 to 0.27, 60 eyes, low-quality evidence).

Data from seven RCTs did not demonstrate a difference between groups in the need for additional intraoperative anaesthesia (odds ratio 0.88, 95% CI 0.56 to 1.39, 1194 eyes of 1161 participants; low-quality evidence), although this result is uncertain.

A variety of measures were reported relating to possible intraocular toxicity. Data from four RCTs did not demonstrate a difference between groups in mean percentage corneal endothelial cell count change from pre- to postoperatively (mean difference 0.89%, 95% CI −1.12% to 2.9%, 254 eyes of 221 participants, moderate-quality evidence).

Synthesis of the evidence from eight RCTs identified no difference in intraoperative adverse events between groups (odds ratio 1.00, 95% CI 0.32 to 3.16, 1726 eyes, low-quality evidence). This result should be interpreted with caution, mainly due to a lack of clear definitions of adverse events, low numbers of events, heterogeneity between studies, and large confidence intervals. Large observational studies may have been more appropriate for looking at this outcome.

Authors' conclusions

There is moderate-quality evidence that supplementation of topical anaesthesia with intracameral lidocaine 0.5% to 1% for phacoemulsification cataract surgery in adults reduces participant perception of intraoperative pain. The odds of experiencing any pain (as opposed to no pain) were 60% less for the topical anaesthesia plus intracameral lidocaine group versus the topical anaesthesia-only group. However, the numerical amplitude of the effect may not be of great clinical significance on the continuous pain score scale. Generally, the pain scores were consistently low for both techniques. We found moderate-quality evidence that there is no additional benefit of intracameral lidocaine on postoperative pain. There is insufficient evidence to determine the impact on participant satisfaction and need for additional intraoperative anaesthesia due to low-quality evidence. There is moderate-quality evidence that intracameral lidocaine supplementation does not increase measures of intraocular toxicity, specifically loss of corneal endothelial cells. There is low-quality evidence that the incidence of intraoperative adverse events is unchanged with intracameral lidocaine supplementation, but as RCTs are not the optimum medium for looking at this, this result should be interpreted with caution.

Further research specifically investigating the adverse effects of intracameral anaesthesia might help to better determine its safety profile. Economic evaluations would also be useful for detailing cost implications.

PLAIN LANGUAGE SUMMARY

Local anaesthetics in cataract surgery: do eye drops work better with, or without, an injection of anaesthetic?

What are cataracts?

A cataract starts when cloudy patches develop on the lens of your eye. The lens is a small, clear disc inside the eye that focuses light rays to make clear images of objects seen. As the cloudy patches get bigger over time, sight becomes misty and blurred. Cataracts are more common in older people, and can affect your ability to do everyday activities, such as driving. Untreated cataracts will lead to blindness.

How are cataracts treated?

Surgery is the only way to improve your eyesight if you have cataracts. In cataract surgery (phacoemulsification), a tiny cut is made in your eye; the old, cloudy lens is removed and a new, plastic lens is put in its place.

During the operation you are usually awake. Doctors use eye drops containing a numbing medicine (local anaesthetic) to stop the nerves in your eye sending pain signals to your brain during the operation. Sometimes, in addition to anaesthetic eye drops, lidocaine (a type of local anaesthetic) may be injected inside your eye. This may reduce pain during and after the operation.

Why did we do this review?

In this Cochrane Review, we wanted to identify the potential benefits and harms of lidocaine injection into the eye in addition to anaesthetic eye drops during cataract surgery.

What did we do?

In February 2020, we searched for studies that looked at the effects of giving a lidocaine injection and anaesthetic eye drops, compared with giving anaesthetic eye drops alone, during cataract surgery. We looked for randomized controlled studies, a type of study in which treatments are given at random to people in the people in the study because these studies usually give the most reliable evidence about treatments.

Search date: we included evidence published up to 4 February 2020.

What we found

We found 13 studies in 2355 adults, aged 34 to 95 years, who had cataract surgery in one or both eyes. The studies were conducted in hospitals and eye day-care centres in the USA, Canada, Australia, the UK, Italy, Taiwan, Singapore, India, and Pakistan.

What are the results of the review?

Compared with giving anaesthetic eye drops alone, lidocaine injection with anaesthetic eye drops probably:

· reduced the level of pain experienced during the operation;

· reduced the number of people who said they felt any pain during their operation;

· did not reduce the level of pain people said they felt after the operation; and

· did not cause additional eye damage (measured before the operation and after 1 and 12 months).

Lidocaine injection with anaesthetic eye drops may make little or no difference to:

· how many people needed extra anaesthesia during their operation; and

· people's satisfaction with their cataract surgery (we are uncertain about this result because it is based on only one study).

The numbers of unwanted (adverse) effects associated with local anaesthetics were similar between people who had eye drops alone and those who had eye drops and a lidocaine injection. But we are uncertain about this result because the type of study we looked at may not have been the best to assess unwanted effects.

Our confidence in the results

We are moderately confident (certain) in most of our results. However, we only looked at a small number of studies, and in some studies the doctors were aware of which treatment they were giving, which could have affected the study's results. Our results may change if more research becomes available.

Conclusions

Lidocaine injection plus anaesthetic eye drops probably reduced the level of pain during a cataract operation more than using anaesthetic eye drops alone, and led to fewer people reporting pain during the operation. However, pain ratings for this operation were generally low both with and without a lidocaine injection, so this difference may not be clinically important.

Lidocaine injection plus anaesthetic eye drops did not reduce the level of pain people said they felt after their operation. Although lidocaine injection did not cause additional eye damage, we are uncertain whether its use causes more unwanted effects than eye drops alone.

SUMMARY OF FINDINGS

Summary of findings 1. Topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults

Topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults

Patient or population: adults undergoing phacoemulsification cataract surgery
Settings: hospitals and ophthalmic surgical day centres in the USA, the UK, Taiwan, Australia, Canada, Singapore, Italy, India, and Pakistan
Intervention: topical anaesthesia plus intracameral lidocaine
Comparison: topical anaesthesia alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of eyes (studies)	Quality of the evidence (GRADE)	Comments
	Risk with topical anaesthesia alone	Risk with topical anaesthesia plus intracameral lidocaine				
Intraoperative pain or discomfort (continuous data) Assessed with 0-to-10 analogue rating scales Assessed from time of surgery to 1 day postoperatively	Mean pain score ranged from 0.67 to 3 on a 0-to-10 scale.	Mean intraoperative pain in the intervention group was **0.26 lower** (0.39 lower to 0.13 lower).	-	1692 (8 RCTs)	⊕⊕⊕⊖ **moderate** [1]	It is uncertain whether 0.26 on a 0-to-10 scale is likely to be of great clinical significance.
Intraoperative pain or discomfort (dichotomous data) Assessed with a variety of rating scales; results transformed into 2 groups: 'no pain' and 'pain' Assessed from time of surgery to 1 day postoperatively	Study population 424 per 1000	227 per 1000 (176 to 296)	OR 0.40 (0.29 to 0.57)	1268 (7 RCTs)	⊕⊕⊕⊖ **moderate** [2]	Participants were 60% less likely to experience any pain (as opposed to no pain) in the topical anaesthesia plus intracameral lidocaine group compared to the topical anaesthesia-alone group.
Postoperative pain or discomfort Assessed with 0-to-10 analogue rating scales Assessed from immediately after surgery to 1 day postoperatively	Mean pain score ranged from 0.29 to 1.88 on a 0-to-10 scale.	Mean postoperative pain in the intervention group was **0.12 lower** (0.29 lower to 0.05 higher).	-	751 (4 RCTs)	⊕⊕⊕⊖ **moderate** [3]	
Participant satisfaction	Mean participant satisfaction was	Mean participant satisfaction in the inter-	-	60	⊕⊕⊖⊖ **low** [4]	

Assessed with 5-point Likert scale Assessed from immediately after surgery to 1 day postoperatively	4.6 on a 1-to-5 scale.	vention group was **0.1 higher** (0.47 lower to 0.27 higher).		(1 RCT)		
Need for additional anaesthesia during surgery Assessed dichotomously, as 'additional anaesthesia given' or 'additional anaesthesia not given'	Study population 73 per 1000	65 per 1000 (42 to 98)	OR 0.88 (0.56 to 1.39)	1194 (7 RCTs)	⊕⊕⊖⊖ **low** [5]	
Measures relating to possible intraocular toxicity Assessed by mean percentage change in corneal endothelial cell count from pre- to postoperatively in operated eye Assessed from 1 month to 1 year postoperatively	Mean percentage change in pre- to postoperative endothelial cell count ranged from 6.1% to 12.9%.	Mean percentage change in pre- to postoperative corneal endothelial cell count in the intervention group was **0.89% higher (worse)** (1.12 lower to 2.9 higher).	-	254 (4 RCTs)	⊕⊕⊕⊖ **moderate** [6]	No between-group difference was demonstrated. 2 studies suggested no difference in postoperative change in corneal pachymetry and anterior chamber inflammatory activity between groups, but no numeric data were analysed. 2 studies suggested no difference in postoperative generalized corneal oedema between groups, but no numeric data were analysed.
Intraoperative adverse surgical events attributable to choice of anaesthesia	Study population 7 per 1000	7 per 1000 (2 to 23)	OR 1.00 (0.32 to 3.16)	1726 (8 RCTs)	⊕⊕⊖⊖ **low** [7]	

*__The risk in the intervention group__ (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; **RCT:** randomized controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[1]Downgraded one level as surgeon was not blinded in two studies that accounted for 22.3% of the weighting.
[2]Downgraded one level as surgeon was not blinded, and adequate randomization and allocation concealment did not take place in one study that accounted for 4.3% of the weighting, and heterogeneity in the outcome-measuring method between studies (I^2 = 32%).
[3]Downgraded one level as surgeon was not blinded in one study, and for indirectness of evidence, whereby one study included a restricted population of myopic participants only.
[4]Downgraded two levels as based on only one RCT with a low number of participants, unclear risk of selection, detection, and reporting bias, and no validated outcome measure used.
[5]Downgraded two levels as surgeon was not blinded in two studies, for study heterogeneity with respect to criteria for and administration of supplemental anaesthesia, and for imprecision.
[6]Downgraded one level due to low number of eyes included and wide confidence interval.
[7]Downgraded two levels as surgeon was not blinded in two studies, for lack of clear definitions of adverse events and heterogeneity between studies, and for low numbers of events leading to non-estimable effect sizes and wide confidence intervals.

BACKGROUND

Description of the condition

A cataract is the natural lens of the eye losing its transparency and becoming opaque. This most commonly occurs due to the oxidative stress that occurs during the natural aging process (Vinson 2006). Other risk factors include genetics (Hammond 2001), diet (Agte 2010), drugs such as topical and systemic corticosteroids (Li 2008), metabolic disorders such as diabetes mellitus (Li 2014), smoking (Galor 2011), alcohol (Gong 2015), and ionizing radiation (Ainsbury 2009).

Cataracts typically cause blurred or reduced vision, but can also cause other symptoms such as glare, haloes, increased myopia and monocular diplopia (Liu 2017). Age-related cataracts are generally progressive (Petrash 2013), and without treatment can cause a restriction of daily activities and independent living. Poor vision is associated with reduced quality of life (Vos 2016), affecting both physical and cognitive function in the elderly (Hajek 2016). Globally, cataracts are one of the leading causes of visual impairment, causing moderate to severe visual impairment in 52.6 million people worldwide (Flaxman 2017). Cataracts affect more than 24.4 million Americans age 40 and older (National Eye Institute). In the UK, one-quarter of the population will have developed cataracts by age 75 years (RCOphth 2010).

The only treatment available for cataract at present is surgery (RCOphth 2010), where the cataract is removed and replaced with a synthetic intraocular lens (IOL). Various techniques exist, but in middle- and high-income countries, the most common method is phacoemulsification of the lens (Ashwin 2009), which accounts for 99.7% of cataract operations in the UK (Jaycock 2009). Cataract surgery is the most commonly performed elective procedure in the UK's National Health Service (NHS), with around 400,000 operations undertaken each year in England (RNIB 2016). In the USA, about 3.6 million cataract operations are performed each year (Lindstrom 2015).

Description of the intervention

There are a number of options for anaesthesia in cataract surgery. As for some other types of surgery (St George 2018; Tayeb 2017), local anaesthesia is standard, with general anaesthesia reserved for exceptional cases when local anaesthesia is deemed unsuitable (such as in children or those with behavioural issues).

Sharp needle techniques for delivering local anaesthesia include retrobulbar blocks, where anaesthetic agent is delivered into the muscular cone, and peribulbar blocks, where anaesthetic agent is delivered into the extraconal space. However, both techniques, in particular retrobulbar blocks, have been associated with vision and life-threatening complications such as globe perforation, retrobulbar haemorrhage, optic nerve trauma, brainstem anaesthesia, and extraocular muscle injury (Davis 1994; Wong 1993), and there has been no clear advantage demonstrated in terms of effectiveness of anaesthesia of one technique over the other (Alhassan 2008). Both techniques have now been mostly replaced by sub-Tenon's and topical anaesthesia.

Sub-Tenon's anaesthesia is a blunt needle technique whereby, after incision of the conjunctiva and Tenon's capsule, local anaesthetic, with or without hyaluronidase (Rüschen 2018), is delivered into the sub-Tenon's space using a blunt cannula. Topical anaesthesia became popular in the 1990s (Fichman 1992), and involves instilling anaesthetic eye drops into the fornix before, and onto the surface of the eye during, surgery. It is cost-effective and allows for rapid patient turnover, as well as rapid patient postoperative visual recovery. A recent Cochrane Review concluded that both techniques were accepted and safe methods of anaesthesia with no clear advantage of one over the other (Guay 2015).

Topical anaesthesia has become the most commonly used anaesthesia for cataract surgery (Malot 2011), and particularly so with those performing high-volume surgery. In the USA, the majority of surgeons using topical anaesthesia use it with intracameral lidocaine (Leaming 2004).

How the intervention might work

Patients undergoing topical anaesthesia often report discomfort at certain points in the surgery, usually during either direct iris manipulation or movement of the iris diaphragm, as a result of rapid hydrodynamic changes. Whilst topical anaesthesia provides for corneal anaesthesia, it is thought that intracameral anaesthesia may reduce any discomfort that may be caused by manipulation of intraocular structures. The rationale for using supplementary intracameral lidocaine is to provide anaesthesia for these intraocular structures. The anterior chamber (camera) of the eye is bounded by the cornea anteriorly, and the lens posteriorly. This is the working area for instrumentation during cataract surgery. Intracameral anaesthesia involves the intraoperative administration of anaesthetic agent into this chamber.

These anaesthetic modalities have been used alone as well as combined with oral or intravenous sedation.

Why it is important to do this review

Safe and effective local anaesthesia for cataract surgery is necessary for good surgical outcomes and patient satisfaction. Preventing pain during surgery by using local anaesthesia seems to lead to less long-term pain for patients (Weinstein 2018). There is a considerable amount of published data comparing topical anaesthesia alone to topical anaesthesia with intracameral anaesthesia for phacoemulsification. These data indicate conflicting outcomes. We conducted this systematic review to analyse the results of different trials; to collate information regarding the value of this additional intervention; and to help guide cataract surgeons and patients in their choice of anaesthesia. This is an update of a previous review (Ezra 2007). The original review demonstrated that supplementation of topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery did reduce participant intraoperative pain reception, although the difference was small. No difference was demonstrated between groups receiving topical anaesthesia alone and topical combined with intracameral anaesthesia in terms of the need for supplemental intraoperative anaesthesia and the occurrence of intraoperative adverse events or corneal toxicity. We undertook this updated review to look for new studies and to update the methods.

OBJECTIVES

To assess whether supplementing topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults reduces intraoperative and postoperative pain, and to assess differences in participant satisfaction, need for additional

intraoperative anaesthesia, surgeon satisfaction, measures of intraocular toxicity and adverse effects attributable to choice of anaesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) comparing topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone, either in two eyes of the same participant or in different participants. We also included studies that used oral or intravenous sedation in addition to local anaesthesia.

Types of participants

We included studies with adult participants only who underwent phacoemulsification for cataract under topical anaesthesia with, or without, intracameral lidocaine.

We excluded studies that only included low-risk participants and excluded more difficult operative cases, for example people with hard lens nuclei or small pupils. We also excluded studies assessing only participants with Fuchs' endothelial dystrophy.

Types of interventions

We included studies involving the administration of topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification. We did not place any restrictions on specific topical anaesthetic agent drugs, concentrations, or method of delivery. We did not place any restrictions on concentration of intracameral lidocaine.

Types of outcome measures

We evaluated primary and secondary outcomes as follows.

Primary outcomes

1. Intraoperative pain or discomfort.
2. Postoperative pain or discomfort.
3. Participant satisfaction with anaesthesia.

Our first primary outcome was the participant's subjective measure of intraoperative pain or discomfort, defined as at any time point between the surgeon's instruments first touching the eye and the surgeon's instruments last touching the eye. We assessed differences in scores on validated and novel pain scales, such as the 10-point visual analogue scales of Stevens 1992 and Scott 1976. We also assessed pain as a dichotomous outcome, namely the presence versus the absence of intraoperative pain. We accepted individual studies' definitions of pain and no pain, even though these definitions varied at times, for example using different thresholds on a continuous pain scale. Data collection could have taken place during surgery, immediately after surgery, or up to one day postoperatively.

Our second primary outcome was the participant's subjective measure of postoperative pain or discomfort, defined as at any time point between the surgeon's instruments last touching the eye and the first postoperative day. We assessed differences in scores on validated and novel pain scales, such as the 10-point visual analogue scales of Stevens 1992 and Scott 1976. Data collection could have taken place immediately after the surgery or up to one day postoperatively.

Our third primary outcome was measure of participant satisfaction with anaesthesia, assessed as differences in scores on any validated or novel satisfaction scale, such as a five-point Likert scale. Data collection could have taken place immediately after the operation or up to one day postoperatively.

Secondary outcomes

1. Need for additional anaesthesia during surgery.
2. Surgeon satisfaction with operative procedure.
3. Measures relating to possible intraocular toxicity.
4. Intraoperative adverse events (complications) attributable to choice of anaesthesia.

Need for additional anaesthesia during surgery was measured as a dichotomous outcome, namely additional anaesthesia given or not given.

Surgeon satisfaction with the operative procedure was assessed as differences in scores on any validated or novel satisfaction scale, such as a five-point Likert scale. Data collection could have taken place immediately after the operation or up to one day postoperatively.

Measures relating to possible intraocular toxicity included assessment of corneal toxicity and anterior chamber inflammatory activity. With respect to corneal toxicity, acceptable methods of measurement included subjective assessment of corneal oedema by a clinician, measured on any validated or novel scale, at any postoperative time point from one day to one month postoperatively; changes in corneal pachymetry (measured in micrometres) between preoperatively and one day to one month postoperatively; and changes in corneal endothelial cell count (measured in cell numbers or as a percentage using specular microscopy) between preoperatively and one month to one year postoperatively. When there is corneal toxicity, the endothelial cell count will reduce (i.e. change). With respect to anterior chamber inflammatory activity, acceptable methods of measurement included subjective assessment by a clinician of flare or anterior chamber inflammatory cells on any validated or novel scale.

Intraoperative adverse events considered were those that could potentially have a lasting effect on the final visual outcome, including posterior capsule rupture, supra-choroidal haemorrhage, iris prolapse, and vitreous loss.

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive strategies as outlined in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply any restrictions to language or publication status.

We searched the following databases for relevant trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL; searched 4 February 2020);
2. MEDLINE (OvidSP, 1980 to 4 February 2020);

3. Embase (OvidSP, 1980 to 4 February 2020);
4. LILACS BIREME iAH (1982 to 4 February 2020).

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies for the other databases listed. Where appropriate, the search strategy was expanded with search terms for identifying RCTs. All search strategies can be found in the Appendices (Appendix 1; Appendix 2; Appendix 3; Appendix 4).

We scanned the following trials registries for ongoing and unpublished trials on 4 February 2020:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov);
2. ISRCTN registry (isrctn.org);
3. University hospital Medical Information Network Clinical Trials Registry (Japan) (umin.ac.jp/ctr/index.htm);
4. Australian New Zealand Clinical Trials Registry (anzctr.org.au);
5. Netherlands Trial Register (trialregister.nl);
6. EU Clinical Trials Register (clinicaltrialsregister.eu).

The search strategy was developed in consultation with the Information Specialist. The original search was run in 2006 (Ezra 2007).

Searching other resources

We scanned the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials.

We did not manually search any conference abstracts for this review.

Data collection and analysis

Selection of studies

Two review authors (NM, DGE) independently reviewed the titles and abstracts resulting from the searches. We obtained and assessed full-text copies of possibly and definitely relevant trials according to the definitions in Criteria for considering studies for this review. We assessed only the trials meeting these criteria for methodological quality. We contacted the study corresponding authors for any clarification of details needed to permit a complete assessment of the relevance of the study. Any disagreements were resolved either by discussion or by consulting additional referees.

Data extraction and management

We collected data using prespecified data collection forms developed by Cochrane Anaesthesia (CARG). We compared data, resolving any disagreements by discussion. We entered data into Cochrane's software Review Manager 5 (Review Manager 2014). We contacted trial authors for information regarding any missing data.

Assessment of risk of bias in included studies

Two review authors (NM, DGE) independently assessed risk of bias in accordance with the tools and methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We considered the following domains:

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. masking of participants and personnel (performance bias);
4. masking of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective reporting (reporting bias); and
7. other sources of bias.

For each study, we documented relevant information on each domain in a 'Risk of bias' table, assigning a judgement for each domain as 'high risk', 'low risk', or 'unclear risk'. Any disagreements in 'Risk of bias' assessment were resolved either by discussion or by consulting additional referees. Review authors were not masked to any trial details during the assessment. We contacted study authors where a decision regarding the classification of a study was hampered by lack of information (see Characteristics of included studies).

Measures of treatment effect

We performed data synthesis in accordance with Cochrane methods and statistics guidelines. We summarized data from studies collecting comparable outcome measures with similar follow-up times. For dichotomous outcomes, we presented data as odds ratios (ORs) with 95% confidence intervals (CIs); when the outcomes were small in number, we employed a Peto odds ratio. For continuous outcomes, we presented the mean difference (MD) between treatment groups with 95% CIs.

Unit of analysis issues

For parallel trials, the unit of analysis was the individual participant for pain and participant satisfaction scores; the eye for adverse effects and events data and endothelial cell counts; and the surgeon for surgeon satisfaction scores. As there was just one paired-eye trial (where the two eyes of the same participant received different anaesthesia), with a relatively low number of participants, we opted to combine these data with the parallel trials in the same meta-analyses for pain scores. In order to investigate potential unit of analysis error in doing this, we performed sensitivity analyses by also excluding the paired-eye trial data from the meta-analyses.

Dealing with missing data

We contacted authors for missing data. When authors did not respond, we imputed missing data. Where the median was presented, we imputed the mean and standard deviation from the median, range, and sample size, using the method described by Hozo 2005. Where the mean was presented but no standard deviation, and we were unable to impute standard deviations from P values (e.g. as non-parametric tests had been used), we imputed the standard deviation by borrowing results from other studies in the meta-analysis (Furukawa 2006). We performed sensitivity analyses looking at the effect on the meta-analysis outcomes of excluding trials that utilized imputed data.

Assessment of heterogeneity

We considered clinical heterogeneity (variability in participants, interventions, and outcomes studied), methodological heterogeneity (variability in study design), and statistical heterogeneity (variability in the intervention effects being evaluated) by examining study characteristics and forest plots of the results. We used the I^2 statistic to quantify inconsistency across studies, and the Chi^2 test to assess statistical heterogeneity

for meta-analysis. We interpreted an I^2 value of 30% or more as moderate, and 50% or more as substantial, as this suggests that more than 50% of the variability in effect estimates was due to heterogeneity rather than sampling error (chance). We considered $P < 0.10$ to represent significant statistical heterogeneity for the Chi^2 test.

Assessment of reporting biases

In order to assess for possible selective outcome reporting, we searched for study protocols on the following trial registers, although many of the studies were performed prior to roll-out of these databases:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov);
2. ISRCTN registry (iscrtn.org);
3. University hospital Medical Information Network Clinical Trials Registry (Japan) (umin.ac.jp/ctr/index.htm);
4. Australian New Zealand Clinical Trials Registry (anzctr.org.au);
5. Netherlands Trial Register (trialregister.nl);
6. EU Clinical Trials Register (clinicaltrialsregister.eu).

We planned to create and examine funnel plots to explore possible small-study and publication biases if we were able to pool more than 10 studies. However, this was not the case in this review, therefore we did not create funnel plots.

Data synthesis

When at least two studies performed similar comparisons and reported the same outcome measures, with heterogeneity indicating that reporting the pooled effect was appropriate, we performed meta-analyses using Review Manager 5 (Review Manager 2014). We used a fixed-effect model for meta-analysis when we considered that heterogeneity was not important. If we found moderate or greater heterogeneity amongst studies, we used a random-effects model (Higgins 2011). This was the case for analysis of intraoperative pain measured as a dichotomous outcome, as the included studies used different methods and scales of measurement for the primary outcome and utilized different interpretations of pain versus no pain. We presented the 'Risk of bias' assessment on a 'Risk of bias' graph. We presented results for each comparison as forests plots when appropriate.

Subgroup analysis and investigation of heterogeneity

We planned a priori to perform subgroup analyses for measures of pain or discomfort, participant or surgeon satisfaction, and the need for additional anaesthesia based on whether or not participants in the trials received routine oral or intravenous sedation. It is likely that having sedation affects one's perception and recall of pain, therefore we felt that being sedated could potentially affect these outcomes. We performed these subgroup analyses to answer a specific question rather than to investigate heterogeneity.

We planned that if data exhibited substantial heterogeneity (I^2 greater than 50%), we would investigate possible causes, including:

1. topical anaesthetic drug used;
2. jelly versus drops for topical anaesthesia;
3. use of preoperative oral analgesia.

If the causes of the heterogeneity could not be addressed, we would not perform meta-analysis. We did not find substantial heterogeneity in this review, therefore no subgroup analyses were performed for the purpose of investigating heterogeneity.

Sensitivity analysis

We performed sensitivity analyses to determine the effect of including or excluding trials graded as inadequate on any parameter of quality, and of including or excluding trials with imputed data. We also performed sensitivity analyses of the effect of combining paired-eye with parallel trial data in meta-analyses where there were potential unit of analysis error issues.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the quality of the evidence, as per the GRADE handbook (Schünemann 2013), and created the Summary of findings 1 for the comparison of topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone, using GRADEpro GDT. The outcomes for the comparison included intraoperative pain (continuous data), intraoperative pain (dichotomous data), postoperative pain, participant satisfaction, need for additional anaesthesia during surgery, measures relating to possible intraocular toxicity, and intraoperative adverse surgical advents attributable to choice of anaesthesia. Two review authors (NM and DE) independently undertook the downgrading of evidence, reaching agreement by consensus. The GRADE approach assesses the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the certainty of a body of evidence involved considering the methodological quality of studies, the directness of the evidence, the heterogeneity of the data, the precision of the effect estimates and the risk of publication bias. Throughout this review, we refer to the quality of evidence, rather than certainty, when referring to GRADE assessments.

RESULTS

Description of studies

Results of the search

The original searches were undertaken in June 2006 (Ezra 2007), and yielded a total of 1558 studies matching the predefined search parameters. These were screened, and full-text copies of 17 studies were obtained for further assessment. Of these, eight studies were deemed suitable for inclusion (Boulton 2000; Carino 1998; Crandall 1999; Gillow 1999; Gills 1997; Martin 1998; Roberts 2002; Tseng 1998). No studies where different eyes were allocated different treatments were identified.

An updated electronic search in February 2020 identified a further 1010 studies. Of these, 13 new studies of potential interest were identified and their full-text copies obtained for further assessment. Of these 13 studies, five were deemed suitable for inclusion (Chuang 2007; Hussain 2017; Joshi 2013; Lofoco 2008; Tan 2011). One of these studies was a paired-eye study with different eyes of the same participant allocated different treatments (Chuang 2007).

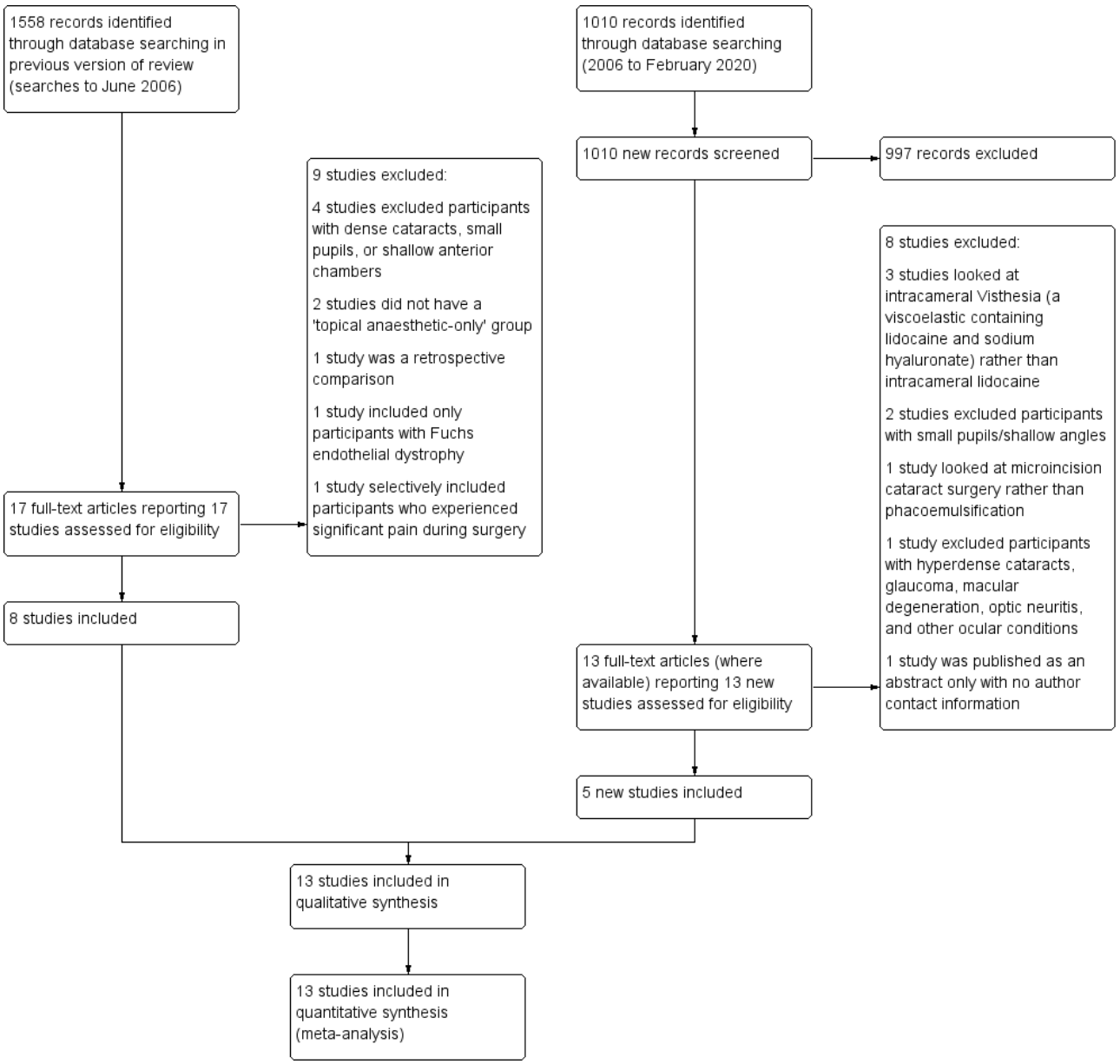
We included a total of 13 studies in this updated review.

Where we required clarification of study methodology or any further unpublished data, we contacted the study authors. We

contacted the authors of 10 of the included studies, and in this regard we acknowledge the responses of the authors of four studies (Gillow 1999; Gills 1997; Joshi 2013; Roberts 2002). We independently extracted trial details using prespecified data extraction sheets. The trials and data were clear, and there were no disagreements between the review authors with regard to data extraction, study inclusion, and quality assessment.

For the PRISMA study flow diagram, see Figure 1.

Figure 1. PRISMA flow diagram for updated review.



Included studies

For further details of the included studies, see Characteristics of included studies.

Types of participants

A total of 2388 eyes of 2355 participants were recruited in the included studies. Where specified, the age range of participants was between 34 and 95 years. The inclusion and exclusion criteria of the studies were mostly clear, with the exception of Martin 1998. All of the studies for which inclusion criteria were clearly stated considered all participants undergoing cataract surgery who were suitable for topical anaesthesia, except for Lofoco 2008, which included only participants with high myopia (axial length > 26 mm). The main exclusion criteria reflected barriers in communication such as hearing impairment, poor native language skills, dementia and confusion (Boulton 2000; Carino 1998; Hussain 2017; Joshi 2013; Tan 2011; Tseng 1998). Other exclusion criteria included ophthalmic risk factors such as nystagmus or involuntary eye movement, Boulton 2000; Chuang 2007; Hussain 2017; Joshi 2013; Tseng 1998, and previous intraocular surgery, Carino 1998, and participant-specific factors such as involuntary movement

disorders, Lofoco 2008; Tseng 1998, and American Society of Anesthesiologists (ASA) score above three (Crandall 1999). Some studies also excluded participants undergoing cataract surgery when combined with other procedures (Boulton 2000; Gills 1997).

Setting

All studies took place in hospital or ophthalmic day centre settings. Three studies were conducted in the USA (Crandall 1999; Gills 1997; Martin 1998), two in the UK (Boulton 2000; Gillow 1999), two in Taiwan (Chuang 2007; Tseng 1998), and one each in Canada (Carino 1998), Pakistan (Hussain 2017), India (Joshi 2013), Italy (Lofoco 2008), Australia (Roberts 2002), and Singapore (Tan 2011).

Types of interventions

Six different types of topical anaesthesia were employed. Tetracaine (amethocaine) 0.5% to 1% drops were used in five trials (Boulton 2000; Carino 1998; Gillow 1999; Roberts 2002; Tseng 1998), bupivacaine 0.75% drops in one trial (Crandall 1999), lidocaine 2% drops in one trial (Chuang 2007), lidocaine gel in two trials (2% concentration in Lofoco 2008; unspecified concentration in Tan 2011), proparacaine 0.5% drops in one trial (Joshi 2013), and combinations of anaesthesia in two trials (proparacaine 0.5% and lidocaine 4% in Martin 1998, and proparacaine 0.5% and bupivacaine 0.75% in Gills 1997). Hussain 2017 did not specify the agent used for topical anaesthesia.

The application regimen was also variously described. Boulton 2000 described four sets of two drops preoperatively. Carino 1998 described two drops 15 minutes preoperatively, and then another two drops immediately prior to surgery. Crandall 1999 described three sets of two drops every five minutes beginning 15 minutes prior to surgery. Chuang 2007 described four sets of drops at the start of surgery. Gillow 1999 described one drop every five minutes until the stinging sensation stopped. Gills 1997 described the use of two drops of proparacaine and bupivacaine four times preoperatively: the details of the timing were unclear. Joshi 2013 described just a single drop given two minutes preoperatively. Lofoco 2008 described instilling lidocaine gel 20 minutes and 5 minutes preoperatively. Martin 1998 described one drop of proparacaine 10 minutes before surgery followed by two drops of lidocaine immediately preoperatively. Roberts 2002 described the application of drops one hour prior to surgery then three drops immediately before the participant arrived at the operating theatre followed by one drop immediately prior to the application of topical povidone-iodine (Betadine). Tan 2011 described instilling lidocaine gel five minutes before the procedure. Tseng 1998 described the application of three sets of two drops in the 10 minutes prior to surgery, two drops prior to phacoemulsification, and two drops prior to intraocular lens insertion. Of note, all participants in this study also received oral analgesia in the form of 1 g paracetamol one hour prior to the surgery. Hussain 2017 did not describe when or how the topical anaesthesia was instilled.

In contrast, the choice of intracameral anaesthesia was fairly consistent. Ten of the 13 trials employed the use of 1% preservative-free lidocaine as the intracameral anaesthetic agent. Chuang 2007 and Joshi 2013 used 0.5% preservative-free lidocaine, and Hussain 2017 did not specify the concentration of lidocaine. However, the point of administration of the intracameral anaesthesia varied between trials. Four studies administered the intracameral anaesthetic immediately after the corneal section (Boulton 2000; Carino 1998; Crandall 1999; Tan 2011), and one study after the side port was created (Chuang 2007). Martin 1998 and Roberts 2002 introduced the intracameral anaesthesia prior to capsulorhexis, whereas Gillow 1999 and Tseng 1998 applied it immediately after capsulorhexis, and Lofoco 2008 at the time of hydrodissection. Gills 1997 applied the intracameral anaesthesia one minute before the phacoemulsification. Hussain 2017 and Joshi 2013 did not specify at which stage of surgery the intracameral lidocaine was given.

Six studies did not routinely use any oral or intravenous (iv) sedation, nor did they offer it at any point during the surgery (Boulton 2000; Chuang 2007; Gillow 1999; Hussain 2017; Joshi 2013; Martin 1998). Four studies gave sedation only if required, for example for preoperative anxiety or breakthrough pain during the procedure (Carino 1998: iv 0.5 mg midazolam and 250 µg alfentanil hydrochloride if more than mild pain experienced intraoperatively; Crandall 1999: iv fentanyl (0.5 µg/kg) given for breakthrough pain and repeated in three minutes if necessary; Gills 1997: iv midazolam given for preoperative anxiety, and during surgery for breakthrough pain; Tan 2011: if required according to hospital anaesthesia protocols). Three studies used sedation routinely for all cases (Lofoco 2008: iv diazepam (0.05 mg/kg); Tseng 1998: 0.5 mg oral fludiazepam; Roberts 2002: iv midazolam 1 to 2 mg five minutes before surgery).

Types of outcomes

Primary outcomes

1. Intraoperative pain or discomfort

All included studies employed an instrument to subjectively measure participant pain or discomfort levels. Several pain scales were used. A 10-point visual analogue scale validated by Stevens 1992 was employed by seven authors (Boulton 2000; Chuang 2007; Crandall 1999; Joshi 2013; Roberts 2002; Tan 2011; Tseng 1998). Gillow 1999 used an alternative 10-point scale described by Scott 1976. Hussain 2017 used a 10-point visual analogue scale but did not specify if this was a validated scale or a novel one. Two studies employed two different novel 4-point scales (Carino 1998; Martin 1998), and Gills 1997 used a novel 5-point scale. Lofoco 2008 noted any sensation of pain or ocular discomfort spontaneously reported by participants. Pain scores were recorded at a variety of different points in the procedure. Carino 1998 recorded preoperative scores. Eleven studies recorded intraoperative pain scores (Boulton 2000; Carino 1998; Chuang 2007; Crandall 1999; Gillow 1999. Hussain 2017; Joshi 2013; Martin 1998; Roberts 2002; Tan 2011; Tseng 1998). Gills 1997 recorded intraoperative pain twice, and Lofoco 2008 three times, at different points of the procedure.

2. Postoperative pain or discomfort

Five studies recorded postoperative pain. Four authors used the Stevens 1992 10-point visual analogue scale (Crandall 1999; Gillow 1999; Joshi 2013; Lofoco 2008), whilst Carino 1998 used a novel 4-point scale.

3. Participant satisfaction with anaesthesia

General participant satisfaction was recorded by Carino 1998 using a 5-point scale.

Secondary outcomes

1. Need for additional anaesthesia during surgery

Nine studies reported the need for supplemental anaesthesia (Boulton 2000; Carino 1998; Chuang 2007; Crandall 1999; Gillow

1999; Gills 1997; Joshi 2013; Lofoco 2008; Roberts 2002). The types of additional anaesthesia varied, and included peribulbar, sub-Tenon's, extra topical anaesthetic, and intravenous sedation. With the exception of two studies (Carino 1998; Gills 1997), we noted a lack of defined criteria for giving additional anaesthesia. Carino 1998 administered supplemental anaesthesia if a pain score of greater than one was recorded, and Gills 1997 described giving supplemental anaesthesia if the participant specifically requested it by means of a predefined hand signal.

2. Surgeon satisfaction with operative procedure

Surgeon satisfaction was recorded by Carino 1998 using a 5-point scale.

3. Measures relating to possible intraocular toxicity

The potential toxic effects of preservative-free intracameral anaesthesia were investigated using a variety of outcome measures. Pre- and postoperative endothelial cell counts were measured by five studies (Carino 1998; Chuang 2007; Crandall 1999; Gills 1997; Martin 1998). Postoperative corneal oedema was assessed by Crandall 1999 and Chuang 2007. Pre- and postoperative corneal pachymetry were recorded by two studies (Gills 1997; Martin 1998). Postoperative anterior chamber activity (cells/flare) was assessed by two studies (Gills 1997; Martin 1998).

4. Intraoperative adverse events (complications) attributable to choice of anaesthesia

Nine studies reported intraoperative complications (Boulton 2000; Chuang 2007; Crandall 1999; Gills 1997; Joshi 2013; Lofoco 2008; Martin 1998; Roberts 2002; Tan 2011).

Excluded studies

We excluded 17 studies (Garcia 1998; Goodarzi 2011; Koch 1997; Labetoulle 2016; Lopez Valladares 2007; Malecaze 2000; Masket 1998; Moschos 2011; Nebbioso 2018; Pandey 2001; Papaconstantinou 2014; Perone 2007; Roux 1998; Shah 2004; Tan 2000; Wang 2013; Weller 2002). Six studies excluded participants due to higher surgical complexity, such as small pupils, dense cataract, or shallow anterior chamber (Labetoulle 2016; Nebbioso 2018; Pandey 2001; Roux 1998; Shah 2004; Tan 2000), and one study only included participants with Fuchs' endothelial dystrophy (Weller 2002). One study looked at participants undergoing microincision cataract surgery (MICS) rather than phacoemulsification (Wang 2013). Two studies did not have a topical anaesthetic control group (Garcia 1998; Koch 1997). Four studies used Visthesia, an ophthalmic viscosurgical device (OVD) containing lidocaine rather than intracameral lidocaine (Lopez Valladares 2007; Moschos 2011; Papaconstantinou 2014; Perone 2007). One study selected participants into the trial dependent on their experience of significant pain during surgery (Malecaze 2000), and one study was a retrospective comparison only (Masket 1998). One study was published as an abstract in conference proceedings only, with no extractable data and no author contact details (Goodarzi 2011).

For details see Characteristics of excluded studies.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

The 'Risk of bias' assessments of the included studies are detailed in the 'Risk of bias' tables (Characteristics of included studies), the 'Risk of bias' graph (Figure 2), and summarized in the methodological quality summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

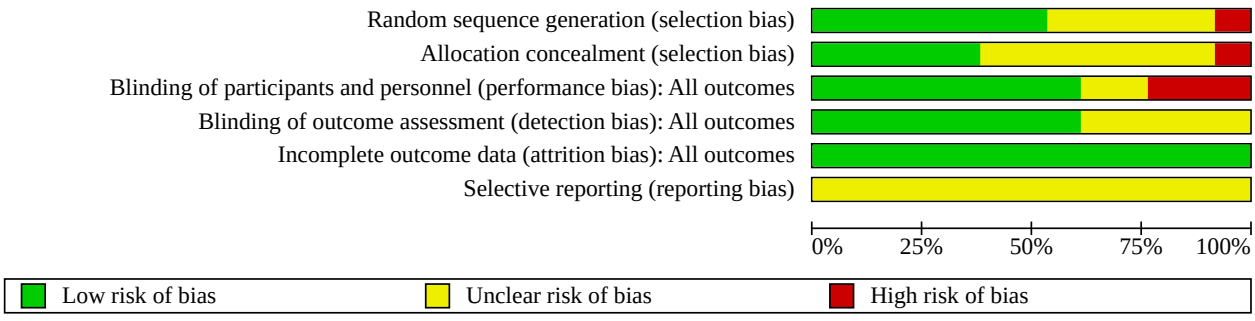
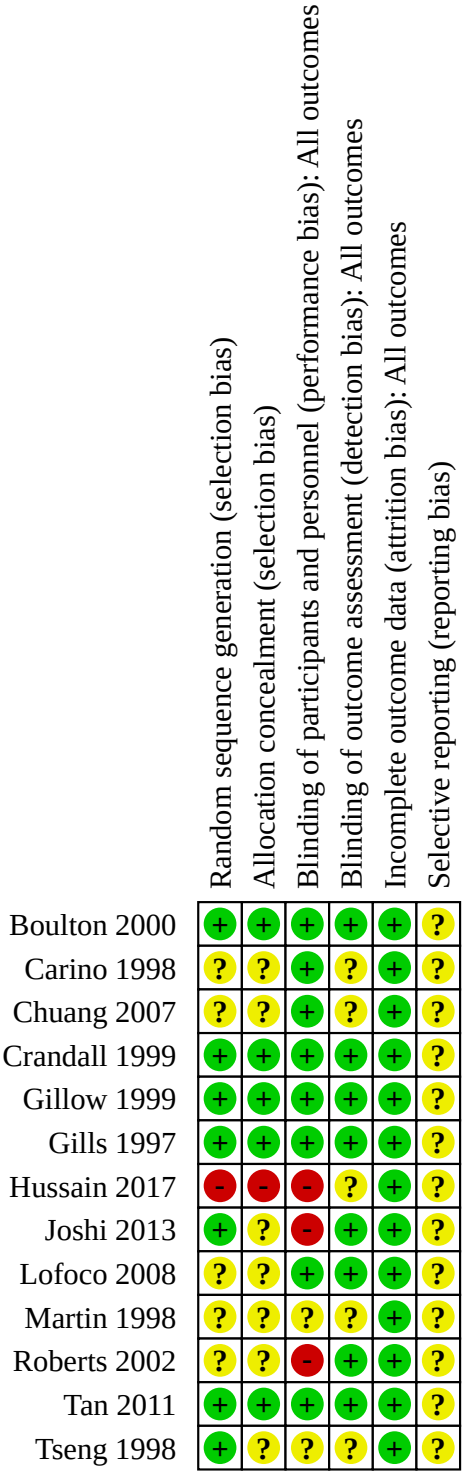


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged there to be low risk of bias for random sequence generation in seven studies (Boulton 2000; Crandall 1999; Gillow 1999; Gills 1997; Joshi 2013; Tan 2011; Tseng 1998). We judged there to be unclear risk in five studies (Carino 1998; Chuang 2007; Lofoco 2008; Martin 1998; Roberts 2002), as the investigators did not explicitly report the process of random sequence generation, and were unable to provide further sufficient information on request. We judged there to be high risk of bias for this domain for one study (Hussain 2017), where the paper discussed dividing the participants into "two equal groups" using the "lottery method". We concluded that by explicitly dividing participants into two equal groups this could not be considered true randomization, and the author was unable to provide further details.

We judged there to be low risk of bias for allocation concealment in five studies (Boulton 2000; Crandall 1999; Gillow 1999; Gills 1997; Tan 2011), and unclear risk of bias in seven studies (Carino 1998; Chuang 2007; Joshi 2013; Lofoco 2008; Martin 1998; Roberts 2002; Tseng 1998). Again, we judged there to be high risk in Hussain 2017 for the same reason as given above.

Blinding

We judged eight studies to be at low risk with respect to performance bias (Boulton 2000; Carino 1998; Chuang 2007; Crandall 1999; Gillow 1999; Gills 1997; Lofoco 2008; Tan 2011). Two studies were at unclear risk of bias for this domain (Martin 1998; Tseng 1998). When we contacted the authors of Joshi 2013, they stated that the surgeon and participants were blinded; however, in the paper there was no mention of any placebo intracameral agent being used, therefore the blinding of the surgeon is questionable. For this reason we assessed this study as at high risk of performance bias. We judged two other studies to have a high risk of performance bias (Hussain 2017; Roberts 2002). In Hussain 2017 no placebo intracameral drug was administered, so the surgeon could not have been blinded to the group allocation of the participant. Roberts 2002 stated that the surgeon was not blinded. Given that when operating under topical anaesthesia, the surgeon's manual handling of the eye, and the manner in which the surgeon talks to the participant during the procedure, affects the participant's perception of pain, both physically and psychologically respectively, we felt that surgeon blinding (in addition to participant blinding) was an important contributor to performance bias.

We judged eight studies to be at low risk of detection bias (Boulton 2000; Crandall 1999; Gillow 1999; Gills 1997; Joshi 2013; Lofoco 2008; Roberts 2002; Tan 2011), and the other five studies at unclear risk (Carino 1998; Chuang 2007; Hussain 2017; Martin 1998; Tan 2011).

Incomplete outcome data

All included studies had a very similar rate of loss to follow-up, that is either very small loss to follow-up rates or no loss at all; we therefore assessed all 13 studies to be at low risk of attrition bias.

Selective reporting

We were unable to review prespecified primary and secondary outcomes for any of the trials, as none appeared in the trials registries searched, and no prospective study protocols were available. Whilst all studies presented results for the outcomes described in the methods section of the papers, we judged all 13 included studies to be at unclear risk of selective reporting due to the lack of study protocols.

Other potential sources of bias

Chuang 2007 was a paired-eye study, the design of which could include potential carry-over effects and selective reporting issues.

Of additional note is the disparate numbers between the randomized groups in Gills 1997, where 183 participants were assigned to the topical anaesthesia plus intracameral lidocaine group, and 120 assigned to the topical anaesthesia-only group; and in Tan 2011, where these numbers were 277 and 229, respectively. Although both trials described an appropriate randomization technique, there was no information in either publication to explain this. We contacted the authors, but they were unable to offer any further information.

Effects of interventions

See: **Summary of findings 1** Topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults

See Summary of findings 1.

Primary outcomes

1. Intraoperative pain or discomfort

All 13 trials included in this review, comprising 2388 eyes of 2355 participants, reported on intraoperative pain or discomfort. Where trials measured pain at several points during surgery, we took the greatest pain score for the analysis.

1. Continuous data

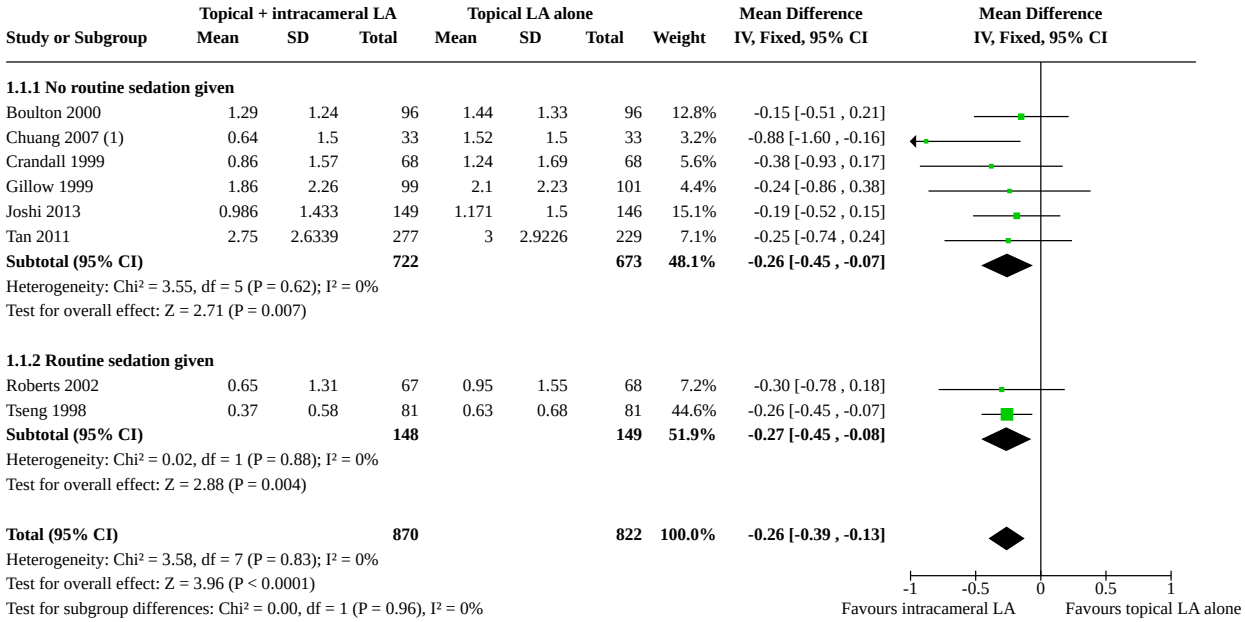
Nine studies employed a 10-point visual analogue pain scale (Boulton 2000; Chuang 2007; Crandall 1999; Gillow 1999; Hussain 2017; Joshi 2013; Roberts 2002; Tan 2011; Tseng 1998). Although the resultant data were derived from a 10-point ordinal scale, we planned to analyse these as continuous data, as outlined in the guidelines for long ordinal scales in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

However, it was not possible to combine the results of all nine studies in one analysis. Hussain 2017 did not present mean or median pain scores, only numbers perceiving "no pain" (score 0 to 3) or "some pain" (score 3+), so we excluded this study from this analysis, and instead included it in the dichotomous analysis described later. Chuang 2007 presented the mean pain score for each group and range, but did not give the standard deviation, and this could not be directly imputed from the data provided (Mann-Whitney test used for P value). Instead, we imputed the standard deviation by borrowing standard deviation data from similar-sized studies in the meta-analysis. This was included in the main meta-analysis, but the effect of excluding these data was explored in a sensitivity analysis. The study did also present numbers of participants experiencing "none to mild pain" (score 0 to 1) or "pain" (scores 1+), and we used these data in the dichotomous analysis described later. Tan 2011 did not present mean pain scores, only median scores and range. We imputed the mean and standard deviation using the method described by Hozo 2005, and included this in the main meta-analysis, but the effect of excluding these data was also explored in a sensitivity analysis.

The study also presented numbers that perceived "no pain" (score 0 to 1) or "pain" (scores 1+), and so we used these data in the dichotomous analysis described later.

Data from the eight studies (62% of total studies) for which the mean and standard deviation was available or imputed (Boulton 2000; Chuang 2007; Crandall 1999; Gillow 1999; Joshi 2013; Roberts 2002; Tan 2011; Tseng 1998), comprising 1692 eyes of 1659 participants (71% of total eyes), demonstrated that there was benefit resulting from the use of intracameral preservative-free lidocaine in addition to topical anaesthesia (P < 0.001). The mean difference in pain score was 0.26 points lower in the intracameral lidocaine group (95% confidence interval (CI) −0.39 to −0.13). We detected no heterogeneity between the results of these studies (I^2 = 0%) (see Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, outcome: 1.1 Intraoperative pain or discomfort (continuous 10-point scale).



Footnotes
(1) Study was in paired eyes

When we split the studies into subgroups receiving no routine sedation, Boulton 2000; Chuang 2007; Crandall 1999; Gillow 1999; Joshi 2013; Tan 2011, and those receiving routine sedation, Roberts 2002; Tseng 1998, there was still benefit from using intracameral lidocaine in both groups (pain score 0.26 points lower, P = 0.007; and pain score 0.30 points lower, P = 0.004, respectively).

We performed a number of sensitivity analyses. We excluded the two trials with imputed data (Chuang 2007; Tan 2011). This did not change the overall result; there was still benefit from using intracameral lidocaine (pain score 0.24 points lower, P < 0.001). We excluded the data from the paired-eye trial that had been combined with the parallel trial data (Chuang 2007). This also did not change the overall result (pain score 0.24 points lower, P < 0.001). We excluded the trial that was rated as having a high risk of bias in any one domain (Roberts 2002), and this also did not change the overall result (pain score 0.26 points lower, P < 0.001).

Using the GRADE approach, we found the quality of the evidence to be moderate. We downgraded by one level, as in two of the studies, which contributed 22.3% of the total weight in the meta-analysis (Joshi 2013; Roberts 2002), the surgeon was not blinded, putting these studies at high risk of performance bias. We did not downgrade any further as the other studies in the analysis were mainly at low risk of bias, and of note the two studies contributing 57.4% of the total weight were at low risk for all categories of bias other than reporting bias (Boulton 2000; Tseng 1998). Furthermore, all studies gave results in the same direction (in favour of topical anaesthesia plus intracameral lidocaine).

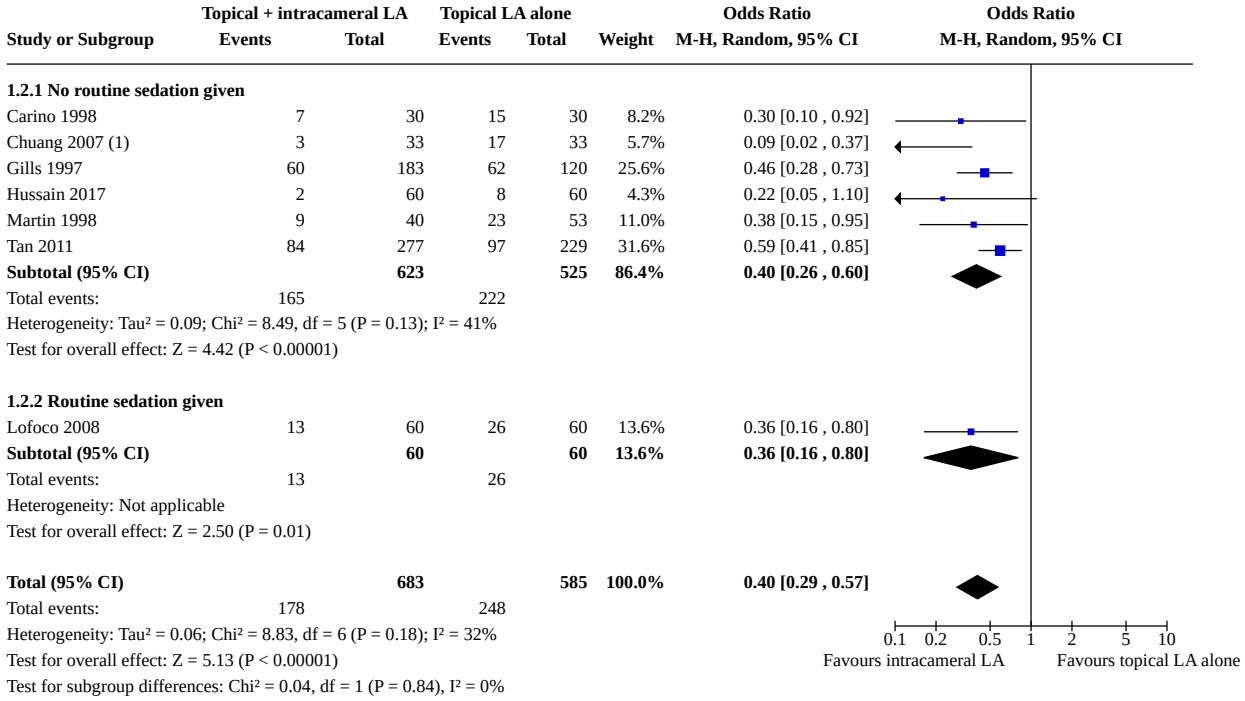
2. Dichotomous data

Three studies used smaller ordinal scales to record subjective pain experienced by participants (Carino 1998; Gills 1997; Martin 1998). The vast majority of these participants scored zero, that is to say they did not experience any pain at all. We have therefore transformed these data into dichotomous data for the purposes of our review, and divided into groups scoring zero (no pain at all) or greater than zero (pain experienced). In addition, three studies using 10-point visual analogue scales also presented their data as numbers experiencing no pain or some pain (Chuang 2007; Hussain 2017; Tan 2011). One study presented numbers of participants spontaneously reporting pain during the surgery (Lofoco 2008).

We combined the data from these seven studies (54% of total studies), comprising 1268 eyes of 1235 participants (53% of total eyes), and demonstrated benefit in favour of the use of

preservative-free intracameral lidocaine (P < 0.001). The odds ratio of experiencing pain in the topical anaesthesia with intracameral lidocaine group was 0.40 versus the topical anaesthesia-only group (95% CI 0.29 to 0.57). There was moderate heterogeneity between the results of these studies (I^2 = 32%) (see Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, outcome: 1.2 Intraoperative pain or discomfort (dichotomous).



Footnotes
(1) Study was in paired eyes

When we split the studies into subgroups receiving no routine sedation (Carino 1998; Chuang 2007; Gills 1997; Hussain 2017; Martin 1998; Tan 2011), and those receiving routine sedation (Lofoco 2008), there was still benefit from using intracameral lidocaine in both groups (odds ratio 0.40, P < 0.001; and odds ratio 0.36, P = 0.01, respectively).

When we excluded the data from the paired-eye trial that had been combined with the parallel trial data in a sensitivity analysis (Chuang 2007), this did not change the overall results (odds ratio 0.48, P < 0.001). Excluding this trial did reduce the heterogeneity between the results of the studies to I^2 = 0%. We excluded the trial that was judged as having a high risk of bias in any domain (Hussain 2017), and this also did not change the result (odds ratio 0.41, P < 0.001).

Using the GRADE approach, we found the quality of the evidence to be moderate. We downgraded by one level due to one of the studies having a high risk of performance and selection bias, as the surgeon was not blinded, and adequate randomization and allocation concealment did not take place (Hussain 2017), as well as the heterogeneity between the studies. We did not downgrade further, as the one study that was deemed at high risk of selection and performance bias contributed only 4.3% to the total weight of the meta-analysis result. Furthermore, the heterogeneity was potentially accounted for by the inclusion of the paired-eye trial, Chuang 2007, with the other parallel studies, as excluding this study from the meta-analysis reduced the heterogeneity yet maintained the same result. Also, all studies gave results in the same direction (in favour of topical anaesthesia plus intracameral lidocaine).

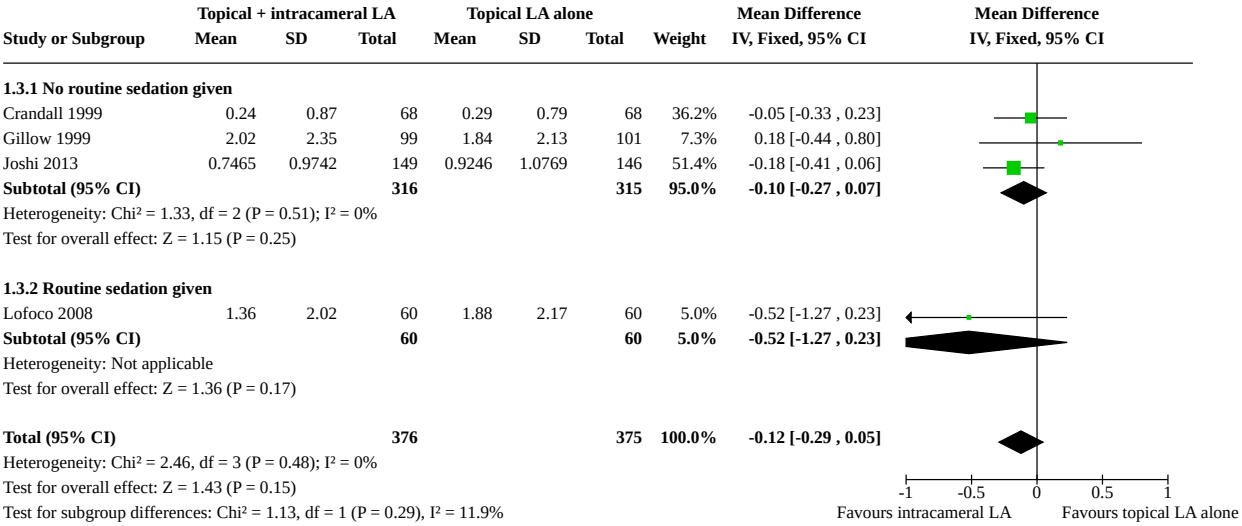
2. Postoperative pain or discomfort

Five studies, comprising 811 eyes of 811 participants, measured postoperative pain (Carino 1998; Crandall 1999; Gillow 1999; Joshi 2013; Lofoco 2008).

Carino 1998 used a novel 4-point scale, however the other four studies used a 10-point scale and were compatible for meta-analysis (Crandall 1999; Gillow 1999; Joshi 2013; Lofoco 2008).

The data derived from these four trials (31% of total studies), comprising 751 eyes of 751 participants (31% of total eyes), did not show any benefit of intracameral lidocaine in addition to topical anaesthesia on postoperative pain (mean difference in pain score was 0.12 points lower in the intracameral lidocaine group; 95% CI −0.29 to 0.05; P = 0.15) (see Analysis 1.3; Figure 6). There was no heterogeneity between the results of the studies (I^2 = 0%).

Figure 6. Forest plot of comparison: 1 Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, outcome: 1.3 Postoperative pain or discomfort (10-point scale).



This result was the same for both the subgroup that did not receive routine sedation (P = 0.25) (Crandall 1999; Gillow 1999; Joshi 2013), and the subgroup with routine sedation (P = 0.17) (Lofoco 2008).

Using the GRADE approach, we found the quality of the evidence to be moderate. We downgraded by one level due to one of the studies, contributing 51.4% of the weight in the meta-analysis, having a high risk of performance bias as the surgeon was not blinded (Joshi 2013), and due to indirectness of evidence, whereby one trial met the eligibility criteria for inclusion but involved a restricted population of myopic participants only with axial length greater than 26 mm (Lofoco 2008).

3. Participant satisfaction with anaesthesia

Only one trial (8% of total studies), comprising 60 eyes of 60 participants (3% of total eyes), recorded participant satisfaction independently (Carino 1998). A 5-point scale was employed, and no difference in participant satisfaction was found between the topical anaesthesia plus intracameral lidocaine (mean satisfaction score 4.7) and topical anaesthesia-only (mean satisfaction score 4.6) groups (mean difference 0.1 points, 95% CI −0.47 to 0.27; P = 0.18).

Using the GRADE approach, we found the quality of the evidence to be low. We downgraded by two levels as there was just one RCT, which had an unclear risk of selection bias, detection bias, and reporting bias; included only a small number of participants; and used an unvalidated outcome measure.

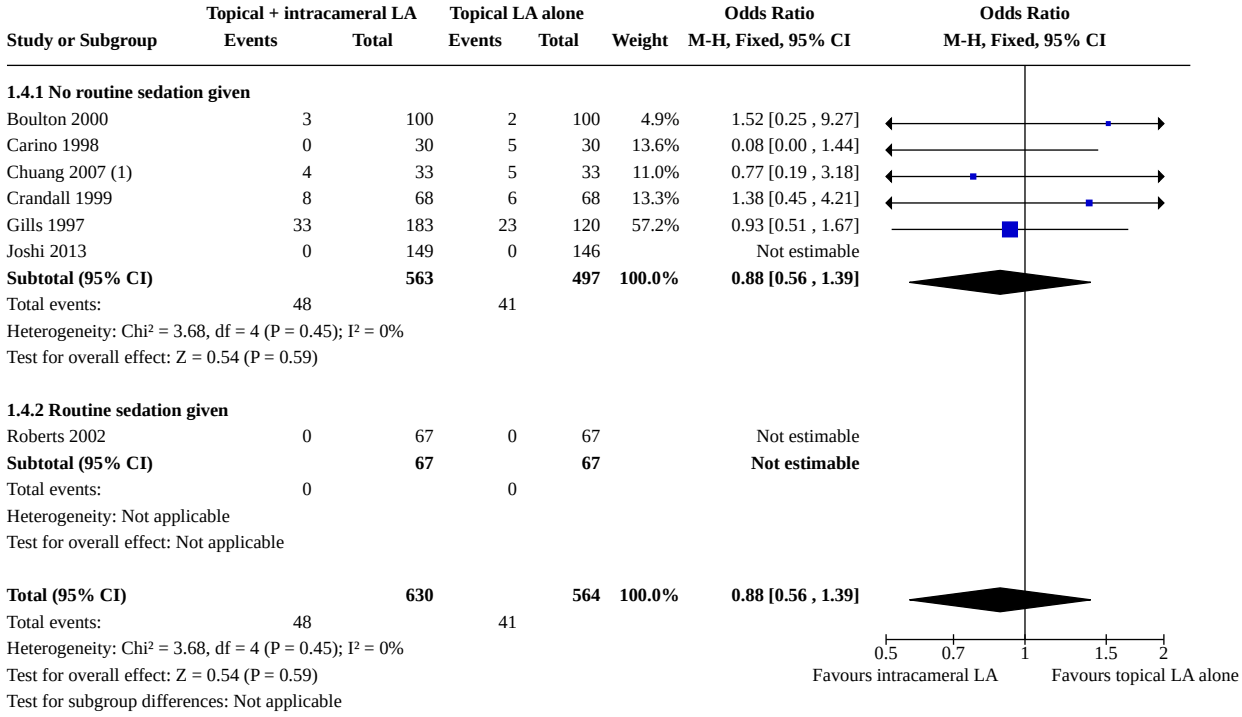
Secondary outcomes

1. Need for additional anaesthesia during surgery

Seven trials, comprising 1194 eyes of 1161 participants, recorded any participants receiving supplemental anaesthesia (Boulton 2000; Carino 1998; Chuang 2007; Crandall 1999; Gills 1997; Joshi 2013; Roberts 2002). Gillow 1999, whilst recording extra intraoperative anaesthesia, did not define the numbers requiring anaesthetic supplementation in each group. Lofoco 2008 commented that there was no difference between the two groups in terms of need for additional anaesthesia, but did not provide any data to support this. We did not include these two trials in the meta-analysis. Additional anaesthesia was defined as: extra topical drops; subconjunctival, sub-Tenon's, or peribulbar injections; or additional intravenous sedation.

Our analysis of the data from these 7 trials (54% of total studies), comprising 1194 eyes of 1161 participants (50% of total eyes), showed no difference between the topical anaesthesia plus intracameral lidocaine and topical anaesthesia-only groups in the need for supplementary anaesthesia (odds ratio 0.88, 95% CI 0.56 to 1.39; P = 0.59) (see Analysis 1.4; Figure 7). Although there was no heterogeneity between the results of the studies (I^2 = 0%), we note that due to the undefined and heterogeneous criteria for the administration of supplemental anaesthesia, this result should be interpreted with caution.

Figure 7. Forest plot of comparison: 1 Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, outcome: 1.4 Need for additional anaesthesia during surgery.



Footnotes
(1) Study was in paired eyes

We excluded the paired-eye trial that had been combined with the parallel group studies in a sensitivity analysis (Chuang 2007), and this did not change the overall result (P = 0.66). We excluded the trial that was judged as having a high risk of bias in any one domain (Roberts 2002), and this also did not change the overall result (P = 0.59).

Using the GRADE approach, we found the quality of the evidence to be low. We downgraded by two levels as two trials had a high risk of performance bias due to the surgeon not being blinded (Joshi 2013; Roberts 2002); the trials as a group had undefined and heterogeneous criteria for the administration of supplemental anaesthesia as mentioned previously; and for imprecision as there was wide variance of point estimates across studies.

2. Surgeon satisfaction with operative procedure

Only one trial (8% of total studies), comprising 60 eyes of 60 participants (3% of total eyes), recorded surgeon satisfaction (Carino 1998). A 5-point scale was employed, and the authors recorded a higher level of surgeon satisfaction in the topical anaesthesia plus intracameral lidocaine group (mean difference in surgeon satisfaction score was 0.83 points higher in topical anaesthesia plus intracameral lidocaine group, 95% CI 0.3 to 1.36; P = 0.0007).

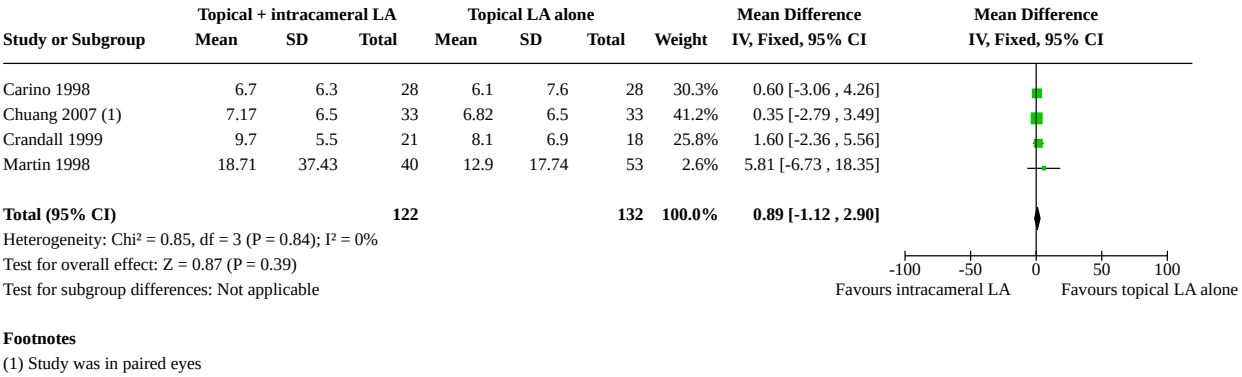
3. Measures relating to possible intraocular toxicity

Changes in corneal endothelial cell count postoperatively

Carino 1998 measured pre- and postoperative corneal endothelial cell counts at one month, presenting mean endothelial cell change as a percentage with standard deviation. Crandall 1999 measured endothelial cell counts pre- and postoperatively at three months in a subset of participants, presenting mean endothelial cell change as a percentage with standard deviation. Martin 1998 recorded endothelial cell counts preoperatively and at 69 days postoperatively at the earliest, presenting mean endothelial cell change in numbers with standard deviation; for this analysis, these were converted into percentage change from preoperative mean cell counts. Chuang 2007 measured pre- and postoperative endothelial cells counts (time frame not specified); the authors presented mean endothelial cell change as a percentage but did not give the standard deviation or the actual P value for comparison between groups. For meta-analysis, the standard deviation was imputed by borrowing data from the other similar studies in the meta-analysis. Gills 1997 measured pre- and postoperative endothelial cell counts (time frame not specified) in a subset of 20% of cases, and stated that there were no differences between topical anaesthesia plus intracameral lidocaine and topical anaesthesia-only groups with respect to percentage cell loss, but did not publish the numerical data, and so this study was not included in the meta-analysis.

We undertook a meta-analysis of mean percentage corneal endothelial cell count change from pre- to postoperatively for these four studies (31% of total studies) (Carino 1998; Chuang 2007; Crandall 1999; Martin 1998), comprising 254 eyes of 221 participants (11% of total eyes). The higher the mean percentage change in endothelial cell count, the greater the negative effect of the surgery on the health of the cornea (i.e. the greater the corneal toxicity). The analysis demonstrated no difference between the topical anaesthesia plus intracameral lidocaine and topical anaesthesia-only groups (mean difference in percentage endothelial cell count change was 0.89% higher in the topical anaesthesia plus intracameral lidocaine group, 95% CI −1.12% to 2.9%; P = 0.39). There was no heterogeneity between the results of the studies (I^2 = 0%) (see Analysis 1.5; Figure 8).

Figure 8. Forest plot of comparison: 1 Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, outcome: 1.5 Mean change in corneal endothelial cell count from pre- to postoperatively (%).



Footnotes
(1) Study was in paired eyes

We excluded the study where the standard deviation had been imputed in a sensitivity analysis (Chuang 2007), and this did not change the overall result (P = 0.34).

Using the GRADE approach, we found the quality of the evidence to be moderate. There were no studies with high risk of bias in any domain, no significant heterogeneity, and no evidence of publication bias. However, we downgraded by one level for imprecision as the number of eyes was small and the confidence interval wide.

Corneal oedema postoperatively

Crandall 1999 measured corneal oedema postoperatively in 136 eyes of 136 participants using a subjective 4-point scale and found that grade 1 corneal oedema, defined in the study as oedema confined to the corneal wound site, was more prevalent in the topical anaesthesia plus intracameral lidocaine group (P = 0.034) versus the topical anaesthesia-alone group. There was no difference in corneal striae between the two groups (generalized corneal oedema). Chuang 2007 reported that, for 66 eyes of 33 participants, there was no difference in corneal oedema between topical anaesthesia plus intracameral lidocaine and topical anaesthesia-alone groups, but did not present any formal data or analysis.

Changes in corneal pachymetry postoperatively

Martin 1998 measured postoperative pachymetry (time frame not specified) but did not report the results. Gills 1997 also measured postoperative pachymetry (time frame not specified) and stated that measurements were equivalent between the topical anaesthesia plus intracameral lidocaine and topical anaesthesia-alone groups, but did not publish the data.

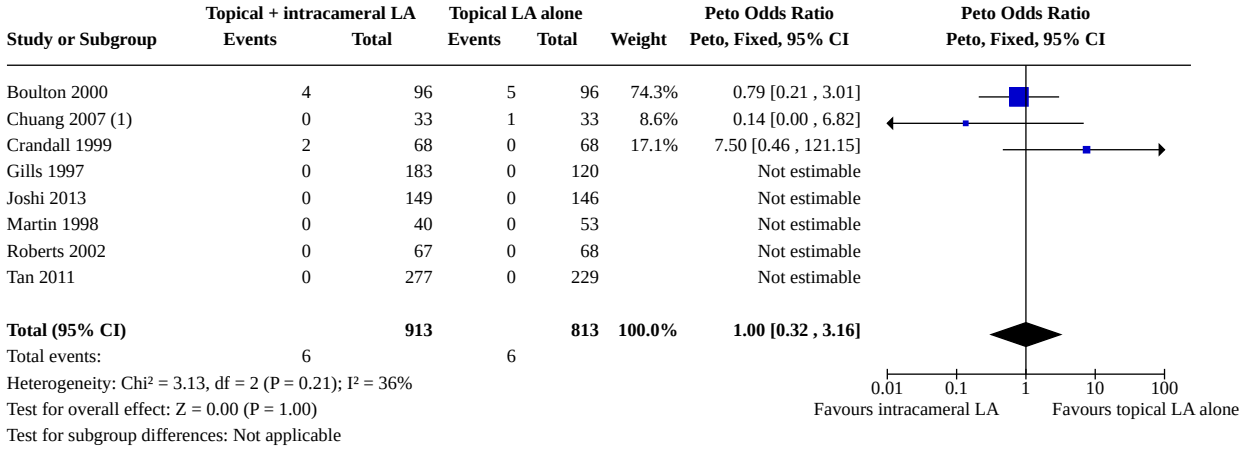
Anterior chamber inflammatory activity postoperatively

Martin 1998 objectively measured mean postoperative anterior chamber flare at 10 days using the Kowa laser flare-cell metre on 100 eyes of 100 participants and found no difference between the topical anaesthesia plus intracameral lidocaine and topical anaesthesia-only groups. Gills 1997 measured postoperative anterior chamber cells and flare at one day (method unspecified) and stated that there was no difference between the groups, but did not publish the data.

4. Intraoperative adverse events (complications) attributable to choice of anaesthesia

Eight studies recorded adverse intraoperative events (Boulton 2000; Chuang 2007; Crandall 1999; Gills 1997; Joshi 2013; Martin 1998; Roberts 2002; Tan 2011). Whilst these included iris prolapse, capsule tears with or without vitreous loss, the need for corneal suturing, and the placement of a sulcus fixated lens, no clear definitions of intraoperative adverse events were provided by any of the trials. Lofoco 2008 commented that there was no difference in adverse events between groups, but did not provide any data to support this and so was not included in the meta-analysis. A total of 1726 eyes of 1693 participants (72% of total eyes) from the eight trials (62% of total studies) were included in this analysis, although effect sizes were not estimable for five of the studies, as neither group had any adverse events (Gills 1997; Joshi 2013; Martin 1998; Roberts 2002; Tan 2011). No association was identified between intraoperative adverse events and either the topical anaesthesia plus intracameral lidocaine or topical anaesthesia-only group (P = 1.00). There was moderate heterogeneity between the results of these studies (I^2 = 36%) (see Analysis 1.6; Figure 9).

Figure 9. Forest plot of comparison: 1 Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, outcome: 1.6 Intraoperative adverse surgical events attributable to choice of anaesthesia.



Footnotes

(1) Study was in paired eyes

We excluded the study judged to have a high risk of bias in any one domain in a sensitivity analysis (Roberts 2002), and this did not change the overall result (P = 1.00).

Using the GRADE approach, we found the quality of the evidence to be low. We downgraded by two levels due to two studies having a high risk of performance bias related to the surgeon not being blinded (Joshi 2013; Roberts 2002), lack of clear definitions of adverse events, low numbers of events leading to non-estimable effect sizes, heterogeneity between the studies, and wide confidence intervals.

DISCUSSION

Summary of main results

In this updated review, we included 13 RCTs that met our inclusion criteria for evaluating topical anaesthesia plus intracameral lidocaine versus topical anaesthesia only for phacoemulsification cataract surgery in adults. Ten of the 13 studies used 1% preservative-free intracameral lidocaine; two studies used a concentration of 0.5%; and one study did not specify the concentration. There was some variation in stage of surgery at which the lidocaine was instilled, although when specified in all cases this was at or before hydrodissection. We did not consider these differences in intracameral instillation significant, given the dilution of the anaesthetic agent that takes place within the aqueous of the eye, and that instillation of the anaesthetic was always prior to stages of the surgery when most pain would be experienced. Many different drugs and regimens were used for the topical anaesthetic instillation across the 13 trials, but given that within each trial the topical anaesthetic was consistent between the two groups examined, this was also judged not to be significant.

Moderate-quality evidence from eight trials employing a 10-point visual analogue pain scale with continuous data combined (Boulton 2000; Chuang 2007; Crandall 1999; Gillow 1999; Joshi 2013; Roberts 2002; Tan 2011; Tseng 1998), comprising 1692 eyes of 1659 participants, demonstrated that participants undergoing surgery with topical anaesthesia plus intracameral lidocaine had a mean intraoperative pain score of 0.26 points lower than those with topical anaesthesia alone (95% CI −0.39 to −0.13; P < 0.001). Moderate-quality evidence from seven trials with dichotomous data combined (Carino 1998; Chuang 2007; Gills 1997; Hussain 2017; Lofoco 2008; Martin 1998; Tan 2011), comprising 1268 eyes of 1235 participants, demonstrated that participants undergoing surgery with topical anaesthesia plus intracameral lidocaine had an odds ratio of 0.40 (95% CI 0.29 to 0.57) of experiencing intraoperative pain compared to those with topical anaesthesia alone; P < 0.001. Results were similar whether or not routine sedation was given (sedation can affect pain perception and recollection of events). These results suggest that participants were 60% less likely to experience any pain (as opposed to no pain) when topical anaesthesia plus intracameral lidocaine was used compared to topical anaesthesia alone. However, the numerical amplitude of the reduction in pain score with intracameral lidocaine supplementation (0.26 points on a 0-to-10 pain scale) may not be of great clinical significance. Generally, the pain scores were consistently low for both techniques, with the vast majority of scores being either one or zero.

A smaller number of trials measured postoperative pain, and moderate-quality evidence from four trials (Crandall 1999; Gillow 1999; Joshi 2013; Lofoco 2008), comprising 751 eyes of 751 participants, found no difference between the topical anaesthesia plus intracameral lidocaine and topical anaesthesia-only groups (P = 0.15).

Impact on participant satisfaction and need for supplementary anaesthesia were less certain. Low-quality evidence from just one trial (Carino 1998), comprising 60 eyes of 60 participants, demonstrated no difference between the topical anaesthesia plus intracameral lidocaine and topical anaesthesia-only groups (P = 0.18). Low-quality evidence from seven trials (Boulton 2000; Carino 1998; Chuang 2007; Crandall 1999; Gills 1997; Joshi 2013; Roberts 2002), comprising 1194 eyes of 1161 participants,

demonstrated no difference in the need for supplementary anaesthesia during phacoemulsification (P = 0.59). It would thus appear that numerically, despite a statistical reduction in pain when using topical anaesthesia with intracameral lidocaine over topical anaesthesia alone, there is no improvement in participant satisfaction and no reduction in the need for supplemental anaesthesia. However, this result and conclusion should be interpreted with caution.

Although the toxic effects of anaesthetic agents on the corneal epithelium have been well characterized (Rosenwasser 1989), much less is known about their effects on the corneal endothelium. Some studies have suggested that intracameral lidocaine can produce significant endothelial cell loss and corneal oedema in a rabbit model. However, these effects appeared to be associated only with higher concentrations of anaesthetic, and the effects were transient (Judge 1997; Kadonosono 1998; Kim 1998). Five of the included trials attempted to identify any corneal toxicity by using a variety of endpoints such as corneal pachymetry, endothelial cell counts, and anterior chamber inflammatory activity. Moderate-quality evidence from four of these studies (Carino 1998; Chuang 2007; Crandall 1999; Martin 1998), comprising 254 eyes of 221 participants, found no difference in percentage pre- to postoperative endothelial cell count change between the topical anaesthesia plus intracameral lidocaine and topical anaesthesia-only groups (P = 0.39).

Eight trials (Boulton 2000; Chuang 2007; Crandall 1999; Gills 1997; Joshi 2013; Martin 1998; Roberts 2002; Tan 2011), comprising 1726 eyes of 1693 participants, specifically recorded any intraoperative complications. We found that the choice of anaesthesia does not predispose to adverse surgical events during phacoemulsification. Whilst complications were uncommon in both of the study groups, there was no increased risk of intraoperative complications for either the topical anaesthesia with intracameral lidocaine or topical anaesthesia-only group (P = 1.00). However, the low quality of the evidence means this result should be interpreted with caution.

The objective of this review was to assess the effectiveness and safety of intracameral lidocaine as a supplement to topical anaesthesia for phacoemulsification cataract surgery in adults. Overall, the combined data from the trials we have identified demonstrates that both methods (topical anaesthesia plus intracameral lidocaine, and topical anaesthesia alone) are effective methods of providing anaesthesia for cataract surgery. Whilst participants were less likely to experience any intraoperative pain (as opposed to no pain) with topical anaesthesia plus intracameral lidocaine compared to topical anaesthesia alone, pain scores were generally very low for both techniques. The numerical reduction in intraoperative pain score with intracameral lidocaine supplementation was statistically significant, but is it unclear whether the magnitude is of clinical significance. Our data do support the safety profile of lidocaine supplementation with regard to intraocular (specifically corneal) toxicity.

Overall completeness and applicability of evidence

We are confident that our search strategy identified all available studies. The results of this review are applicable to all adult patients undergoing phacoemulsification cataract surgery who would be suitable for topical anaesthesia. The included studies took place in a variety of ophthalmology settings in a large range of countries that use this method of cataract surgery (the UK, the USA, Australia, Italy, Canada, Taiwan, Singapore, India, and Pakistan). A range of different topical anaesthetic agents were employed in the studies, which were delivered at slightly different times and with different methods. The intracameral lidocaine was also delivered at slightly different stages of surgery amongst the trials. These differences support the applicability of the evidence to real-life settings whereby different hospitals may have different topical anaesthetic agents available, and different surgeons use slightly different operative techniques.

Whilst we made every attempt to exclude studies that were 'selective' with respect to the cases they included (i.e. we excluded studies that only included low-risk participants and excluded more complex cases such as dense nuclei and small pupils), it was not obvious from the papers what percentage of the cases were low-risk versus high-risk/complex. It is likely that the low-risk cases heavily outnumbered the more complex cases in this meta-analysis. Furthermore, the surgeons who performed the operations in the included studies were all experienced surgeons. It is likely that pain scores would be higher with less experienced surgeons and more complex cases, and our review does not address this.

With respect to the intervention, during the search process for the updated review it became apparent that there were a number of more recent trials comparing topical anaesthetic alone with topical anaesthetic plus intracameral Visthesia, which is a viscoelastic device containing lidocaine 1%. We decided not to change the original inclusion criteria for the systematic review, and so not to include these studies, especially as Visthesia is not in common use internationally. However, this may be a potential limitation of this review with respect to overall completeness. We also did not include intracameral mixtures, such as Mydrane (lidocaine, plus phenylephrine, plus tropicamide) in the review. Furthermore, 8 of the 13 included studies are 16 to 22 years old. Since that time there have been some advances in phacoemulsification surgical technique, with evolvement in the fluid dynamics of the phacoemulsification equipment and smaller incision microsurgical instruments available. It is possible that with these changes, the procedure as a whole has become less painful under topical anaesthesia alone, and so this should be considered also as a potential limitation with respect to applicability of the evidence.

Quality of the evidence

We rated the quality of the evidence using the GRADE approach. The 'Risk of bias' graph gives an overview of risk of bias in the included studies (Figure 2), detailed in the methodological quality summary (Figure 3). Whilst only seven included studies explicitly gave details of randomization method (Boulton 2000; Crandall 1999; Gillow 1999; Gills 1997; Joshi 2013; Tan 2011; Tseng 1998), only one study was judged as at high risk for selection bias (Hussain 2017). This same study and two other studies, Joshi 2013; Roberts 2002, were the only studies also judged as at high risk of performance bias, as the surgeon was not blinded. No other studies were judged as at high risk of bias for any of the other domains.

For intraoperative pain on a continuous scale, we downgraded the quality of the evidence by one level to moderate due to the surgeon not being blinded in two of the studies. For intraoperative pain on a dichotomous scale, we downgraded the quality of the evidence by one level due to one study having high risk of performance and selection bias, and heterogeneity between the studies. For postoperative pain, we downgraded the quality of the evidence by

one level to moderate as in one study the surgeon was not blinded, and in a second study the population included was restricted to those with a high axial length (indirectness). For participant satisfaction, we downgraded the quality of the evidence by two levels due to the result being based on data from just one RCT with a small number of participants; unclear risk of selection bias, detection bias, and reporting bias; and use of an unvalidated outcome measure. For need for additional anaesthesia during surgery, we downgraded the quality of the evidence by two levels due to two trials being high risk for performance bias; heterogeneity between studies; and imprecision. For measures relating to possible intraocular toxicity, specifically mean percentage corneal endothelial cell count change from pre- to postoperatively, we downgraded the quality of the evidence by one level due to the low number of included eyes and wide confidence interval. For intraoperative adverse events (complications) attributable to choice of anaesthesia, we downgraded the quality of the evidence by two levels to low due to two studies being at high risk of performance bias because the surgeon was not blinded; a lack of clear definitions of adverse events in the studies; low numbers of events leading to non-estimable effect sizes for the majority of studies; and heterogeneity between the studies and wide confidence intervals.

Potential biases in the review process

A potential bias arises from the exclusion of studies that compared topical anaesthesia alone with topical anaesthesia plus intracameral Visthesia, an ophthalmic viscoelastic device containing lidocaine 1%. This form of intracameral lidocaine was not available when the original review was undertaken, and is still not commonly used internationally. For this reason we decided not to include this as a form of intracameral lidocaine in the review, and recognize this to be a potential limitation of the review.

Another potential bias comes from our decision not to include studies in which participants were excluded when they were judged to be difficult operative cases, for example participants with hard lens nuclei and small pupils. We felt that including these studies would bias the results, as only straightforward operative cases would be included that perhaps would only require milder levels of anaesthesia. However, it must be considered that in real-life situations, some surgeons would opt to perform the more difficult operative cases under sub-Tenon's anaesthesia rather than topical anaesthesia alone or topical anaesthesia plus intracameral lidocaine, not just for extended duration or efficacy of anaesthesia, but also for the ability to immobilise the eye to a degree. Consequently, the decision by some of the study authors to exclude such participants may have been justified.

We included the data from a paired-eye study, Chuang 2007, alongside the data from the parallel studies in the review. Potential bias may have arisen due to inherent potential carry-over effects and selective reporting issues with a paired-eye design.

Finally, with regard to the search, we limited our review to the inclusion of RCTs only, which may not have been adequate for detecting all adverse events. The inclusion of observational studies for this outcome may have been a more comprehensive approach.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic review of intracameral lidocaine and topical anaesthesia versus topical anaesthesia alone for phacoemulsification cataract surgery. The previous version of this review, Ezra 2007, had similar results with regard to primary outcomes. There was a difference between review versions in the conclusions relating to measures of intraocular toxicity. The measure used in the meta-analysis in the original review (postoperative endothelial cell count), despite showing no difference between groups, did have a high level of heterogeneity, therefore it was concluded that this result should be interpreted with caution. In this updated review, mean percentage change in endothelial cell count from pre- to postoperatively was used, and again showed no difference between groups, but this time with no heterogeneity. The conclusion that there was no additional corneal toxicity from using intracameral lidocaine in terms of effect on endothelial cell count can thus be made with more certainty.

AUTHORS' CONCLUSIONS

Implications for practice

Our review demonstrates there is moderate-quality evidence that supplementation of topical anaesthesia with intracameral lidocaine (concentration 0.5% to 1%) for phacoemulsification cataract surgery in adults likely reduces participant perception of intraoperative pain or discomfort. Whilst supplemental intracameral lidocaine does reduce the likelihood of the participant experiencing any pain (as opposed to no pain) intraoperatively, the absolute difference in mean pain scores on the 10-point scale is small, and it is not clear whether this is of great clinical significance. Overall, supplementation with intracameral lidocaine probably results in a slight reduction in intraoperative pain perception. Both topical anaesthesia plus intracameral lidocaine, and topical anaesthesia alone, generally had low intraoperative pain scores. As such, both would be acceptable methods of anaesthesia for cataract surgery.

Our review does not demonstrate a benefit of supplemental intracameral lidocaine in addition to topical anaesthesia for reduction of postoperative pain (moderate-quality evidence). Evidence was insufficient to determine the impact on participant satisfaction (low-quality evidence) or on the need for additional intraoperative anaesthesia (low-quality evidence).

There is moderate-quality evidence that supplementation of topical anaesthesia with intracameral lidocaine likely does not increase measures of intraocular toxicity, specifically loss of corneal endothelial cells. There is low-quality evidence that the incidence of intraoperative adverse events may be unchanged when topical anaesthesia is supplemented with intracameral lidocaine. However, as randomized controlled trials are not the optimum medium for looking at this, this result should be interpreted with caution. Overall, however, the review supports the safety of using intracameral lidocaine in addition to topical anaesthesia.

Implications for research

We have demonstrated that data from a number of randomized controlled trials support the effectiveness of both topical anaesthesia plus intracameral lidocaine and topical anaesthesia

alone for cataract surgery. Further studies comparing the anaesthetic effects of adjunctive intracameral lidocaine with a placebo control group may be considered unnecessary. However, if phacoemulsification surgical techniques continue to evolve, instrumentation becomes more minimally invasive, and laser-assisted surgery becomes more commonplace, then requirements for local anaesthesia for phacoemulsification cataract surgery may change, as the pain provoked by the procedure itself may change. As such, it would then be useful to conduct these randomized controlled trials again.

In any future research, it would be useful to look particularly at whether the timing of instillation of intracameral lidocaine (before or after viscoelastic) makes any difference to intraoperative pain scores, as viscoelastic may act as a barrier to the lidocaine reaching the iris/ciliary body. Also, one of the most important indicators of pain is change in the autonomic outflow, which in turn is reflected in the haemodynamic changes (e.g. heart rate, blood pressure) of the participant. The majority of the studies in this review did not address this, so future research could be directed at looking at these parameters.

Further research directed specifically at investigating adverse effects of intracameral anaesthesia may help to better determine the safety profile of this intervention. Whilst we demonstrated that there was no increased corneal toxicity from using intracameral lidocaine, the number of eyes included in this analysis was low, and so larger studies exploring this would further support this conclusion. Also, larger observational studies looking at adverse events and surgical complications attributable to choice of anaesthesia are necessary.

If Visthesia is used increasingly as a supplement to topical anaesthesia for phacoemulsification cataract surgery internationally, a priority for research would be to review its efficacy and safety profile versus topical anaesthesia alone and versus topical anaesthesia with intracameral lidocaine.

Lastly, whilst we did not explicitly search for it, in our comprehensive search of the literature we did not come across any studies looking at the economical impact of using supplemental intracameral lidocaine. Economical analysis and cost-effectiveness is crucial information when making recommendations and policy decisions, and for financial planning, and as such any further studies should incorporate this aspect.

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CHARACTERISTICS OF STUDIES

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* Indicates the major publication for the study

Boulton 2000

Study characteristics	
Methods	**Study design**: single-centre, prospective, parallel-group, randomized double-blinded, placebo-controlled trial
Participants	**Site and country**: cataract surgery unit within a multispecialty hospital, UK **Total number**: 200 eyes of 200 participants randomized; 192 with primary outcome data 1. Topical LA and placebo group, n = 100 eyes (96 with primary outcome data) 2. Topical LA and intracameral lidocaine group, n = 100 eyes (96 with primary outcome data) **Inclusion criteria** 1. All phacoemulsification cataract surgery suitable for topical anaesthesia considered **Exclusion criteria** 1. Combination surgery 2. Deafness 3. Poor English 4. Dementia 5. Nystagmus 6. Involuntary movement disorder 7. High anxiety score 8. Adverse reaction to lidocaine **Age of participants**: mean 76 years (range 39 to 95 years). No difference between groups. **Sex of participants**: 40% male, 60% female; uneven distribution between groups (comparatively more males in placebo group, P = 0.0393)
Interventions	**Trial drug**: intracameral 0.5 mL unpreserved epinephrine-free 1% lidocaine in BSS **Placebo**: intracameral 0.5 mL BSS 1. Topical LA (both groups): 1% tetracaine 2. Topical LA method (both groups): up to 4 sets of 2 drops 3. Intracameral lidocaine/BSS injected via Rycroft cannula into anterior chamber immediately after clear corneal incision Surgery performed by 3 surgeons. No IV sedation
Outcomes	**Primary outcome** 1. Participant intraoperative pain score, measured using standard 0-to-10 visual analogue scale (Stevens 1992), recorded immediately postoperatively **Secondary outcomes** 1. Any requirement for additional intraoperative injected anaesthetic (N.B. this prevented assessment of primary outcome) 2. Intraoperative complications
Notes	**Study dates**: 25 June 1997 to 10 December 1997 **Funding sources**: not stated

Boulton 2000 *(Continued)*

Conflicts of interest: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used permuted block, individual, randomization schedule of 300 allocations (A or B) using 6 permuted blocks of 4; blocks selected by dice rolling
Allocation concealment (selection bias)	Low risk	Randomization schedule retained in pharmacy and not seen by investigators. Each participant allocated unique trial number with content of bottle for surgery matching the number.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, surgeons, and nurse administering pain score fully masked from bottle contents.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurse administering pain score fully masked from bottle contents. Surgeon not present in room whilst pain score was conducted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 participants (of 100) in each group asked for additional anaesthesia and were not included in the assessment of pain (primary outcome).
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Carino 1998

Study characteristics

Methods	**Study design**: single-centre, prospective, parallel-group, randomized double-blinded, placebo-controlled trial
Participants	**Site and country**: The Toronto Hospital - Western Division, Toronto, Canada **Total numbe**r: 60 eyes of 59 participants randomized 1. Topical LA and placebo group, n = 30 eyes 2. Topical LA and intracameral lidocaine group, n = 30 eyes **Inclusion criteria** 1. All phacoemulsification cataract surgery **Exclusion criteria** 1. Dementia 2. Confusion 3. Previous intraocular surgery in same eye 4. Requested systemic sedation **Age of participants**: mean age placebo group 69.9 years (range 40 to 82 years); mean age lidocaine group 67.1 years (range 34 to 81 years). No difference between groups.

Carino 1998 *(Continued)*

	Sex of participants: 43% male, 57% female. No difference between groups.
Interventions	**Trial drug**: intracameral 0.2 mL 1% unpreserved lidocaine **Placebo**: intracameral 0.2 mL BSS 1. Topical LA (both groups): 0.5% tetracaine 2. Topical LA method (both groups): 2 drops 15 minutes preoperatively, and a further 2 drops immediately prior to surgery 3. Intracameral lidocaine/BSS injected into anterior chamber immediately after first corneal section No routine IV sedation IV sedation (0.5 mg midazolam and 250 µg alfentanil HCl) if more than mild pain experienced intraoperatively Surgery performed by 1 surgeon.
Outcomes	1. Participant's baseline, intraoperative, and postoperative pain scores measured using 4-point pain scale (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain). Scores measured at 4 points: prior to surgery (after preparation and drape = baseline); after capsulorhexis; after phacoemulsification of lens; and immediately postoperatively. 2. Anaesthetic failure (pain score > 2 intraoperatively, requiring addition of intravenous anaesthesia) 3. Participant satisfaction (5-point scale: 1 = extremely dissatisfied; 5 = extremely satisfied), measured immediately postoperatively 4. Surgeon satisfaction (5-point scale: 1 = extremely dissatisfied; 5 = extremely satisfied), measured immediately postoperatively 5. Participant preference for anaesthesia of the other eye, noted immediately postoperatively 6. Mean central corneal endothelial cell loss of operated eye 1 month postoperatively. Endothelial cell count measured preoperatively and 1 month postoperatively, using Keeler Konan specular microscope. 7. Visual outcome of operated eye: improvement in best-corrected visual acuity from baseline (preoperatively) measured 1 hour, 1 day, 1 week, and 1 month postoperatively 8. Rate of recovery of potential visual acuity of operated eye
Notes	Authors contacted for further information but no response received. **Study dates**: February 1997 to May 1997 **Funding sources**: not stated **Conflicts of interest**: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided about method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description provided about allocation concealment. Study said (quote): "intracameral solution was prepared by a research assistant".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeon and anaesthetist blinded regarding intracameral solution.

Carino 1998 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear who was recording participant pain and participant/surgeon satisfaction, or endothelial cell count. If this was the investigator, then they were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results obtained for all participants, except 4 for endothelial cell count (2 in each group).
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Chuang 2007

Study characteristics	
Methods	**Study design**: single-centre, prospective, paired-eye, randomized double-blinded, placebo-controlled trial Cross-over study
Participants	**Site and country**: Chuang Gung Memorial Hospital, Taoyuan, Taiwan, Republic of China **Total number**: 66 eyes of 33 participants randomized 1. Topical LA and placebo group, n = 33 eyes 2. Topical LA and intracameral lidocaine group, n = 33 eyes of same 33 participants **Inclusion criteria** 1. Participants undergoing cataract surgery **Exclusion criteria** 1. Anxiety 2. Unintentional eye movement 3. Small pupil with an inability to completely dilate 4. Baseline endothelial count less than 1500 cells/mm^2 5. Other ocular entities affecting the corneal endothelium 6. Allergy to relevant medications 7. Mature cataracts with total cortical opacity requiring indocyanine green staining **Age of participants**: mean 70 years (+/− 10.8 years SD) (for both groups, as same participants in each group) **Sex of participants**: 36% female, 64% male (for both groups, as same participants in each group)
Interventions	**Trial drug**: intracameral 0.15 mL of 0.5% preservative-free lidocaine **Placebo**: intracameral 0.15 mL BSS 1. Topical LA (both groups): unpreserved lidocaine 2% drops 2. Topical LA method (both groups): 4 drops instilled at start of surgery; any supplemental LA during surgery recorded 3. Intracameral lidocaine/BSS method: 0.15 mL agent injected after side-port made (after main section) No sedation

Chuang 2007 *(Continued)*

Outcomes	1. Participant's intraoperative pain score, measured using standard 0-to-10 visual analogue scale (Stevens 1992), recorded within 30 minutes of participant being sent to recovery room 2. Corneal endothelial cell changes of operated eye: mean endothelial cell count (cells/mm^2), mean coefficient variation of cell size and percentage of hexagonal cells, measured preoperatively and postoperatively (time frame not stated) using specular microscope. Percentage mean cell loss calculated. 3. Corneal oedema in operated eye, recorded as present or absent postoperatively (time frame not stated)
Notes	Authors contacted for further information but no response received. **Paired human eyes**: fellow eye had surgery at least 2 weeks after first (mean 40 days) **Data analysis:** paired Student t-test and Mann-Whitney U test used to analyse correlated data **Study dates**: July 2004 to February 2005 **Funding sources**: not stated **Conflicts of interest**: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description provided regarding method of randomization.
Allocation concealment (selection bias)	Unclear risk	No description provided regarding allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both patients and physician were double-blinded to the anesthesia strategy"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear who was assessing the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented for all participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Crandall 1999

Study characteristics

Methods	**Study design**: single-centre, prospective, parallel-group, randomized double-blinded, placebo-controlled trial
Participants	**Site and country**: John A. Moran Eye Center, University of Utah School of Medicine, Salt Lake City, Utah, USA **Total number**: 136 eyes of 136 participants randomized

Crandall 1999 *(Continued)*

1. Topical LA and placebo group, n = 68 eyes
2. Topical LA and intracameral lidocaine group, n = 68 eyes

Inclusion criteria

1. All cataract surgery in patients aged 45 to 85 years suitable for topical anaesthesia

Exclusion criteria

1. ASA score > 3
2. Monocular patients

Age of participants: details not stated

Sex of participants: details not stated

Interventions	**Trial drug**: intracameral 0.3 mL 1% unpreserved lidocaine **Placebo**: intracameral 0.3 mL BSS 1. Topical LA (both groups): bupivacaine hydrochloride 0.75% 2. Topical LA method (both groups): 3 sets of 2 drops every 5 minutes 3. Intracameral lidocaine/BSS injected into anterior chamber immediately after first corneal section No routine IV sedation If breakthrough pain occurred during surgery, IV fentanyl (0.5 µg/kg) given and repeated in 3 minutes if necessary. Surgery performed by 1 surgeon.
Outcomes	1. Participant's intraoperative pain score, measured using standard 0-to-10 visual analogue scale (Stevens 1992), recorded immediately postoperatively 2. Participant's postoperative pain score, measured using standard 0-to-10 visual analogue scale (Stevens 1992), recorded immediately postoperatively 3. Participant's discomfort from sensation of tissue manipulation intraoperatively, measured on a 3-point scale (0 = none, 1 = a little, 2 = a lot), recorded immediately postoperatively 4. Participant's microscope light discomfort, measured on a 3-point scale (0 = none, 1= a little, 2 = a lot), recorded immediately postoperatively 5. Changes in participant's autonomic intraoperative recordings (pulse, blood pressure) 6. Surgeon's assessment of intraoperative difficulties and complications, recorded immediately post-operatively 7. Surgeon's assessment of operative conditions on an analogue scale (10 = excellent; 7.5 = good; 5 = fair; 2.5 = poor; 0 = extremely poor), recorded immediately postoperatively 8. Surgeon's assessment of patient co-operation (0 = poor; 1 = good; 2 = excellent), recorded immediately postoperatively 9. Supplemental IV sedation given 10. Postoperative corneal oedema of operated eye, measured by operating surgeon on first postoperative day on 4-point scale (0 = none; 1 = oedema confined to the surgical wound; 2 = oedema extending beyond the wound but not involving the central cornea; 3 = oedema of the central cornea) 11. Postoperative corneal striae of operated eye, measured by operating surgeon on first postoperative day on 4-point scale (0 = none; 1 = striae confined to the surgical wound; 2 = striae extending beyond the wound but not involving the central cornea; 3 = striae of the central cornea) 12. Subset of participants (first 40 randomized) had preoperative and postoperative endothelial cell counts of operated eye measured (3 and 6 months postoperatively). Percentage change in cell counts calculated.
Notes	**Study dates**: September 1996 to June 1997

Crandall 1999 *(Continued)*

Funding sources: study supported in part by an unrestricted grant from Research to Prevent Blindness Inc, New York, to the Department of Ophthalmology, University of Utah, Salt Lake City, Utah

Conflicts of interest: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomization
Allocation concealment (selection bias)	Low risk	Circulating and scrub nurse drew up solutions in identical syringes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeon and anaesthetist blinded until after conclusion of study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All people involved in measuring/evaluating outcomes blinded until after conclusion of study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data available for all participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Gillow 1999

Study characteristics

Methods	**Study design**: single-centre, prospective, parallel-group, randomized double-blinded, placebo-controlled trial
Participants	**Site and country**: Victoria Eye Hospital, Hereford, England, UK **Total number**: 204 eyes of 204 participants randomized; 200 with outcome data 1. Topical and placebo group, n = 101 eyes 2. Topical and intracameral lidocaine group, n = 99 eyes **Inclusion criteria** 1. All patients undergoing topical anaesthesia for cataract surgery **Exclusion criteria** 1. Communication difficulties 2. Allergy to lidocaine **Age of participants**: mean 76 years (range 51 to 99 years) **Sex of participants**: 38% male, 62% female

Gillow 1999 *(Continued)*

Interventions	**Trial drug**: intracameral 0.5 mL 1% unpreserved lidocaine **Placebo**: intracameral 0.5 mL BSS 1. Topical LA (both groups): tetracaine 0.5% 2. Topical LA method (both groups): 1 drop every 5 minutes until stinging stopped 3. Intracameral lidocaine/placebo given via 25-gauge Rycroft cannula after hydrodissection. Left for 1 minute before phacoemulsification started No IV sedation Surgery performed by more than 1 surgeon (number not stated).
Outcomes	1. Participant's intraoperative pain score, measured using a validated 0-to-10 vertical visual analogue scale with 20 linear gradations but no numeric clues (Scott 1976), recorded on day 1 postoperatively 2. Participant's postoperative pain score, measured using Scott 1976, recorded on day 1 postoperatively 3. Participant's intraoperative microscope light discomfort, measured using Scott 1976, recorded on day 1 postoperatively 4. Use of supplementary anaesthetic
Notes	Authors contacted for further information and response received. **Study dates**: not stated **Funding sources**: not stated **Conflicts of interest**: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assisting surgical nurse used computer-generated randomization charts.
Allocation concealment (selection bias)	Low risk	Surgeon and anaesthetist blinded to contents of intracameral syringe.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeon and anaesthetist blinded to contents of intracameral syringe.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent observer (day-case nurse) questioned participants about pain.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of the 204 participants recruited were excluded from analysis.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Gills 1997

Study characteristics	
Methods	**Study design**: single-centre, prospective, parallel-group, randomized double-blinded, placebo-controlled trial
Participants	**Site and country**: St Luke's Cataract and Laser Institute's ambulatory surgical centre, Tarpon Springs, Florida, USA **Total number**: 303 eyes of 303 participants 1. Topical LA and placebo group: 120 eyes 2. Topical LA and intracameral lidocaine group: 183 eyes **Inclusion criteria** 1. All patients undergoing phacoemulsification cataract surgery suitable for topical anaesthetic **Exclusion criteria** 1. Allergy to lidocaine 2. Allergy to topical anaesthetics 3. Multiple procedures **Age of participants**: mean topical LA plus intracameral lidocaine group 75.5 years (range 55 to 93 years); mean topical LA plus placebo group 73.6 years (range 45 to 87 years); no difference between groups **Sex of participants:** 33% male in topical LA plus intracameral lidocaine group, 44% male in topical LA plus placebo group; no difference between groups
Interventions	**Trial drug**: intracameral 0.1 cm^3 1% unpreserved epinephrine-free lidocaine **Placebo**: intracameral 0.1 cm^3 unpreserved BSS 1. Topical LA (both groups): proparacaine 0.5%, bupivacaine hydrochloride 0.75% 2. Topical LA method (both groups): 1 drop proparacaine twice, 1 drop bupivacaine 4 times Intracameral lidocaine/BSS given 1 minute prior to phacoemulsification. Supplemental IV sedation and intracameral lidocaine for breakthrough/anxiety Any participant with anxiety preoperatively given IV sedation with midazolam just before surgery. Surgery performed by 1 surgeon.
Outcomes	1. Participant's intraoperative pain score, measured using a 5-point scale (0 = no sensation; 1 = mild pressure; 2 = increased pressure (uncomfortable); 3 = moderate pain; 4 = sharp pain; 5 = severe pain), recorded midway through phacoemulsification of lens and midway through IOL insertion 2. Need for additional anaesthesia/sedation intraoperatively 3. Participant's pre-, intra-, and postoperative blood pressure 4. Mean postoperative endothelial cell count for the operated eye (time frame not stated) 5. Postoperative anterior chamber cells and flare for the operated eye, measured on day 1 postoperatively (method not specified) 6. Postoperative central pachymetry for the operated eye (time frame not specified) 7. Visual acuity for the operated eye, measured on day 1 postoperatively
Notes	Authors contacted for further information and response received. Study stopped prematurely as lidocaine shown to be so effective. This may explain discrepancy in numbers in each group.

Gills 1997 *(Continued)*

A secondary, non-placebo-controlled study took place after this, giving 0.5 mL 1% intracameral lidocaine.

Study dates: not stated

Funding sources: not stated

Conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization schedule used to assign lidocaine or BSS to consecutive surgery days (rather than participants).
Allocation concealment (selection bias)	Low risk	Scrub technician prepared the assigned treatment in masked fashion.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeon masked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurse anaesthetist who was the grader masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Hussain 2017

Study characteristics

Methods	**Study design**: single-centre, prospective randomized trial
Participants	**Site and country**: Department of Ophthalmology, University Medical and Dental College, Faisalabad, Pakistan **Total number**: 120 eyes of 120 participants 1. Topical LA only group: 60 eyes 2. Topical LA and intracameral lidocaine group: 60 eyes **Inclusion criteria** 1. Patients undergoing phacoemulsification surgery (no further details provided) **Exclusion criteria** 1. Patients with known history of hearing impairment 2. Poor native language skills 3. Mental sickness

Hussain 2017 *(Continued)*

4. Nystagmus
5. Involuntary movement disorder
6. Intraoperative complications such as capsular rupture or vitreous loss

Age of participants: mean control group 54.55 years; mean lidocaine group 56.00 years

Sex of participants: overall 50.8% male, 49.2% female; breakdown per group not given

Interventions	**Trial drug**: intracameral preservative-free lidocaine **Placebo**: no intracameral placebo used 1. Topical LA (both groups): not specified 2. Topical LA method (both groups): not specified Stage at which intracameral lidocaine given not specified. No sedation mentioned.
Outcomes	1. Participant's intraoperative pain score, measured on 10-point visual analogue scale; not specified if this was a validated scale. Time pain score recorded not stated.
Notes	Authors contacted for further information but no response received. **Study dates**: May 2016 to December 2016 **Funding sources**: not stated **Conflicts of interest**: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	120 participants were divided into "equal groups" using a "lottery method", which is not true randomization.
Allocation concealment (selection bias)	High risk	Description of dividing participants into "equal groups" suggests that allocation concealment did not take place.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Details of blinding not given, but as there was no placebo intracameral drug, the surgeon could not have been blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Joshi 2013

Study characteristics	
Methods	**Study design**: single-centre, prospective, parallel-group, randomized trial
Participants	**Site and country**: Department of Ophthalmology, Shri Vasantrao Naik Government Medical College, Yavatmal, Maharashtra, India **Total number**: 295 eyes of 295 participants 1. Topical LA only group, n= 146 eyes 2. Topical LA and intracameral lidocaine group: 149 eyes **Inclusion criteria** 1. Patients with operable cataracts of various grades **Exclusion criteria** 1. Allergy to topical anaesthetics 2. Deafness 3. Nystagmus 4. Barrier to communication 5. Extreme anxiety 6. Neurological disorders 7. Monocular patients 8. Complicated and subluxed cataracts 9. Non-dilating pupil 10. Unable to understand a visual analogue scale **Age of participants**: mean topical group 61.00 +/− 11.09 years; mean intracameral group 58.71 +/− 10.09 years **Sex of participants**: 146 females (71 in topical LA only group, 75 in topical LA plus intracameral lidocaine group) and 149 males (75 in topical LA only group, 74 in topical LA plus intracameral lidocaine group)
Interventions	**Trial drug**: intracameral 0.5% preservative-free lidocaine (Xylocaine) **Placebo**: no intracameral placebo used 1. Topical LA (both groups): proparacaine hydrochloride 0.5% drops 2. Topical LA method (both groups): single drop placed in lower fornix 2 minutes before start of surgery **Intracameral method**: not stated No preoperative or intraoperative sedation used. Surgery performed by 1 surgeon.
Outcomes	1. Participant's intraoperative and postoperative pain score, measured using a 10-point visual analogue scale (Stevens 1992), recorded 30 minutes after completion of surgery 2. Participant's choice of similar anaesthetic for fellow eye, recorded 30 minutes after completion of surgery 3. Surgeon's subjective impression of intraoperative corneal haze (0 = clear; 1 = mild haze; 2 = moderate haze; 3 = severe haze) 4. Surgeon's subjective impression of participant discomfort during surgery (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain) 5. Surgical complications 6. Supplemental anaesthesia use

Joshi 2013 *(Continued)*

	7. Participant's intraoperative vital parameters (blood pressure, pulse rate, oxygen saturation) 8. Need for supplemental intravenous sedation
Notes	Authors contacted for further information and response received. No mention in paper of whether participant, surgeon, or postoperative examiner was blinded. The study author said they were blinded in personal communication, but no placebo used so this could not be possible with respect to surgeon. **Study dates**: not stated **Funding sources**: none **Conflicts of interest**: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No description provided about method of randomization in the paper, but when contacted the author stated that the "coin toss" method was used.
Allocation concealment (selection bias)	Unclear risk	No description provided regarding allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not mentioned in the paper, but when contacted, the author stated that the surgeon and participant were blinded. However, the surgeon could not have been blinded as no placebo intracameral agent was used in the topical-only group.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Para-ophthalmic technician performed the pain grading, but no mention made in the paper as to whether or not they were blinded to group allocation. When contacted the author stated that they were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Lofoco 2008

Study characteristics

Methods	**Study design**: single-centre, prospective, parallel-group, randomized double-blinded, placebo-controlled trial
Participants	**Site and country**: Department of Ophthalmology, Ospedale San Pietro-Fatebenefratelli, Rome, Italy **Total number**: 120 eyes of 120 participants 1. Topical LA and placebo group, n = 60 eyes 2. Topical and intracameral lidocaine group, n = 60 eyes **Inclusion criteria** 1. Highly myopic eyes with axial length > 26 mm scheduled for routine cataract surgery

Lofoco 2008 *(Continued)*

	Exclusion criteria 1. Monocularity 2. Degeneration and dystrophy of the cornea 3. Involuntary movement disorders 4. High anxiety 5. Reported allergy to lidocaine 6. Unwillingness to have topical anaesthesia **Age of participants**: mean topical LA and placebo group 65.57 years; mean topical LA and intracameral lidocaine group 63.98 years; P = 0.24 **Sex of participants**: topical LA and placebo group 37% male; topical LA and intracameral lidocaine group 45% male; P = 0.45
Interventions	**Trial drug**: 0.1 mL intracameral preservative-free lidocaine hydrochloride 1% **Placebo**: intracameral BSS 1. Topical LA (both groups): lidocaine 2% jelly 2. Topical LA method (both groups): 1 mL lidocaine 2% jelly administered 20 minutes and 5 minutes before participant taken to operating room 3. Intracameral method: agent injected into the capsular bag during hydrodissection **Sedation**: all participants received intravenous diazepam (0.05 mg/kg) before procedure Surgery performed by 2 surgeons.
Outcomes	1. Participant intraoperative pain: any sensation of pain spontaneously reported by participant during 3 surgical stages: phaco tip insertion, I/A system insertion for aspiration of cortex, I/A system insertion for OVD removal 2. Participant postoperative pain, measured using a 10-point visual analogue scale (Stevens 1992), recorded immediately postoperatively
Notes	Authors contacted for further information but no response received. **Study dates**: January 2006 to March 2008 **Funding sources**: not stated **Conflicts of interest**: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	During preoperative assessment, eligible cases randomly assigned by dice roll.
Allocation concealment (selection bias)	Unclear risk	Assignment was performed during the preoperative assessment, but no details given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeon, participant, anaesthetist, and staff interviewing participant blind to anaesthesia used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeon, participant, anaesthetist, and staff interviewing participant blind to anaesthesia used.

Lofoco 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Martin 1998

Study characteristics	
Methods	**Study design**: single-centre, prospective, parallel-group, randomized placebo-controlled trial
Participants	**Site and country**: Carolina Eye Associates, Southern Pines, North Carolina, USA **Total number**: 93 eyes of 93 participants 1. Topical LA and placebo group, n = 53 eyes 2. Topical and intracameral group, n = 40 eyes **Inclusion criteria** 1. Not stated **Exclusion criteria** 1. Not stated **Age of participants**: details not stated; 2 groups were "comparable in distribution" **Sex of participants**: details not stated; 2 groups were "comparable in distribution"
Interventions	**Trial drug**: intracameral 0.5 cm^3 1% unpreserved lidocaine **Placebo**: intracameral 0.5 cm^3 BSS 1. Topical LA (both groups): proparacaine 0.5%, lidocaine 4% 2. Topical LA method (both groups): 1 drop of proparacaine 10 minutes prior to surgery and 2 drops of lidocaine immediately prior to surgery 3. Intracameral lidocaine/BSS given using 30-gauge cannula immediately before capsulorhexis performed No IV sedation
Outcomes	1. Participant's intraoperative pain score, measured on a 4-point scale (0 = no sensation; 1 = mild pressure; 2 = increased pressure; 3 = mild pain), recorded immediately postoperatively 2. Anterior chamber flare in operated eye, measured using Kowa laser flare-cell metre, at 1 and 10 days postoperatively 3. Corneal endothelial cell count of operated eye, measured using the Konan system, preoperatively and 2 to 3 months postoperatively, with mean change calculated 4. Other corneal endothelial cell density parameters of operated eye: mean postoperative percentage of hexagonal cells; mean postoperative coefficient of variation, measured with the Konan system at 2 to 3 months postoperatively 5. Mean postoperative pachymetry (time frame not stated)
Notes	Authors contacted for further information but no response received. **Study dates**: not stated

Martin 1998 *(Continued)*

Funding sources: not stated

Conflicts of interest: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of surgeon/anaesthetist blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants had outcome data.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Roberts 2002

Study characteristics

Methods	**Study design**: single-centre, prospective, parallel-group, randomized placebo-controlled trial
Participants	**Site and country**: private ophthalmic day surgery unit, The Eye Institute, Sydney, Australia **Total number**: 135 eyes of 135 participants 1. Topical LA and placebo group, n = 67 eyes 2. Topical LA and intracameral lidocaine group, n = 68 eyes **Inclusion criteria** 1. All cataract surgery undergoing topical anaesthesia **Exclusion criteria** 1. None **Age of participants**: mean age topical LA and intracameral lidocaine group 75 years; mean age topical LA and placebo group 74 years (range 47 to 92 years) **Sex of participants**: details not stated
Interventions	**Trial drug**: intracameral 0.3 mL 1% unpreserved lidocaine **Placebo**: intracameral 0.3 mL BSS

Roberts 2002 *(Continued)*

	1. Topical LA (both groups): tetracaine 1% 2. Topical LA method (both groups): 1 drop 1 hour before surgery, 3 drops 5 minutes prior to surgery, and 1 drop prior to povidone-iodine (Betadine) prep Intracameral lidocaine/BSS given prior to capsulorhexis. All participants given IV sedation (midazolam 1 to 2 mg) 5 minutes before surgery. Music played throughout procedures. All surgery performed by 1 surgeon.
Outcomes	1. Participant's intraoperative pain score, measured using a 10-point visual analogue scale (Stevens 1992), recorded immediately postoperatively 2. Participant's autonomic intraoperative recordings: heart rate, blood pressure, oxygen saturation
Notes	Authors contacted for further information and response received. **Study dates**: not stated **Funding sources**: not stated **Conflicts of interest**: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description regarding random sequence generation
Allocation concealment (selection bias)	Unclear risk	No description regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Surgeon not masked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Anaesthetist, participant, and recovery nurse who made outcome measurements masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all participants enrolled in study.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Tan 2011

Study characteristics

Methods	**Study design**: 2-centre, prospective, parallel-group, randomized double-blinded, placebo-controlled trial
Participants	**Site and country**: Tan Tock Seng Hospital and Alexandra Hospital, Singapore

Tan 2011 *(Continued)*

	Total number: 506 eyes of 506 participants 1. Topical LA and placebo group, n = 229 eyes 2. Topical LA and intracameral lidocaine group, n = 277 eyes **Inclusion criteria** 1. Consecutive participants undergoing routine phacoemulsification under topical anaesthesia **Exclusion criteria** 1. Severe co-existing ocular pathology such as Fuchs' endothelial dystrophy, end-stage glaucoma, severe diabetic maculopathy, and proliferative diabetic retinopathy 2. Patients unsuitable for topical anaesthesia (anxious/anticipated high manipulation of intraocular tissues) 3. Unable or unwilling to give consent for the study 4. Intraoperative complications such as posterior capsule rupture **Age of participants**: mean topical LA and placebo group 67.5 years; mean topical LA and intracameral lidocaine group 66.8 years; P = 0.468 **Sex of participants**: topical LA and placebo group 47.2% male; topical LA and intracameral lidocaine group 51.3% male; P = 0.373
Interventions	**Trial drug**: intracameral 0.5 mL 1% preservative-free lidocaine **Placebo**: intracameral 0.5 mL BSS 1. Topical LA (both groups): lidocaine gel 2. Topical LA method (both groups): standardized volume of lidocaine gel instilled into conjunctival sac 5 min prior to surgery 3. Intracameral method: 0.5 mL of agent injected into anterior chamber immediately after corneal incision **Sedation**: not routinely given; if required, given based on standard anaesthesia protocols in the hospitals Surgery performed by 4 surgeons.
Outcomes	1. Participant's intraoperative pain score, measured using a 10-point visual analogue scale (Stevens 1992), administered immediately postoperatively in the recovery room
Notes	**Study dates**: 2003 to 2004 **Funding sources**: Tan Tock Seng Hospital small project research grant **Conflicts of interest**: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers generated and placed in sequentially numbered envelopes.
Allocation concealment (selection bias)	Low risk	Envelopes prepared by study co-ordinator.
Blinding of participants and personnel (performance bias)	Low risk	The surgeon, nurse assisting the surgery, participant, and investigator who performed the postoperative interview were blinded.

Tan 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The surgeon, nurse assisting the surgery, participant, and investigator who performed the postoperative interview were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all participants enrolled in study.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Tseng 1998

Study characteristics	
Methods	**Study design**: single-centre, prospective, randomized placebo-controlled trial
Participants	**Site and country**: Department of Ophthalmology, College of Medicine, National Cheng Kung Huniversity, Tainan, Taiwan, Republic of China **Total number**: 162 eyes of 162 participants 1. Topical LA and placebo group, n = 81 eyes 2. Topical LA and intracameral lidocaine group, n = 81 eyes **Inclusion criteria** 1. All undergoing cataract surgery **Exclusion criteria** 1. Movement disorders 2. Hearing difficulties 3. Excessive anxiety 4. Poor fixation due to nystagmus or strabismus 5. Not native language speakers for consent 6. Allergy to lidocaine or topical anaesthetic 7. Corneal/ocular problem precluding use of topical anaesthetic **Age of participants**: mean age topical LA plus intracameral lidocaine group 67.8 years; mean age topical LA plus placebo group 66.1 years; range 43 to 84 years; no difference between groups **Sex of participants**: topical LA plus intracameral lidocaine group 62.3% female; topical LA plus placebo group 59.3% female; no difference between groups
Interventions	**Trial drug**: intracameral 0.5 mL of 1% preservative-free lidocaine **Placebo**: intracameral 0.5 mL BSS 1. Topical LA (both groups): tetracaine 0.5% 2. Topical LA method (both groups): 3 doses of 2 drops in the 10 minutes prior to surgery. Intraoperatively, 2 drops before phaco and 2 drops before IOL insertion. Additional drops if patient discomfort or when procedure prolonged. Intracameral lidocaine/BSS given immediately after corneal incisions and entry into anterior chamber.

Tseng 1998 *(Continued)*

	Sedation: all participants given oral fludiazepam 0.5 mg and paracetamol 1.0 g 1 hour prior to surgery. All surgery performed by 1 surgeon.
Outcomes	1. Participant's intraoperative pain score, measured using a 10-point visual analogue scale (Stevens 1992), recorded immediately postoperatively
Notes	Authors contacted but no response received. **Study dates**: January 1997 to July 1997 **Funding sources**: not stated **Conflicts of interest**: authors declared no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table used.
Allocation concealment (selection bias)	Unclear risk	No details regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details regarding blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details regarding blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all participants enrolled in study.
Selective reporting (reporting bias)	Unclear risk	No study protocol available. Results covered all outcomes described in the methods.

Acronyms and abbreviations used in this table
ASA: American Society of Anesthesiologists
BP: blood pressure
BSS: balanced salt solution
HCI: hydrochloride
HR: heart rate
I/A: irrigation/aspiration
IOL: intraocular lens
IV: intravenous
LA: local anaesthetic
OVD: ophthalmic viscosurgical device
sd: standard deviation
VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Garcia 1998	Corneal endothelial toxicity effect assessed by comparing a topical and intracameral group with a peribulbar group rather than with a topical-alone group.
Goodarzi 2011	Only abstract in conference proceedings was published, with no extractable data and no author contact details.
Koch 1997	This prospective study looked only at the efficacy of "intracameral and topical" anaesthesia. No topical-only group was included.
Labetoulle 2016	Study did not include participants with pupil diameter less than 7 mm.
Lopez Valladares 2007	Both groups had intracameral anaesthesia but in different forms (lidocaine versus Visthesia).
Malecaze 2000	Selection of participants into trial was dependent on the experience of significant pain during surgery.
Masket 1998	Retrospective comparison only
Moschos 2011	Intracameral anaesthesia used was Visthesia (cohesive OVD consisting of sodium hyaluronate 1.5% and lidocaine hydrochloride 1%).
Nebbioso 2018	Study excluded more complicated operative cases, including hyperdense cataracts and participants with age-related macular degeneration, neovascular membranes, chorioretinal disease, glaucoma, optic neuritis, and ocular trauma.
Pandey 2001	Study excluded all patients with a pupil diameter of less than 5 mm or a shallow anterior chamber.
Papaconstantinou 2014	Intracameral anaesthesia used was Visthesia (cohesive OVD consisting of sodium hyaluronate 1.5% and lidocaine hydrochloride 1%).
Perone 2007	Intracameral anaesthesia used was Visthesia (cohesive OVD consisting of sodium hyaluronate 1.5% and lidocaine hydrochloride 1%).
Roux 1998	Dense cataracts were excluded.
Shah 2004	Study looked at endothelial damage associated with lidocaine (Xylocaine) use as topical anaesthesia. Dense cataracts were excluded.
Tan 2000	Study excluded all participants with a pupil diameter of less than 5 mm.
Wang 2013	Surgical technique for cataract surgery was not phacoemulsification, but rather MICS.
Weller 2002	Only Fuchs endothelial dystrophy participants were included.

Acronyms and abbreviations used in this table
MICS: microincision cataract surgery
OVD: ophthalmic viscosurgical device

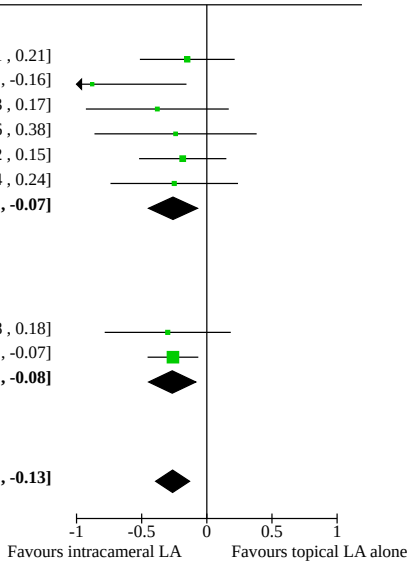
DATA AND ANALYSES

Comparison 1. Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Intraoperative pain or discomfort (continuous 10-point scale)	8	1692	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.39, -0.13]
1.1.1 No routine sedation given	6	1395	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.45, -0.07]
1.1.2 Routine sedation given	2	297	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.45, -0.08]
1.2 Intraoperative pain or discomfort (dichotomous)	7	1268	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.29, 0.57]
1.2.1 No routine sedation given	6	1148	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.26, 0.60]
1.2.2 Routine sedation given	1	120	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.16, 0.80]
1.3 Postoperative pain or discomfort (10-point scale)	4	751	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.29, 0.05]
1.3.1 No routine sedation given	3	631	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.27, 0.07]
1.3.2 Routine sedation given	1	120	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.27, 0.23]
1.4 Need for additional anaesthesia during surgery	7	1194	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.56, 1.39]
1.4.1 No routine sedation given	6	1060	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.56, 1.39]
1.4.2 Routine sedation given	1	134	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5 Mean change in corneal endothelial cell count from pre- to postoperatively (%)	4	254	Mean Difference (IV, Fixed, 95% CI)	0.89 [-1.12, 2.90]
1.6 Intraoperative adverse surgical events attributable to choice of anaesthesia	8	1726	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.32, 3.16]

Analysis 1.1. Comparison 1: Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, Outcome 1: Intraoperative pain or discomfort (continuous 10-point scale)

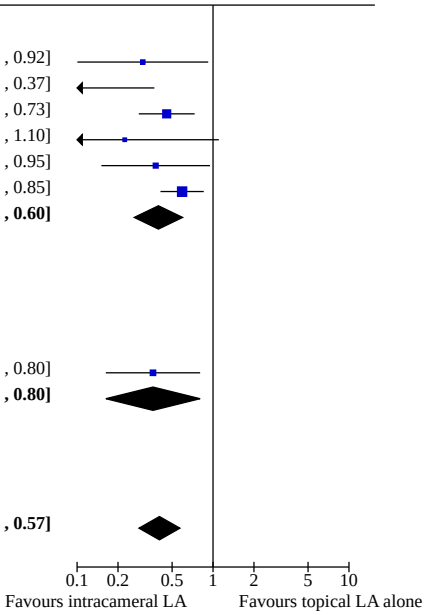
Study or Subgroup	Topical + intracameral LA Mean	SD	Total	Topical LA alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 No routine sedation given								
Boulton 2000	1.29	1.24	96	1.44	1.33	96	12.8%	-0.15 [-0.51 , 0.21]
Chuang 2007 (1)	0.64	1.5	33	1.52	1.5	33	3.2%	-0.88 [-1.60 , -0.16]
Crandall 1999	0.86	1.57	68	1.24	1.69	68	5.6%	-0.38 [-0.93 , 0.17]
Gillow 1999	1.86	2.26	99	2.1	2.23	101	4.4%	-0.24 [-0.86 , 0.38]
Joshi 2013	0.986	1.433	149	1.171	1.5	146	15.1%	-0.19 [-0.52 , 0.15]
Tan 2011	2.75	2.6339	277	3	2.9226	229	7.1%	-0.25 [-0.74 , 0.24]
Subtotal (95% CI)			**722**			**673**	**48.1%**	**-0.26 [-0.45 , -0.07]**
Heterogeneity: Chi² = 3.55, df = 5 (P = 0.62); I² = 0%								
Test for overall effect: Z = 2.71 (P = 0.007)								
1.1.2 Routine sedation given								
Roberts 2002	0.65	1.31	67	0.95	1.55	68	7.2%	-0.30 [-0.78 , 0.18]
Tseng 1998	0.37	0.58	81	0.63	0.68	81	44.6%	-0.26 [-0.45 , -0.07]
Subtotal (95% CI)			**148**			**149**	**51.9%**	**-0.27 [-0.45 , -0.08]**
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 2.88 (P = 0.004)								
Total (95% CI)			**870**			**822**	**100.0%**	**-0.26 [-0.39 , -0.13]**
Heterogeneity: Chi² = 3.58, df = 7 (P = 0.83); I² = 0%								
Test for overall effect: Z = 3.96 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%								



Footnotes
(1) Study was in paired eyes

Analysis 1.2. Comparison 1: Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, Outcome 2: Intraoperative pain or discomfort (dichotomous)

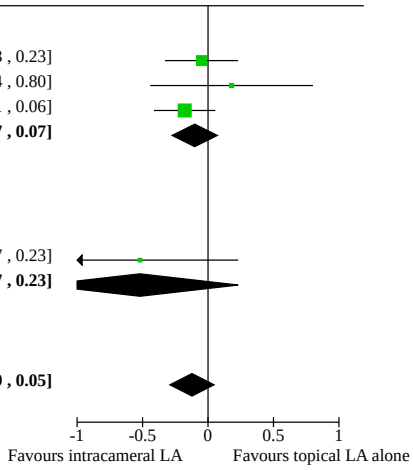
Study or Subgroup	Topical + intracameral LA Events	Total	Topical LA alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 No routine sedation given						
Carino 1998	7	30	15	30	8.2%	0.30 [0.10 , 0.92]
Chuang 2007 (1)	3	33	17	33	5.7%	0.09 [0.02 , 0.37]
Gills 1997	60	183	62	120	25.6%	0.46 [0.28 , 0.73]
Hussain 2017	2	60	8	60	4.3%	0.22 [0.05 , 1.10]
Martin 1998	9	40	23	53	11.0%	0.38 [0.15 , 0.95]
Tan 2011	84	277	97	229	31.6%	0.59 [0.41 , 0.85]
Subtotal (95% CI)		**623**		**525**	**86.4%**	**0.40 [0.26 , 0.60]**
Total events:	165		222			
Heterogeneity: Tau² = 0.09; Chi² = 8.49, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
1.2.2 Routine sedation given						
Lofoco 2008	13	60	26	60	13.6%	0.36 [0.16 , 0.80]
Subtotal (95% CI)		**60**		**60**	**13.6%**	**0.36 [0.16 , 0.80]**
Total events:	13		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)		**683**		**585**	**100.0%**	**0.40 [0.29 , 0.57]**
Total events:	178		248			
Heterogeneity: Tau² = 0.06; Chi² = 8.83, df = 6 (P = 0.18); I² = 32%						
Test for overall effect: Z = 5.13 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						



Footnotes
(1) Study was in paired eyes

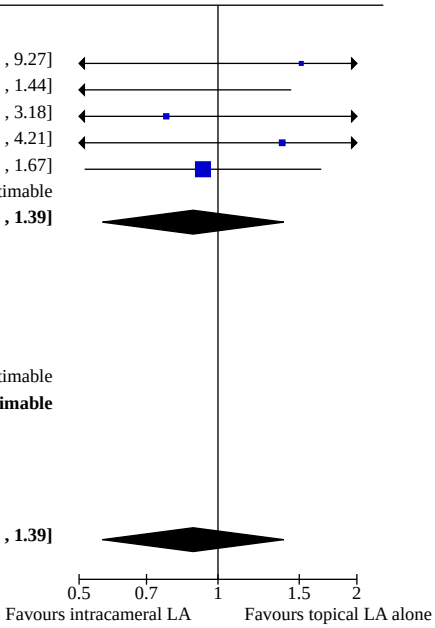
Analysis 1.3. Comparison 1: Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, Outcome 3: Postoperative pain or discomfort (10-point scale)

Study or Subgroup	Topical + intracameral LA Mean	SD	Total	Topical LA alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 No routine sedation given								
Crandall 1999	0.24	0.87	68	0.29	0.79	68	36.2%	-0.05 [-0.33 , 0.23]
Gillow 1999	2.02	2.35	99	1.84	2.13	101	7.3%	0.18 [-0.44 , 0.80]
Joshi 2013	0.7465	0.9742	149	0.9246	1.0769	146	51.4%	-0.18 [-0.41 , 0.06]
Subtotal (95% CI)			**316**			**315**	**95.0%**	**-0.10 [-0.27 , 0.07]**
Heterogeneity: Chi² = 1.33, df = 2 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.15 (P = 0.25)								
1.3.2 Routine sedation given								
Lofoco 2008	1.36	2.02	60	1.88	2.17	60	5.0%	-0.52 [-1.27 , 0.23]
Subtotal (95% CI)			**60**			**60**	**5.0%**	**-0.52 [-1.27 , 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.17)								
Total (95% CI)			**376**			**375**	**100.0%**	**-0.12 [-0.29 , 0.05]**
Heterogeneity: Chi² = 2.46, df = 3 (P = 0.48); I² = 0%								
Test for overall effect: Z = 1.43 (P = 0.15)								
Test for subgroup differences: Chi² = 1.13, df = 1 (P = 0.29), I² = 11.9%								



Analysis 1.4. Comparison 1: Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, Outcome 4: Need for additional anaesthesia during surgery

Study or Subgroup	Topical + intracameral LA Events	Total	Topical LA alone Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 No routine sedation given						
Boulton 2000	3	100	2	100	4.9%	1.52 [0.25 , 9.27]
Carino 1998	0	30	5	30	13.6%	0.08 [0.00 , 1.44]
Chuang 2007 (1)	4	33	5	33	11.0%	0.77 [0.19 , 3.18]
Crandall 1999	8	68	6	68	13.3%	1.38 [0.45 , 4.21]
Gills 1997	33	183	23	120	57.2%	0.93 [0.51 , 1.67]
Joshi 2013	0	149	0	146		Not estimable
Subtotal (95% CI)		**563**		**497**	**100.0%**	**0.88 [0.56 , 1.39]**
Total events:	48		41			
Heterogeneity: Chi² = 3.68, df = 4 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.4.2 Routine sedation given						
Roberts 2002	0	67	0	67		Not estimable
Subtotal (95% CI)		**67**		**67**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**630**		**564**	**100.0%**	**0.88 [0.56 , 1.39]**
Total events:	48		41			
Heterogeneity: Chi² = 3.68, df = 4 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Not applicable						



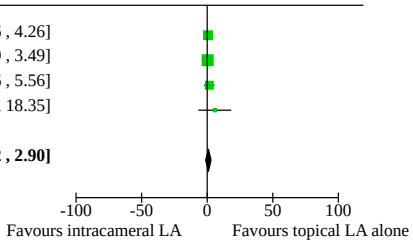
Footnotes

(1) Study was in paired eyes

Analysis 1.5. Comparison 1: Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, Outcome 5: Mean change in corneal endothelial cell count from pre- to postoperatively (%)

Study or Subgroup	Topical + intracameral LA Mean	SD	Total	Topical LA alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carino 1998	6.7	6.3	28	6.1	7.6	28	30.3%	0.60 [-3.06 , 4.26]
Chuang 2007 (1)	7.17	6.5	33	6.82	6.5	33	41.2%	0.35 [-2.79 , 3.49]
Crandall 1999	9.7	5.5	21	8.1	6.9	18	25.8%	1.60 [-2.36 , 5.56]
Martin 1998	18.71	37.43	40	12.9	17.74	53	2.6%	5.81 [-6.73 , 18.35]
Total (95% CI)			**122**			**132**	**100.0%**	**0.89 [-1.12 , 2.90]**

Heterogeneity: Chi² = 0.85, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Not applicable

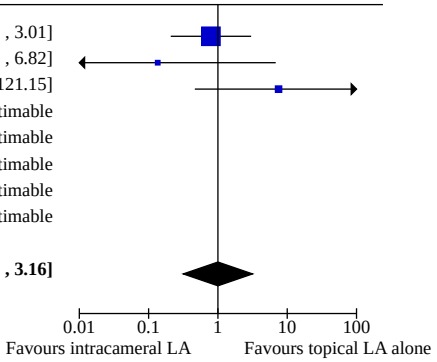


Footnotes
(1) Study was in paired eyes

Analysis 1.6. Comparison 1: Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification cataract surgery in adults, Outcome 6: Intraoperative adverse surgical events attributable to choice of anaesthesia

Study or Subgroup	Topical + intracameral LA Events	Total	Topical LA alone Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Boulton 2000	4	96	5	96	74.3%	0.79 [0.21 , 3.01]
Chuang 2007 (1)	0	33	1	33	8.6%	0.14 [0.00 , 6.82]
Crandall 1999	2	68	0	68	17.1%	7.50 [0.46 , 121.15]
Gills 1997	0	183	0	120		Not estimable
Joshi 2013	0	149	0	146		Not estimable
Martin 1998	0	40	0	53		Not estimable
Roberts 2002	0	67	0	68		Not estimable
Tan 2011	0	277	0	229		Not estimable
Total (95% CI)		**913**		**813**	**100.0%**	**1.00 [0.32 , 3.16]**
Total events:	6		6			

Heterogeneity: Chi² = 3.13, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Footnotes
(1) Study was in paired eyes

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Cataract] explode all trees
#2 MeSH descriptor: [Cataract Extraction] explode all trees
#3 MeSH descriptor: [Phacoemulsification] explode all trees
#4 Cataract* near surg*
#5 Cataract* near extract*
#6 Cataract and (surg* or extract*)
#7 cataract* or sutureless or nonstitch* or non stitch* or no stitch* or nostitch*
#8 phako* or phaco*
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Anesthesia, Local] explode all trees
#11 MeSH descriptor: [Anesthetics, Local] explode all trees
#12 MeSH descriptor: [Lidocaine] explode all trees

#13 (anaesthe* or anesthe*) and (local or topical)
#14 lignocain* or lidocain* or intracamer* or intra camer*
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15 in trials

Appendix 2. MEDLINE (OvidSP) search strategy

1 exp Cataract/ or exp Cataract Extraction/ or exp Phacoemulsification/ or (cataract adj3 (surg* or extract*)).mp. or (cataract* or sutureless or nonstitch* or non stitch* or no stitch* or nostitch or phako* or phaco*).ti,ab.
2 exp Anesthesia, Local/ or exp Anesthetics, Local/ or exp Lidocaine/ or (an?esthe* adj3 (local or topical)).mp. or (lignocain* or lidocain* or intracamer* or intra camer*).mp.
3 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
4 1 and 2 and 3

Appendix 3. Embase (OvidSP) search strategy

1 exp cataract/ or exp cataract extraction/ or exp extracapsular cataract extraction/ or exp intracapsular cataract extraction/ or exp phacoemulsification/ or (cataract adj3 (surg* or extract*)).mp. or (cataract* or sutureless or nonstitch* or non stitch* or no stitch* or nostitch or phako* or phaco*).ti,ab.
2 exp local anesthesia/ or exp local anesthetic agent/ or exp local anesthesia/ or exp topical anesthesia/ or exp lidocaine/ or exp intracameral drug administration/ or (an?esthe* adj3 (local or topical)).mp. or (lignocain* or lidocain* or intracamer* or intra camer*).mp.
3 (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 multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.
4 1 and 2 and 3

Appendix 4. LILACS (BIREME iAH) search strategy

"CATARACT" or "CATARACT EXTRACTION/" or "CATARACT/" or "CATARACTS" or "PHACOEMULSIFICATION" or "cataract*" or "phako$" or "phaco$" [Words] and "ANESTHESIA" or "ANESTHETICS" or "ANESTHETICS/" or "LIDOCAINE" or anesthe$ or anaesthe$ or lignocaine$ or lidocain$ or intracamer$ or intra camer$ [Words]

WHAT'S NEW

Date	Event	Description
28 July 2020	New search has been performed	We updated the review. We ran the search to 4 February 2020. We identified five new randomized controlled trials that met the inclusion criteria of the review (Chuang 2007; Hussain 2017; Joshi 2013; Lofoco 2008; Tan 2011).
28 July 2020	New citation required and conclusions have changed	One new author has joined the team since publication of the previous review (Minakaran N). The overall conclusions with respect to primary outcomes are not changed by the inclusion of new studies, although stronger inferences are made. The conclusion with respect to corneal toxicity is changed, in that the reduction in heterogeneity compared with the previous review means that the result can be interpreted with more certainty. We updated the methodology to include 'Risk of bias' graphs and summaries, sensitivity analyses, and assessment of the quality of the evidence with the inclusion of a 'Summary of findings' table. We performed subgroup analyses to account for the potential influence of using sedation on the pain score results. We changed the parameter used to compare corneal toxicity between groups from postoperative endothelial cell count to change in endothelial cell count (preoperative to postoperative).

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 3, 2007

Date	Event	Description
11 April 2017	New search has been performed	New studies awaiting classification included.
6 March 2017	New search has been performed	New search January 2017
9 November 2010	Amended	Contact details updated.
18 February 2009	Amended	Minor editing of text
1 September 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Neda Minakaran (NM) Daniel G Ezra (DGE), Bruce DS Allan (BDA)

Conceiving the review: BDA
Designing the review: BDA, DGE (and Anil K Nambiar; Nambiar 2005)
Co-ordinating the review: BDA
Undertaking manual searches: DGE, Anil K Nambiar, NM
Screening search results: BDA, DGE, NM
Organizing retrieval of papers: DGE, NM
Screening retrieved papers against inclusion criteria: BDA, DGE, NM
Appraising quality of papers: DGE, BDA, NM
Abstracting data from papers: DGE, BDA, NM
Writing to authors of papers for additional information: DGE, NM
Providing additional data about papers: DGE, NM
Obtaining and screening data on unpublished studies: DGE, NM
Data management for the review: DGE, BDA, NM
Entering data into Review Manager 5 (Review Manager 2014): DGE, NM
Analysis of data: DGE, BDA, NM
Interpretation of data: DGE, BDA, NM
Writing the review: DGE, BDA, NM
Securing funding for the review: not applicable
Performing previous work that was the foundation of the present study: BDA, DGE
Guarantor for the review (one author): NM
Statistical analysis: DGE, NM

DECLARATIONS OF INTEREST

Neda Minakaran: none known

Daniel G Ezra: none known

Bruce DS Allan: none known

SOURCES OF SUPPORT

Internal sources

- Moorfields Eye Hospital NHS Foundation Trust, UK

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the protocol and first version of this review (Ezra 2007).

Updating the review title

We updated the review title from "Topical anaesthesia alone versus topical anaesthesia with intracameral lidocaine for phacoemulsification" to "Topical anaesthesia plus intracameral lidocaine versus topical anaesthesia alone for phacoemulsification cataract surgery in adults". We did this to clarify that 'topical anaesthesia plus intracameral lidocaine' was the experimental intervention, and to include the population in the title.

Change in authors

Neda Minakaran joined the review team for the update.

Improved details regarding types of interventions

We clarified that we did not place any restrictions on concentration of intracameral lidocaine.

Improved details regarding outcome measures

We clarified details of outcome measures, including methods of obtaining measurements, scales and ranges, and timing of measurement. We used the measure "percentage change in corneal endothelial cell count from pre- to postoperatively" as a proxy for corneal toxicity instead of "postoperative endothelial cell count". We felt that this was a more useful and accurate measure to show how much damage had been done to the corneal endothelium from the surgery and anaesthesia, as it showed a change from baseline. Comparing postoperative cell counts alone is less meaningful, as we do not know what the baseline preoperative cells counts were. To compare this between groups assumes that all eyes had the same baseline cell count, which is unlikely.

Inclusion of search of trial registries

We searched a number of electronic trial registries for the update, for ongoing and unpublished trials and for published trial protocols.

Improved assessment of risk of bias in included studies

We improved the assessment of trial quality in accordance with the tools and methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We created more detailed and complete 'Risk of bias' tables for each study, and created a 'Risk of bias' graph.

Explanation of how missing data were dealt with

In the update, where there were missing data and the study authors did not respond when contacted, we imputed missing data to include in the statistical evaluations.

Improved assessment of heterogeneity

We improved our methodology for assessing heterogeneity.

Improved assessment of reporting biases

In the update, we performed a more thorough search for reporting bias.

New subgroup analyses

We planned to look at subgroups of participants receiving or not receiving oral or intravenous sedation for the update, as we considered that being sedated could potentially affect outcomes relating to pain perception and satisfaction.

More extensive sensitivity analyses

We included sensitivity analyses in the update looking at the effects of imputing missing data, and of combining paired-eye with parallel trial data.

Inclusion of 'Summary of findings' table and GRADE

We improved our methodology for assessing the quality of evidence by employing the GRADE approach for the update, and created a 'Summary of findings' table.

Improved 'Characteristics of included studies' table

We improved our 'Characteristics of included studies' table to include more detailed information about trials, including sources of funding and conflicts of interests of the authors, as per the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards.

INDEX TERMS

Medical Subject Headings (MeSH)

Anesthesia, Local [*methods]; Anesthetics, Combined [administration & dosage]; Anesthetics, Local [*administration & dosage]; Bupivacaine [administration & dosage]; Lidocaine [*administration & dosage]; *Phacoemulsification; Propoxycaine [administration & dosage]; Randomized Controlled Trials as Topic; Tetracaine [administration & dosage]

MeSH check words

Humans