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SYSTEMATIC REVIEW

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Regenerative surgical treatment of furcation defects: A systematic review and Bayesian network meta-analysis of randomized clinical trials

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Abstract

Aims: To investigate the clinical performance of regenerative periodontal surgery in the treatment of furcation defects versus open flap debridement (OFD) and to compare different regenerative modalities.

Material and Methods: A systematic search was conducted to identify RCTs evaluating regenerative surgical treatment of furcations with a minimum of 12-month follow-up. Three authors independently reviewed, selected and extracted data from the search conducted and assessed risk of bias. Primary outcomes were tooth loss, furcation improvement (closure/conversion) (FImp), gain of horizontal bone level (HBL) and attachment level (HCAL). Secondary outcomes were gain in vertical attachment level (VCAL), probing pocket depth (PPD) reduction, PROMs and adverse events. Data were summarized into Bayesian standard and network meta-analysis in order to estimate direct and indirect treatment effects and to establish a ranking of treatments.

Results: The search identified 19 articles, reporting on 20 RCTs (19 on class II, 1 on class III furcations) with a total of 575 patients/787 defects. Tooth loss was not reported. Furcation closure ranged between 0% and 60% (10 trials), and class I conversion from 29% to 100% (six trials). Regenerative techniques were superior to OFD for FImp (OR = 20.9; 90% CrI = 5.81, 69.41), HCAL gain (1.6 mm), VCAL gain (1.3 mm) and PPD reduction (1.3 mm). Bone replacement grafts (BRG) resulted in the highest probability (Pr = 61%) of being the best treatment for HBL gain. Non-resorbable membranes + BRG ranked as the best treatment for VCAL gain (Pr = 75%) and PPD reduction (Pr = 56%).

Conclusions: Regenerative surgery of class II furcations is superior to OFD. FImp (furcation closure or class I conversion) can be expected for the majority of defects. Treatment modalities involving BRG are associated with higher performance.

KEYWORDS
furcation defect, meta-analysis, periodontal regeneration, periodontitis, systematic review

Jepsen and Gennai contributed equally to this work.

1 | INTRODUCTION

It is well established that periodontitis-affected multi-rooted teeth presenting with furcation involvement, exhibit a higher rate of tooth loss than those without furcation defects (Nibali et al., 2016). Furcation defects represent a challenge for the clinician due to their anatomy, their accessibility and the complexity of the healing. The main clinical challenge for the treatment of the furcation defects is in the complexity of their topography that impairs a proper debridement (Al-Shammari, Kazor, & Wang, 2001; Jepsen, Deschner, Braun, Schwarz, & Eberhard, 2011; Svärdström & Wennström, 1988). Various types of treatments have been evaluated for treating furcation defects. Non-surgical periodontal treatment has been shown to have limited results (Loos, Nylund, Claffey, & Egelberg, 1989; Nordland et al., 1987). A recent systematic review reports that surgical debridement of furcation defects could result in a modest improvement in clinical parameters (Graziani et al., 2015).

In contrast, it has been demonstrated that compared to open flap surgery regenerative treatment led to superior outcomes (Jepsen, Eberhard, Herrera, & Needleman, 2002). This has been further confirmed and regenerative surgery, particularly in class II defects, has become the treatment that should be considered before resective therapy or extraction (Avila-Ortiz, Buitrago, & Reddy, 2015). Various surgical regenerative techniques have been proposed in order to treat furcation defects of periodontitis-affected teeth. Among them, most frequently described are guided tissue regeneration (GTR) using either resorbable or non-resorbable membranes; bone replacement grafts (autografts, allografts or xenografts) (BRG), bioactive agents such as enamel matrix derivative (EMD), platelet-derived growth factor (PDGF), platelet-rich plasma, platelet-rich fibrin (PRP/PRF), and combinations of them (Jepsen & Jepsen, 2018; Sanz et al., 2015). Indeed, there is also evidence from human histological studies for periodontal regeneration in class II furcation defects (Laugisch et al., 2019).

So far the comparative efficacy of different periodontal regenerative approaches for furcation defects has not been established. Therefore, the aim of this systematic review was to evaluate the performance and the added value of surgical regenerative techniques in terms of tooth loss, furcation closure/conversion, horizontal bone level gain and other periodontal parameters of teeth affected by periodontitis-related furcation defects, at least 12 months after surgery. A Bayesian network meta-analysis (NM) model was considered in order to summarize quantitative data from included RCTs to establish a ranking in efficacy of the treatment options, and to identify the best regenerative technique.

Clinical Relevance

Scientific rationale for the study: To investigate the effects of regenerative surgical treatment of furcation defects in a systematic review and Bayesian network meta-analysis of RCTs with at least 12 months of follow-up.
Principal findings: Various regenerative approaches, including the use of (non)-resorbable barrier membranes, bone replacement grafts, EMD and their combinations, have been evaluated in class II furcation defects and have been shown to be superior compared to open flap debridement.
Practical implications: Regenerative procedures can be recommended to improve the clinical outcomes of periodontal surgery in class II furcation defects.

2 | MATERIALS AND METHODS

2.1 | Protocol development and eligibility criteria

A detailed protocol was reported according to the PRISMA (Preferred Reporting Items Systematic review and Meta-Analyses) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (Hutton et al., 2015; Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009). The protocol for this systematic review was registered (PROSPERO, International Prospective Register of Systematic Reviews, # CRD42019124466).

The following focused question was phrased: "What is the efficacy of regenerative periodontal surgery in terms of tooth loss, furcation conversion and closure, horizontal clinical attachment level (HCAL) and bone level (HBL) gain as well as other periodontal parameters in teeth affected by periodontitis-related furcation defects, at least 12 months after surgery?"

Articles to be included had to follow the following PICO (Glossary of Evidence-Based Terms 2007):

(P) Type of participants: patients with a clinical diagnosis of periodontitis-related furcation defects of any type (class I, II and III).
(I) Type of interventions: any type of surgical regenerative treatment including possible combination therapies for treatment of periodontitis-related furcation defects.
(C) Comparison between interventions: open flap debridement (OFD) and any type of possible comparison between surgical regenerative treatments of periodontitis-related furcation defects, excluding variations of the same technique, with at least 12 months of post-surgical follow-up.
(O) Type of outcome measures: Primary outcomes were tooth loss, furcation conversion and closure, horizontal clinical attachment level (HCAL) and bone level (HBL) gain; secondary outcomes were vertical clinical attachment level (VCAL) gain and probing pocket depth (PPD) reduction as well as patient-reported outcomes and adverse events.

Only RCTs of at least 12 months' duration and a population of at least 10 subjects were considered for inclusion in this review. No time and language limitations were applied. No time limitation was applied. Only articles in the English language were considered for this review after the electronic search.

2.2 | Information sources and search

Search on electronic databases up to and including December 2018. The search was applied to the Cochrane Oral Health Group specialist trials, MEDLINE via PubMed and EMBASE via Ovid. The strategy used was a combination of MeSH terms and free-text words:

- Intervention: guided periodontal tissue regeneration [MeSH Terms] OR surgical flaps [MeSH Terms] OR perio* [Text word] OR regener* [Text word]

AND

- Disease: furc* [Text Word] OR molar* [Text Word] OR multi-rooted* [Text Word] OR multi-rooted* [Text Word] OR radicular [Text Word]

AND

- Study design: longitudinal study [MeSH Terms] OR randomized controlled trial [MeSH Terms] OR clinical trial [MeSH Terms] OR prospective study [Mesh Terms]

Hand searching was also performed on Journal of Clinical Periodontology, the Journal of Periodontal Research, and the Journal of Periodontology from January 1985 up to December 2018 and on bibliographies of all retrieved papers and review articles. In addition experts, groups and industry involved in periodontal surgical research were contacted to find other trials or to clarify ambiguous or missing data.

2.3 | Study selection and data collection

Eligibility assessment was performed through titles and abstract analysis and full-text analysis. Titles and abstracts of the search results were initially screened by two reviewers for possible inclusion in the review (SG and JH). Reviewers were calibrated for study screening against another reviewer (FG) with experience in conducting systematic reviews. Each round of calibration consisted of a duplicate, independent validity assessment of 20 titles, and abstracts from the search. Reviewer had to achieve a consistent level of agreement (K score > .8). In order not to exclude potentially relevant articles, unclear abstracts were included in the full-text analysis. The full text of all studies of possible relevance was then obtained for independent assessment by three reviewers (SG, JH and SJ) against the stated inclusion criteria. Any disagreement was resolved by discussion among the reviewers. The three reviewers conducted all quality assessments independently and data of the included articles were extracted through an ad hoc extraction sheet.

2.4 | Data items

Tooth loss was defined as the percentage of teeth that were lost. Because of some ambiguity and heterogeneity in the definition of complete and partial furcation closure, a binary outcome “Furcation Improvement (FImp)” was created, where “improved” meant that furcation defects had a furcation class reduction (conversion from class II to class I) or complete closure after surgical intervention; while “not improved” meant that furcation defects did not improve or had worsened after surgical intervention. HCAL and HBL gain, VCAL gain and PPD reduction had to be expressed as the average difference baseline/follow-up of the treated sites in millimetres. HCAL gain was the change in horizontal depth of the furcation (soft tissue measurement); HBL gain was defined as the change of horizontal component of the osseous defect (hard-tissue measurement); VCAL was the distance between the bottom of the pocket and a fixed reference point (i.e. cemento-enamel junction). The reviewers did not make any additional calculations on these parameters. Thus, studies not reporting differences between baseline and follow-up examinations were excluded unless data of each patient was provided. In the latter case, the average difference was calculated by the authors. Patient-reported outcomes and adverse events reporting were also collected.

2.5 | Summary measures

Mean differences between post-treatment and pre-treatment along with respective standard deviations were extracted from each primary study for all continuous outcomes. If standard deviation of the mean difference was not reported it was calculated by using the standard deviation of the pre- and post-treatment means, assuming the smallest correlation coefficient calculated by other studies reporting complete summary data (Elbourne et al., 2002). Subsequently, difference between treatments was calculated for each study. For split-mouth studies, the standard error of between-groups mean difference was obtained by the same aforementioned method using a between sites (within the same patient) correlation coefficient of .5. For dichotomous outcomes (FImp), a logarithmic transformation was applied.

Data were structured to gather firstly the adjunctive effect of surgical regeneration versus open flap debridement and then to compare the various technique among themselves.

2.6 | Geometry of the network

Graphical representation of evidence base was performed through plots of networks (Chaimani, Higgins, Mavridis, Spyridonos, & Salanti, 2013) generated using Stata version 13 (StataCorp, Stata Statistical Software). The geometry of the treatment network was estimated in terms of diversity and co-occurrence of treatments using the PIE index and the *C*-score (Salanti, Higgins, Ades, & Ioannidis, 2008).

2.7 | Data synthesis and analysis

Network meta-analyses (NMs) were performed within a Bayesian framework for comparing the effect of multiple treatments on the same outcome (JB, ZK). Direct and indirect treatment comparisons were analysed at the same time by using the Bayesian random-effects model for NM proposed by Buti, Baccini, Nieri, La Marca, and Pini-Prato (2013). An efficacy ranking among the tested treatments and the probability (Pr) that each of the surgical techniques included in the analysis was the best were also estimated (Higgins & Thompson, 2002; Lu & Ades, 2004). Bayesian pairwise single meta-analyses (SM) were performed when possible. Model specification details, assessment of network heterogeneity and inconsistency, estimation of treatment ranking, best probabilities and cumulative ranking curves and surfaces under these curves (SUCRA) as well as software used for NM and SM are reported in Appendix S1. Variability around treatment estimates was reported as 90% Credibility Intervals (90% CrI).

2.8 | Publication bias

Possible publication bias was assessed plotting the intervention effect (centred at comparison-specific pooled effect for network meta-analyses) against the standard error when at least 10 studies could be included in the meta-analyses. Publication bias was evaluated looking at asymmetry in the funnel plots using the methods described by Begg and Egger (Begg & Mazumdar, 1994; Egger, Smith, Schneider, & Minder, 1997).

2.9 | Risk of bias within individual studies

Risk of bias was evaluated through a process of quality analysis performed by two reviewers. Quality analysis of randomized clinical trial (RCT) according to the Cochrane Reviewers' Handbook (Higgins & Green, 2011) implied the assessment of six RCT issues: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants, personnel and outcome assessors, (d) handling of incomplete outcome data, (e) selective outcome reporting and (f) other sources of bias. All the six included issues were finally deemed as adequate, inadequate, or unclear (Higgins, Altman, & Sterne, 2009). In order to properly assess other sources of bias, the CONSORT guidelines for non-pharmacological treatments (NPT) were used such as information concerning the study design, the source of funding, the setting of the study, the therapist's expertise, the definition of level analysis, the calibration, the statistical methods, the definition of the furcation defect, the participants' smoking habits, the initial oral hygiene conditions, and the supportive periodontal treatment (Boutron, Moher, Altman, Schulz, & Ravaud, 2008).

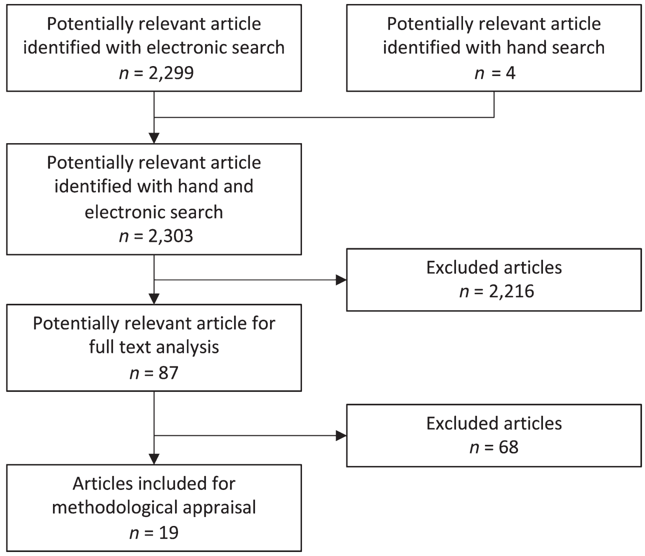

FIGURE 1 Flow chart of study selection

2.10 | Risk of bias across studies

Assessment of risk of bias across all studies was performed using the "Possible approach for summary assessment of the risk of bias" (Higgins & Green, 2011).

3 | RESULTS

3.1 | Study selection

A total of 2,303 studies were identified for inclusion in the review. The electronic search determined a total of 2,299 articles. Hand searching identified a further four articles for the full-text analysis (Figure 1). Screening of titles and abstracts led to rejection of 2,216 articles, and thus, the full text of the remaining 87 articles was obtained. After full-text analysis and the exclusion of further 68 articles, the remaining 19 articles were analysed for methodological quality and availability of data for meta-analysis. These 19 publications, representing 20 trials, met the criteria for inclusion in this meta-analysis. Characteristics of the included studies are reported in Table 1. The list of the 68 excluded studies and the reasons for their exclusion are shown in Appendix S2.

3.2 | Study characteristics

3.2.1 | Study design and study population

Characteristics of the included studies are depicted in Table 2. All studies had a follow-up of at least 12 months. The included population consisted of 575 subjects, with an age range of 31–80 years and a total of 787 furcation-involved molars were treated. Fifteen studies included only mandibular (buccal and/or lingual) furcation defects, three studies both mandibular and maxillary (buccal) defects, whereas one trial included exclusively maxillary (buccal) defects. No studies on class I furcations were identified. Only one study included class III furcation defects, whereas the remaining were class II defects. Nine trials had a split-mouth design, whereas the others had a parallel-group design. In all the studies, a cycle of non-surgical periodontal treatment was reported that had been conducted prior to the surgical intervention with the exception of the studies by Gantes, Synowski, Garrett, and Egelberg (1991) and Garrett, Martin, and Egelberg (1990).

3.2.2 | Type of interventions

A variety of interventions were employed (Table 2). GTR technique with non-resorbable membrane (GTR-NONRES) using expanded poly-tetra-fluoro-ethylene (ePTFE) was reported in 11 trials. The GTR technique with resorbable membrane (GTR-RES) was tested in 10 studies. EMD was used in three trials. Bone replacement grafts (BRG) were used alone in two studies, in combination with GTR techniques in six trials and in combination with EMD in one study. Open flap debridement (OFD) served in five trials as non-regenerative control group.

3.3 | Synthesis of the results

The following treatment grouping was created:

- GTR techniques with non-resorbable membrane (GTR-NONRES) made of: expanded PTFE, synthetic wound dressing or teflon;
- GTR techniques with resorbable membrane (GTR-RES) made of collagen, polylactic/polyglycolic acid, periostal, calcium sulphate or cellulose. The application of autologous connective tissue graft was also considered in this group;
- Regenerative techniques with bone replacement grafts (BRG) including autografts, demineralized freeze-dried bone allografts, xenografts, hydroxyapatite with b-tricalcium phosphate or bioactive glass;
- Regenerative techniques with enamel matrix derivative (EMD);
- Open flap debridement (OFD).

Nine treatment alternatives could be considered for BNM and SM analyses: (a) GTR-NONRES, (b) GTR-RES; (c) GTR-NONRES + BRG; (d) GTR-RES + BRG; (e) GTR-RES + BRG+EMD; (f) BRG alone; (g) EMD alone; (h) EMD + BRG; and (i) OFD.

Standard Bayesian meta-analysis (SM) was performed to compare all regenerative techniques combined in a single group (ALLREG) versus OFD procedures for FImp, HCAL gain, VCAL gain and PPD reduction (Figure 2a–d), and to evaluate HCAL gain comparing GTR-NONRES + BRG versus OFD (Figure S1), and comparing GTR-NONRES versus GTR-RES (Figure S2).

Bayesian network meta-analysis (NM) was possible for HBL gain, PPD reduction and VCAL gain. Network plots are depicted in Figure 3a–c.

3.3.1 | Tooth loss, furcation closure and furcation conversion

Tooth loss was not reported in any of the studies.

Furcation closure was reported in 10 studies. Frequencies of furcation closure ranged between 22% and 36% for GTR-NONRES (three studies, 113 defects), between 0% and 24% for GTR-RES (five studies, 172 defects), between 0% and 18% for EMD (two studies, 58 defects), between 0% and 56% for BRG (two studies, 30 defects) and between 0% and 60% for combination therapies (seven studies, 106 defects) (Table 3).

Furcation conversion from class II to class I was specified in six studies including 371 defects and the reported frequencies ranged from 20% to 100% (Table 3).

Furcation Improvement (FImp) was obtained in 19 out of 30 (63%) surgically treated defects for BRG, 48 out of 58 (83%) for EMD, 12 out of 14 (86%) for BRG + EMD, 68 out of 114 (60%) for GTR-NONRES, 23 out of 45 (51%) for GTR-NONRES + BRG, 113 out of 173 (65%) for GTR-RES, 22 out of 37 (59%) for GTR-RES + BRG, 10 out of 10 (100%) for GTR-RES + BRG+EMD and 3 out of 55 (6%) for OFD.

3.3.2 | Comparison of regenerative techniques versus OFD (SM)

FImp

The Bayesian SM for FImp (three RCTs) comparing all the regenerative techniques (ALL REG) versus OFD estimated a significant OR of 20.91 (90% CrI = 5.81, 69.41; I^2 = 31.5, 90% CrI = 1.07; 8.37317E + 29) in favour of regenerative techniques (Figure 2a).

HCAL gain

The Bayesian SM for HCAL gain (three RCTs) comparing all the regenerative techniques (ALL REG) versus OFD estimated a significant mean difference of 1.6 mm (90% CrI = 0.79, 2.39; I^2 = 94.0, 90% CrI = 81.60; 99.08) in favour of regenerative techniques (Figure 2b).

VCAL gain, PPD reduction

The Bayesian SM for VCAL gain and PPD (four RCTs) reduction comparing all the regenerative techniques (ALL REG) versus OFD estimated significant mean differences of 1.34 mm (90% CrI = 0.58, 2.08; I^2 = 91.30, 90% CrI = 78.54; 98.06) and of 1.29 mm (90% CrI = 0.3; 2.26; I^2 = 93.90, 90% CrI = 84.35; 98.65), respectively in favour of regenerative techniques (Figure 2c,d).

TABLE 1 Publications/Studies included in the final review: citations

Queiroz, L.A., Santamaria, M.P., Casati, M.Z., Ruiz, K.S., Nociti, F., Sallum, A.W. & Sallum, E.A. (2016) Enamel matrix protein derivative and/or synthetic bone substitute for the treatment of mandibular class II buccal furcation defects. A 12-month randomized clinical trial. *Clinical Oral Investigations* **20**, 1597–1606.
Leite, A.C., Oliveira, R.R., Novaes, A.B., O'Connell, P.A., Grisi, M.F., Taba, M., Palioto, D.B. & Souza, S.L. (2013) Effect of early membrane removal on the treatment of mandibular class II furcation defects--a controlled clinical trial with re-entry after 12 months. *Brazilian Dental Journal* **24**, 402–409.
Jaiswal, R. & Deo, V. (2013) Evaluation of the effectiveness of enamel matrix derivative, bone grafts, and membrane in the treatment of mandibular Class II furcation defects. *International Journal of Periodontics & Restorative Dentistry* **33**, e58–64.
Santana, R.B., de Mattos, C.M.L. & Van Dyke, T. (2009) Efficacy of combined regenerative treatments in human mandibular class II furcation defects. *Journal of Periodontology* **80**, 1756–1764.
Villaça, J.H., Rodrigues, D.C., Novaes, A.B., Taba, M., Souza, S.L. & Grisi, M.F. (2004) Root trunk concavities as a risk factor for regenerative procedures of class II furcation lesions in humans. *Journal of Periodontology* **75**, 1493–1499.
Jepsen, S., Heinz, B., Jepsen, K., Arjomand, M., Hoffmann, T., Richter, S., Reich, E., Sculean, A., Gonzales, J.R., Bödeker, R.H. & Meyle, J. (2004) A randomized clinical trial comparing enamel matrix derivative and membrane treatment of buccal Class II furcation involvement in mandibular molars. Part I: study design and results for primary outcomes. *Journal of Periodontology* **75**, 1150–1160.
Maragos, P., Bissada, N.F., Wang, R. & Cole, B.P. (2002) Comparison of three methods using calcium sulfate as a graft/barrier material for the treatment of Class II mandibular molar furcation defects. *International journal of Periodontics & Restorative Dentistry* **22**, 493–501.
Pruthi, V.K., Gelskey, S.C. & Mirbod, S.M. (2002) Furcation therapy with bioabsorbable collagen membrane: a clinical trial. *Journal of the Canadian Dental Association* **68**, 610–615.
Karapataki, S., Falk, H., Hugoson, A., Olsson, G. & Slotte, C. (1999) Treatment of class II furcation defects using resorbable and non-resorbable GTR barriers. *Swedish Dental Journal* **23**, 173–183.
De Leonardis, D., Garg, A.K., Pedrazzoli, V. & Pecora, G.E. (1999) Clinical evaluation of the treatment of class II furcation involvements with bioabsorbable barriers alone or associated with demineralized freeze-dried bone allografts. *Journal of Periodontology* **70**, 8–12.
de Santana, R.B., Gusman, H.C. & Van Dyke, T.E. (1999) The response of human buccal maxillary furcation defects to combined regenerative techniques--two controlled clinical studies. *Journal of the International Academy of Periodontology* **1**, 69–77.
Bouchard, P., Giovannoli, J.L., Mattout, C., Davarpanah, M. & Etienne, D. (1997) Clinical evaluation of a bioabsorbable regenerative material in mandibular class II furcation therapy. *Journal of Clinical Periodontology* **24**, 511–518.
Garrett, S., Polson, A.M., Stoller, N.H., Drisko, C.L., Caton, J.G., Harrold, C.Q., Bogle, G., Greenwell, H., Lowenguth, R.A., Duke, S.P. & DeRouen, T.A. (1997) Comparison of a bioabsorbable GTR barrier to a non-absorbable barrier in treating human class II furcation defects. A multi-center parallel design randomized single-blind trial. *Journal of Periodontology* **68**, 667–675.

(Continues)

TABLE 1 (Continued)

Hugoson, A., Ravald, N., Fornell, J., Johard, G., Teiwik, A. & Gottlow, J. (1995) Treatment of class II furcation involvements in humans with bioresorbable and nonresorbable guided tissue regeneration barriers. A randomized multi-center study. *Journal of Periodontology* **66**, 624–634.
Wang, H.L., O'Neal, R.B., Thomas, C.L., Shyr, Y. & MacNeil, R.L. (1994) Evaluation of an absorbable collagen membrane in treating Class II furcation defects. *Journal of Periodontology* **65**, 1029–1036.
Blumenthal, N.M. (1993) A clinical comparison of collagen membranes with e-PTFE membranes in the treatment of human mandibular buccal class II furcation defects. *Journal of Periodontology* **64**, 925–933.
Bouchard, P., Ouhayoun, J.P. & Nilvéus, R.E. (1993) Expanded polytetrafluoroethylene membranes and connective tissue grafts support bone regeneration for closing mandibular Class II furcations. *Journal of Periodontology* **64**, 1193–1198.
Gantes, B.G., Synowski, B.N., Garrett, S. & Egelberg, J.H. (1991) Treatment of periodontal furcation defects. Mandibular class III defects. *Journal of Periodontology* **62**, 361–365.
Garrett, S., Martin, M. & Egelberg, J. (1990) Treatment of periodontal furcation defects. Coronally positioned flaps versus dura mater membranes in class II defects. *Journal of Clinical Periodontology* **17**, 179–185.

Publication bias for FImp, HCAL and VCAL gain and PPD reduction could not be assessed as <10 studies could be included in the network meta-analysis.

3.3.3 | Direct and indirect comparisons between regenerative techniques (NM)

HBL gain

Five treatment options (GTR-NONRES, GTR-RES, GTR-RES + BRG, BRG, EMD) were analysed for HBL gain, with a total of 10 possible pairwise comparisons (four direct comparisons based on data from six RCTs and six based on indirect evidence (Figure 3a). All pairwise comparisons are reported in Figure 4a and in a supplementary results section (Appendix S2).

The combined technique with the highest Pr of being the best treatment in terms of HBL gain was the BRG (Pr = 61%), followed by EMD (Pr = 19%) and GTR-RES + BRG (Pr = 15%). The therapies with the highest ranking were as follows: (a) BRG (mean rank [Mr]=1.81), (b) GTR-RES + BRG (Mr = 2.45) and (c) EMD (Mr = 2.96) (Table S1). The surface under the cumulative ranking curve (SUCRA) for HBL was 64% for BRG, 51% for GTR-RES + BRG and 41% for EMD (Figure S3a, Appendix S2).

Heterogeneity and inconsistency of the network

The percentage of total variability due to the between-trials heterogeneity was moderate to high (I^2 = 65.29, 90% CrI = 14.85; 95.09) while the percentage due to the network inconsistency ($I_w^{\,2}$ = 26.66, 90% CrI = 0.31; 81.04) was low. The network inconsistency ($\tau_w^{\,2}$) was compared to the between-trials heterogeneity

TABLE 2 Characteristics of the included studies

Study	Method, follow-up	Smoking habits	Control Group participants	Test Group participants	Control Group defects	Test Group defects
Queiroz et al. (2016)	Parallel group 12 months H	Smokers were excluded	1. 14 individuals 53.14 ± 5.92 years 2. 14 individuals 54.57 ± 5.63 years	13 individuals 53.69 ± 6.58 years	1. 14 teeth II furcation class Mandibular Buccal Average PPD 4.93 ± 0.73 mm 2. 14 teeth II furcation class Mandibular Buccal Average PPD 4.79 ± 0.70 mm	13 teeth II furcation class Mandibular Buccal Average PPD 4.92 ± 0.49 mm
Leite et al. (2013)	Split mouth 12 months H	Smokers were excluded	15 individuals (3 lost to follow-up) 37–60 years	15 individuals (3 lost to follow-up) 37–60 years	12 teeth II furcation class Mandibular Buccal & lingual Average PPD 3.43 ± 1.20 mm	12 teeth II furcation class Mandibular Buccal & lingual Average PPD 3.47 ± 1.32 mm
Jaiswal & Deo (2013)	Parallel group 12 months H	Smokers were excluded	10 individuals 36.6 ± 1.3 years	1. 10 individuals 2. 10 individuals 36.6 ± 1.3 years	10 teeth II furcation class Mandibular Buccal & lingual Average PPD 3.02 ± 0.73 mm Average HCAL 4.50 ± 1.71 mm	1. 10 teeth II furcation class Mandibular Buccal & lingual Average PPD 3.28 ± 0.76 mm Average HCAL 3.30 ± 0.40 mm 2. 10 teeth II furcation class Average PPD 3.14 ± 0.53 mm Average HCAL 3.50 ± 0.70 mm
Santana et al., (2009)	Parallel group 12 months	Smokers were excluded	30 individuals 48.3 years	30 individuals 48.3 years	30 teeth II furcation class Mandibular Buccal Average PPD 5.95 ± 1.3 mm Average HCAL 6.10 ± 1.4 mm	30 teeth II furcation class Mandibular Buccal Average PPD 6.36 ± 1.0 mm Average HCAL 4.85 ± 0.90 mm
Villaça et al. (2004)	Split mouth 12 months	Smokers were excluded	10 individuals	10 individuals	10 teeth II furcation class Mandibular Buccal Average PPD 2.93 ± 1.35 mm	10 teeth II furcation class Mandibular Buccal Average PPD 3.27 ± 1.34 mm
Jepsen et al., (2004)	Split mouth 14 months	Nine of the patients were current smokers (seven to 20 cigarettes per day)	45 individuals 53 years	45 individuals 53 years	45 teeth II furcation class Mandibular Buccal	45 teeth II furcation class Mandibular Buccal

Control Group interventions (Group for NM)	Test group interventions (Group for NM)	Outcomes	Control group tooth loss	Test group tooth loss	Control Group furcation closure/ furcation conversion	Test Group furcation closure/ furcation conversion	Site and funding
1. β-Tricalcium phosphate/ hydroxyapatite (BRG) 2. Enamel matrix derivative + β-tricalcium phosphate/ hydroxyapatite (EMD + BRG)	Enamel matrix derivative (EMD)	HCAL, VCAL, PPD, REC	0	0	1. 0 furcation closure 10 (71%) conversion class II to class I 2. 0 furcation closure 12 (85%) class II to class I	0 furcation closure 13 (100%) conversion class II to class I	University, NR
ePTFE membrane removed after 4 weeks (GTR-NONRES)	ePTFE membrane removed after 2 weeks (GTR-NONRES)	HBL (re-entry), VCAL, PPD, REC, VBL	0	0	NR	NR	University, grants
OFD (OFD)	1. EMD + DFDBA+PLA membrane (GTR-RES + BRG+EMD) 2. DFDBA + PLA membrane (GTR-RES + BRG)	HCAL, VCAL, PPD, REC	0	0	0 furcation closure 2 (20%) conversion class II to class I	1. 3 (30%) furcation closure 7 (70%) conversion class II to class I 2. 0 furcation closure 8 (80%) conversion class II to class I	University, NR
OFD (OFD)	ePTFE membrane + HA (GTR-NONRES + BRG)	HCAL, PPD, VCAL, REC	0	0	0 furcation closure* *if HCAL ≤ 2mm	18 (60%) furcation closure* *if HCAL ≤ 2mm	University, self-funded
Non-modified ePTFE membrane (GTR-NONRES)	Modified ePTFE membrane (GTR-NONRES)	HBL (re-entry), PPD, VCAL, VBL	0	0	NR	NR	University, NR
PLA membrane (GTR-RES)	Enamel matrix derivative (EMD)	HBL (re-entry)	0	0	3 (7%) furcation closure 27 (60%) conversion class II to class I	8 (18%) furcation closure 27 (60%) conversion class II to class I	University, private practice, industry

(Continues)

TABLE 2 (Continued)

Study	Method, follow-up	Smoking habits	Control Group participants	Test Group participants	Control Group defects	Test Group defects
Maragos et al. (2002)	Parallel group 12 months H	Smokers were excluded	17 individuals 55.8 years	17 individuals 55.8 years	11 teeth II furcation class Mandibular Buccal & lingual	1. 11 teeth II furcation class Mandibular 2. 14 teeth II furcation class Mandibular Buccal & lingual
Pruthi et al. (2002)	Split mouth 12 months H	Smokers were excluded	17 individuals 56.5 ± 13.3 years	17 individuals 56.5 ± 13.3 years	17 teeth II furcation class Mandibular Buccal & lingual Average PPD 4.53 ± 1.77 mm Average HCAL 2.0 mm	17 teeth II furcation class Mandibular Buccal & lingual Average PPD 4.73 ± 1.16 mm Average HCAL 2.0 mm
Karapataki et al. (1999)	Split mouth 12 months	All patients were smokers	11 individuals 43.4 years	11 individuals 43.4 years	11 teeth II furcation class Mandibular Buccal & lingual Average HCAL 5.9 ± 1.5 mm	11 teeth II furcation class Mandibular Buccal & lingual Average HCAL 6.0 ± 1.4 mm
De Leonardis et al. (1999)	Split mouth 12 months H	Smokers were excluded	12 individuals 49.8 years	12 individuals 49.8 years	12 teeth II furcation class mandibular Average PPD 7.1 ± 1 mm	12 teeth II furcation class mandibular Average PPD 7.3 ± 1 mm
de Santana et al. (1999)	Parallel group 12 months	Smokers were excluded	15 individuals 48.3 years	15 individuals 48.3 years	15 teeth II furcation class Maxillary Buccal Average PPD 5.83 ± 1.12 mm Average HCAL 5.1 ± 0.8 mm	15 teeth II furcation class Maxillary Buccal Average PPD 5.6 ± 1.3 mm Average HCAL 5.2 ± 0.7 mm
de Santana et al. (1999)	Parallel group 12 months	Smokers were excluded	15 individuals 48.3 years	15 individuals 48.3 years	15 teeth II furcation class Maxillary Buccal Average PPD 6.06 ± 0.9 mm Average HCAL 5.53 ± 1.2 mm	15 teeth II furcation class Maxillary Buccal Average PPD 6.06 ± 1.4 mm Average HCAL 4.93 ± 1.1 mm
Bouchard et al. (1997)	Parallel group 12 months	Only non-smokers or light smokers (<5 cigarettes/day) were included	15 individuals (9 females) 48.5 ± 8.1 years	15 individuals (9 females) 50.9 ± 10.4 years	15 teeth II furcation class Mandibular Buccal Average PPD 4.8 ± 1.9 mm Average HCAL 6.1 ± 1.5 mm	15 teeth II furcation class Mandibular Buccal Average PPD 4.7 ± 1.2 mm Average HCAL 6.5 ± 1.2 mm

Control Group interventions (Group for NM)	Test group interventions (Group for NM)	Outcomes	Control group tooth loss	Test group tooth loss	Control Group furcation closure/ furcation conversion	Test Group furcation closure/ furcation conversion	Site and funding
Calcium sulphate membrane (GTR-RES)	1. Calcium sulphate membrane doxycycline hyclate (GTR-RES) 2. Calcium sulphate membrane + DFDBA (GTR-RES + BRG)	HBL (re-entry), HCAL, PPD, VCAL, VBL	0	0	NR	NR	University, NR
ePTFE membrane (GTR-NONRES)	Collagen membrane (GTR-RES)	HBL (re-entry), PPD, VCAL, VBL, REC	0	0	NR	NR	University, industry
ePTFE membrane (GTR-NONRES)	PLA membrane (GTR-RES)	HCAL, VCAL, REC	0	0	NR	NR	University, grants
PLA membrane (GTR-RES)	PLA membrane + DFDBA (GTR-RES + BRG)	HCAL, PPD, VCAL, REC	0	0	6 of 12 (50%) converted into class I	11 of 12 (91%) converted into class I	University, private practice, grants
OFD (OFD)	CAF (OFD)	HCAL, PPD, VCAL, REC	0	0	1 of 30	2 (13%) furcation closure	University, NR
OFD (OFD)	ePTFE membrane + HA (GTR-NONRES + BRG)	HCAL, PPD, VCAL, REC	0	0	1 of 30	5 (33%) furcation closure	University, NR
PGA/PLA membrane (GTR-RES)	ePTFE membrane (GTR-NONRES)	HCAL, PPD, VCAL, REC	0	0	6 (40%) closed or converted to class I	8 (53%) closed or converted to class I	University, industry

(Continues)

TABLE 2 (Continued)

Study	Method, follow-up	Smoking habits	Control Group participants	Test Group participants	Control Group defects	Test Group defects
Garrett et al. (1997)	Parallel group 12 months	Not reported	64 individuals	66 individuals	64 teeth II furcation class Both mandibular & maxillary Buccal & lingual for mandibular Only Buccal for maxillary Average PPD 5.5 mm Average HCAL 4.7 mm	66 teeth II furcation class Both mandibular & maxillary Buccal & lingual for mandibular Only Buccal for maxillary Average PPD 5.6 mm Average HCAL 4.6 mm
Hugoson et al. (1995)	Split mouth 12 months	Not reported	38 individuals 34–63 years	38 individuals 34–63 years	38 teeth II furcation class Mandibular and maxillary Buccal & lingual for mandibular Only Buccal for maxillary Average PPD 5.6 ± 1.4 mm	38 teeth II furcation class Mandibular and maxillary Buccal & lingual for mandibular Only Buccal for maxillary Average PPD 5.3 ± 1.2 mm
Wang et al. (1994)	Split mouth 12 months	Not reported	12 individuals 46.42 ± 9.15 years	12 individuals 46.42 ± 9.15 years	12 teeth II furcation class Mandibular Buccal & lingual Average PPD 6.92 mm	12 teeth II furcation class Mandibular Buccal & lingual Average PPD 6.92 mm
Blumenthal (1993)	Split mouth 12 months	Not reported	12 individuals 31–80 years	12 individuals 31–80 years	12 teeth II furcation class Mandibular Buccal Average PPD 5.17 ± 1.47 mm Average HCAL 4.42 ± 0.93 mm	12 teeth II furcation class Mandibular Buccal Average PPD 5.75 ± 1.61 mm Average HCAL 4.50 ± 0.87 mm
Bouchard et al. (1993)	Split mouth 12 months	Not reported	12 individuals 45 years	12 individuals 45 years	12 teeth II furcation class Mandibular Buccal Average PPD 5.1 ± 1.4 mm	12 teeth II furcation class Mandibular Buccal Average PPD 5.2 ± 2.0 mm
Gantes et al. (1991)	Parallel group 12 months	Not reported	14 individuals	13 individuals	14 teeth **III furcation class** Mandibular Average PPD 7.43 ± 1.41	13 teeth **III furcation class** Mandibular Average PPD 7.23 ± 1.75
Garrett et al. (1990)	Parallel group 12 months	Not reported	12 individuals	13 individuals	16 teeth II furcation class Mandibular Buccal & lingual 5.9 ± 1.3	15 teeth II furcation class Mandibular Buccal & lingual 6.0 ± 0.7

Abbreviations: OFD = open flap debridement; GTR-RES = membrane technique (resorbable); GTR-NONRES = membrane technique (non-resorbable); EMD = enamel matrix derivative; DFDBA = allograft from bio-banking; GF = growth factor; HA = alloplastic materials (hydroxyapatite); b-TCP = alloplastic materials (b-tricalcium phosphate); CAF = coronally advanced flap with special suturing; PLA = polylactide; H = Hamp classification (Hamp et al. 1975) for furcation defects stated in the article; NR = not reported.

Control Group interventions (Group for NM)	Test group interventions (Group for NM)	Outcomes	Control group tooth loss	Test group tooth loss	Control Group furcation closure/ furcation conversion	Test Group furcation closure/ furcation conversion	Site and funding
ePTFE membrane (GTR-NONRES)	PGA/PLA membrane (GTR-RES)	HCAL, PPD, VCAL, VBL, REC	0	0	14/64 (22%) furcation closure 33/64 (52%) furcation conversion class II to class I	16/66 (24%) furcation closure 35/66 (53%) furcation conversion class II to class I	University, industry
ePTFE membrane (GTR-NONRES)	PLA (GTR-RES)	HCAL, PPD, VCAL, REC	0	0	4/38 (10%) furcation closure 13/38 (34%) furcation conversion class Ii to class I	13/38 (34%) furcation closure 11/38 (29%) furcation conversion class II to class I	University, private practice, industry
OFD (OFD)	Collagen membrane (GTR-RES)	PPD, VCAL, VBL, REC	0	0	NR	NR	University, private practice, self-funded, industry
ePTFE membrane (GTR-NONRES)	Collagen membrane (GTR-RES)	HCAL, HBL (re-entry), PPD, VCAL, REC, VBL	0	0	NR	NR	University, industry
ePTFE membrane (GTR-NONRES)	CTG (GTR-RES)	HCAL, HBL (re-entry), PPD, VCAL, VBL, REC	0	0	4/11 (36%) furcation closure	2/11 (18%) furcation closure	University
CAF + citric acid (OFD)	CAF + DFDBA +citric acid (BRG)	PPD, VCAL, REC	0	0	1/14 “soft tissue” furcation closure	3/13 “soft tissue” furcation closure	University, public grant
CAF + citric acid + DFDBA (BRG)	Collagen membrane + DFDBA (GTR-RES + BRG)	HBL (re-entry), PPD, VBL, REC	0	0	9/16 (56%) furcation closure	3/15 (20%) furcation closure	University, public grant

(τ^2) and expressed in terms of probability of ${\tau_w}^2$ to be larger than τ^2, *Pr* (${\tau_w}^2 > \tau^2$) (Lu & Ades, 2006). The value of *Pr* (${\tau_w}^2 > \tau^2$) was equal to 0.50.

Publication bias could not be assessed as <10 studies could be included in the network meta-analysis.

VCAL gain

Six treatment modalities (GTR-NONRES, GTR-RES, GTR-RES + BRG, GTR-NONRES + BRG, GTR-RES + BRG+EMD, OFD) were analysed for VCAL gain, with a total of 15 possible pairwise comparisons (seven direct comparisons based on data from 13 RCTs and eight based on indirect evidence (Figure 3b). All pairwise comparisons are reported in Figure 4b and in the supplementary results section (Appendix S2).

The procedure with the highest Pr of being the best treatment in terms of VCAL gain was the GTR-NONRES + BRG (Pr = 75%) followed by GTR-RES + BRG+EMD (Pr = 19%), GTR-NONRES (Pr = 3%) and GTR-RES + BRG (Pr = 2%). The treatments with the highest ranking were as follows: (a) GTR-NONRES + BRG (Mr = 1.44), (b) GTR-RES + BRG+EMD (Mr = 2.08), (c) GTR-RES + BRG (Mr = 3.42) (Table S2). The surface under the cumulative ranking curve (SUCRA) for VCAL was 76% for GTR-NONRES + BRG, 65% for GTR-RES + BRG+EMD and 43% for GTR-RES + BRG (Figure S3b, Appendix S2).

Heterogeneity and inconsistency of the network

The percentage of total variability due to the between-trials heterogeneity was low (I^2 = 28.50, 90% CrI = 4.20; 80.77) as well as the percentage due to the network inconsistency was higher (${I_w}^2$ = 60.87, 90% CrI = 1.31; 92.95). The network inconsistency (${\tau_w}^2$) was compared to the between-trials heterogeneity (τ^2) and expressed in terms of probability of ${\tau_w}^2$ to be larger than τ^2, *Pr* (${\tau_w}^2 > \tau^2$) (Lu & Ades, 2006). The value of *Pr* (${\tau_w}^2 > \tau^2$) was equal to 0.64.

Publication bias

Study publication bias for VCAL was examined using funnel plots (Appendix S3). Intervention effect centred at comparison-specific pooled effect for network meta-analyses plotted against the standard error showed symmetrical distribution with no obvious skewness of treatment effects.

PPD reduction

PPD reduction was the most reported outcome in all the studies (Figure 3c). Nine treatment options (GTR-NONRES, GTR-RES, GTR-RES + BRG, GTR-NONRES + BRG, BRG, GTR-RES + BRG+EMD, BRG + EMD, EMD and OFD) were analysed for PPD reduction, with a total of 36 possible pairwise comparisons (16 direct comparisons based on data from 13 RCTs and 20 based on indirect evidence (Figure 3c). All results are reported in Figure 4c and in a supplementary results section (Appendix S2).

The procedure with the highest Pr of being the best treatment in terms of PPD reduction was the GTR-NONRES + BRG (Pr = 56%) followed by GTR-RES + BRG+EMD (Pr = 14%) and EMD (Pr = 13%). The treatments with the highest ranking were as follows: (a) GTR-NONRES + BRG (Mr = 2.2), (b) GTR-RES + BRG+EMD (Mr = 3.31), (c) EMD (Mr = 4.2) (Table S3). The surface under the cumulative ranking curve (SUCRA) for PPD was 77% for GTR-NONRES + BRG, 64% for GTR-RES + BRG+EMD and 54% for EMD (Figure S3c, Appendix S2).

Heterogeneity and inconsistency of the network

The percentage of total variability due to the between-trials heterogeneity was moderate to high (I^2 = 62.89, 90% CrI = 14.99; 89.87) while the percentage due to the network inconsistency was low (${I_w}^2$ = 24.86, 90% CrI = 0.26; 81.80). The network inconsistency (${\tau_w}^2$) was compared to the between-trials heterogeneity (τ^2) and expressed in terms of probability of ${\tau_w}^2$ to be larger than τ^2, Pr (${\tau_w}^2 > \tau^2$) (Lu & Ades, 2006). The value of Pr (${\tau_w}^2 > \tau^2$) was equal to 0.31.

Publication bias

Study publication bias for PPD was examined using funnel plots (Appendix S3). Intervention effect centred at comparison-specific pooled effect for network meta-analyses plotted against the standard error showed symmetrical distribution with no obvious skewness of treatment effects.

3.3.4 | Standard Bayesian meta-analysis (SM)

HCAL gain

Network meta-analysis was not possible for HCAL gain.

A Bayesian SM for HCAL gain (two RCTs) showed that GTR-NONRES + BRG was superior to OFD by 2.49 mm (90% CrI = 2.44; 2.54) (Figure S1). Evidence from six RCTs was summarized in a random-effects Bayesian SM where no statistically significant difference was observed between GTR-RES versus GTR-NONRES (mean difference = −0.01 mm; 90% CrI = −0.64; 0.6, I^2 = 72.39, 90% CrI = −2.74; 94.52) (Figure S2).

3.3.5 | Patient-reported outcomes and adverse events

Patient-reported outcomes were documented in one study (Jepsen et al., 2004) by questionnaires. During the first post-operative week there was a frequency of no pain or no swelling of 62% and 44%, respectively, in the group treated with EMD and 12% and 6%, respectively in the GTR-RES with PLA/membrane group.

Adverse events were reported in seven studies (Bouchard, Giovannoli, Mattout, Davarpanah, & Etienne, 1997; Bouchard, Ouhayoun, & Nilvéus, 1993; De Leonardis, Garg, Pedrazzoli, & Pecora, 1999; Garrett et al., 1997; Hugoson et al., 1995; Jepsen et al., 2004; Karapataki, Falk, Hugoso, Olsson, & Slotte, 1999) and are described in the supplementary results section (Appendix S2).

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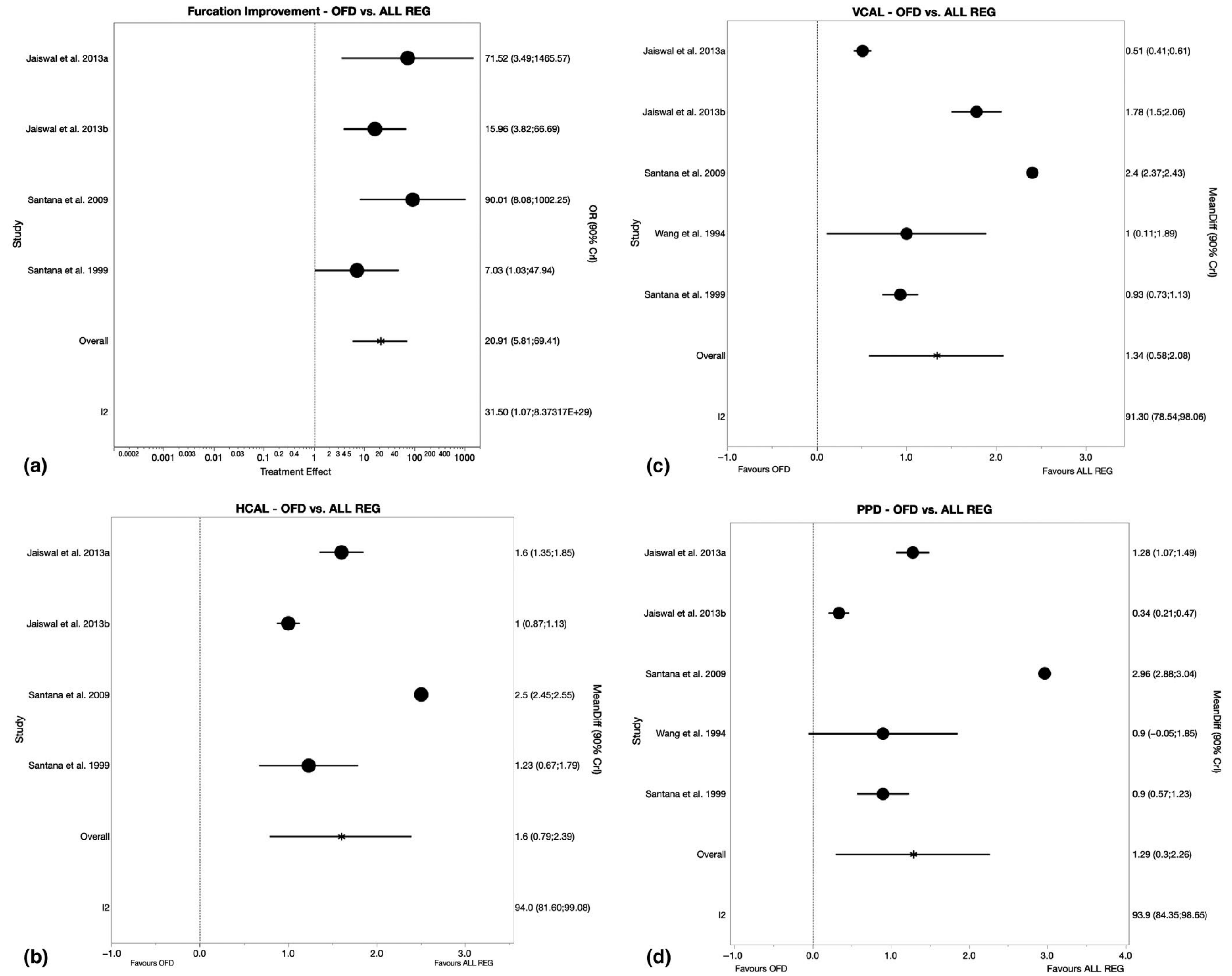

FIGURE 2 (a) FImp SM forest plot for OFD versus all others regenerative techniques. (b) HCAL gain SM forest plot for OFD versus all others regenerative techniques. (c) VCAL gain SM forest plot for OFD versus all others regenerative techniques. (d) PPD reduction SM forest plot for OFD versus all others regenerative techniques

3.3.6 | Class III furcation defects

Only one study on class III furcation defects (in mandibular molars) could be identified that fulfilled the inclusion criteria of the present systematic review (Gantes et al., 1991). The only outcome assessed after 12 months was "soft tissue closure" by a panel of three examiners. This endpoint was obtained in one out of 14 non-grafted control defects and in three out of 13 DFDBA-grafted (BRG) class III furcations. Bone fill could be demonstrated in one of these cases during a re-entry procedure.

3.4 | Risk of bias

Risk of bias of individual studies is reported in Table 4. Only one study was adequate with regard to all items including blinding of the statistician (Queiroz et al., 2016). Adequate methods of random sequence generation, allocation concealment and blinding of assessors were reported in three studies (Garrett et al., 1997; Jepsen et al., 2004; Queiroz et al., 2016). Adequate random sequence generation was also reported in five other studies (Blumenthal, 1993; Jaiswal & Deo, 2013; Leite et al., 2013; Maragos, Bissada, Wang, & Cole, 2002; Santana, Mattos, & Dyke, 2009), and blinding of assessors was performed in another four studies (Garrett et al., 1990; Hugoson et al., 1995; Karapataki et al., 1999; Santana et al., 2009). All studies were adequate with regard to reporting incomplete outcome data. Other sources of bias are shown in Table 4.

4 | DISCUSSION

This systematic review was designed to evaluate the adjunctive clinical benefits of regenerative procedures in the treatment of furcation defects when compared to open flap debridement and to compare the various types of regenerative treatment among each other.

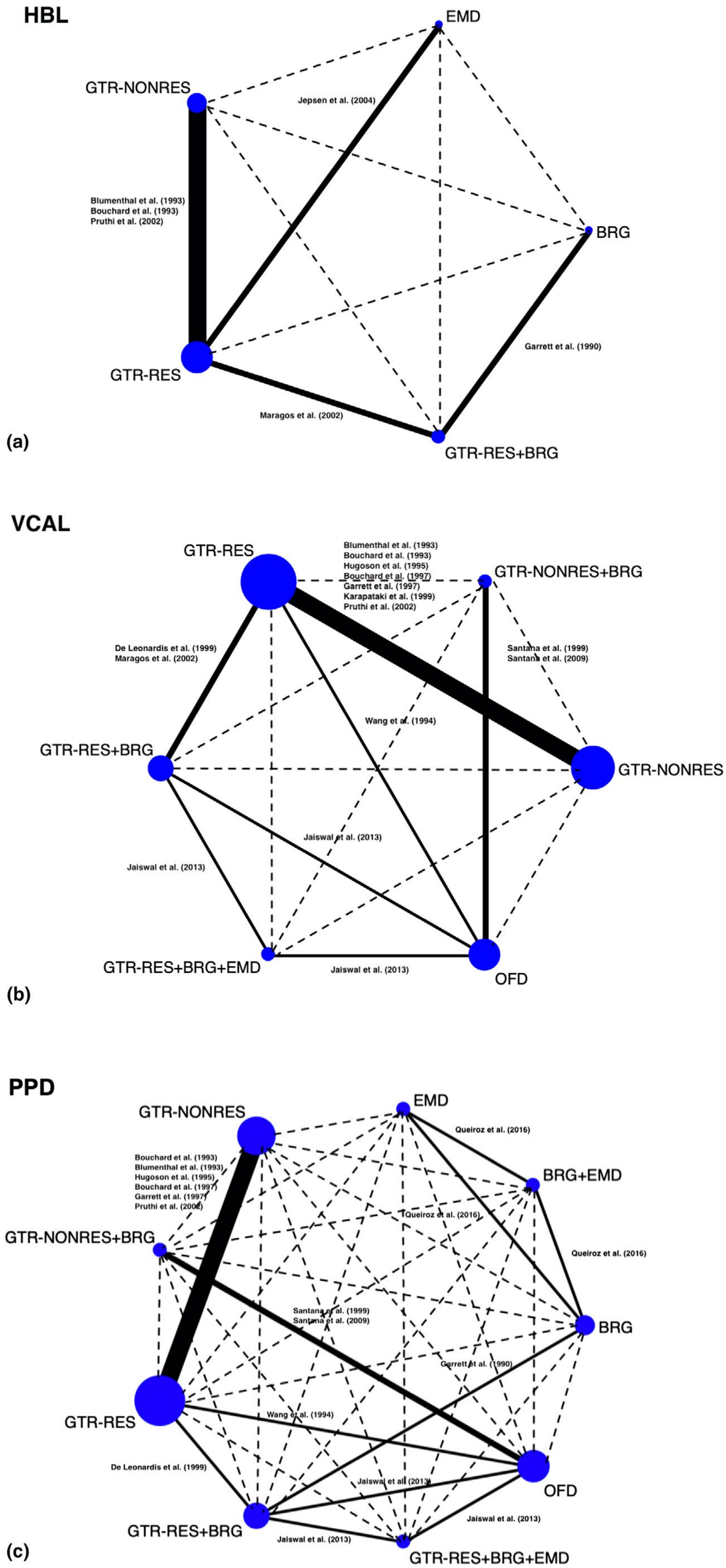

FIGURE 3 Network plots for HBL gain (a), PPD reduction (b) and VCAL gain (c). Nodes are weighted according to the number of studies including the respective intervention. Edges are weighted according to the number of studies including the respective comparison. Solid lines refer to direct comparisons (the width of the lines is proportional to the number of randomized controlled trials (RCTs) included for each comparison) while dotted lines refer to those comparisons that have not been tested directly in RCTs

TABLE 3 Furcation closure/conversion (class II to class I)

Study	Treatment arms	Furcation closure	Furcation conversion
Queiroz et al. (2016)	EMD	0 (0%)	13 (100%) to class I
	BRG	0 (0%)	10 (71.4%) to class I
	EMD + BRG	0 (0%)	12 (85.7%) to class I
Jaiswal & Deo (2013)	OFD	0 (0%)	2 (20%) to class I
	GTR-RES + BRG+EMD	3 (30%)	7 (70%) to class I
	GTR-RES + BRG	0 (0%)	8 (80%) to class I
Santana et al. (2009)	OFD	0 (0%) if HCAL ≤ 2 mm	NR
	GTR-NONRES + BRG	18 (60%) if HCAL ≤ 2 mm	NR
Jepsen et al. (2004)	GTR-RES	3 (7%)	27 (60%) to class I
	EMD	8 (18%)	27 (60%) to class I
De Leonardis et al. (1999)	GTR-RES	0 (0%)	6 (50%) to class I
	GTR-RES + BRG	0 (0%)	11 (91%) to class I
de Santana et al. (1999)	OFD	1	NR
	GTR-NONRES + BRG	5 (33%)	NR
Garrett et al. (1997)	GTR-NONRES	14 (22%)	33 (52%) to class I
	GTR-RES	16 (24%)	35 (53%) to class I
Hugoson et al. (1995)	GTR-NONRES	4 (10%)	13 (34%) to class I
	GTR-RES	13 (34%)	11 (29%) to class I
Bouchard et al. (1993)	GTR-NONRES	4 (36%)	NR
	GTR-RES	2 (18%)	NR
Garrett et al. (1990)	BRG	9 (56%)	NR
	GTR-RES + BRG	3 (20%)	NR

No studies on class I furcation defects were identified. Only one RCT addressed class III mandibular furcation defects and showed very limited success in improving the furcation status. The findings of the remaining 19 studies included in this systematic review indicate that for mandibular (buccal/lingual) and maxillary (buccal) class II furcation defects a variety of regenerative techniques produced a significant advantage if compared to OFD in terms of primary outcomes (furcation closure/conversion) and surrogate periodontal outcomes. Moreover, some procedures, such as the use of bone replacement grafts, with or without barrier membrane application, appear to have a higher probability to show better results.

The present systematic review is unique as it is based on the best available evidence, by including only randomized clinical trials with of at least 12 months' duration, and as it has used, to the best of our knowledge, for the first time Bayesian network meta-analyses to allow for direct and indirect comparisons between various regenerative techniques. This is in contrast to previous systematic reviews on regenerative furcation therapy, that were either not limited to RCTs, and/or did not perform meta-analyses, and/or included studies of shorter duration, and/or were focused on specific procedures only (Avila-Ortiz et al., 2015; Chen, Tu, Yen, & Lu, 2013; Jepsen et al., 2002; Kinaia, Steiger, Neely, Shah, & Bhola, 2011; Panda et al., 2019).

Tooth loss was not reported in any of the studies included in this systematic review. This may be not surprising, as an observation period of 12 months is probably not long enough to evaluate this important outcome. In fact, long-term data on regenerative furcation therapy are sparse (Figueira et al., 2014). Clinical furcation closure was reported in about half of the studies and frequencies ranged between 0% and 60%. No meta-analysis of furcation closure rates was performed, as the methods to establish furcation closure varied substantially and ranged from direct measurements at re-entry as demanded at a previous European Workshop (Jepsen et al., 2002) to defining a furcation as closed if the horizontal CAL at 12 months was equal or smaller than 2 mm. Based on the available data, furcation closure following regenerative therapy cannot be considered to be a predictable outcome. Furcation conversion from class II to class I was specified in about one third of the studies and the reported frequencies ranged from 20% to 100%. The two multicentre studies (Garrett et al., 1997; Jepsen et al., 2004) having a low risk of bias and providing by far the largest numbers of participants and defects indicated conversion rates between 52% and 60% using either GTR or EMD. A meta-analysis on FImp (either closure or conversion to class I) was performed and showed evidence that the furcation status can be significantly improved by various regenerative therapies when compared to open flap debridement (OR = 20.91). This outcome is relevant as it has been shown previously that there is no significant difference in the long-term prognosis (risk for tooth loss) of molars with class I furcation involvement and molars without

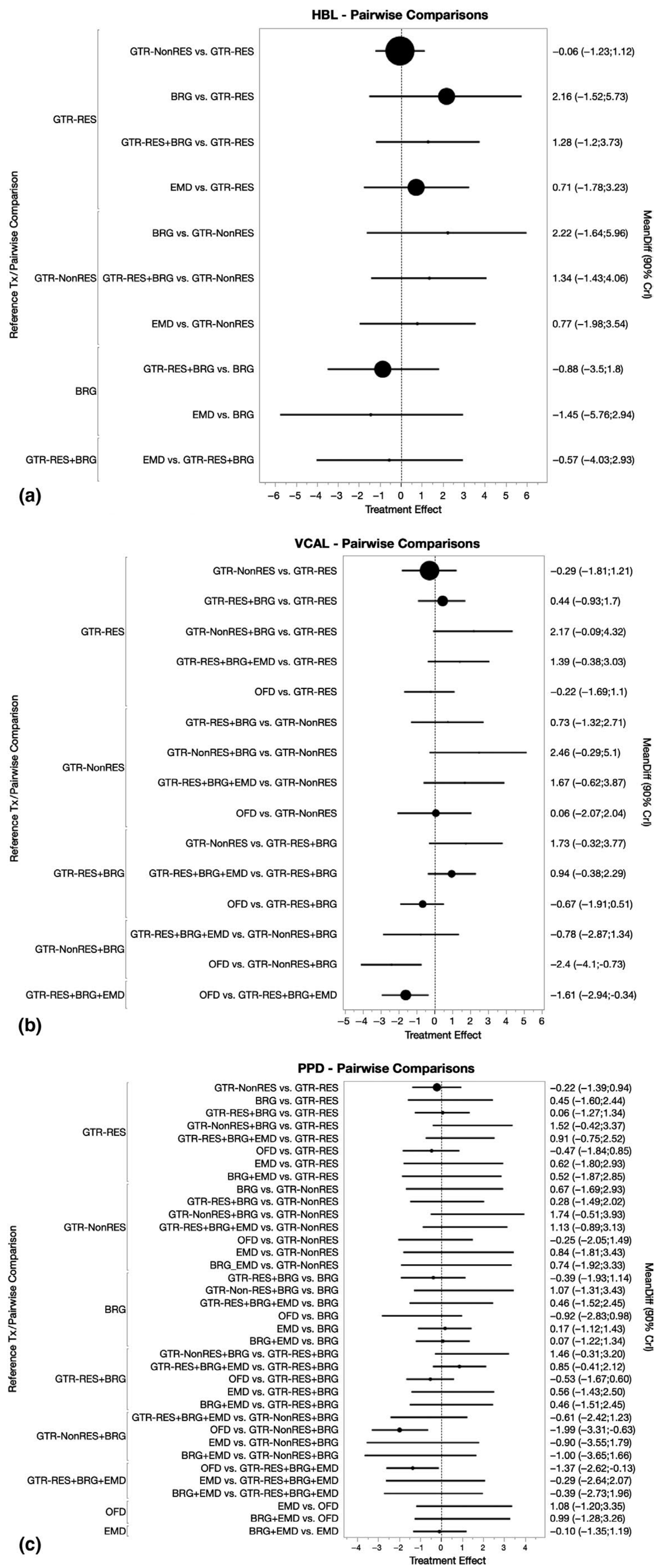

FIGURE 4 (a) HBL gain NM forest plot for pairwise comparisons. Size of the spheres is proportional to the number of studies with direct evidence supporting the comparison. (b) VCAL gain NM forest plot for pairwise comparisons. Size of the spheres is proportional to the number of studies with direct evidence supporting the comparison. (c) PPD reduction NM forest plot for pairwise comparisons. Size of the spheres is proportional to the number of studies with direct evidence supporting the comparison

TABLE 4 Summary of risk of bias in individual studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of assessor	Blinding of statistician	Incomplete outcome data	Other sources of bias
Queiroz et al. (2016)	+ Computer	+	+	+	+	US, DTD, DFD, SR, SMD, ISPT, DLA, C, SZC, OHLR
Leite et al. (2013)	+ Coin toss	?	?	?	+	DTD, SFD, US, DLA, DFD, ISPT, SR, C, SMD, OHLR
Jaiswal & Deo (2013)	+ Computer	?	?	?	+	DTD, US, DFD, SR, SMD
Santana et al. (2009)	+ Coin toss	?	+	?	+	US, SFD, DTD, DFD, SR, SMD, ISPT, SZC, DLA, C
Villaça et al. (2004)	?	?	–	?	+	US, DTD, DFD, SR, SMD, ISPT
Jepsen et al. (2004)	+ Computer	+	+	?	+	US, SFD, DTD, DFD, SR, SMD, ISPT, SZC, DLA, C
Maragos et al. (2002)	+	+	?	?	+	US, DTD, DFD, SR, SMD, ISPT
Pruthi et al. (2002)	?	?	?	?	+	US, SFD, DTD, DFD, SR, SMD, ISPT
Karapataki et al. (1999)	?	?	+	?	+	US, SFD, DTD, DFD, SMD, ISPT, SR
De Leonardis et al. (1999)	?	?	?	?	+	US, SFD, DTD, DFD, SR, SMD, ISPT
de Santana et al. (1999)	?	?	?	?	+	US, DTD, DFD, SR, ISPT, OHLR
Bouchard et al. (1997)	?	?	–	?	+	US, SFD, DTD, DFD, SR, SMD, ISPT, OHLR
Garrett et al. (1997)	+	+	+	?	+	US, DTD, DFD, SR, SMD, ISPT, C
Hugoson et al. (1995)	?	?	+	?	+	US, SFD, DTD, DFD, SMD, ISPT
Wang et al. (1994)	?	?	?	?	+	US, SFD, DTD, DFD, SMD, ISPT, OHLR
Blumenthal (1993)	+ Coin toss	?	?	?	+	US, SFD, DTD, DFD, SMD
Bouchard et al. (1993)	?	?	–	?	+	US, DTD, DFD, SMD
Gantes et al. (1991)	?	?	?	?	+	DTD, ISPT, DLA, C, OHLR
Garrett et al. (1990)	?	?	+	?	+	US, SFD, DFD, SMD, ISPT, DLA

Note: – = inadequate; ? = unclear; + = adequate; US, university setting; SFD, source of funding disclosed; DTD, definition of trial design; DFD, definition of furcation defect; SR, smoking reporting; SMD, statistical method definition; SZC, sample size calculation; ISPT, information of supportive therapy provided; DLA, definition of level analysis; C, calibration; OHLR, oral hygiene level reporting.

furcation involvement (Dannewitz et al., 2016; Graetz et al., 2015; McGuire & Nunn, 1996; Salvi et al., 2014). Only in patients not undergoing periodontal care class I furcation involvement was associated with an increased risk of molar loss (Nibali et al., 2017).

Calculation of numbers needed to treat (NNT) was considered for the present systematic review. However, NNT is more complex from meta-analysis than from single trials. Treating the data as if it all came from one trial may lead to misleading results when the trial arms are imbalanced. While NNT from meta-analysis can be calculated from pooled risk differences, this is unlikely to be a stable method unless the event rates in the control groups are very similar. Therefore, in this work, the use of a relative measure, such as the odds ratio, was preferred (Cates, 2002).

Regenerative techniques yielded 1.6 mm more horizontal clinical attachment gain than OFD. However, it has to be emphasized that this is based on a limited number of direct comparisons and regenerative techniques. Regarding the other primary outcome HBL gain, Bayesian network meta-analysis showed that BRG was the technique with the highest probability of being the best treatment, followed by EMD and GTR-RES + BRG. The therapies with the highest ranking were as follows: (a) BRG, (b) GTR-RES + BRG and (c) and EMD.

With regard to the secondary outcomes VCAL gain and PPD reduction the adjunctive clinical benefit of regenerative procedures was approximately of 1.3 mm for both parameters, values similar to the regenerative benefits noted in intraosseous defects (Nibali et al., 2019). In addition, NM analysis showed that treatments using bone replacement grafts, alone or combined with GTR showed the highest rankings for VCAL gain and PPD reduction.

Surprisingly, even though an earlier European Workshop had concluded that more emphasis should be given to patient-centred outcomes and adverse effects (Jepsen et al., 2002) patient-reported outcomes were only addressed in one study (Jepsen et al., 2004), indicating that less post-operative swelling and pain was found following EMD compared to GTR-RES. Adverse events such as suppuration were reported in seven studies and mostly associated with GTR procedures.

Strengths of the present systematic review are as follows: (a) it included only RCTs and not study designs with an inherent higher risk of bias; (b) studies included had at least 12 months' duration what appears to be critical for the evaluation of the outcomes of periodontal regeneration; and (c) inclusion was not limited to certain types of regenerative techniques. Furthermore, for the first time network meta-analyses were employed to combine evidence from direct and indirect comparisons among a set of different trials on regenerative furcation surgery in a unique network of treatments. This approach has been shown to be a useful method for analysing the performance of different root coverage procedures (Buti et al., 2013) and regenerative therapies of infrabony defects (Tu, Needleman, Chambrone, Lu, & Faggion Jr, 2012). Network meta-analysis made it possible to investigate treatment comparisons never directly tested in RCTs. Another important advantage of the Bayesian NM is the possibility of obtaining a ranking of the treatments included in the analysis and assessing the probability for each treatment to be the best. Traditional meta-analytical methods do not permit grading treatments by effectiveness, while this is a fundamental issue in the clinical decision-making process, especially in the presence of a large number of available treatment options (Buti et al., 2013).

Limitations of the present systematic review are the relatively small number of studies available for the various different regenerative techniques, due to the stringent inclusion criteria. Very few studies could be retrieved that had chosen open flap debridement as a control, what is needed to establish the added benefit of a regenerative technique in direct comparison. This may be due to the fact, that OFD has not been shown to improve the furcation status (Graziani et al., 2015) and may thus be considered unethical as control in an RCT. Moreover, most of the studies that were finally included had an unclear risk of bias. Based on the available data, it was not possible to evaluate the influence of oral hygiene, smoking, antibiotics and other patient, site and technique factors associated with successful outcomes of regenerative therapy in furcations.

Interventions and assessments of outcomes were rather heterogeneous. In SM models heterogeneity for FImp (I^2 = 31%) was deemed low to moderate, while it was high for VCAL gain, HCAL gain and PPD reduction. This could be explained by the fact that an overall regenerative group was created including different surgical procedures. In NM models, the percentage of total variability due to the between-trials heterogeneity was consistently lower than 75%; it was deemed low for VCAL gain (I^2 = 29%), moderate to high for PPD reduction (I^2 = 63%) and moderate to high for HBL gain network meta-analysis models (I^2 = 65%). In combining the data from a set of different studies, NM approach shares all difficulties with standard meta-analysis. In particular, precise definition of treatment procedures, reproducibility of measurement methods/landmarks at furcation sites and consistency of outcome measures together with differences in the characteristics of the participants certainly affect variability in the models. In fact, all these factors are potential sources of heterogeneity among studies and inconsistency of the network.

While the statistical combination of direct and indirect evidence is a powerful and welcome addition to evidence synthesis techniques, it also raises the issue of properly assessing a source of variability emerging in NM models: the inconsistency. In the present work, heterogeneity and inconsistency did not show particularly high values in the estimates of NM models; the percentage of total variability due to the network inconsistency (I_w^2) was generally low to moderate (ranging between 25% and 61%), showing that network inconsistency was generally not a concern for HBL gain (I_w^2 = 27%) and PPD reduction (I_w^2 = 25%), while VCAL gain (I_w^2 = 61%) results appeared less consistent with direct evidence. Overall, the estimates seem to account for the reliability of the results.

A variety of outcome measures can be considered to assess the effectiveness of regenerative furcation therapies (Jepsen & Jepsen, 2018; Sanz et al., 2015). From a clinical point of view, complete elimination of the inter-radicular defect appears to be the most important outcome. Decreasing furcation degree is associated with a decreased long-term tooth loss risk (Nibali et al., 2016). Thus, the main outcome variables for studies evaluating the efficacy of regenerative techniques in furcations are change of furcation status (conversion into class I or complete closure) and horizontal hard-tissue fill. As histological evidence for successful furcation regeneration is not a practical outcome variable for controlled clinical trials, changes in direct bone measurements (horizontal probing bone level, at surgery and during re-entry, open measurements) serve as primary outcome variables for evaluating clinical success, while closed measurements such as clinical attachment level gain (horizontal/ vertical probing attachment level), probing depth reduction (horizontal/vertical), and radiographic assessments may serve as secondary outcomes (Machtei, 1997). Bone fill during a re-entry procedure is the only component of a regenerated periodontium that can be accurately assessed clinically. In fact, it was stated at a European consensus conference that it would be desirable for all future GTR studies to report the reduction in horizontal probing during re-entry, and also the frequency (predictability) of complete furcation closure (Jepsen et al., 2002); however, this may not always be feasible due to ethical considerations. Patient-reported outcomes following regenerative furcation surgery may include post-operative pain, the rate of complications, perceived benefit, and change in quality of life.

The clinical performance of conservative surgery (OFD) in the treatment of class II furcation defects has been evaluated (Graziani et al., 2015). Based on prospective data of the control groups of RCTs, most of them with 6 months' duration, the following outcomes could be established and can serve as reference: furcation closure after OFD was never reported, mean HBL gain was almost imperceptible, mean HCAL gain amounted to 1mm, mean VCAL gain to 0.55 mm and mean PPD reduction to 1.4 mm.

The efficacy of various regenerative approaches in furcation defects has been evaluated by several systematic reviews with or without meta-analyses (Avila-Ortiz et al., 2015; Chen et al., 2013; Jepsen et al., 2002; Kinaia et al., 2011; Murphy & Gunsolley, 2003; Reynolds, Aichelmann-Reidy, Branch-Mays, & Gunsolley, 2003) and has also been addressed in recent comprehensive narrative reviews (Jepsen & Jepsen, 2018; Sanz et al., 2015).

Evaluating the effect of GTR compared to OFD by meta-analyses, Jepsen et al. (2002), found furcation closure at re-entry to be a rare finding. However, GTR was superior to OFD for HBL and HCAL gain. Kinaia et al. (2011) performed meta-analyses to investigate the effects of GTR-NONRES versus OFD, GTR-RES versus OFD, and GTR-NONRES versus GTR-RES in class II furcations, including only studies with re-entry data. They concluded that both GTR-NONRES and GTR-RES were significantly superior to OFD for HBL gain, PPD reduction, and VCAL gain. However, no significant differences between GTR-NONRES and GTR-RES were found. These findings are confirmed by the present network meta-analysis. Chen et al. (2013) systematically compared GTR versus OFD, GTR + BRG versus OFD, and GTR versus GTR-BRG. Regarding furcation closure in mandibular defects, the results indicated that GTR + BRG was the most effective therapeutic approach. Their results also showed a superiority of GTR in combination with BRG compared with both OFD and GTR alone, as previously indicated by Murphy and Gunsolley (2003). These findings could be confirmed by our network meta-analyses. A recent systematic review with meta-analysis by Panda et al. (2019) evaluated the adjunctive effect of autologous platelet concentrates for the treatment of furcation defect. As currently there are no RCTs available with a duration of at least 12 months, this treatment modality was not analysed in the present systematic review.

Exemplary human histology is needed to supplement the information obtained from clinical regenerative studies (Machtei, 1997). The histological evidence for periodontal regeneration in furcations was recently reviewed and information derived from human histology was found to be scarce (Laugisch et al., 2019). Regarding the treatment groups of the present systematic review supportive human histology is available for GTR (Gottlow, Nyman, Lindhe, Karring, & Wennstrom, 1986; Stoller, Johnson, & Garrett, 2001). Regarding a combination of GTR-RES + BRG one study by Harris (2002), and for BRG two studies (Camelo, Nevins, & Schenk, 2003; Nevins, Camelo, Nevins, Schenk, & Lynch, 2003) observed new bone, cementum, and connective tissue attachment coronal or limited to the notch area.

Thus, for the treatment modalities that ranked highest in the present network meta-analysis, BRG with or without GTR, there is some supportive evidence from human histology. However, no human histological data are available for the use of EMD in this indication.

In summary, the findings from the present systematic review could consolidate and expand the evidence on regenerative treatment of class II furcation defects. Bearing in mind that most of the studies included mandibular and few studies maxillary buccal furcations in non-smoking patients, the following conclusions can be drawn:

5 | CONCLUSIONS

- The likelihood to obtain FImp (closure or conversion to class I) is significantly higher (OR = 20.91; 90% CrI = 5.81, 69.41) for regenerative techniques than for open flap debridement.
- Adjunctive regenerative techniques lead to a significant gain of HCAL, VCAL and reduction of PPD compared to OFD.
- The procedures with the highest ranking for HBL gain are BRG, GTR-RES + BRG and EMD.
- GTR-NONRES and GTR-RES lead to similar improvements of HBL, VCAL and PPD.
- GTR-RES + BRG leads to more HBL gain than GTR-RES alone.
- PROMS show less post-operative swelling and pain following EMD compared to GTR-RES.
- No gold standard in the regenerative treatment of class II furcations can be defined.
- No conclusions can be made for interproximal maxillary furcation defects because of lack of studies.

IMPLICATIONS FOR FUTURE RESEARCH

- RCTs assessing the efficacy of novel therapies (such as biologics) of at least 12 months' duration should be performed.

- RCTs assessing efficacy of treatment in interproximal maxillary class II furcation defects are needed.
- RCTs assessing efficacy of treatment in class III furcation defects are advocated.
- RCTs assessing the long-term outcomes of furcation regeneration, including tooth loss, furcation closure/conversion and PROMs and cost–benefit analyses are needed.
- Adherence to CONSORT guidelines should be mandatory to improve reporting and reduce risk of bias.
- Research into novel approaches for the regenerative treatment of class II furcations is encouraged.

CONFLICT OF INTEREST

The other authors declared no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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