Received: 27 July 2019 | Revised: 12 December 2019 | Accepted: 14 December 2019

DOI: 10.1111/jcpe.13237

SYSTEMATIC REVIEW

Journal of Clinical Periodontology WILEY

Regenerative surgery versus access flap for the treatment of intra-bony periodontal defects: A systematic review and meta-analysis

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Abstract

Background: The aim of this systematic review was to compare clinical, radiographic and patient-reported outcomes (PROMs) in intra-bony defects treated with regenerative surgery or access flap.

Materials and Methods: A systematic review protocol was written following the PRISMA checklist. Electronic and hand searches were performed to identify randomized clinical trials (RCTs) on regenerative treatment of deep intra-bony defects (≥3 mm) with a follow-up of at least 12 months. Primary outcome variables were probing pocket depth (PPD) reduction, clinical attachment level (CAL) gain and tooth loss. Secondary outcome variables were Rec, radiographic bone gain, pocket "closure," PROMs and adverse events. Meta-analysis was carried out when possible. To evaluate treatment effect, odds ratios were combined for dichotomous data and mean differences for continuous data using a random-effect model.

Results: A total of 79 RCTs (88 articles) published from 1990 to 2019 and accounting for 3,042 patients and 3,612 intra-bony defects were included in this systematic review. Only 10 of included studies were rated at low risk of bias. A total of 13 meta-analyses were performed. All regenerative procedures provided adjunctive benefit in terms of CAL gain (1.34 mm; 0.95–1.73) compared with open flap debridement alone. Both enamel matrix derivative (EMD) and guided tissue regeneration (GTR) were superior to OFD alone in improving CAL (1.27 mm; 0.79–1.74 mm and 1.43 mm; 0.76–2.22, respectively), although with moderate–high heterogeneity. Among biomaterials, the addition of deproteinized bovine bone mineral (DBBM) improved the clinical outcomes of both GTR with resorbable barriers and EMD. Papillary preservation flaps enhanced the clinical outcomes. The strength of evidence was low to moderate.

Conclusion: EMD or GTR in combination with papillary preservation flaps should be considered the treatment of choice for residual pockets with deep (≥3 mm) intra-bony defects.

KEYWORDS

enamel matrix derivatives, intra-bony defect, meta-analysis, periodontal pocket, periodontal regeneration, systematic review

1 | BACKGROUND

Periodontal intra-bony defects (also called "vertical" defects) are an anatomical sequela of periodontal disease progression, with a base apical to the inter-dental alveolar crest, surrounded by one, two or three bony walls (Lang, 2000). These defects are associated with a higher risk of progression (Papapanou & Wennstrom, 1991) and, as such, are often considered to require surgical intervention beyond cause-related periodontal therapy. Pioneering studies in the 1970s and 1980s have shown that intra-bony defects have potential for healing through regeneration using barrier membranes, including the formation of new attachment, re-growth of periodontal ligament and bone measurable clinically, radiographically and histologically (Nyman, Lindhe, Karring, & Rylander, 1982). Among the various materials employed today, there is currently evidence of true periodontal regeneration (periodontal ligament, cementum and bone) for decalcified freeze-dried bone allograft (DFDBA) (Bowers et al., 1989), demineralized bovine bone mineral (DBBM) (Mellonig, 2000) and enamel matrix derivative (EMD) (Bosshardt, Sculean, Windisch, Pjetursson, & Lang, 2005). On the contrary, bioactive glass (BG) (Nevins et al., 2000), hydroxyapatite (HA) (Stahl & Froum, 1987) and tricalcium phosphate (TCP) (Froum & Stahl, 1987), although efficient for improving clinical parameters, have histologically shown limited evidence of regeneration. Furthermore, the regenerative effect was demonstrated for platelet-derived factors (Ridgeway, Mellonig, & Cochran, 2008), although no histologic evidence for periodontal regeneration is yet available for autogenous platelet-rich plasma (PRP) and platelet-rich fibrin (PRF).

A plethora of human clinical studies followed, showing variable improvements in clinical and radiographic measurements of periodontal disease after regenerative surgical procedures compared with access flaps (Cortellini & Tonetti, 2015; Esposito, Grusovin, Papanikolaou, Coulthard, & Worthington, 2009; Needleman, Worthington, Giedrys-Leeper, & Tucker, 2006). Several techniques and biomaterials have been employed for periodontal regeneration of intra-osseous defects, including minimally invasive techniques with or without regenerative devices, proposed to reduce treatment time, costs and morbidity (Cortellini & Tonetti, 2011; Harrel, 1999; Trombelli, Farina, & Franceschetti, 2007). A recent consensus report of the American Academy of Periodontology considers surgical intervention the treatment of choice for intra-bony defects (Reynolds et al., 2015). However, guidelines for the surgical treatment of intra-bony defects are needed, to improve the clarity on indications of different techniques and biomaterials.

The aim of this systematic review was to compare clinical, radiographic and patient-reported outcomes in the treatment of intra-bony defects treated with regenerative surgery or access flap. Based on this, guidelines for the regenerative treatment of periodontal intra-bony defects will be proposed.

Clinical Relevance

Scientific rationale for the study: The aim of this systematic review was to assess the clinical efficacy of regenerative procedures in the treatment of residual pockets associated with intra-bony defects ≥3 mm.

Principal findings: The use of enamel matrix derivative (EMD) or resorbable barriers (res-GTR) was associated with higher clinical benefit compared with open flap for debridement (OFD) alone. No significant difference was reported when comparing EMD and res-GTR. Among biomaterials, deproteinized bovine bone mineral (DBBM) seems to provide additional clinical benefits to both EMD and res-GTR. Non-resorbable membranes for GTR were associated with higher post-operative morbidity and higher incidence of complications, compared with resorbable membranes. The use of papillary preservation flap is critical to obtain successful outcomes. Initial and heterogeneous data seem to support the use of platelet-rich plasma (PRP)/platelet-rich fibrin (PRF) in addition to OFD, although no definitive proof of histologic regeneration of new attachment is available.

Practical implications: Evidence supports the use of EMD or res-GTR as the treatment of choice for deep intra-bony defects. The addition of DBBM should be considered especially for the treatment of wider defects. Soft tissue management according to the principles of papilla preservation techniques should be routinely applied to obtain successful outcomes.

2 | MATERIALS AND METHODS

A systematic review protocol was written in the planning stages, and the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009) was followed in both the planning and reporting of the review. The protocol was registered on 08 February 2019 with PROSPERO (available from ID: CRD42019124022).

2.1 | Focused question

The present review aimed to answer two focused questions:

- Does regenerative surgery of intra-bony defects provide additional clinical benefits measured as probing pocket depth (PPD) reduction, clinical attachment level (CAL) gain, recession (Rec) and bone gain (BG) in periodontitis patients compared with access flap?

- Is there a difference among regenerative procedures in terms of clinical and radiographic gains in intra-bony defects?

2.2 | Eligibility criteria

Criteria used in this systematic review (SR) for studies selection were based on the PICOS method and were the following:

- (P) Types of participants: Adult human patients with periodontitis who have completed a cycle of non-surgical periodontal therapy and present with residual pockets and intra-bony defects (defects with a base apical to the inter-dental alveolar crest, surrounded by one, two or three bony walls or a combination with at least 3 mm of intra-bony component).
- (I) Types of interventions: (A) Any type of regenerative surgery with guided tissue regeneration (GTR), enamel matrix derivative (EMD), bone filler or substitutes, growth factors (GF) or combination. (B) Access flap surgery (any type of mucoperiosteal flap providing access to the root for debridement followed by re-positioning of the gingiva at pre-surgical level).
- (C) Comparison between interventions: All possible comparisons between access flap surgery and regenerative procedures or between regenerative procedures.
- (O) Type of outcome measures:
  Primary outcomes: CAL gain, PD reduction and tooth loss.
  Secondary outcomes: Rec, radiographic bone gain (BG), pocket "closure" (namely presence of PD at experimental site ≤4 mm at study follow-up), PROMs (patient-reported outcome measures) and adverse events (AE).
- (S) Types of studies: Only randomized controlled clinical trials (RCTs) were considered.

The following additional inclusion criteria were considered:

- RCTs, with or without a split-mouth design comparing the results of at least 2 of the investigated surgical techniques above in patients with periodontal intra-bony defects ≥3 mm;
- including at least 10 patients per arm;
- with at least 12-month follow-up. According to follow-up duration, the studies were divided into short-term observations (1–3 years) and long-term observations (>3 years);
- only studies published in English were considered (due to the time constraints of this review).

In this SR, the following items were considered as exclusion criteria:

- RCTs comparing variations of a same technique (i.e. EMD with or without doxycycline).
- RCTs with unclear/not specified type of treated intra-bony defects.
- RCTs treating multiple intra-bony defects, furcation defects or both single intra-bony defects and furcation defects.
- RCTs with multiple treated sites into a single patient without appropriate statistical analysis and unavailable individual patient data (IPD).

2.3 | Information sources and search

An expert reviewer (U.P.) conducted a search on electronic databases until 31 January 2019 to identify studies suitable for this review. Three online evidence sources were used:

1. The National Library of Medicine (MEDLINE by PubMed).
2. The Cochrane Database Trials Register.
3. Scopus.

The search strategies used for each online database are published in Appendix S1; Appendix S2; Appendix S3.

Hand searching included a complete search of *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research* and *Journal of Dental Research* from January 2000 to January 2019.

The search was complemented by a screening of the Open Grey database and of the reference lists of included studies and previous systematic reviews or guidelines dealing with regenerative surgical procedures for the treatment of periodontal intra-bony defects (Călin & Pătraşcu, 2016; Castro et al., 2017; Darby & Morris, 2013; Del Fabbro, Bortolin, Taschieri, & Weinstein, 2011; Esposito et al., 2009; Giannobile & Somerman, 2003; Graziani et al., 2012; Hou, Yuan, Aisaiti, Liu, & Zhao, 2016; Kao, Nares, & Reynolds, 2015; Khojasteh, Sogeilifar, Mohajerani, & Nowzari, 2013; Khoshkam et al., 2015; Koop, Merheb, & Quirynen, 2012; Matarasso et al., 2015; Miron et al., 2017; Murphy & Gunsolley, 2003; Needleman et al., 2006; Pagliaro et al., 2008; Panda, Doraiswamy, Malaiappan, Varghese, & Fabbro, 2016; Parrish, Miyamoto, Fong, Mattson, & Cerutis, 2009; Patel, Wilson, & Palmer, 2012; Rathe, Junker, Chesnutt, & Jansen, 2009; Reynolds, Aichelmann-Reidy, Branch-Mays, & Gunsolley, 2003; Roselló-Camps et al., 2015; Sculean et al., 2015; Stoecklin-Wasmer et al., 2013; Troiano et al., 2017; Trombelli, Heitz-Mayfield, Needleman, Moles, & Scabbia, 2002; Yen, Tu, Chen, & Lu, 2014; Zanatta, Souza, Pinto, Antoniazzi, & Rösing, 2013; Zhou et al., 2018).

2.4 | Study selection

Study selection was conducted by independent reviewers in the following stages:

1. *Initial screening of potentially suitable titles and abstracts against the inclusion criteria to identify potentially relevant papers (authors L.B. and U.P.).* Before initial screening, all the items found

through electronic and manual searches were grouped into a single list, excluding duplicates by means of EndNote™ software (L.B.). Subsequently, two review authors (L.B. and U.P.) independently screened the titles and abstracts (when available) of all reports identified in the EndNote™ single list (step 1). When studies met the inclusion criteria or when insufficient data from abstracts for evaluating inclusion criteria were gained, the full article was obtained.

2. *Eligibility of the full papers identified as possibly relevant in the initial screening (L.B., F.C., V.K., U.P.).* Four review authors (L.B., F.C., V.K. and U.P.) independently assessed the full text of all studies of possible relevance.

Interrater agreement among examiners was calculated using the kappa score after article selection. The following outcomes were reported, leading moderate to substantial reliability (Landis & Koch, 1977):

Examiner 1 versus Examiner 2: K = 0.63 (95% CI from 0.52 to 0.74)
Examiner 1 versus Examiner 3: K = 0.67 (95% CI from 0.57 to 0.78)
Examiner 1 versus Examiner 4: K = 0.61 (95% CI from 0.49 to 0.72)
Examiner 2 versus Examiner 3: K = 0.55 (95% CI from 0.43 to 0.67)
Examiner 2 versus Examiner 4: K = 0.55 (95% CI from 0.43 to 0.67)
Examiner 3 versus Examiner 4: K = 0.72 (95% CI from 0.63 to 0.82)

When disagreement between the four reviewers was revealed, consensus was achieved by discussion between all reviewers (step 2).

An attempt was made to contact authors of potentially relevant papers in order to obtain summary data, which may not have been reported in the published document and clarify potential inclusion of such papers.

2.5 | Data collection process and data items

All studies meeting the inclusion criteria then underwent quality assessment and data recording. A standardized specifically designed data extraction form was used to record data from each included study, encompassing number of patients, demographics, definition and diagnosis of periodontitis, clinical methods (assessment and treatment), follow-up duration, clinical and radiographic outcomes and patient-reported outcomes. Two review authors (L.B. and V.K.) independently extracted data. When disagreement between the two reviewers was detected, consensus was achieved by discussion with the third reviewer/statistical advisor (M.N.).

2.6 | Study characteristics

Only RCTs, with or without a split-mouth design, were included in the systematic review.

CAL gain had to be expressed as mean clinical attachment level increase in millimetres of the treated sites of each study arm at follow-up visit. *PD reduction* had to be expressed as mean periodontal probing depth reduction in millimetres of the treated sites of each study arm at follow-up visit. *Rec* had to be expressed as mean recession in millimetres of the treated sites of each study arm at baseline and follow-up visits. *Radiographic BG (bone gain)* had to be expressed as mean intra-bony component decrease in millimetres of the treated intra-bony defects of each study arm at follow-up visit. *Tooth loss* had to be expressed as the number or the percentage of treated teeth of each considered study arm that resulted missing (extracted) at the follow-up visit. Pocket "closure" had to be reported as the presence of PD ≤ 4 mm at experimental site at study follow-up. *PROMs (patient-reported outcome measures)* and *AE (adverse events)* had to be described at least in a narrative form.

2.7 | Risk of bias in individual studies

The quality assessment of the included studies was independently performed in a duplicate form by two review authors (L.B. and M.N.) through risk of bias analysis as it could impact on the overall results and conclusions ("Systematic reviews, CRD's guidance for undertaking reviews in health care," University of York, 2008). The Cochrane Collaboration's tool was used for assessing risk of bias (Higgins & Green, 2011) (Figure 2).

Briefly, seven domains (sequence generation, allocation concealment, blinding of the outcome assessor, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other bias) were considered and included in a specific table.

Risk of bias in the included studies was categorized as below:

A Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
B Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were partly met.
C High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

2.8 | Summary measures and planned method of analysis

Studies were initially narratively summarized by chief characteristics and according to type of regenerative surgery, for example GTR, bone filler material and type of membrane. A meta-analysis was considered appropriate and was performed in the presence of at least two studies of similar design. Mean differences were used for CAL

gain, PD reduction, Rec reduction (RecRed), bone gain, aesthetic and functional satisfaction. The odds ratio of tooth loss and for complications was used as a summary measure.

The variables were registered at patient level. In each patient, only one tooth per technique was assessed. When studies with multiple teeth were identified, the presence of individual patient data (IPD) was checked and the mean of the multiple sites was used for the analysis. If the IPD were not reported in the study, the number of patients was used in the meta-analysis.

Forest plots were produced when appropriate to graphically represent the difference in outcomes between groups using the patient as the analysis unit.

The techniques described by Elbourne et al. were used to calculate the standard error of the difference in split-mouth studies, where the appropriate data were not presented (Elbourne et al., 2002).

Meta-analyses were performed on an intention-to-treat basis using the generic inverse variance method with random-effect models. Ninety-five per cent confidence intervals for each outcome variable were calculated. The significance of any discrepancies in the estimates of the treatment effects from different trials was assessed by means of the Cochran test for heterogeneity and the I^2 statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than change. The suggested interpretation of I^2 is as follows: 0%–40% may represent low heterogeneity, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity and 75%–100% considerable heterogeneity (Higgins & Green, 2011). Funnel plots and Egger's test were planned to explore the presence of publication bias if at least 10 studies were included in the meta-analysis (Song, Hooper, & Loke, 2013; Sterne, Egger, & Moher, 2008). Sensitivity analysis was also planned considering only studies in the single meta-analysis at low risk of bias.

The statistical analyses were carried out using the RevMan software version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) by a single reviewer (MN).

2.9 | Evaluation of the strength of evidence

Evidence regarding provided by RTCs was rated using different levels of methodological strength modified from GRADE (Grading of Recommendations Assessments Development and Evaluation) (Guyatt et al., 2008). Three different strength of evidence were considered:

- High: At least 3 RCTs at low risk of bias and low heterogeneity.
- Moderate: More than 1 RCT and at least 1 RCT at low risk of bias and low heterogeneity.
- Low: Lack of RCTs or RCTs at high risk of bias or high heterogeneity.

3 | RESULTS

3.1 | Study selection

The search results are presented in Figure 1.

The electronic search in MEDLINE (by PubMed), in the Cochrane Collaboration databases and in Scopus provided, respectively, 646, 766 and 1,544 articles published until January 2019. After grouping into a single list and discarding duplicates, 1,012 articles were identified by electronic search.

The hand searching found 421 articles, 7 of which were not found by the electronic search.

The search in the reference lists of included studies and previous systematic reviews or guidelines provided 10 additional articles not found by electronic and hand searching.

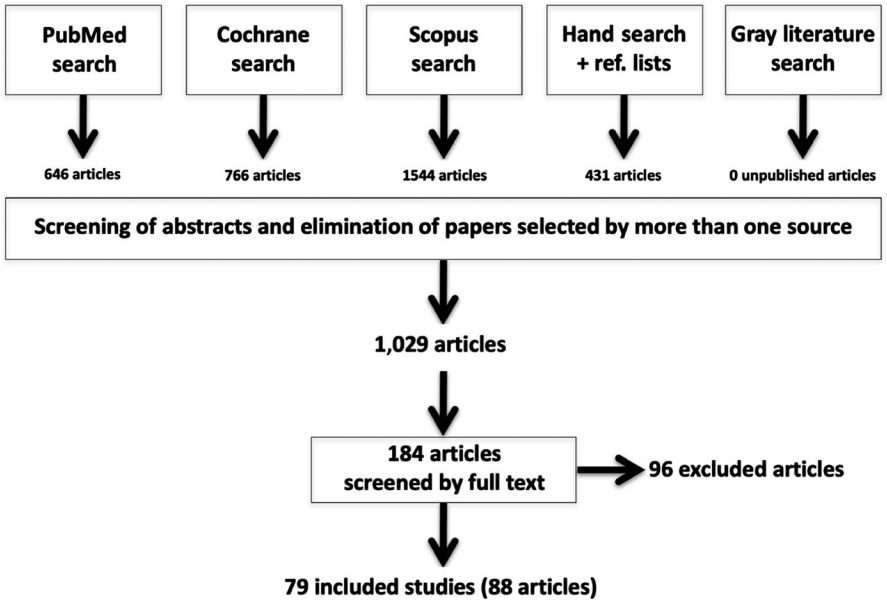

FIGURE 1 Literature search process and results

The search of the "grey literature" (unpublished data) by e-mail contact with all the authors of the identified studies and clinical experts or researchers in the field of periodontal surgery did not provide additional data.

Finally, by merging the literature searches (electronic, manual and unpublished data searches), 1,029 articles (1,012 by electronic, 7 by hand search and 10 by reference lists) were selected.

Subsequently, by first-stage reading all titles and abstracts, 184 articles were screened as potentially relevant papers.

The full-text reading of the 184 articles allowed the selection of 88 articles (79 studies) that met the inclusion criteria of this systematic review and the exclusion of 96 articles from the analysis. Rejected studies at this stage are listed in Appendix S4 (Characteristics of excluded studies), and the reason for exclusion was recorded.

3.2 | Study characteristics

All 79 studies (88 articles) included in the systematic review are presented in Tables 1 and 2. All included studies were published between 1990 and 2019 and accounted for 3,042 patients and 3,612 intra-bony defects. Out of the 79 studies, 11 reported data after 3 years of follow-up, 8 studies between 1 and 3 years of follow-up, and the residual 60 studies have a follow-up of 1 year. The use of systemic antibiotics was reported in 58 studies, while in 10 RTCs, no systemic antibiotics were used. In the residual 11 studies, no information was reported.

3.3 | Source of funding

Regarding the source of funding, 15 included studies received private financial support, 17 public support and 12 combination of public and private funding. In addition, 2 studies reported no funding, whereas the majority (33 studies) did not report the source of funding.

3.4 | Results of the analyses

Based on available studies, the following comparisons were considered (at least 2 available studies for each comparison):

1. Open flap for debridement (OFD) versus all regenerative procedures (RP)
2. OFD versus OFD + enamel matrix derivative (EMD)
3. OFD versus OFD + guided tissue regeneration (GTR)
4. OFD versus OFD + deproteinized bovine bone mineral (DBBM) + GTR
5. OFD versus OFD + platelet-rich fibrin (PRF)
6. OFD + demineralized freeze-dried bone allograft (DFDBA) versus OFD + DFDBA + platelet-rich plasma (PRP)
7. OFD + DBBM versus OFD + DBBM + other
8. OFD + GTR versus OFD + EMD
9. OFD + EMD versus OFD + EMD + other
10. OFD + EMD versus OFD + filler
11. OFD + non-resorbable GTR (GTR-NR) versus OFD + resorbable GTR (GTR-R)
12. OFD + filler + GTR versus OFD + filler + GTR + PRP
13. OFD + GTR versus OFD + GTR + filler

Clinical outcomes from a total of 50 RCTs (52 articles) were included in the meta-analyses. Table 3 reports the results of meta-analyses for all investigated variables including CAL, PD reduction, recession and bone gain.

The main results of the meta-analyses can be summarized as:

- OFD versus all RP: Regenerative procedures resulted in improved CAL gain, greater PD and bone gain compared with OFD alone. Moderate to substantial heterogeneity in the size of the adjunctive effect was observed. This could be partly explained by the use of specific biomaterials or flap designs.
- OFD versus EMD + OFD: EMD results in greater CAL gain, PD reduction and bone gain compared with OFD alone. RecRed is not significantly different between the two treatments. Substantial to considerable heterogeneity is present for the variables. In part, the heterogeneity could be due to the presence or not of the placebo in the control group.
- OFD versus OFD + GTR: GTR results in greater CAL gain and PD reduction compared with OFD alone. RecRed and bone gain are not significantly different between the two interventions. Moderate to substantial heterogeneity is present. In part, the heterogeneity could be due to the presence of resorbable or non-resorbable membranes.
- OFD versus OFD + DBBM + GTR: OFD + DBBM + GTR results in greater CAL gain, PD reduction, RecRed and CAL gain stability in the long term compared with OFD. Moderate to substantial heterogeneity is present. In part, the heterogeneity could be due to the presence of OFD or papilla preservation flaps (PPF).
- OFD versus OFD + PRF: OFD + PRF results in greater CAL gain and PD reduction compared with OFD. Substantial to considerable heterogeneity is present.
- OFD + DFDBA versus OFD + DFDBA + PRP: OFD + DFDBA + PRP results in greater CAL gain, RecRed and bone gain compared with OFD + DFDBA. PD reduction is not significantly different between the two treatments. Low to substantial heterogeneity is present. In part, the heterogeneity could be due to the presence of PRP or PRF.
- OFD + GTR versus OFD + EMD: CAL gain, PD reduction and RecRed are not significantly different when comparing OFD + GTR versus OFD + EMD. Moderate to substantial heterogeneity is present. For PD reduction, the heterogeneity could be due to the presence of resorbable or non-resorbable membranes.
- OFD + EMD versus OFD + EMD + Other: OFD + EMD + Other results in greater CAL gain, PD reduction and bone gain compared

TABLE 1 Comparison between OFD and regenerative procedures

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
OFD versus OFD + EMD								
Silvestri et al. (2000)	OFD versus OFD + EMD	P	1.2 ± 1.0	4.5 ± 1.6	1.4 ± 1.3	4.8 ± 1.6	–	–
De Leonardis and Paolantonio (2013)	PPF versus PPF + EMD	SM	1.40 ± 1.13	2.95 ± 0.74	2.38 ± 1.01	3.76 ± 0.74	1.01 ± 0.46	0.80 ± 0.39
Fickl, Thalmair, Kebschull, Bohm, and Wachtei (2009)		SM	1.7 ± 0.3	3.7 ± 0.4	2.4 ± 0.3	4.2 ± 0.3	0.7 ± 0.2	0.5 ± 0.2
Francetti, Del Fabbro, Basso, Testori, and Weinstein (2004)		P	2.71 ± 0.76	4.29 ± 1.38	3.00 ± 1.15	4.86 ± 1.95	–	–
Tonetti et al. (2002)		P	2.5 ± 1.5	3.1 ± 1.5	3.3 ± 1.7	3.9 ± 1.7	0.8 ± 1.2	0.8 ± 1.2
Zucchelli et al. (2002)		P	2.6 ± 0.8	4.2 ± 0.9	4.5 ± 1.0	5.1 ± 0.7	1.9 ± 0.8	1.0 ± 0.5
Francetti et al. (2005)[a]		P	2.51	3.51	3.51	4.02	–	–
Wachtel et al. (2003)		SM	1.7 ± 1.4	3.6 ± 1.6	2.1 ± 1.1	3.9 ± 1.4	0.4 ± 0.9	0.3 ± 0.8
Heijl, Heden, Svärdström, and Ostgren (1997)	OFD + placebo versus OFD + EMD	SM	1.7 ± 1.3	2.2 ± 1.1	2.3 ± 1.1	3.1 ± 1.0	–	–
Okuda et al. (2000)		SM	0.83 ± 0.86	1.72 ± 1.07	2.22 ± 0.81	3.00 ± 0.97	1.22 ± 0.16	1.22 ± 0.88
Grusovin and Esposito (2009)	PPF + placebo versus PPF + EMD	P	3.3 ± 1.2	3.4 ± 1.1	3.9 ± 1.0	4.2 ± 1.6	−0.6 ± 1.1	−0.8 ± 1.0
Rösing, Aass, Mavropoulos, and Gjermo (2005)[a]		SM	[b]	[b]	[b]	[b]	–	–
OFD versus OFD + GTR								
Mora, Etienne, and Ouhayoun (1996)	OFD versus OFD + GTR-NR	SM	2.55 ± 1.0	3.85 ± 0.9	3.55 ± 1.1	5.35 ± 1.3	−0.9 ± 0.5	−1.25 ± 0.7
Silvestri et al. (2000)		P	1.2 ± 1.0	4.8 ± 2.1	1.4 ± 1.3	5.9 ± 1.1	–	–
Zucchelli et al. (2002)	PPF versus PPF + GTR-NR	P	2.6 ± 0.8	4.9 ± 1.6	4.5 ± 1.0	6.5 ± 1.6	1.9 ± 0.8	1.6 ± 1.0
Mayfield et al. (1998)	OFD versus OFD + GTR-R	P	1.3 ± 1.7	1.5 ± 1.9	2.5 ± 1.9	2.9 ± 1.8	−1.2 ± 1.0	−1.4 ± 0.9
Paolantonio et al. (2008)[a]		P	1.5	3.1	2.8	5.2	1.4	2.1
Loos et al. (2002)[d]		SM	0.5	1.5	–	–	–	–
	OFD + GTR-R (AB+)[d]	SM	2.0	1.3	–	–	–	–
Blumenthal and Steinberg (1990)[a]		P	0.75 ± 0.2	1.17 ± 0.1	1.51 ± 0.2	1.99 ± 0.3	1.24 ± 0.2	0.96 ± 0.1
Tonetti et al. (1998)	PPF versus PPF + GTR-R	P	2.18 ± 1.46	3.04 ± 1.64	3.09 ± 1.67	4.03 ± 1.81	1.01 ± 1.18	1 ± 1.4
Cortellini et al. (2001)		P	2.6 ± 1.8	3.5 ± 2.1	3.6 ± 2.1	4.4 ± 2.4	0.9 ± 1.3	0.9 ± 1
Stavropoulos et al. (2003)		P	1.5	2.9	2.9	3.9	1.3	1.1
Stavropoulos and Karring (2010)[a] (F-up Stavropoulos et al. (2003))		P	1.2	2.4	[b]	[b]	–	–

(Continues)

TABLE 1 (Continued)

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
OFD versus OFD + DBBM + GTR								
Sculean et al. (2003)	OFD versus OFD + DBBM + GTR-R	P	2.1 ± 1.7	4.0 ± 1.3	3.8 ± 1.8	5.3 ± 1.6	1.7 ± 1.2	1.3 ± 0.8
Sculean, Chiantella, et al. (2005))		P	1.9 ± 1.1	4.1 ± 0.9	3.6 ± 1.3	5.4 ± 0.9	1.6 ± 0.9	1.3 ± 1.0
Sculean, Schwarz, et al. (2007)) (F-up Sculean et al., 2003)		P	[b]	[b]	[b]	[b]	[b]	[b]
Stavropoulos et al. (2003)[c]	PPF versus PPF + DBBM + GTR-R	P	1.5	2.5	2.9	3.8	1.3	2.8
Stavropoulos and Karring (2010) (F-up Stavropoulos et al. (2003))		P	1.2	2.3	[b]	[b]	–	–
Tonetti, Cortellini, et al. (2004))		P	2.5 ± 1.5	3.3 ± 1.7	3.2 ± 1.5	3.7 ± 1.8	0.7 ± 0.9	0.3 ± 1.2
OFD versus OFD + PRF								
Thorat, Baghele, and S, P.R. (2017)		SM	0.33 ± 1.21	4.0 ± 0.63	1.50 ± 0.34	4.0 ± 0.63	0.16 ± 0.40	−0.32 ± 0.50
Patel, Gaekwad, Gujjari, and S C, V.K. (2017)		SM	2.1 ± 0.74	3.70 ± 0.67	2.4 ± 0.84	4.2 ± 1.69	–	–
Bokan, Bill, and Schlagenhauf (2006)[a]	OFD versus PPF + EDM + bTCP	P	2.1 ± 1.4	4.0 ± 1.0	3.8 ± 1.8	4.1 ± 1.2	1.5 ± 0.7	0.7 ± 1.1
	OFD versus PPF + EMD	P	2.1 ± 1.4	3.7 ± 1.0	3.8 ± 1.8	3.9 ± 1.3	1.5 ± 0.7	0.7 ± 1.3
Blumenthal and Steinberg (1990)[a]	OFD versus OFD + AAA	P	0.75 ± 0.2	1.43 ± 0.1	1.51 ± 0.2	2.03 ± 0.1	1.24 ± 0.2	1.47 ± 0.4
	OFD versus OFD + AAA + CG		0.75 ± 0.2	1.88 ± 0.2	1.51 ± 0.2	2.61 ± 0.1	1.24 ± 0.2	1.03 ± 0.2
	OFD versus ODS versus OFD + AAA + CG + GTR-R		0.75 ± 0.2	2.01 ± 0.1	1.51 ± 0.2	2.73 ± 0.1	1.24 ± 0.2	0.91 ± 0.1
De Leonardis and Paolantonio (2013)[a]	PPF versus PPF + EMD + HA/bTCP	SM	1.40 ± 1.13	3.63 ± 0.91	2.38 ± 1.01	4.25 ± 0.63	1.01 ± 0.46	0.63 ± 0.42
Ferrarotti et al. (2018)[a]	PPF versus PPF + DPSCs	P	2.9 ± 2.2	4.5 ± 1.9	3.4 ± 1.7	4.9 ± 1.4	0.5 ± 0.9	0.4 ± 1.1
Kasaj, Röhrig, Reichert, and Willershausen (2008)	OFD versus OFD + HA/P−15	P	1.8 ± 1.0	3.9 ± 1.7	2.5 ± 1.1	4.3 ± 1.3	0.7 ± 0.7	0.3 ± 0.6
Kim et al. (1998)[a]	OFD versus OFD + DFDBA + CS barrier	P	1.7 ± 1.5	2.9 ± 0.8	3.0 ± 1.3	4.3 ± 0.5	–	–
Minenna, Herrero, Sanz, and Trombelli (2005)[a]	OFD versus PLA/PGA	P	3.4 ± 1.4	3.6 ± 1.5	3.9 ± 1.4	4.6 ± 2.0	0.6 ± 1.3	1.1 ± 1.5
Paolantonio et al. (2008)[a]	OFD versus OFD + CS	P	1.5	2.7	2.8	4.4	1.4	1.6
Pietruska, Pietruski, et al. (2012)), Pietruska, Skurska, et al. (2012))[a]	OFD versus OFD + HA	P	2.0 ± 1.5	2.0 ± 2.7	2.6 ± 1.6	2.9 ± 2.5	0.6 ± 0.6	0.9 ± 1.2

(Continues)

TABLE 1 (Continued)

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
Shirakata et al. (2008)[a]	OFD versus OFD + CPC	P	1.4 ± 0.8	2.3 ± 1.0	3.3 ± 1.2	3.4 ± 1.2	1.9 ± 0.9	1.1 ± 1.1
De Santana and de Santana (2015)[a]	PPF versus PPF + rhFGF–2/HyAc	SM	2.2 ± 0.5	4.8 ± 0.2	2.9 ± 0.9	5.5 ± 1.4	−0.7 ± 0.1	−0.7 ± 0.2
Slotte, Askiöw, Sultan, and Norderyd (2012)[a]	OFD versus OFD + DBBM	P	2.8 ± 0.6	2.3 ± 0.8	4.0 ± 0.5	3.2 ± 0.7	1.1 ± 0.3	0.9 ± 0.4

Abbreviations: AAA, autolysed antigen-extracted allogenic freeze-dried bone; bTCP, tricalcium phosphate; CG, microfibrillar collagen gel; CPC, calcium phosphate bone cement; CS, calcium sulphate; DBBM, demineralized bovine bone matrix; DFDBA, demineralized freeze-dried bone allograft; DPSCs, dental pulp stem cells; EMD, enamel matrix derivative; GTR-NR, guided tissue regeneration using a non-resorbable membrane; GTR-R, GTR using a resorbable membrane; HA, hydroxyapatite; HA/P-15, anorganic bovine-derived hydroxyapatite matrix/cell-binding peptide; HyAc, hyaluronic acid; OFD, open flap debridement; P, parallel; PLA/PGA polylactide/polyglycolide copolymer as biomaterial; PPF, papilla preservation flap; PRF, platelet-rich fibrin; rhFGF-2, recombinant human fibroblast growth factor; SM, split mouth.

[a]Not in meta-analysis.

[b]Reported the baseline and follow-up data but not the mean difference.

[c]For this review the group adding gentamicin to the graft was not included.

[d]For Loos et al. (2002) were considered two comparisons: Loos et al. (2002) OFD versus OFD + GTR-R and OFD(AB+) versus OFD + GTR-R (AB+); Loos et al. (2002), the patients in the second comparison received an antibiotic (AB+).

with to OFD + EMD. RecRed is not significantly different between the two interventions. Low to moderate heterogeneity is present. Assessing the different materials added to OFD + EMD, only DBBM is significant for CAL gain and PD reduction, while HA/bTCP is significant for bone gain.

- OFD + GTR-NR versus OFD + GTR-R: CAL gain, PD reduction and RecRed are not significantly different comparing OFD + GTR-NR versus OFD + GTR-R. The heterogeneity was low.

Sensitivity analysis was also performed considering only studies in the single meta-analysis at low risk of bias.

The following meta-analyses were than available for this evaluation:

- OFD versus OFD + EMD, one RCT, (De Leonardis & Paolantonio, 2013)
- OFD versus OFD + GTR, three RCTs (2 studies by Loos et al., 2002 and Stavropoulos, Karring, Kostopoulos, & Karring, 2003)
- OFD versus OFD + DBBM + GTR, one RCT (Stavropoulos et al., 2003)
- OFD + GTR versus OFD + EMD, two RCTs (Iorio Ghezzi, Ferrantino, Bernandini, Lencioni, & Masiero, 2016; Siciliano et al., 2011)
- OFD + EMD versus OFD + EMD + Other, three RCTs (De Leonardis & Paolantonio, 2013; Meyle et al., 2011; Sipos, Loos, Abbas, Timmerman, & Velden, 2005)

Interestingly, sensitivity analysis did not change the results of primary analysis, apart from the comparison OFD versus OFD + GTR, which showed no significant difference between treatments.

4 | TOOTH LOSS

Very limited data are available for the tooth loss variable. Only 1 tooth in the papilla preservation flap group was lost in Tonetti, Cortellini, et al. (2004)) due to periodontal reason in a 12-month follow-up (Tonetti, Cortellini, et al., 2004). Considering the long-term observation, after 7 years of follow-up, 2 teeth were lost due to periodontal reason out of 36 treated with a GTR procedure (Stavropoulos & Karring, 2010). Similarly, patients treated with OFD + AB with or without a membrane lost one tooth on each group after 10 years (Nygaard-Østby, Bakke, Nesdal, Susin, & Wikesjö, 2010).

4.1 | Secondary outcomes

4.1.1 | PROMs

Only very few studies reported PROMs, and no meta-analysis was possible. Testing the benefit of the EMD, Tonetti, Fourmousis, et al.

TABLE 2 Comparison between regenerative procedures

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
OFD + DFDBA versus OFD + DFDBA + PRP								
Agarwal and Gupta (2014)	OFD + DFDBA versus OFD + DFDBA + PRP	SM	2.40 ± 0.61	3.15 ± 0.63	3.65 ± 0.52	3.65 ± 0.63	1.23 ± 0.47	0.54 ± 0.59
Piemontese, Aspriello, Rubini, Ferrante, and Procaccini (2008)		P	2.4 ± 2.2	3.6 ± 1.8	3.5 ± 1.9	4.6 ± 1.3	1.1 ± 2.1	1.0 ± 1.3
Agarwal et al. (2016)	OFD + DFDBA versus OFD + DFDBA + PRF	SM	2.61 ± 0.68	3.73 ± 0.74	3.60 ± 0.51	4.15 ± 0.84	1.00 ± 0.61	0.47 ± 0.56
OFD + DBBM versus OFD + DBBM + Other								
Sculean, Chiantella, Chiantella, Windisch, Gera, and Reich (2002))	OFD + DBBM versus OFD + DBBM + EMD	P	4.9 ± 2.1	4.7 ± 1.9	6.5 ± 2.0	5.7 ± 1.5	1.5 ± 1.0	0.8 ± 0.7
Döri et al. (2009)	OFD + DBBM versus OFD + DBBM + PRP	P	4.7 ± 1.6	4.6 ± 1.7	5.3 ± 1.7	5.2 ± 1.6	0.6 ± 1.6	0.6 ± 1.7
Qiao, Duan, Zhang, Chu, and Sun (2016)[a]	OFD + DBBM versus OFD + DBBM + PRP (CGF)	P/SM	2.4 ± 1.1	3.7 ± 1.3	3.0 ± 1.6	4.2 ± 1.3	0.7 ± 0.5	0.5 ± 0.6
OFD + GTR versus OFD + EMD								
Crea et al. (2008)	OFD + GTR-NR versus OFD + EMD	P	2.0 ± 1.1	2.4 ± 1.2	3.2 ± 1.1	3.1 ± 1.4	–	–
Siciliano et al. (2011)		P	4.1 ± 1.4	2.4 ± 2.2	5.5 ± 1.0	2.9 ± 2.1	0.5 ± 0.6	0.7 ± 1.2
Silvestri et al. (2003)		P	4.3 ± 1.9	4.1 ± 1.8	5.6 ± 1.5	5.3 ± 1.9	–	–
Zucchelli et al. (2002)		P	4.9 ± 1.6	4.2 ± 0.9	6.5 ± 1.6	5.1 ± 0.7	1.6 ± 1.0	1.0 ± 0.5
Pontoriero, Wennström, and Lindhe (1999)[a]		P	2.9	2.9	4.7	4.4	1.8	1.7
Silvestri et al. (2000)[a]		P	4.8 ± 2.1	4.5 ± 1.6	5.9 ± 1.1	4.8 ± 1.6	–	–
Sanz et al. (2004)	OFD + GTR-R versus OFD + EMD	P	2.5 ± 1.9	3.1 ± 1.8	3.3 ± 1.5	3.8 ± 1.5	0.7 ± 0.9	0.6 ± 0.9
Pontoriero et al. (1999)[a,e]		P	2.9	3.4	4.7	4.8	1.8	1.4
		P	2.9	3.0	4.7	4.1	1.8	1.1
Minabe et al. (2002)		P	2.8 ± 0.9	2.6 ± 1.0	3.7 ± 1.2	3.8 ± 0.9	0.9 ± 0.8	1.2 ± 0.8
Siciliano et al. (2014)	OFD + DBBM + GTR-R versus OFD + DBBM + EMD	P	3.7 ± 1.2	3.8 ± 1.5	4.4 ± 1.7	4.6 ± 1.9	0.7 ± 0.9	0.6 ± 1.0
Ghezzi et al. (2016)	PPF + DBBM + GTR-R versus PPF + DBBM + EMD	P	4.0 ± 1.82	4.4 ± 1.17	4.7 ± 2.36	4.9 ± 1.20	0.7 ± 0.95	0.5 ± 0.85
OFD + EMD versus OFD + EMD + Other								
Guida et al. (2007)	OFD + EMD versus OFD + EMD + AB	SM	4.6 ± 1.3	4.9 ± 1.8	5.6 ± 1.7	5.1 ± 1.7	1.1 ± 0.7	0.3 ± 0.8

(Continues)

TABLE 2 (Continued)

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
Yilmaz, Cakar, Yildirim, and Sculean (2010)		P	3.4 ± 0.8	4.2 ± 1.1	4.6 ± 0.4	5.6 ± 0.9	1.2 ± 0.8	1.4 ± 0.9
Bokan et al. (2006)	OFD + EMD versus OFD + EMD + bTCP	P	3.7 ± 1.0	4.0 ± 1.0	3.9 ± 1.3	4.1 ± 1.2	0.7 ± 1.3	0.7 ± 1.1
De Leonardis and Paolantonio (2013)	OFD + EMD versus OFD + EMD + HA/bTCP	SM	2.95 ± 0.74	3.63 ± 0.91	3.76 ± 0.74	4.25 ± 0.63	0.80 ± 0.39	0.63 ± 0.42
Losada et al. (2017)		P	2.65 ± 2.18	2.38 ± 2.17	3.30 ± 1.89	3.14 ± 1.95	0.65 ± 1.3	0.85 ± 1.45
Meyle et al. (2011)		P	1.93 ± 1.7	1.69 ± 2.1	2.90 ± 1.8	2.80 ± 2.1	0.97 ± 1.1	1.11 ± 1.3
Hoffmann, Al-Machot, Meyle, Jervøe-Storm, and Jepsen (2016)[a] (F-up Meyle et al., 2011)		P	3.81 ± 2.2	4.07 ± 3.6	3.93 ± 2.3	3.88 ± 2.0	−0.12 ± 2.9	0.19 ± 2.3
Pietruska, Pietruski, et al. (2012)), Pietruska, Skurska, et al. (2012))[a]		P	[b]	[b]	[b]	[b]	[b]	[b]
Sculean, Pietruska, et al. (2005))	OFD + EMD versus OFD + EMD + BG	P	3.9 ± 1.8	3.2 ± 1.7	4.5 ± 2.0	4.2 ± 1.4	0.9 ± 0.7	1.1 ± 0.8
Sculean, Pietruska, Pietruska, Arweiler, Auschill, and Nemcovsky (2007))[a] (F-up Sculean, Pietruska, et al., 2005)		P	[b]	[b]	[b]	[b]	[b]	[b]
Zucchelli et al. (2003)	OFD + EMD versus OFD + EMD + DBBM	P	4.9 ± 1.0	5.8 ± 1.1	5.8 ± 0.8	6.2 ± 0.4	0.9 ± 0.5	0.4 ± 0.6
Sipos et al. (2005)	OFD + EMD versus OFD + EMD + GTR-R	SM	1.28 ± 2.04	1.65 ± 1.29	2.86 ± 0.75	3.02 ± 1.55	1.56 ± 2.30	1.38 ± 1.63
Minabe et al. (2002)		P	2.6 ± 1.0	3.0 ± 1.3	3.8 ± 0.9	4.3 ± 1.6	1.2 ± 0.8	1.2 ± 0.9
OFD + EMD versus OFD + Filler								
Leknes, Andersen, Bøe, Skavland, and Albandar (2009)	OFD + EMD versus OFD + BG	SM	0.6 ± 1.0	1.2 ± 0.2	2.5 ± 1.9	2.6 ± 1.1	2.3 ± 2.0	0.7 ± 1.3
Al Machot, Hoffman, Lorenz, Khalili, and Noack (2014)	OFD + EMD versus OFD + HA	P	1.4 ± 1.8	2.1 ± 1.6	2.6 ± 1.8	3.2 ± 1.8	1.1 ± 1.1	1.2 ± 1.2
OFD + GTR-NR versus OFD + GTR-R								
Christgau et al. (1997)		SM	3.7 ± 3.0	3.8 ± 1.9	3.9 ± 2.3	4.0 ± 1.4	−0.4 ± 1.2	0.1 ± 0.9
Zybutz et al. (2000)		P	2.4 ± 0.8	2.4 ± 1.9	3.1 ± 1.2	3.3 ± 2.1	3.3 ± 1.2	3.0 ± 2.0
OFD + Filler + GTR versus OFD + Filler + GTR + PRP								
Christgau et al. (2006)	OFD + bTCP + GTR-R versus OFD + bTCP + GTR-R + PRP	SM	5.2 ± 1.6	5.0 ± 1.5	6.0 ± 1.1	6.3 ± 1.2	1.0 ± 1.2	1.3 ± 1.3

(Continues)

TABLE 2 (Continued)

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
Moder, Taubenhansl, Hiller, Schmalz, and Christgau (2012)[a] (F-up Christgau et al. (2006))		SM	5.0	3.5	5.5	4.5	1.0	1.0
Döri, Huszár, et al. (2008))	OFD + bTCP + GTR-NR versus OFD + bTCP + GTR-NR + PRP	P	3.9 ± 0.9	4.1 ± 0.7	5.4 ± 0.7	5.8 ± 0.6	1.5 ± 0.7	1.4 ± 0.8
Döri et al. (2007b)	OFD + DBBM + GTR-R versus OFD + DBBM + GTR-R + PRP	P	4.6 ± 0.8	4.7 ± 1.1	5.7 ± 1.2	5.5 ± 1.2	1.2 ± 0.9	1.2 ± 1.1
Döri et al. (2007a)	OFD + DBBM + GTR-NR versus OFD + DBBM + GTR-NR + PRP	P	4.6 ± 1.1	4.5 ± 1.1	5.5 ± 1.7	5.5 ± 1.3	1.3 ± 0.8	1.1 ± 0.7
OFD + GTR versus OFD + GTR + Filler								
Trejo, Weltman, and Caffesse (2000)	OFD + GTR versus OFD + GTR + DFDBA	P	3.27 ± 1.10	2.29 ± 0.61	4.12 ± 0.84	3.37 ± 1.16	1.08 ± 1.07	0.85 ± 0.91
Paolantonio (2002)	OFD + GTR versus OFD + GTR + DBBM	P	4.00 ± 1.27	5.05 ± 1.56	5.58 ± 1.00	5.76 ± 1.60	1.52 ± 1.60	0.75 ± 0.44
Aspriello, Ferrante, Rubini, and Piermontese (2011)[a]	OFD + DFDBA versus OFD + DFDBA + EMD	P	3.25	4.0	4.0	5.0	1.0	1.0
Blumenthal and Steinberg (1990)[a]	OFD + GTR-R versus OFD + AAA	P	1.17 ± 0.1	1.43 ± 0.1	1.99 ± 0.3	2.03 ± 0.1	0.96 ± 0.1	1.47 ± 0.4
	OFD + GTR-R versus OFD + AAA + CG		1.17 ± 0.1	1.88 ± 0.2	1.99 ± 0.3	2.61 ± 0.1	0.96 ± 0.1	1.03 ± 0.2
	OFD + GTR-R versus OFD + AAA + CG + GTR-R		1.17 ± 0.1	2.01 ± 0.1	1.99 ± 0.3	2.73 ± 0.1	0.96 ± 0.1	0.91 ± 0.1
	OFD + AAA versus OFD + AAA + CG		1.43 ± 0.1	1.88 ± 0.2	2.03 ± 0.1	2.61 ± 0.1	1.47 ± 0.4	1.03 ± 0.2
	OFD + AAA versus OFD + AAA + CG + GTR-R		1.43 ± 0.1	2.01 ± 0.1	2.03 ± 0.1	2.73 ± 0.1	1.47 ± 0.4	0.91 ± 0.1
	OFD + AAA + CG versus OFD + AAA + CG + GTR-R		1.88 ± 0.2	2.01 ± 0.1	2.61 ± 0.1	2.73 ± 0.1	1.03 ± 0.2	0.91 ± 0.1
Cetinkaya, Keles, Pamuk, Balli, and Keles (2014)[a]	OFD + PP + GTR-R versus OFD + BG + GTR-R	SM	2.36 ± 0.92	2.64 ± 1.12	2.91 ± 0.94	3.45 ± 0.93	–	–
Döri, Arweiler, Gera, and Sculean (2005)[a]	OFD + DBBM + EMD versus OFD + EMD + bTCP	P	4.3 ± 0.8	4.1 ± 0.8	4.8 ± 0.9	4.6 ± 0.8	[b]	[b]
Döri et al. (2016)[a] (F-up Döri et al. (2005))		P	[b]	[b]	[b]	[b]	[b]	[b]
Döri, Nikolidakis, et al. (2008))[a]	OFD + DBBM + EMD versus OFD + DBBM + EMD + PRP	P	5.0 ± 0.9	4.8 ± 1.3	5.9 ± 1.3	5.8 ± 1.8	0.9 ± 1.3	1.0 ± 1.0

(Continues)

TABLE 2 (Continued)

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
Döri, Arweiler, Huszár, et al. (2013))[a] (F-up Döri, Nikolidakis, et al., 2008)		P	[b]	[b]	[b]	[b]	[b]	[b]
Mengel, Soffner, and Flores-de-Jacoby (2003)[a]	OFD + GTR-R versus OFD + BG	P	3.4 ± 2.3	2.8 ± 1.8	4.0 ± 2.1	3.8 ± 1.9	0.6 ± 1.5	1.0 ± 1.4
Mengel, Schreiber, and Flores-de-Jacoby (2006)[a] (F-up of Mengel et al. (2003))		P	3.0 ± 2.0	3.3 ± 2.1	3.6 ± 2.0	3.5 ± 1.4	0.6 ± 1.4	0.2 ± 1.7
Minabe et al. (2002)[a]	OFD + GTR-R versus OFD + EMD + GTR-R	P	2.8 ± 0.9	3.0 ± 1.3	3.7 ± 1.2	4.3 ± 1.6	0.9 ± 0.8	1.2 ± 0.9
Nevins et al. (2013)[a]	OFD + bTCP + Placebo versus OFD + bTCP + PDGF 0.3 mg/ml	P	[c]	[c]	[c]	[c]	[c]	[c]
	OFD + bTCP + Placebo versus OFD + bTCP + PDGF 1.0 mg/ml		[c]	[c]	[c]	[c]	[c]	[c]
	OFD + bTCP + PDGF 0.3 mg/ml versus OFD + bTCP + PDGF 1.0 mg/ml		[c]	[c]	[c]	[c]	[c]	[c]
Nygaard-Østby et al. (2010)[a]	OFD + AB versus OFD + AB + GTR-NR	P	2.2 ± 0.7	3.8 ± 0.5	2.7 ± 0.5	4.2 ± 0.5	0.6 ± 0.5	0.7 ± 0.3
Okuda et al. (2005)[a]	OFD + HA + saline versus OFD + HA + PRP	P	2.0 ± 1.2	3.4 ± 1.7	3.7 ± 2.0	4.7 ± 1.6	1.8 ± 1.6	1.3 ± 1.2
Orsini, Orsini, Benlloch, Aranda, and Sanz (2008)[a]	OFD + AB + CSM versus OFD + AB + GTR-R	SM	2.6 ± 1.2	2.4 ± 1.1	3.3 ± 1.6	4.2 ± 1.2	–	–
Paolantonio et al. (2008)[a]	OFD + CS versus OFD + GTR-R	P	2.7	3.1	4.4	5.2	1.6	2.1
Scabbia and Trombelli (2004)[a]	PPF + DBBM versus PPF + HA/collagen/chondroitin sulphate	P	4.0 ± 2.4	2.9 ± 1.9	4.4 ± 2.3	4.2 ± 2.1	0.4 ± 1.8	1.2 ± 1.9
Sculean, Barbé, et al. (2002))[a]	OFD + BG versus OFD + EMD + BG	P	[b]	[b]	[b]	[b]	[b]	[b]
Stavropoulos et al. (2003)[a,d]	OFD + GTR-R versus OFD + DBBM + GTR	P	2.9	2.5	3.9	3.8	1.1	1.3
Stavropoulos and Karring (2010)[a] (F-up Stavropoulos et al. (2003))		P	3.0	2.5	[b]	[b]	–	–
Yassibag-Berkman, Tuncer, Subasioglu, and Kantarci (2007)[a]	OFD + bTCP versus OFD + bTCP + PRP	P	2.5	2.1	4.1	3.6	–	–
	OFD + bTCP versus OFD + bTCP + PRP + GTR-R		2.5	2.4	4.1	4.0	–	–

(Continues)

TABLE 2 (Continued)

Study	Comparison (control vs. test)	Design	CAL change control (mm)	CAL change test (mm)	PD reduction control (mm)	PD reduction test (mm)	REC control (mm)	REC test (mm)
	OFD + bTCP + PRP versus OFD + bTCP + PRP + GTR-R		2.1	2.4	3.6	4.0	–	–
Yamamiya et al. (2008)[a]	OFD + HA + PRP versus OFD + PRP + HA + HCPC	P	3.9 ± 1.6	2.7 ± 1.3	4.8 ± 1.1	4.3 ± 1.1	0.9 ± 1.5	1.7 ± 1.3

Abbreviations: AAA, autolysed antigen-extracted allogenic freeze-dried bone; BG, bioactive glass; bTCP, tricalcium phosphate; CG, microfibrillar collagen gel; CPC, calcium phosphate bone cement; CS, calcium sulphate; CSM, calcium sulphate membrane; DBBM, demineralized bovine bone matrix; DFDBA, demineralized freeze-dried bone allograft; DPSCs, dental pulp stem cells; EMD, enamel matrix derivative; GTR-NR, guided tissue regeneration using a non-resorbable membrane; GTR-R, GTR using a resorbable membrane; HA, hydroxyapatite; HA/P-15, anorganic bovine-derived hydroxyapatite matrix/cell-binding peptide; HCPC, human-cultured periosteum used in sheet as a membrane; OFD, open flap debridement; P, parallel; PDGF, platelet-derived growth factor; PLA/PGA, polylactide/polyglycolide copolymer as biomaterial; PP, platelet pellet; PPF, papilla preservation flap; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; SM, split mouth.

[a]Not in meta-analysis.

[b]Reported the baseline and follow-up data but not the mean difference.

[c]Data presented in graphs.

[d]For this review the group adding gentamicin to the graft was not included.

[e]In this study in two groups were used two types of resorbable membrane.

(2004) reported no difference for post-operative discomfort and number of analgesic tablets when compared to PPF alone. Similar results were reported when a resorbable membrane (GTR-R) was used with a PPF procedure (Cortellini et al., 2001). These data are scarce and not conclusive, even if the influence of EMD or resorbable membrane on post-operative discomfort seems to be minimal compared with OFD.

4.1.2 | Adverse events

No authors reported serious adverse events in the included studies. Due to heterogeneity of the techniques and data, no meta-analysis was possible. A common reported complication was the exposure of non-resorbable membranes. This was frequently reported in 4 studies testing GTR-NR (Crea, Dassatti, Hoffmann, Zafiropoulos, & Deli, 2008; Siciliano et al., 2011; Zucchelli, Bernardi, Montebugnoli, & De, 2002; Zybutz, Laurell, Rapoport, & Persson, 2000), with a rate of exposure ranging from 15% to 66% during the first 6 post-operative weeks. Similarly, the studies testing resorbable membranes (GTR-R) reported a rate of exposure ranging from 20% (Sculean et al., 2003; Siciliano et al., 2014) to 62% (Sanz et al., 2004) and 86% (Zybutz et al., 2000). Usually, the exposure for resorbable membranes is minimal with no serious effect on the clinical outcomes. There is also no definitive evidence regarding the complexity of regenerative procedure and the rate of exposure. A series of studies tested different combinations using bTCP, DBBM and both GTR-R and GTR-NR (Döri et al., 2007a, 2007b; Döri, Huszár, et al., 2008; Döri, Nikolidakis, et al., 2008) and described higher rate of complications when using bTCP + GTR-NR (Döri, Huszár, et al., 2008).

4.1.3 | Pocket "closure" (PD ≤ 4 mm)

Only a few studies reported data on "pocket closure." Included studies seem to show an increased probability of pocket closure for GTR procedures (Cortellini et al., 2001; Siciliano et al., 2011; Zucchelli et al., 2002) compared to OFD alone. However, in one no difference was reported between GTR and OFD (Tonetti et al., 1998).

4.1.4 | Risk of bias

Out of the 79 included studies, 14 were rated at high risk of bias, 55 at unclear and only 10 at low risk of bias. Among the seven domains, the lack of blinding of the outcome assessor (18%) and incomplete outcome data (5%) were the most frequent sources of bias (Figure 2 and Appendix S5).

5 | DISCUSSION

The focused question of this systematic review was "*Does regenerative surgery of intra-bony defect provide additional clinical benefits*

TABLE 3 Meta-analysis results

Comparisons between OFD and regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
1. OFD vs. OFD + RP (regenerative procedures)	**Better OFD + RP**	**Better OFD + RP**	No SSD	**Better OFD + RP**
	p < .00001	*p* < .00001	*p* < .04	*p* < .0006
	MD = 1.34	MD = 1.20	MD = 0.14	MD = 1.57
	95% CI: 0.95, 1.73	95% CI: 0.85, 1.55	95% CI: 0.00, 0.28	95% CI: 0.67, 2.47
	I^2 = 86%	I^2 = 82%	I^2 = 39%	I^2 = 93%
	22 studies RoB: 4 low, 13 unclear, 5 high *Low strength of evidence*	22 studies RoB: 4 low, 13 unclear, 5 high *Low strength of evidence*	19 studies RoB: 4 low, 10 unclear, 5 high *Low strength of evidence*	6 studies RoB: 2 low, 3 unclear, 1 high *Low strength of evidence*
2. OFD vs. OFD + EMD	**Better OFD + EMD**	**Better OFD + EMD**	No SSD	**Better OFD + EMD**
	p < .00001	*p* < .00001	*p* = .19	*p* < .0004
	MD = 1.31	MD = 1.04	MD = 0.18	MD = 1.70
	95% CI: 0.86, 1.86	95% CI: 0.85, 1.22	95% CI: −0.09, 0.44	95% CI: 0.76, 2.64
	I^2 = 79%	I^2 = 74%	I^2 = 68%	I^2 = 91%
	10 studies RoB: 1 low, 7 unclear, 3 high *Low strength of evidence*	10 studies RoB: 1 low, 7 unclear, 3 high *Low strength of evidence*	8 studies RoB: 1 low, 5 unclear, 3 high *Low strength of evidence*	4 studies RoB: 1 low, 2 unclear, 1 high *Low strength of evidence*
Sub-Group				
2.1 OFD	**Better OFD + EMD**	**Better OFD + EMD**	No SSD	No data
	p < .00001	*p* < .00001	*p* = .42	
	MD = 3.30	MD = 3.40	MD = −0.30	
	95% CI: 2.12, 4.48	95% CI: 2.13, 4.67	95% CI: −1.03, 0.43	
	I^2 = not applicable	I^2 = not applicable	I^2 = not applicable	
	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	
2.2 PPF	**Better PPF + EMD**	**Better PPF + EMD**	**Better PPF + EMD**	**Better PPF + EMD**
	p < .00001	*p* < .00001	*p* = .002	*p* < .00001
	MD = 1.46	MD = 1.09	MD = 0.30	MD = 2.08
	95% CI: 1.01, 1.91	95% CI: 0.87, 1.32	95% CI: −0.03, 0.63	95% CI: 1.34, 2.82
	I^2 = 69%	I^2 = 72%	I^2 = 76%	I^2 = 73%
	6 studies RoB: 1 low, 4 unclear, 1 high *Low strength of evidence*	6 studies RoB: 1 low, 4 unclear, 1 high *Low strength of evidence*	5 studies RoB: 1 low, 3 unclear, 1 high *Low strength of evidence*	2 studies RoB: 1 low, 4 unclear *Low strength of evidence*
2.3 OFD + Placebo	**Better OFD + EMD**	**Better OFD + EMD**	No SSD	**Better OFD + EMD**
	p = .001	*p* < .0001	*p* = 1.00	*p* < .00001
	MD = 0.69	MD = 0.79	MD = 0.00	MD = 2.60
	95% CI: 0.27, 1.11	95% CI: 0.42, 1.16	95% CI: −0.43, 0.43	95% CI: 1.95, 3.25
	I^2 = 0%	I^2 = 0%	I^2 = Not applicable	I^2 = not applicable
	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*

(Continues)

TABLE 3 (Continued)

Comparisons between OFD and regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
2.4 PPF + placebo	No SSD	No SSD	No SSD	No SSD
	p < .82	*p* = .54	*p* = .61	*p* = 1.00
	MD = 0.10	MD = 0.30	MD = −0.20	MD = 0.00
	95% CI: −0.74, 0.94	95% CI: −0.66, 1.26	95% CI: −0.96, 0.56	95% CI: −0.84, 0.84
	I^2 = not applicable	I^2 = 82.8%	I^2 = 68%	I^2 = not applicable
	1 study RoB: 1 high *Low strength of evidence*	1 study RoB: 1 high *Low strength of evidence*	1 study RoB: 1 high *Low strength of evidence*	1 study RoB: 1 high *Low strength of evidence*
3. OFD vs. OFD + GTR	**Better OFD + GTR**	**Better OFD + GTR**	No SSD	No SSD
	p = .0007	*p* = .003	*p* = .76	*p* = .34
	MD = 1.15	MD = 1.24	MD = −0.04	MD = 0.91
	95% CI: 0.48, 1,82	95% CI: 0.41, 2.07	95% CI: −0.27, 0.20	95% CI: −0.95, 2.77
	I^2 = 82%	I^2 = 87%	I^2 = 23%	I^2 = 88%
	9 studies RoB: 3 low, 4 unclear, 2 high *Low strength of evidence*	9 studies RoB: 3 low, 4 unclear, 2 high *Low strength of evidence*	9 studies RoB: 3 low, 4 unclear, 2 high *Moderate strength of evidence*	2 studies RoB: 1 low, 1 unclear *Low strength of evidence*
Sub-Group				
3.1 Not resorbable OFD	**Better OFD + GTR-NR**	**Better OFD + GTR-NR**	**Better OFD + GTR-NR**	No data
	p = .04	*p* = .02	*p* = .05	
	MD = 2.36	MD = 3.14	MD = −0.43	
	95% CI: 0.11, 4.61	95% CI: 0.49, 5.78	95% CI: −0.85, 0.00	
	I^2 = 87%	I^2 = 93%	I^2 = 0%	
	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*	
3.2 Not resorbable PPF	**Better PPF + GTR-NR**	**Better PPF + GTR-NR**	No SSD	No data
	p < .00001	*p* < .00001	*p* = .19	
	MD = 2.30	MD = 2.00	MD = 0.30	
	95% CI: 1.65, 2.95	95% CI: 1.33, 2.67	95% CI: −0.15, 0.75	
	I^2 = not applicable	I^2 = not applicable	I^2 = not applicable	
	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	
3.3 Resorbable OFD	No SSD	No SSD	No SSD	No SSD
	p = .78	*p* = .98	*p* = .90	*p* = 1.00
	MD = 0.16	MD = −0.01	MD = 0.05	MD = 0.00
	95% CI: −0.92, 1.23	95% CI: −0.59, 0.58	95% CI: −0.72, 0.82	95% CI: −0.71, 0.71
	I^2 = 70%	I^2 = 0%	I^2 = 52%	I^2 = not applicable
	3 studies RoB: 2 low, 1 unclear *Low strength of evidence*	3 studies RoB: 2 low, 1 unclear *Moderate strength of evidence*	3 studies RoB: 2 low, 1 unclear *Moderate strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*

(Continues)

TABLE 3 (Continued)

Comparisons between OFD and regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
3.4 Resorbable PPF	**Better PPF + GTR-R** *p* < .0001 MD = 0.91 95% CI: 0.50, 1.32 I^2 = 0% 3 studies RoB: 1 low, 2 high *Moderate strength of evidence*	**Better PPF + GTR-R** *p* < .0001 MD = 0.91 95% CI: 0.46, 1.36 I^2 = 0% 3 studies RoB: 1 low, 2 high *Moderate strength of evidence*	No SSD *p* = .76 MD = 0.02 95% CI: −0.27, 0.31 I^2 = 0% 3 study RoB: 1 low, 2 high *Moderate strength of evidence*	**Better PPF + GTR-R** *p* = .0004 MD = 1.90 95% CI: 0.84, 2.96 I^2 = not applicable 1 study *RoB: 1 low* *Low strength of evidence*
4. OFD vs. OFD + DBBM + GTR	**Better OFD + DBBM + GTR** *p* = .004 MD = 1.50 95% CI: 0.66, 2.34 I^2 = 71% 4 studies RoB: 1 low, 2 unclear, 1 high *Low strength of evidence*	**Better OFD + DBBM + GTR** *p* .002 MD = 1.13 95% CI: 0.42, 1.84 I^2 = 60% 4 studies RoB: 1 low, 2 unclear, 1 high *Low strength of evidence*	**Better OFD + DBBM + GTR** *p* = .01 MD = 0.36 95% CI: 0.07, 0.64 I^2 = 0% 4 studies RoB: 1 low, 2 unclear, 1 high *Moderate strength of evidence*	No data
Sub.Group				
4.1 OFD	**Better OFD + DBBM + GTR** *p* < .00001 MD = 2.11 95% CI: 1.52, 2.71 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	**Better OFD + DBBM + GTR** *p* < .00001 MD = 1.72 95% CI: 1.05, 2.38 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p* = .18 MD = 0.34 95% CI: −0.16, 0.85 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No data
4.2 PPF	**Better PPF + DBBM + GTR** *p* = .003 MD = 0.82 95% CI: 0.28, 1.36 I^2 = 0% 2 studies RoB: 1 low, 1 high *Moderate strength of evidence*	**Better PPF + DBBM + GTR** *p* < .03 MD = 0.58, 95% CI: 0.05, 1.11 I^2 = 0% 2 studies RoB: 1 low, 1 high *Moderate strength of evidence*	**Better PPF + DBBM + GTR** *p* = .04 MD = 0.36 95% CI: 0.01, 0.71 I^2 = 0% 2 studies RoB: 1 low, 1 high *Moderate strength of evidence*	No data
5. OFD vs. OFD + PRF	**Better OFD + PRF** *p* = .01 MD = 2.63 95% CI: 0.60, 4.65 I^2 = 96% 2 studies RoB: 2 unclear *Low strength of evidence*	**Better OFD + PRF** *p* < .00001 MD = 2.29 95% CI: 1.67, 2.92 I^2 = 47% 2 studies RoB: 2 unclear *Low strength of evidence*	No data	No data

(Continues)

TABLE 3 (Continued)

Comparations between regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
6. OFD + DFDBA vs. OFD + DFDBA + PRP	**Better OFD + DFDBA + PRP**	NO SSD	**Better OFD + DFDBA + PRP**	**Better OFD + DFDBA + PRP**
	p < .00001	*p* < .10	*p* < .00001	*p* < .00001
	MD = 0.94	MD = 0.45	MD = 0.59	MD = 0.81
	95% CI: 0.65, 1.24	95% CI: −0.08, 0.98	95% CI: 0.40, 0.78	95% CI: 0.54, 1.08
	I^2 = 40%	I^2 = 80%	I^2 = 0%	I^2 = 40%
	3 studies RoB: 3 unclear *Low strength of evidence*	3 studies RoB: 3 unclear *Low strength of evidence*	3 studies RoB: 3 unclear *Low strength of evidence*	3 studies RoB: 3 unclear *Low strength of evidence*
Sub-Group				
6.1 PRP	**Better OFD + DFDBA + PRP**	No SSD	**Better OFD + DFDBA + PRP**	**Better OFD + DFDBA + PRP**
	p < .00001	*p* < .38	*p* = .03	*p* < .00001
	MD = 0.78	MD = 0.48	MD = 0.55	MD = 0.65
	95% CI: 0.52, 1.05	95% CI: −0.59, 1.55	95% CI: 0.06, 1.04	95% CI: 0.41, 0.90
	I^2 = 0%	I^2 = 84%	I^2 = 36%	I^2 = 0%
	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*
6.2 PRF	**Better OFD + DFDBA + PRF**	**Better OFD + DFDBA + PRF**	**Better OFD + DFDBA + PRF**	**Better OFD + DFDBA + PRF**
	p < .00001	*p* = .0006	*p* < .0002	*p* < .00001
	MD = 1.12	MD = 0.55	MD = 0.53	MD = 1.01
	95% CI: 0.81, 1.43	95% CI: 0.24, 0.86	95% CI: 0.26, 0.80	95% CI: 0.72, 1.30
	I^2 = not applicable	I^2 = not applicable	I^2 = not applicable	I^2 = not applicable
	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*
7. OFD + DBBM vs. OFD + DBBM + Other	No SSD	No SSD	No SSD	No data
	p = .78	*p* = .40	*p* = .11	
	MD = −0.13	MD = −0.39	MD = 0.50	
	95% CI: −1.08, 0.81	95% CI: −1.29, 0.52	95% CI: −0.11, 1–12	
	I^2 = 0%	I^2 = 0%	I^2 = 6%	
	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*	2 studies RoB: 2 unclear *Low strength of evidence*	
Sub-Group				
7.1 EMD	No SSD	No SSD	**Better OFD + DBBM + EMD**	No data
	p = .84	*p* = .27	*p* = .05	
	MD = −0.20	MD = −0.80	MD = 0.70	
	95% CI: −1.81, 1.41	95% CI: −2.21, 0.61	95% CI: 0.01, 1.39	
	I^2 = not applicable	I^2 = not applicable	I^2 = not applicable	
	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	1 study RoB: 1 unclear *Low strength of evidence*	

(Continues)

TABLE 3 (Continued)

Comparations between regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
7.2 PRP	No SSD *p = .87* MD = −0.10 95% CI: −1.28, 1.08 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p = .87* MD = −0.10 95% CI: −1.28, 1.08 I^2 = not applicabe 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p = 1.00* MD = 0.00 95% CI: −1.14, 1.14 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No data
8. OFD + GTR vs. OFD + EMD	No SSD *p = .51* MD = −0.15 95% CI: −0.58, 0.29 I^2 = 56% 8 studies RoB: 2 low, 3 unclear, 3 high *Low strength of evidence*	No SSD *p = .21* MD = −0.44 95% CI: −1.12, 0.24 I^2 = 82% 8 studies RoB: 2 low, 3 unclear, 3 high *Low strength of evidence*	No SSD *p = .17* MD = 0.20 95% CI: −0.09, 0.49 I^2 = 34% 5 studies RoB: 2 low, 1 unclear, 2 high *Moderate strength of evidence*	No data
Sub-Group				
8.1 Non resorbable GTR-RN	No SSD *p = .22* MD = −0.47 95% CI: −1.22, 0.29 I^2 = 73% 4 studies RoB: 1 low, 2 unclear, 1 high *Low strength of evidence*	**Better OFD + GTR-NR** *p = .03* MD = −1.06 95% CI: −2.04, −0.08 I^2 = 85% 4 studies RoB: 1 low, 2 unclear, 1 high *Low strength of evidence*	No SSD *p = .56* MD = 0.23 95% CI: 0.55, 1.01 I^2 = 80% 2 studies RoB: 1 low, 1 unclear *Low strength of evidence*	No data
8.2 Resorbable GTR-R	No SSD *p = .74* MD = 0.13 95% CI: −0.64, 0.91 I^2 = 53% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No SSD *p = .26* MD = 0.28 95% CI: −0.21, 0.76 I^2 = 0% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No SSD *p = .65* MD = 0.10 95% CI: −0.33, 0.53 I^2 = not applicable 1 study RoB: 1 high *Low strength of evidence*	No data
8.3 Resorbable + DBBM	No SSD *p = .61* MD = 0.19 95% CI: −0.54, 0.93 I^2 = 0% 2 studies RoB: 1 low, 1 high *Moderate strength of evidence*	No SSD *p = .67* MD = 0.20 95% CI: −0.72, 1.12 I^2 = 82% 2 studies RoB: 1 low, 1 high *Low strength of evidence*	No SSD *p = .57* MD = 0.14 95% CI: −0.33, 0.61 I^2 = 0% 2 studies RoB: 1 low, 1 high *Moderate strength of evidence*	No data

(Continues)

TABLE 3 (Continued)

Comparations between regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
9. OFD + EMD vs. OFD + EMD + Other	**Better OFD + EMD + Other** *p* = .005 MD = 0.41 95% CI: 0.13, 0.69 I^2 = 36% 10 studies RoB: 3 low, 6 unclear, 1 high *Moderate strength of evidence*	**Better OFD + EMD + Other** *p* = .001 MD = 0.40 95% CI: 0.15, 0.64 I^2 = 32% 10 studies RoB: 3 low, 6 unclear, 1 high *Moderate strength of evidence*	No SSD *p* = .20 MD = 0.15 95% CI: −0.08, 0.38 I^2 = 50% 10 studies RoB: 3 low, 6 unclear, 1 high *Moderate strength of evidence*	No data
Sub-Group				
9.1 AB (Autogenous bone)	No SSD *p* = .48 MD = 0.38 95% CI: −0.67, 1.43 I^2 = 62% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No SSD *p* = .61 MD = 0.37 95% CI: −1.07, 1.82 I^2 = 79% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No SSD *p* = .56 MD = 0.29 95% CI: −0.69, 1.27 I^2 = 84% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No data
9.2 bTCP	No SSD *p* = .35 MD = 0.30 95% CI: −0.33, 0.93 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p* = .63 MD = 0.20 95% CI: −0.60, 1.00 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p* = 1.00 MD = 0.00 95% CI: −0.76, 0.76 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No data
9.3 HA/bTCP	No SSD *p* = .58 MD = 0.21 95% CI: −0.52, 0.94 I^2 = 61% 3 studies RoB: 2 low, 1 unclear *Low strength of evidence*	No SSD *p* = .12 MD = 0.32 95% CI: −0.08, 0.72 I^2 = 19% 3 studies RoB: 2 low, 1 unclear *Moderate strength of evidence*	No SSD *p* = .13 MD = 0.13 95% CI: −0.04, 0.29 I^2 = 0% 3 studies RoB: 2 low, 1 unclear *Moderate strength of evidence*	**Better OFD + EMD + HA/bTCP** *p* < 0.00001 MD = 0.67 95% CI: 0.40, 0.94 I^2 = 0% 3 studies RoB: 2 low, 1 unclear *Moderate strength of evidence*
9.4 Bioactive Glass (BG)	No SSD *p* = .27 MD = −0.70 95% CI: −1.95, 0.55 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p* = .63 MD = −0.30 95% CI: −1.53, 0.93 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p* = .46 MD = −0.20 95% CI: −0.73, 0.33 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No data

(Continues)

TABLE 3 (Continued)

Comparations between regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
9.5 DBBM	**Better OFD + EMD + DBBM** *p = .0009* MD = 0.90 95% CI: 0.37, 1.43 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	**Better OFD + EMD + DBBM** *p = .01* MD = 0.40 95% CI: 0.09, 0.71 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	**Better OFD + EMD + DBBM** *p = .0004* MD = 0.50 95% CI: 0.23, 0.77 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No data
9.6 GTR	No SSD *p = .19* MD = 0.38 95% CI: −0.18, 0.93 I^2 = 0% 2 studies RoB: 1 low, 1 unclear *Moderate strength of evidence*	No SSD *p = .25* MD = 0.36 95% CI: −0.25, 0.97 I^2 = 0% 2 studies RoB: 1 low, 1 unclear *Moderate strength of evidence*	No SSD *p = .82* MD = 0.18 95% CI: −1.33, 1.69 I^2 = not applicable 1 study RoB: 1 low *Low strength of evidence*	No data
10. OFD + EMD vs. OFD + Graft	No SSD *p = .98* MD = 0.02 95% CI: −1.25, 1.29 I^2 = 75% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p = .56* MD = −0.23 95% CI: −1.01, 0.55 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p = .30* MD = 0.78 95% CI: −0.69, 2.24 I^2 = 78% 2 studies RoB: 2 unclear *Low strength of evidence*	No data
Sub-Group				
10.1 Bioactive Glass (BG)	No SSD *p = .09* MD = 0.60 95% CI: −0.09, 1.29 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p = .86* MD = 0.10 95% CI: −0.98, 1.18 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	**Better OFD + BG** *p = .008* MD = 1.60 95% CI: 0.42, 2.78 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No data
10.2 HA	No SSD *p = .20* MD = −0.70 95% CI: −1.78, 0.38 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p = .30* MD = −0.60 95% CI: −1.74, 0.54 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p = .79* MD = 0.10 95% CI: −0.63, 0.83 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No data

(Continues)

TABLE 3 (Continued)

Comparations between regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
11. OFD + GTR-NR vs. OFD + GTR-R	No SSD *p* = .96 MD = 0.02 95% CI: −0.91, 0.96 I^2 = 0% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No SSD *p* = .76 MD = 0.16 95% CI: −0.80, 1.12 I^2 = 0% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No SSD *p* = .34 MD = 0.25 95% CI: −0.26, 0.76 I^2 = 0% 2 studies RoB: 1 unclear, 1 high *Low strength of evidence*	No data
12. OFD + Graft + GTR vs. OFD + Graft + GTR + PRP	No SSD *p* = .86 MD = 0.03 95% CI: −0.32, 0.39 I^2 = 0% 4 studies RoB: 4 unclear *Low strength of evidence*	No SSD *p* = .12 MD = 0.26 95% CI: −0.07. 0.59 I^2 = 0% 4 studies RoB: 4 unclear *Low strength of evidence*	No SSD *p* = .87 MD = 0.03 95% CI: −0.28, 0.33 I^2 = 0% 4 studies RoB: 4 unclear *Low strength of evidence*	No data
Sub-Group				
12.1 bTCP	No SSD *p* = .83 MD = 0.05 95% CI: −0.41, 0.52 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p* = .06 MD = 0.36 95% CI: −0.01, 0.73 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p* = .73 MD = −0.07 95% CI: −0.49, 0.34 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No data
12.2 DBBM	No SSD *p* = .99 MD = 0.00 95% CI: −0.54, 0.55 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p* = .76 MD = −0.11 95% CI: −0.83, 0.61 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p* = .54 MD = 0.14 95% CI: −0.30, 0.58 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No data
13. OFD + GTR vs. OFD + GTR + Graft	No SSD *p* = 1.00 MD = 0.00 95% CI: −1.99, 1.99 I^2 = 92% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p* = .48 MD = −0.33 95% CI: −1.23, 0.58 I^2 = 60% 2 studies RoB: 2 unclear *Low strength of evidence*	No SSD *p* = .08 MD = 0.48 95% CI: −0.05, 1.01 I^2 = 0% 2 studies RoB: 2 unclear *Low strength of evidence*	No data
Sub-Group				
13.1 DFDBA	**Better OFD + GTR** *p* = .003 MD = −0.98	**Better OFD + GTR** *p* = .04 MD = −0.75	No SSD *p* = .53 MD = 0.23	No data

(Continues)

TABLE 3 (Continued)

Comparations between regenerative procedures				
Comparison	**CAL gain**	**PD reduction**	**REC**	**Bone gain**
	95% CI: −1.63, −0.33 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	95% CI: −1.48, −0.02 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	95% CI: −0.50, 0.96 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	
13.2 DBBM	**Better** **OFD + GTR + DBBM** *p* = .03 MD = 1.05 95% CI: 0.09, 2.01 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	No SSD *p* = .70 MD = 0.18 95% CI: −0.72, 1.08 I^2 = not applicable 1 study RoB: 1 unclear *Low strength of evidence*	**Better** **OFD + GTR + DBBM** *p* = .05 MD = 0.77 95% CI: −0.01, 1.55 I^2 = not aplicable 1 study RoB: 1 unclear *Low strength of evidence*	No data

Abbreviations: OFD, open flap debridement; RP, all regenerative procedures; PPF, papilla preservation flap; PRF, platelet rich fibrin; DBBM, demineralized bovine bone mineral; SSD, statistically significant difference; GTR, guided tissue regeneration; GTR-RN, guided tissue regeneration non resorbable; GTR-R, guided tissue regeneration resorbable; DFDBA, demineralized freezed dried bone allograft; PRP, plateler rich plasma; HA, hydroxyapatite; AB, autogenous bone; bTCP, beta-tricalcium phosphate; HA/bTCP, hydroxyapatite/beta-tricalcium phosphate; BG, bioactive glass; HA, hydroxyapatite; RoB, number of studies at low, unclear or high risk of bias among the studies included in the meta-analysis.

measured as probing pocket depth (PD) reduction, clinical attachment level (CAL) gain, recession (Rec) and radiographic bone gain (BG) in periodontitis patients compared with access flap?" A total of 79 RCTs, covering data on 3,042 patients, and a total of 3,612 intra-bony defects were included in this SR. The overall outcomes showed that regenerative procedures, mainly based on the use of EMD or barriers, provided improved clinical outcomes 12 months after surgery compared with flap surgery alone.

A preliminary, large meta-analysis clustered all studies performing regenerative procures versus OFD alone. A total of 22 RCTs covering 1,182 teeth in 1,000 patients were considered. All RP resulted in improved CAL gain (1.34 mm; 0.95–1.73) and greater PD (1.20 mm; 0.85–1.55) compared with OFD alone. Probably due to the variability in terms of specific biomaterials or flap designs, a moderate to substantial heterogeneity in the size of the adjunctive effect was observed. This overall body of evidence, however, showed the superiority of RP in treating infrabony defects, thus decreasing the risk of disease progression and tooth loss in the long term when a regular support periodontal therapy is performed (Cortellini, Buti, Pini Prato, & Tonetti, 2017; Silvestri, Rasperini, & Milani, 2011).

A consistent number of RCTs investigated the effect of EMDs in the treatment of intra-bony defects compared with flap surgery alone, reporting data on a total of 487 defects (Figure 3). These data demonstrated higher benefits at 12 months when EMD was used, in terms of CAL gain (1.31 mm; 0.86–1.86; low strength of evidence) and PD reduction (1.04 mm; 0.85–1.22; low strength of evidence). The present outcome confirms the observation of a large multicentre study where EMD was applied in conjunction with PPF (Tonetti et al., 2002). In this study, higher efficacy of regeneration was observed in non-smokers and for defects with a predominantly 3-wall anatomy, thus suggesting an effective interaction between biologicals and defect configuration (Tsitoura et al., 2004). Interestingly, in this SR the addition of EMD was associated with higher radiographic bone fill than OFD alone (1.70 mm; 0.76–2.64 mm), leading to a positive effect in changing bone defect configuration. No significant difference in the recession of the gingival margin at the last study follow-up

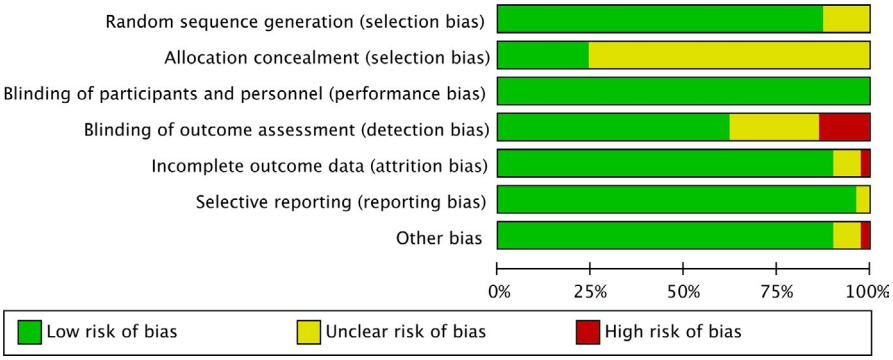

FIGURE 2 Risk of bias for studies in the systematic review

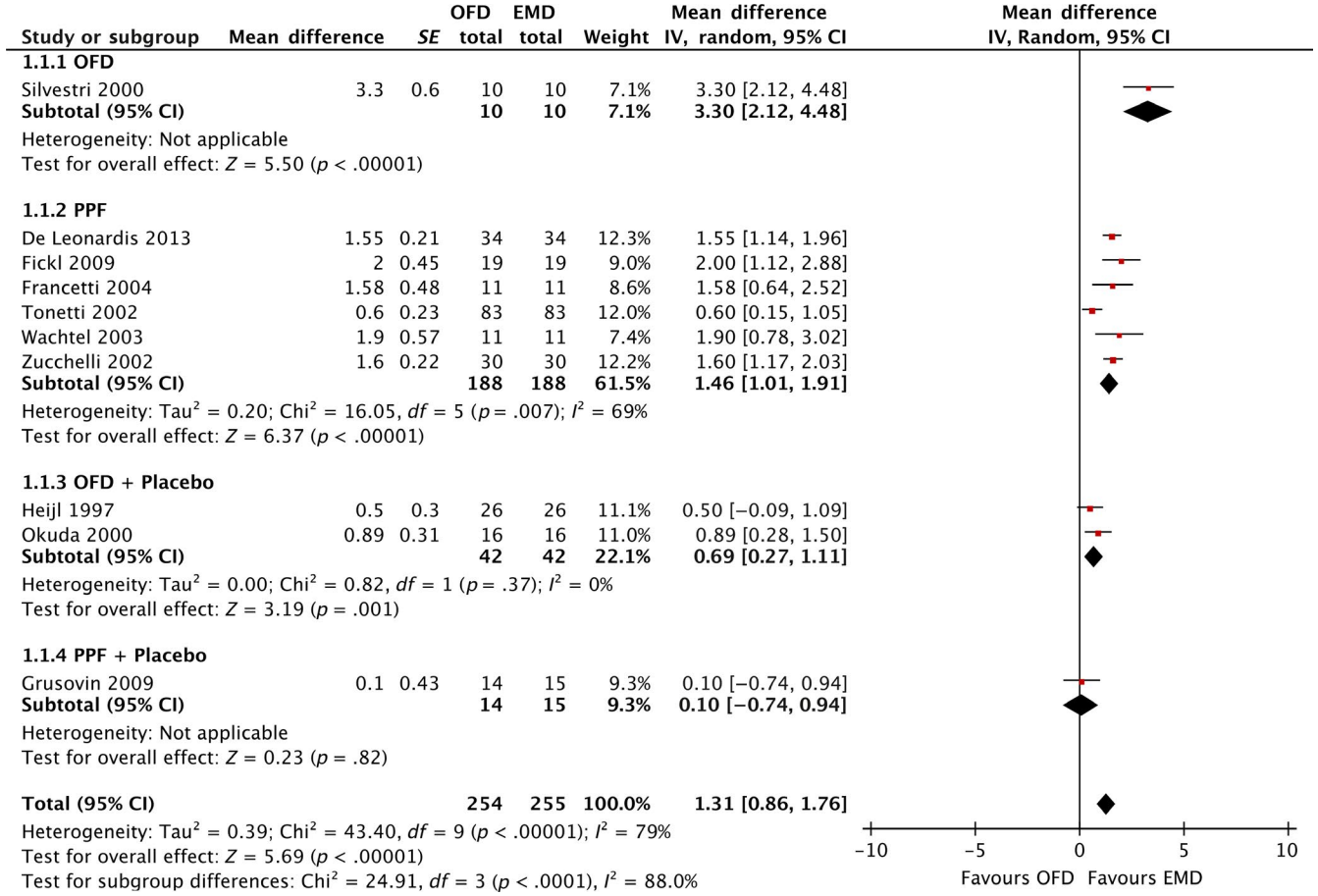

FIGURE 3 Comparison between open flap for debridement plus enamel matrix derivatives (OFD vs. OFD + EMD) versus OFD alone in terms of final clinical attachment level gain (CAL gain)

was observed comparing test and control group. These data clearly support the concept that application of EMD is an effective, tool for regeneration of intra-bony defects.

In recent years, the use of EMD has often been combined with bone filler materials, especially in large/not self-contained intra-bony defects, where a physical support is considered necessary. Overall, the addition of bone filler (AB, bTCP, HAbTCP, Bglass, DBBM) to EMD resulted in improved CAL gain (0.41 mm; 0.13–0.69; moderate strength of evidence), PPD reduction (0.40 mm; 0.15–0.64; moderate strength of evidence) and radiographic bone gain (0.67 mm; 0.40–0.94 mm, moderate strength of evidence) compared with EMD alone. It should be taken in mind that in the present meta-analysis a group of heterogeneous bone filler was considered. Finally, only single study showing statistically significant improvements with the use of bone filler was published by Zucchelli and co-workers, who used DBBM as adjunct to EMD (Zucchelli, Amore, Montebugnoli, & Sanctis, 2003).

The use of GTR compared with OFD alone (Figure 4) showed that the use of membranes was associated with improved CAL gain (1.15 mm; 0.48–1.82; low strength of evidence) and PD reduction (1.24 mm; 0.41–2.07; low strength of evidence) at 12-month follow-up compared with flap surgery alone, although both comparisons resulted in high heterogeneity. No differences were detected between GTR and OFD alone in gingival recession and radiographic bone gain (although this comparison only included two studies). Interestingly, the use of non-resorbable titanium-reinforced barriers was associated with high clinical performance in two clinical studies (Silvestri, Ricci, Rasperini, Sartori, & Cattaneo, 2000; Zucchelli et al., 2002). The only two studies directly comparing resorbable and non-resorbable membranes included in this review (Christgau, Schmalz, Wenzel, & Hiller, 1997; Zybutz et al., 2000) showed similar clinical and radiographic outcomes. Non-resorbable membranes were rarely applied in recent RCTs, owing to the high number of complications reported and the need of second surgery. It should also be taken into account that the popularity of sole barriers for periodontal regeneration decreased in the last 15 years, while combinations of resorbable membranes and replacement biomaterials have become a frequent treatment option. Specific cases where the operator may choose to use non-resorbable membranes based on defect morphology still exist.

Favourable clinical and radiographic results were also detected with the addition of DBBM to GTR, with significantly higher CAL gain (1.5 mm; 0.66–2.34; low strength of evidence) and PD reduction (1.13 mm; 0.42–1.84; low strength of evidence) compared with flap access alone. This finding seems to suggest that this combination may be an effective treatment option especially in larger, not

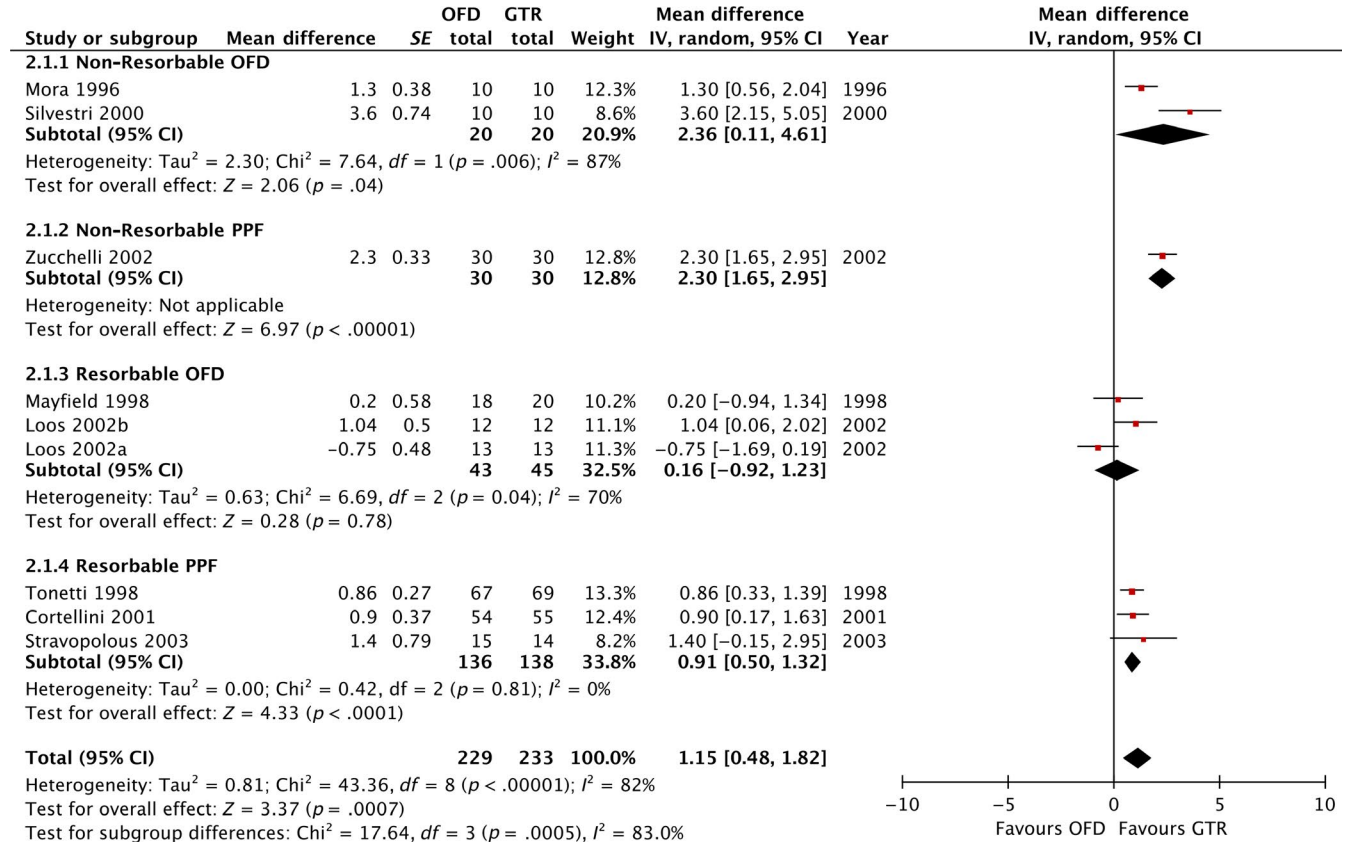

FIGURE 4 Comparison between open flap for debridement plus guided tissue regeneration (OFD vs. OFD + GTR) versus OFD alone in terms of final clinical attachment level gain (CAL gain)

supporting defects where there is a risk of apical collapse of the barrier. Interestingly, two RCTs supported the long-term stability of GTR + DBBM (Sculean, Schwarz, et al., 2007; Stavropoulos & Karring, 2010), thus suggesting that the achieved outcomes in terms of CAL gain (2.09 mm; 1.33–2.86; moderate strength of evidence) were stable after at least 5 years of supportive periodontal therapy. This finding was also confirmed in a 10-year follow-up study comparing EMD + DBBM versus EMD + β TCP (Döri, Arweiler, Szántó, et al., 2013). Conversely, data from the present study recommend caution in applying multiple combinations when treating intra-bony defects, since some specific biomaterials as bioactive glass or HA/bTCP did not improve the efficacy of EMD alone (De Leonardis & Paolantonio, 2013; Losada, Gonzalez, Garcia, Santos, & Nart, 2017; Meyle et al., 2011; Sculean, Pietruska, et al., 2005).

No statistically significant differences in clinical and radiographic outcomes were detected in the comparison between EMD and GTR for intra-bony defects. This is further confirmation of the similar magnitude of differences in PD, CAL and radiographic bone gain seen in the EMD versus open flap and GTR versus open flap analyses above. Equally, no clinical or radiographic differences were detected when EMD was compared with bone filler (with no membrane), although this meta-analysis included only two studies and had high heterogeneity. Noteworthy, EMD is probably more user-friendly and generally associated with limited number of complications compared with barriers (Sanz et al., 2004).

Some of the studies included in both the EMD and GTR comparisons included the use of papilla preservation flaps. It is difficult to make clear conclusions about the differences between simple conventional flaps (sOFD) and papilla preservation flaps (PPF), although the latter seem to be associated with increased CAL gain and reduced gingival recession, in line with what has been suggested elsewhere (Cortellini & Tonetti, 2011; Schincaglia, Hebert, Farina, Simonelli, & Trombelli, 2015). In this context, it is important to highlight how studies have consistently shown no differences in clinical and radiographic outcomes when GTR (Trombelli, Simonelli, Pramstraller, Wikesjo, & Farina, 2010) or EMD (Cortellini & Tonetti, 2011) was used as adjunct to minimally invasive surgeries, as observed in a recent meta-analysis (Liu, Hu, Zhang, Li, & Song, 2016).

The use of PRP/PRF in addition to OFD for intra-bony defects seems to result in improved clinical and radiographic outcomes. However, the meta-analysis included only two studies published by the same research group (Agarwal & Gupta, 2014; Agarwal, Gupta, & Jain, 2016) and reported high levels of heterogeneity. In addition, no human histologic evidence of regeneration has been demonstrated and it should be also kept in mind that additional problems related to possible law restrictions in different countries may complicate the use of this product. Further research, however, is needed to reach a conclusion and clinical guidelines for their use.

Studies included in this review covered almost three decades, ranging in publication year from 1990 to 2019. Interestingly, there is

a tendency in detecting higher clinical performance of regenerative procedures in the last decade compared with studies published in the '90s. This may be related to the growing popularity of papillary preservation flaps for regeneration, which reduced the incidence of early flap dehiscence over the wound area. Furthermore, this positive trend could be also related to the positive learning curve of the operators after early attempts in regeneration, along with the application of modern devices, including biologicals and resorbable barriers, which reduced post-operative morbidity and rate of regeneration failures. Furthermore, in the last 20 years important multicentre studies (Cortellini, Carnevale, Sanz, & Tonetti, 1998; Sanz et al., 2004; Tonetti, Cortellini, et al., 2004; Tonetti et al., 2002) confirmed the clinical efficacy of regeneration procedures but also highlighted a certain degree of variability of the clinical outcomes among different settings. This variability, named "*centre-effect*," accounted for approximately 2 mm in clinical attachment gain and could be explained by possible factors including surgical ability of the operators, different expertise in clinical setting in terms of patient selection, efficacy of previous cause-related therapy and supportive periodontal care programmes. From a clinical perspective, this SR confirmed the superiority of EMD and GTR in combination with papillary preservation flap for the treatment of infrabony defects compared with OFD (Pagliaro et al., 2008). Interestingly, among the selected biomaterials, only DBM seems to promote clinical outcomes.

The "*risk of bias assessment*" in the single studies showed a tendency to improve over time, since 8 out of 10 studies rated at low risk were published after 2011. Twenty-four studies did not report how to conceal the allocation and were considered at unclear risk even if the other six items were rated at low risk showing a good design. Fourteen studies were rated at high risk of bias. In a chronological perspective, it seems that introduction of CONSORT guidelines has improved study quality, leading to a decrease of items with unclear risk of bias.

When evaluating the strength of evidence through the modified GRADE assessment (Guyatt et al., 2008), only one out of twelve meta-analysis was rated at *moderate strength of evidence*, while the others were at *low strength of evidence*. These data seem to suggest caution in data interpretation and also reduce the generalizability of the results. Furthermore, this observation corroborates the need to minimize bias in future studies on periodontal regeneration.

Finally, as it became evident that some limitations of this investigation can be outlined, a thorough literature search for this review gave the authors the opportunity to notice a paucity of data about, "tooth loss," "pocket closure" and "numbers needed to treat" to achieve successful clinical outcomes. This limits the clinical applicability of the conclusions. Furthermore, data on adverse events are not consistently reported in the different studies and there is a lack of data about patient-reported outcomes and health economics of regenerative treatment of intra-bony defects. Only a limited number of studies reporting on long-term results after the regenerative approaches were identified through our search, and meta-analyses over 1 year of follow-up could not be performed, therefore limiting the generalizability of our conclusions. Finally, limited information was provided by the authors in relation to the defect configuration, for example the number of defect walls, the defect depth and the radiographic angulation. Interestingly, the use of systemic antibiotics was reported in 58 studies (Appendix S7), while in the others, it was not reported or unclear. Considering heterogeneity in terms of type of antibiotics and duration of treatment, it was not possible to perform further analysis or to provide specific recommendation.

It is also worth stressing that results observed in this SR refer to deep (≥3 mm radiographically) defects with residual pockets following non-surgical therapy. Modern approach for not-surgical root debridement may achieve optimal outcomes in terms of pocket reduction and elimination of bleeding on probing thus reducing the possible need for further surgery (Nibali, Yeh, Pometti, & Tu, 2018).

6 | CONCLUSIONS

According to data presented in this systematic review, it can be concluded that there is low to moderate strength of evidence that:

- EMD and resorbable GTR appear to be the gold standard for the surgical treatment of deep (≥3 mm) intra-bony defects, which have not resolved following completion of non-surgical therapy.
- Among the possible replacement biomaterials, DBBM improved clinical outcomes of both EMD and resorbable GTR compared with OFD and it should be considered a viable treatment option especially in non-supporting defects.
- Non-resorbable GTR provides higher benefit compared with OFD; however, increased patient morbidity and incidence of post-operative complications, such as membrane exposure, are reported.
- Papillary preservation flaps improve the clinical outcomes and should be considered a surgical pre-requisite when performing any regeneration procedure.
- Limited evidence suggests that PRP/PRF may improve the clinical parameters, but histologic evidence of regeneration has not clearly demonstrated.

7 | INDICATIONS FOR FUTURE RESEARCH

- Increased number of studies assessing clinical efficacy and histologic evidence of regeneration for PRP/PRF is suggested.
- Trials assessing the efficacy of different regenerative procedures for different defect morphologies are suggested, since different techniques may actually have different indications.
- RCTs assessing the long-term outcomes of periodontal regeneration outcomes and including long-term data on PROMs, adverse events and health economics data are encouraged.
- The use of CONSORT guidelines to minimize the risk of bias is strongly encouraged.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest to disclose in connection with this article.

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SUPPORTING INFORMATION

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

How to cite this article: Nibali L, Koidou VP, Nieri M, Barbato L, Pagliaro U, Cairo F. Regenerative surgery versus access flap for the treatment of intra-bony periodontal defects: A systematic review and meta-analysis. *J Clin Periodontol*. 2020;47:320–351. https://doi.org/10.1111/jcpe.13237