Review

Periodontal Regeneration With Enamel Matrix Derivative in Reconstructive Periodontal Therapy: A Systematic Review

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Background: Enamel matrix derivative (EMD) is commonly used in periodontal therapy. The aim of this systematic review is to give an updated answer to the question of whether the additional use of EMD in periodontal therapy is more effective compared with a control or other regenerative procedures.

Methods: A literature search in MEDLINE (PubMed) for the use of EMD in periodontal treatment was performed up to May 2010. The use of EMD in treatment of intrabony defects, furcations, and recessions was evaluated. Only randomized controlled trials with ≥1 year of follow-up were included. The primary outcome variable for intrabony defects was the change in clinical attachment level (CAL), for furcations the change in horizontal furcation depth, and for recession complete root coverage.

Results: After screening, 27 studies (20 for intrabony defects, one for furcation, and six for recession) were eligible for the review. A meta-analysis was performed for intrabony defects and recession. The treatment of intrabony defects with EMD showed a significant additional gain in CAL of 1.30 mm compared with open-flap debridement, EDTA, or placebo, but no significant difference compared with resorbable membranes was shown. The use of EMD in combination with a coronally advanced flap compared with a coronally advanced flap alone showed significantly more complete root coverage (odds ratio of 3.5), but compared with a connective tissue graft, the result was not significantly different. The use of EMD in furcations (2.6 ± 1.8 mm) gave significantly more improvement in horizontal defect depth compared with resorbable membranes (1.9 ± 1.4 mm) as shown in one study.

Conclusions: In the treatment of intrabony defects, the use of EMD is superior to control treatments but as effective as resorbable membranes. The additional use of EMD with a coronally advanced flap for recession coverage will give superior results compared with a control but is as effective as a connective tissue graft. The use of EMD in furcations will give more reduction in horizontal furcation defect depth compared with resorbable membranes. *J Periodontol 2012;83:707-720.*

KEY WORDS

Enamel matrix proteins; furcation defects; gingival recession; guided tissue regeneration, periodontal.

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Periodontitis is a chronic destructive inflammatory disease of the supporting tissues of the teeth.[1] Epidemiologic studies have shown that ≈10% to 15% of the adult population have a severe form of periodontal disease.[1,2] The inflammation of the periodontal tissues results in periodontal pocket formation and bone loss, and the ultimate result of the untreated disease is tooth loss.

A goal of periodontal therapy is to obtain a reduced pocket depth to prevent additional disease progression. In patients with moderate periodontitis, this goal can be accomplished by non-surgical therapy, but in patients with severe periodontitis, residual pockets of ≥6 mm can remain after initial therapy.[3] These pockets can be associated with intrabony defects or furcation involvement. Such pockets have a higher risk for future periodontal destruction,[4] and, for this reason, periodontal surgery is recommended to eliminate these pockets. The elimination is often achieved by resection techniques via gingivectomy or an apically repositioned flap with or without bone recontouring.[5,6] In the past, these techniques were also used in the treatment of intrabony defects or furcations, but currently regenerative procedures are preferred. This envisages regeneration of the tooth-supporting tissues, including cementum, periodontal ligament (PDL), and alveolar bone on a

doi: 10.1902/jop.2011.110266

diseased root surface.[7] This goal can be achieved through several procedures, such as the use of various bone graft (BG) or bone substitute materials,[8-10] guided tissue regeneration (GTR),[11] growth factors,[12-14] enamel matrix derivative (EMD)† proteins,[15] or a combination of the cited procedures.[16,17]

The results from a meta-analysis indicated that the treatment of periodontal osseous defects with intraoral BGs results in periodontal regeneration, but the outcome is not always predictable.[18] A systematic review of GTR has shown that this procedure is more effective than open-flap debridement (OFD), with an additional gain in clinical attachment level (CAL) of 1.2 mm.[19] However, there was a marked variability in results with GTR among different randomized controlled clinical trials (RCTs). Another procedure for periodontal regeneration is the use of EMD. The dominating constituent of the enamel matrix proteins, amelogenin, is shown by means of immunohistochemistry to be expressed in human teeth between the peripheral dentin and the developing cementum during root formation.[20] There is histologic evidence showing that EMD, used on previously periodontally affected root surfaces, will induce new cementum, PDL, and alveolar bone formation.[15,21] A recent systematic review showed that EMD significantly improved CALs in intrabony defects compared with a control.[22] This review concluded that the results had to be interpreted with great caution because of the high degree of heterogeneity between studies.

EMD is also used in root-coverage procedures. A recent systematic review,[23] which investigated the effects of the addition of EMD on a coronally advanced flap (CAF) procedure, showed a significantly higher percentage of complete root coverage (CRC) with the addition of EMD. If EMD was compared with a connective tissue graft (CTG), considered to be the gold standard in most studies, a CTG combined with CAF gave no significant difference.[23]

The evidence on the efficacy of EMD in regenerative procedures is still conflicting. This review aims at giving an updated answer to the question of whether the additional use of EMD in different periodontal treatments is more effective compared with a control or other treatment procedures. The review will look to the use of EMD in intrabony defects, furcations, and recessions.

MATERIALS AND METHODS

In this systematic review, only RCTs with a follow-up of ≥1 year were included.

Search Strategy

For the identification of studies considered relevant for this review and published up to May 2010, a search was performed via The National Library of Medicine (MEDLINE by PubMed) using the following search criteria: emd OR EMD OR emdogain OR enamel matrix proteins OR enamel protein OR dental enamel proteins AND periodontology OR GTR OR guided tissue regeneration OR periodontal defect OR furcation OR angular defect OR infrabony defect OR intrabony defect OR furcation defect OR furcation involvement OR periodontal OR recession coverage OR recession OR root coverage OR recession defect.

Only articles published in the English language and human studies were included.

Selection

The selection criteria and outcome variables are described per treatment.

Intrabony defects. The investigated comparisons were as follows: 1) EMD versus control (OFD, placebo, root conditioning with 24% EDTA); 2) EMD versus resorbable membrane (RM); 3) EMD versus various types of bone or bone substitute grafting procedures (BG); 4) EMD versus RM + BG; 5) EMD versus EMD + BG; and 6) EMD versus EMD + RM + BG.

Criteria for including a study were as follows: 1) non-surgical therapy completed before regenerative therapy, 2) PD ≥6 mm and/or intrabony defect ≥3 mm, 3) no systemic diseases, and 4) a good level of oral hygiene.

The exclusion criteria were: 1) studies in which EMD was compared with non-RMs only and 2) studies with only histologic data.

As a primary outcome the change in CAL was explored. The secondary outcome measures included change in probing depth (PD), change in gingival recession (REC), and change in radiographic bone levels (RAD).

Furcation defects. The same comparisons as mentioned previously were investigated for furcation defects. The inclusion criteria were the same as for intrabony defects except the defect type was different. Defects with a Class II furcation and a zone of keratinized tissue (KT) of ≥2 mm were included. Class I and III furcations and studies in which EMD was compared with non-RMs were excluded. As primary outcome the change in horizontal furcation depth (HFD) was obtained, and CAL, PD, and REC were used as secondary outcomes.

Recession coverage. The investigated comparisons were as follows: 1) CAF + EMD versus CAF; 2) CAF + EMD versus CAF + CTG; 3) CAF + EMD versus CAF + EMD and CTG; 4) CAF + EMD versus CAF + barrier membrane; 5) CAF + EMD versus CAF + acellular dermal matrix; 6) CAF + EMD versus CAF + platelet-rich plasma; and 7) CAF + EMD versus CAF + human fibroblast-derived dermal substitute.

Criteria for including a study were as follows: 1) non-surgical therapy completed before therapy, 2)

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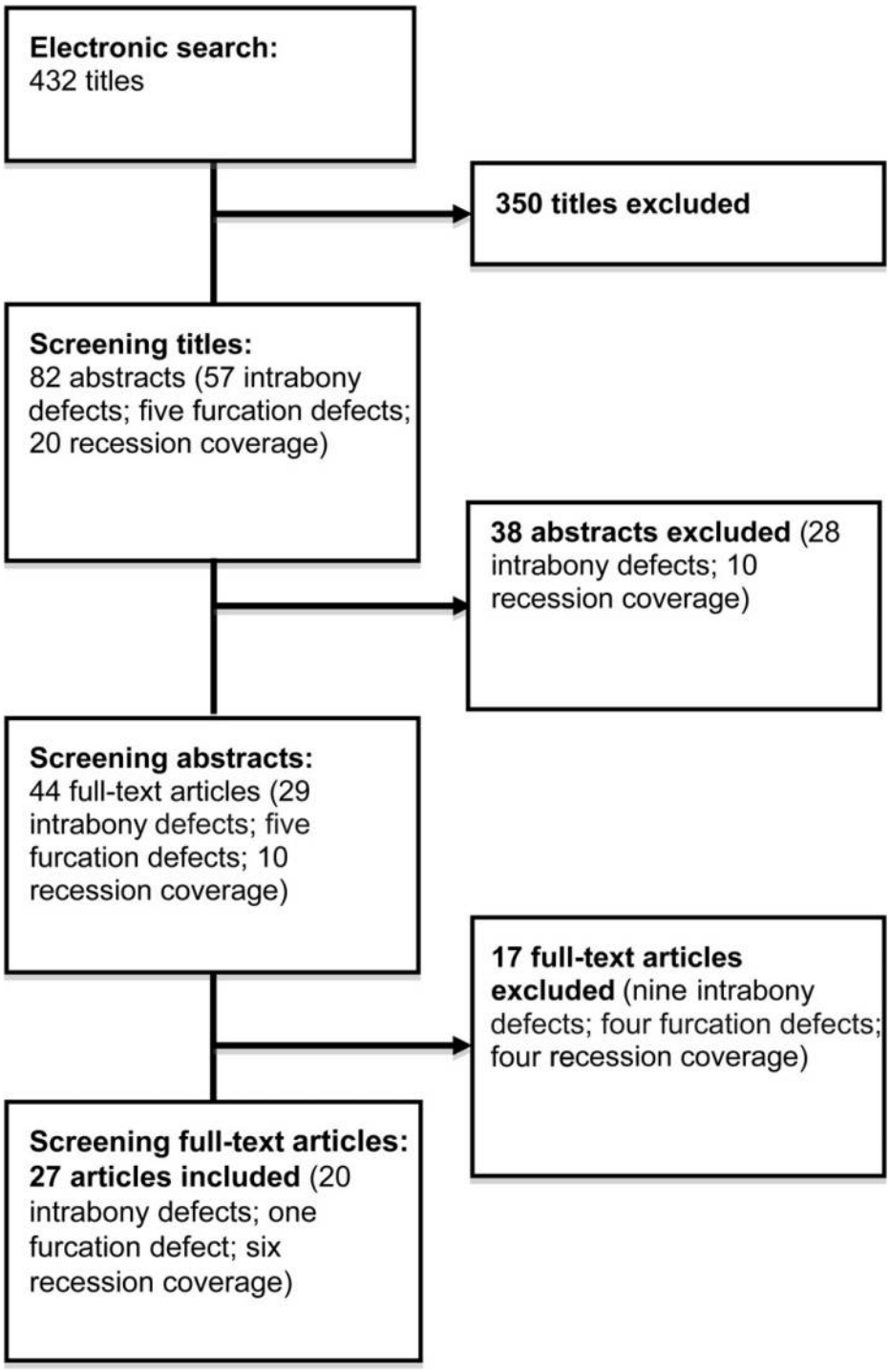

Figure 1.
Search strategy.

patients with Miller Class I or II buccal recession,[24] 3) no systemic diseases, and 4) a good level of oral hygiene.

The exclusion criteria were: 1) patients with Miller Class III or IV buccal recession, 2) patients with PD >3 mm, and 3) studies with only histologic data.

As primary outcome the percentage of recession defects that obtained CRC was explored. The secondary outcome measures included change in REC expressed as recession reduction in millimeters (RecRed), change in recession width (RW), change in height of keratinized tissue (HKT), change in CAL, and change in PD.

Plaque index[25] and gingival index[26] were descriptors to control the level of oral hygiene for every treatment procedure during the study.

Data Collection and Analysis

The titles identified by the search were screened independently by two reviewers (RK and JM). The abstracts of all studies of possible relevance for the review were obtained and screened independently by the reviewers. When studies met the inclusion criteria or when insufficient data from abstracts were available to evaluate inclusion criteria, the full-text article was obtained. The selected articles were screened independently by the reviewers to see whether they met the inclusion criteria. The references of the full-text articles were screened for relevant articles that were not yet included. Also the references of the relevant chapters of a textbook in periodontology were checked.[27] All studies meeting the inclusion criteria underwent quality assessment and data recording. When there was disagreement between the two reviewers, consensus was achieved by discussion with a third reviewer (MQ). Then the data of the included studies were independently extracted and entered into a database by the reviewers. Study design, patient characteristics, treatments, clinical outcomes, and study quality were systematically registered.

Table 1.

Characteristics of the 27 Included Studies

Study	Type of Study	Comparison	Follow up (months)	Group Size		Defect Type		Antibiotics	Smokers	Quality Assessment			
				Test	Control	Number of Walls	Defect Depth			Allocation Concealment	Masking of Assessor	Completeness of Follow Up	Risk of Bias
Intrabony													
Heijl et al., 1997[29]	S	EMD versus placebo	36	31	31	1 to 2	PD ≥6 mm; IBD ≥4 mm	Y	In	Y	Y	Y	Low
Pontoriero et al., 1999[30]	S	EMD versus placebo; EMD versus RM	12	10	10	NR	CAL ≥7 mm; IBD ≥3 mm	Y	NR	Un	Un	Y	High
Okuda et al., 2000[31]	S	EMD versus placebo	12	18	18	1 to 3	PD ≥6 mm; IBD ≥4 mm	Y	Ex	Un	Un	Y	Low
Silvestri et al., 2000[32]	P	EMD versus OFD	12	10	10	NR	PD ≥6 mm; IBD ≥4 mm	Y	NR	Y	Y	Y	High
Pietruska, 2001[33]	P	EMD versus RM + BPBM	12	12	12	NR	PD ≥6 mm; IBD ≥3 mm	Y	NR	Un	Un	Un	High
Tonetti et al., 2002[34]	P	EMD versus EDTA	12	83	83	1 to 3	IBD >3 mm	N	In	Un	Y	N	High
Zucchelli et al., 2002[35]	P	EMD versus EDTA	12	30	30	NR	CAL >7 mm; IBD >3 mm	Y	In	Un	Y	Y	High
Zucchelli et al., 2003[36]	P	EMD versus EMD + BPBM	12	30	30	NR	PD >6 mm; IBD >3 mm	Y	In	Un	Y	Y	High
Francetti et al., 2004[37]	P	EMD versus OFD	24	12	12	NR	PD ≥6 mm; IBD ≥4 mm	Y	NR	Y	Y	Y	Low
Sanz et al., 2004[38]	P	EMD versus RM	12	35	32	1 to 3	IBD ≥3 mm	NR	In	Y	N	Y	High
Rosing et al., 2005[40]	S	EMD versus placebo	12	14	14	ND	PD ≥6 mm; IBD ≥3 mm	Y	In	Un	Y	Y	High
Francetti et al., 2005[39]	P	EMD versus OFD	24	64	46	1 to 3	PD ≥6 mm; IBD ≥4 mm	Y	In	Y	Un	Y	High
Bokan et al., 2006[41]	P	EMD versus OFD; EMD versus EMD + TCP	12	19	18	NR	PD ≥7 mm; IBD ≥3 mm	Y	In	Un	Y	Un	High
Sculean et al., 2006[42]	S	EMD versus RM	96	10	10	NR	PD ≥6 mm	Y	NR	Un	Y	Y	High
Guida et al., 2007[17]	P	EMD versus EMD + AG	12	14	14	NR	PD ≥6 mm; IBD ≥4 mm	Y	In	Un	N	Y	High

Table 1. (continued)

Characteristics of the 27 Included Studies

Study	Type of Study	Comparison	Follow up (months)	Group Size		Defect Type		Antibiotics	Smokers	Quality Assessment			
				Test	Control	Number of Walls	Defect Depth			Allocation Concealment	Masking of Assessor	Completeness of Follow Up	Risk of Bias
Sculean et al., 2007[43]	P	EMD versus EMD + bio. gl.	48	12	13	1 to 3	PD ≥6 mm; IBD ≥3 mm	NR	Ex	Un	Un	N	High
Sculean et al., 2008[44]	P	EMD versus OFD; EMD versus RM	120	10	9	1 to 3	PD ≥6 mm; IBD ≥3 mm	Y	In	Un	Y	Y	High
Fickl et al., 2009[45]	P	EMD versus OFD	12	19	19	1 to 3	PD ≥6 mm; IBD ≥3 mm	NR	In	Un	Y	Un	High
Grusovin and Esposito, 2009[46]	P	EMD versus placebo	12	15	15	2 to 3	IBD ≥4 mm	N	In	Y	Y	Y	Low
Leknes et al., 2009[47]	S	EMD versus BCF	12	13	13	2 to 3	PD ≥6 mm; IBD ≥3 mm	NR	In	Y	Y	Y	Low
Furcation													
Jepsen et al., 2004[48]	S	EMD versus RM	14	45	45	ND	ND	NR	In	Y	Y	Y	Low
Recession													
McGuire and Nunn, 2003[49]	S	CAF + EMD versus CAF + CTG	12	17	17	ND	ND	NR	Ex	Un	Y	Y	High
Del Pizzo et al., 2005[50]	S	CAF + EMD versus CAF	24	15	15	ND	ND	Y	NR	Y	Y	Y	Low
Spahr et al., 2005[51]	S	CAF + EMD versus CAF	24	30	30	ND	ND	NR	In	Y	Y	Y	Low
Castellanos et al., 2006[52]	P	CAF + EMD versus CAF	12	11	11	ND	ND	NR	Ex	Un	Un	N	High
Pilloni et al., 2006[53]	P	CAF + EMD versus CAF	18	15	15	ND	ND	NR	NR	Un	Y	N	High
Abolfazli et al., 2009[54]	S	CAF + EMD versus CAF + CTG	24	12	12	ND	ND	Y	NR	Un	Y	N	High

S = split mouth; IBD = intrabony defect depth; Y = yes; In = included; NR = not reported; Un = unclear; Ex = excluded; P = parallel; BPBM = bovine porous bone mineral; N = no; ND = no data; TCP = tricalcium phosphate; AG = autogenous graft; bio. gl. = bioactive glass; BCF = bioactive ceramic filler.

Table 2.

Characteristics of the 17 Excluded Studies

Study	Reason for Exclusion
Intrabony	
Froum et al., 2001[55]	PD and IBD inclusion criteria not defined
Sculean et al., 2001[56]	Same patient pool with shorter follow-up of a study included in this review[44]
Sculean et al., 2001[57]	Same patient pool with shorter follow-up of a study included in this review[42]
Wachtel et al., 2003[58]	Same patient pool with shorter follow-up of a study included in this review[45]
Silvestri et al., 2003[59]	EMD is compared to non-RMs
Parodi et al., 2004[60]	PD <6 mm included
Sculean et al., 2004[61]	Same patient pool with shorter follow-up of a study included in this review[44]
Sculean et al., 2005[62]	Same patient pool with shorter follow-up of a study included in this review[43]
Crea et al., 2008[63]	EMD is compared to non-RMs
Furcation	
Meyle et al., 2004[64]	Same patient pool as article included in this review[48]
Hoffman et al., 2006[65]	Same patient pool as article included in this review[48]
Chitsazi et al., 2007[66]	Follow-up only 6 months
Casarin et al., 2008[67]	Follow-up only 6 months; proximal furcations included
Recession	
Hägewald et al., 2002[68]	Same patient pool with shorter follow-up of a study included in this review[51]
Nemcovsky et al., 2004[69]	Not an RCT
Moses et al., 2006[70]	Not an RCT
Aroca et al., 2010[71]	Miller Class III REC defects treated

IBD = intrabony defect depth.

When several articles reporting different follow-up durations were published for the same study population, the article with the longest duration was included, and the data from 12 months were extracted for the meta-analysis when available.

Quality Assessment of Included Studies

The quality assessment of the included studies was independently performed by the two reviewers according to the Cochrane Collaboration's tool for assessing risk of bias.[28] Six main quality criteria (adequate sequence generation; allocation concealment; masking of participants, personnel, and outcome assessors; incomplete outcome data; and selective outcome reporting and other sources of bias) were examined. The overall risk of bias was assessed using three key domains: allocation concealment, masking of outcome assessor, and completeness of follow-up. The studies were grouped into two categories: 1) low risk of bias if all three quality criteria were met, and 2) high risk of bias if one or more of the criteria were not met.

Quantitative Data Synthesis

Mean differences, 95% confidence intervals, and standard deviations were used for the outcomes. The patient was considered as the statistical unit. Meta-analyses were conducted, including studies with similar comparisons and reporting the same outcome measures. Mean differences were combined for continuous data using random-effects models. Data from split-mouth studies were combined with data from parallel group trials using the generic inverse variance method in a software program.‡ If the appropriate data were not presented, they were calculated.

The significance of any discrepancies in the estimates of the treatment effects from different trials was assessed by means of the Cochran Q test for heterogeneity and the I^2 statistic, which describes the percentage total variation across studies that is attributable to heterogeneity rather than chance.

RESULTS

Searching Results (Fig. 1)

The initial title search resulted in 432 articles. After screening the titles, 82 abstracts (57 for intrabony defects, five for furcations, and 20 for recession) were selected. A meticulous screening of the abstracts resulted in the selection of 44 articles (29 for intrabony defects, five for furcations, and 10 for recession). The reading of the 44 full-text articles allowed the selection of 27 studies (20 for intrabony defects,[17,29-47] one for furcation defects,[48] and six for recession[49-54]) (Table 1) that met the inclusion criteria of this

‡ Review Manager (RevMan) computer program, version 5.0, The Nordic Cochrane Center, The Cochrane Collaboration, København Ø, Denmark.

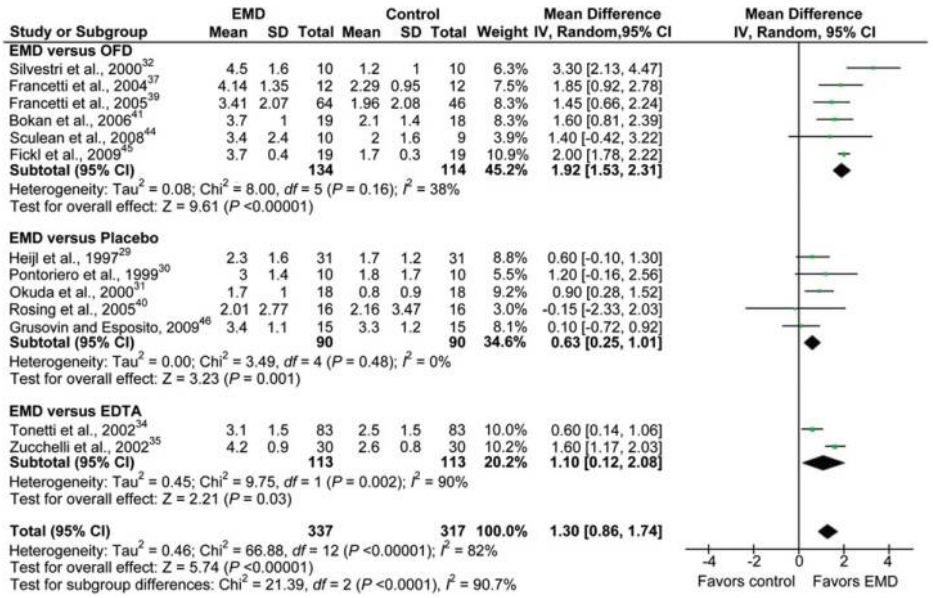

Figure 2.
Comparison of EMD versus control: change in CAL after ≥1 year. Total = number of patients; IV = inverse variance; CI = confidence interval.

systematic review, and 17 articles were excluded[55-71] (Table 2). Three articles[48,64,65] reported about the same patient population, but only the first published article was included.[48]

The screening of the references of all the full-text articles and the relevant chapters in a textbook in periodontology[27] did not result in the inclusion of additional articles.

Study Characteristics and Risk of Bias (Table 1)

Intrabony defects. The 20 selected studies allowed several comparisons, and, in some studies, more than one comparison was done.[30,41,44] Fourteen studies[17,32-39,41,43-46] had a parallel group design, whereas six studies[29-31,40,42,47] had a split-mouth design. The group size per study ranged from nine or 10[30,32,42,44] to 83 patients per group.[34] The included studies used different inclusion criteria for the defects to be treated: intrabony defect depth from 3 to 4 mm and/or PD from 6 to 7 mm and/or CAL from 7 mm. Only 10 studies[29,31,34,38,39,43-47] reported about the number of walls of the defect, and most of them included predominantly 1-, 2-, and 3-wall defects, except one study[29] that included only 1- and 2-wall defects and two studies[46,47] that included only 2- and 3-wall defects.

Most studies[17,29,34-36,38-41,44-47] included smokers (13), but some[30,32,33,37,42] (5) did not mention the smoking status, and two studies[31,43] excluded smokers. In 14 of 20 studies,[17,29-33,35-37,39-42,44] antibiotics were prescribed after surgery, whereas in two studies,[34,46] no antibiotics were indicated and in four studies[38,43,45,47] information was lacking. In all studies except one,[45] postoperative chlorhexidine digluconate mouthrinsing was instructed. The studies had follow-up periods ranging from 12 to 120 months. For all studies, the data of 12 months were extracted, except for one study[29] in which the data of 16 months were extracted.

Five studies[29,31,37,46,47] were classified at a low risk of bias.

Furcation defects. Only one study[48] met the inclusion criteria. The study compared EMD versus RM in the treatment of buccal Class II furcations. Smokers were included in the study, and the use of postoperative antibiotics was not defined. Patients used postoperative chlorhexidine digluconate mouthrinse. The follow-up of the study was 14 months. The study was classified at a low risk of bias.

Recession coverage. The six included studies allowed only two comparisons (CAF + EMD versus CAF and CAF + EMD versus CAF + CTG). Four studies[49-51,54] had a split-mouth group, and two[52,53] had a parallel group design. The group size ranged from 11[52] to 30[51] patients per group. The included studies used the following inclusion criteria: 1) Miller Class I or II buccal REC,[50-53] 2) Miller Class I buccal REC ≥3 mm,[54] and 3) Miller Class II buccal REC.[49] The information on smoking was scarce. Two studies excluded smokers,[49,52] one study included smokers,[51] and three studies gave no information.[50,53,54] Two studies indicated postoperative antibiotics[50,54] whereas the other studies[49,51-53] did not give information. In all studies, postoperative chlorhexidine digluconate mouthrinse was prescribed. The follow-up of the studies ranged from 12 to 24 months. For all studies, the data of 12 months were extracted, except for two studies,[50,51] in which the data of 24 months were extracted because 12-month data were not available. Only two studies[50,51] were classified at a low risk of bias.

Effects of Interventions

Intrabony defects. The primary outcome (change in CAL) showed a significant additional CAL gain for EMD (1.30 mm, $P < 0.00001$) compared with the control treatments (OFD/EDTA/placebo) (Fig. 2). The CAL gain for the use of EMD was not significantly different (0.42 mm, $P = 0.14$) from the use of an RM (Fig. 3).

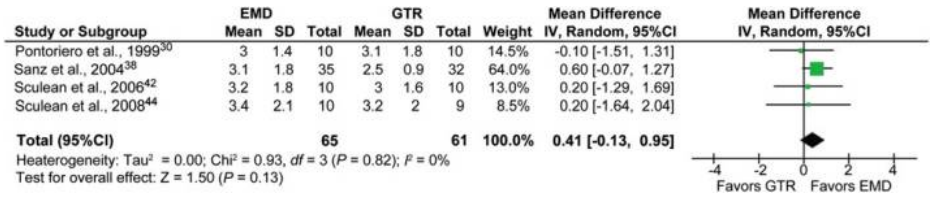

Figure 3.
Comparison of EMD versus GTR: change in CAL after 1 year. Total = number of patients; IV = inverse variance; CI = confidence interval.

For the other comparisons, only one study per comparison was available (Fig. 4). Only the addition of bovine porous bone mineral (BPBM) to EMD gave a significant additional CAL gain (0.9 mm, P = 0.0009).[36] For the secondary outcomes (PD, REC, and RAD), separate meta-analyses were performed.

The results of the change in PD included the following: 1) EMD was superior to OFD, with a mean difference of 1.52 mm, P = 0.0001; 2) EMD was superior to placebo, with a mean difference of 0.48 mm, P = 0.04; 3) EMD was superior to EDTA, with a mean difference of 0.60 mm, P = 0.0004; 4) EMD was superior to OFD/EDTA/placebo, with a mean difference of 0.92 mm, P = 0.0003; and 5) there was no statistically significant difference between EMD versus RM (0.03 mm, P = 0.92). The other comparisons showed only a significant additional PD reduction for EMD + BPBM (0.4 mm, P = 0.01).[36]

The results of the change in REC included the following: 1) no statistically significant difference between EMD versus OFD (–0.45 mm, P = 0.07); 2) no statistically significant difference between EMD versus placebo (0.03 mm, P = 0.83); 3) no statistically significant difference between EMD versus EDTA (–0.45 mm, P = 0.31); 4) EMD was superior to OFD/EDTA/placebo, with a mean difference of –0.29 mm, P = 0.04; and 5) no statistically significant difference between EMD versus RM (–0.10 mm, P = 0.53).

The results of the change in RAD included the following: 1) EMD was superior to OFD, with a mean difference of 1.41 mm, P <0.00001; 2) no statistically significant difference between EMD versus placebo (0.93 mm, P = 0.33); 3) no statistically significant difference between EMD versus EDTA (–0.50 mm, P = 0.74); 4) EMD was superior to OFD/EDTA/placebo, with a mean difference of 1.04 mm, P = 0.03; and 5) no statistically significant difference between EMD versus RM (–0.10 mm, P = 0.53). The other comparisons showed significantly less recession for EMD + BPBM (0.5 mm, P = 0.0005),[36] EMD + autogenous graft (0.8 mm, P = 0.005),[17] and EMD + bioactive ceramic filler (1.6 mm, P = 0.02)[47] compared with EMD alone. Two studies[17,36] reported about RAD, and, in one study,[36] the use of EMD + BPBM was superior to EMD alone (1.0 mm, P = 0.004).

Furcation defects. In both groups, the primary outcome (HFD) had a significant improvement (EMD, 2.6 ± 1.8 mm; GTR, 1.9 ± 1.4 mm). The EMD group showed significantly more improvement than the GTR group. The CAL and PD measurements revealed no significant improvement, and there were no significant differences between the outcomes. There was significantly more recession after GTR in the mid-furcation site (P = 0.04).

Recession coverage. The primary outcome (CRC) showed significantly better results (odds ratio [OR] = 3.50, P = 0.0008) for CAF + EMD compared with CAF alone (Fig. 5). The result for CAF + EMD compared to CAF + CTG showed no difference (OR = 1.20, P = 0.76) (Fig. 6). For the secondary outcomes (RecRed, CAL, PD, and HKT), separate meta-analyses were undertaken.

The results of RecRed included the following: 1) CAF + EMD was superior to CAF, with a mean difference of 0.56 mm, P = 0.006; 2) no statistically significant differences between CAF + EMD versus CAF + CTG (–0.56 mm, P = 0.36); 3) change in CAL; 4) CAF + EMD was superior to CAF, with a mean difference of 0.59 mm, P = 0.0006; and 5) no statistically significant differences between CAF + EMD versus CAF + CTG (–0.50 mm, P = 0.30). The results of the change in PD included the following: 1) no statistically significant differences between CAF + EMD versus CAF (0.07 mm, P = 0.37); 2) CAF + EMD was superior to CAF + CTG, with a mean difference of 0.26 mm, P = 0.0003; 3) change in HKT; 4) CAF + EMD was superior to CAF, with a mean difference of 0.46 mm, P = 0.03; and 5) CAF + CTG was superior to CAF + EMD, with a mean difference of –1.25 mm, P <0.00001.

Three studies that compared CAF + EMD versus CAF[50-52] reported on the change in RW. In two studies,[51,52] the result was superior for the CAF + EMD procedure.

DISCUSSION

This review examines the benefit of using EMD in the treatment of intrabony defects, furcation defects, and recession coverage. Each topic will be addressed separately.

Intrabony Defects

For intrabony defects, the meta-analysis showed a statistically significant additional improvement in CAL (1.30 mm), PD (0.92 mm), and RAD (1.04) in favor of the use of EMD compared with a control (OFD/EDTA/placebo) 1 year after therapy (Fig. 2).

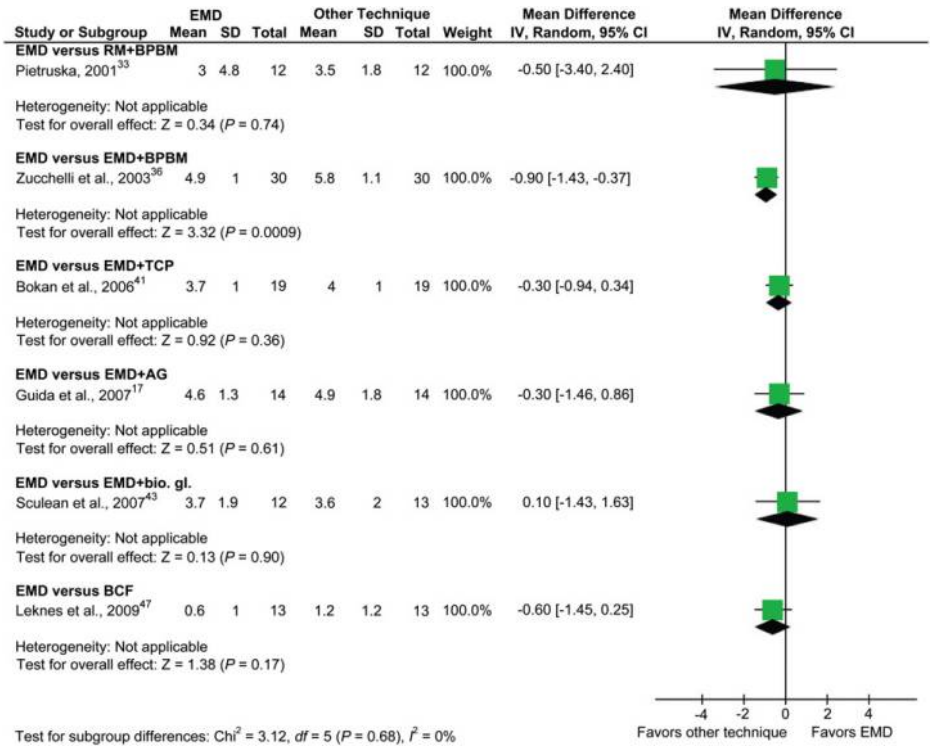

Figure 4.
EMD versus other technique: change in CAL after 1 year. Total = number of patients; IV = inverse variance; CI = confidence interval; BPBM = bovine porous bone mineral; TCP = tricalcium phosphate; AG = autogenous graft; bio. gl. = bioactive glass; BCF = bioactive ceramic filler.

In studies with a longer follow-up,[29,37,39,47-49] the clinical improvement after therapy was maintained for a period of ≤10 years. The heterogeneity between the different studies was high (I^2 = 82% for CAL, I^2 = 86% for PD, and I^2 = 80% for RAD). There was a large variation in results between studies (mean values varied from –0.15 to 4.47 mm for CAL, from –0.30 to 3.4 mm for PD, and from –0.50 to 2.4 mm for RAD). Only in the subgroup of EMD versus placebo with a statistically improvement in CAL (0.59 mm) in favor of EMD might the heterogeneity not be important (I^2 = 0%). A meta-analysis (not reported) for the studies with a low risk of bias[29,31,37,46] showed 0.83 mm for CAL and 0.78 mm for PD, with statistically more gain in favor of EMD. If these observations are taken into consideration, the treatment effect of EMD in intrabony defects for CAL and PD is overestimated in the present meta-analysis.

Several explanations for the high heterogeneity between studies could be found, including the following: operator sensitivity of the technique, difference in surgical techniques, patient and defect characteristics, and postoperative care.

The operator sensitivity of the technique is shown in a multicenter trial.[34] This study showed a significant difference in CAL gain (2.6 ± 0.6 mm) between the best and worst performing center. The observed center variability could depend on differences in the enrolled patients in terms of social background, type of periodontal disease, response to therapy, oral hygiene status, smoking status, and, as mentioned previously, the differences in technical ability and experience of the different clinicians.

In general, the two following surgical techniques were used in the included studies: modified Widman flap[72] and papilla preservation technique.[73,74] A separate meta-analysis (not reported) on the two different techniques used in the included studies showed no significant differences in CAL gain and PD reduction. Today, a minimally invasive surgical technique (MIST) can be used for the treatment of intrabony defects with EMD.[75] This technique (MIST) suggests more favorable results (CAL gain, 4.9 ± 1.7 mm; PD reduction, 5.2 ± 1.7 mm; REC increase, 0.4 ± 0.7 mm) in only one study with respect to the data in this review.[76] The outcomes of this study should be confirmed, and, possibly in the future, the results of periodontal regeneration with EMD in intrabony defects will improve if a MIST technique is used.

The baseline PD to be included in a study was >6 or 7 mm. Some studies[34,35,38] showed in a multivariate analysis that deeper pockets gave significantly more CAL gain. Most studies[31,34,38,39,44] that provided information about the defect type included 1-, 2-, and 3-wall defects. A study in which different treatment modalities were proposed for different intrabony defect configurations suggested better outcomes in defects with a prevalent 3-wall morphology for the use of EMD.[77] One study showed that intrabony defects with 3 walls had a 269% higher chance than 1-wall defects to gain ≥3 mm CAL.[34] Only two studies[37,39] reported about exclusion of teeth with Class 3 mobility, and only one[46] reported about splinting mobile teeth directly after regeneration. Teeth with Class 1 or 2 mobility can respond favorably to regenerative therapy,[78] but it is shown in a review that mobility of the wound margin as well as tooth mobility may cause rupture of the fibrin clot, leading to failure of the treatment.[79] A restriction of the inclusion criteria to only

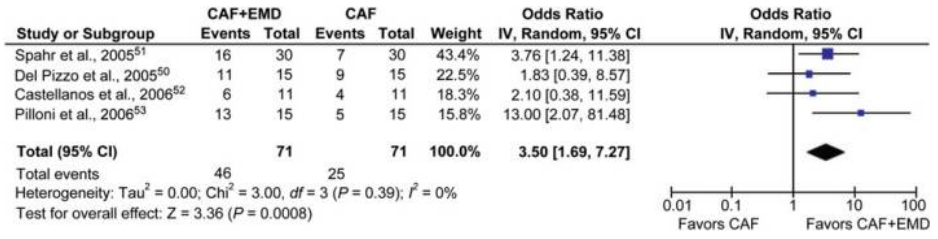

Figure 5.
CAF + EMD versus CAF: CRC after ≥1 year. Total = number of patients; IV = inverse variance; CI = confidence interval.

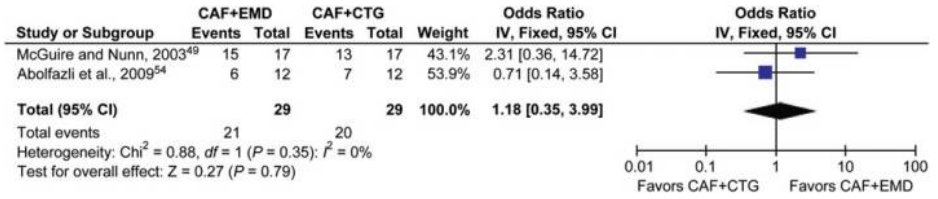

Figure 6.
CAF + EMD versus CAF + CTG: CRC after 1 year. Total = number of patients; IV = inverse variance; CI = confidence interval.

3-wall defects, PD ≥7 mm, and non-mobile teeth could have improved the results.

Smoking has been shown as a major risk factor for periodontitis. The response to periodontal therapy is less in smokers than non-smokers.[80] Also for regenerative therapy, it is shown that non-smokers had higher CAL gains than smokers.[29,34,40,81] The criteria for including smokers (<10 or <20 cigarettes per day or not defined) were different, and in one study smokers were excluded,[31] which may be an explanation for the high heterogeneity between studies. This makes it difficult to draw conclusions regarding smoking as an influencing factor on regeneration with EMD from the data in this review.

In general all studies used the same postoperative protocol, but in two studies,[34,46] no antibiotics were prescribed, and, in four studies,[38,43,45,47] nothing was reported about antibiotics. The beneficial effect of postoperative antibiotics has not been demonstrated.[82] Thus, it is probable that the postoperative prescription of antibiotics will not have had a great effect on the results. In vitro studies[83,84] have shown antimicrobial properties of the EMD vehicle (propylene glycol alginate), which may have contributed to an improved healing of the control defects in which the EMD vehicle was used as a placebo.[29-31,40,46]

The meta-analysis on the use of EMD versus GTR in intrabony defects showed no statistically significant difference between the two treatment modalities (CAL gain, 0.38 mm; PD reduction, 0.23 mm; change in REC, –0.04 mm), and the heterogeneity between the included studies might not be important ($I^2 = 0\%$).

The studies in which EMD was compared with another regeneration material or with combinations of regenerative materials showed better results only for the use of EMD in combination with BPBM for all parameters.[36] In this study, the number of walls per defect was not mentioned. As mentioned previously, EMD gives significantly better results in 3-wall defects and is preferably indicated for these defects. The better results obtained in the test defects may be attributed, at least in part, to the space-maintenance properties of BPBM. Also, the resorption rate of BPBM is very slow, and the bone fill probably consisted of a combination of bovine bone particles and regenerating vital human bone, which is not the case with EMD alone.[85]

Furcation Defects

The literature on the use of EMD in furcation defects is very scarce. There is only one RCT,[48] which compares the use of EMD to a membrane. The EMD group showed significantly more improvement in HFD than the membrane group.

Recession Coverage

The meta-analysis of the use of EMD in combination with a CAF gave significantly better results then CAF alone in CRC (OR = 3.5), RecRed (0.56 mm), change in CAL (0.59 mm), and HKT (0.46 mm). The heterogeneity for CRC (I^2 = 25%) and CAL (I^2 = 25%) might not be important, but RecRed has a substantial (I^2 = 55%) and HKT a considerable (I^2 = 97%) heterogeneity. A meta-analysis of the studies with low risk of bias[50,51] showed only a significant advantage in the change in HKT (0.41 mm) for the use of EMD in combination with CAF. A reason for this observation might be the longer follow-up (24 months). If this is taken into consideration, the additional effect of EMD for RecRed and change in CAL might be overestimated in the present meta-analysis, i.e. EMD might only be useful to increase the KT.

The meta-analysis of the use of CAF + EMD versus CAF + CTG showed no significant difference for change in CRC, RecRed, and CAL. CAF + EMD gave shallower PD (0.26 mm) after treatment, and CAF + CTG gave significantly more HKT (1.25 mm). The

use of the CAF + CTG procedure may be suggested when KT augmentation is the treatment goal. On the contrary, CAF + EMD appears to be an easier procedure with significantly less discomfort in the first postoperative month[49] than CAF + CTG. For this reason, the cost/benefit ratio of CAF + EMD should be carefully evaluated.

Smoking is associated with poorer outcomes in recession coverage with only CAF and CAF + CTG.[86,87] In only two studies[49,52] with different comparisons were smokers excluded, so it is difficult to draw conclusions from these observations.

The major indications for recession coverage procedures are esthetics and root sensitivity,[88] but only one article[49] mentioned that CAF + EMD achieved a more natural-appearing mucogingival complex compared with CAF + CTG.

CONCLUSIONS

In the treatment of intrabony defects, the use of EMD compared with a control showed significantly more gain in CAL (1.30 mm) and PD reduction (0.92 mm). The use of EMD or RMs in intrabony defects is equally effective in CAL gain and PD reduction.Only the addition of BPBM to EMD in intrabony defects gave a superior result in CAL gain (0.9 mm) and PD reduction (0.4 mm) compared with EMD alone, but this was shown in only one RCT. In the treatment of furcations, there is only one RCT available that compared EMD with RM. This study showed significantly more reduction in HFD and less recession and postoperative complications after the use of EMD. In the treatment of recessions, the use of EMD in combination with CAF gave significantly more CRC (OR = 3.50), RecRed (0.56 mm), CAL gain (0.59 mm), and KT gain (0.46 mm) compared with CAF alone. The use of EMD combined with CAF compared with CAF with CTG in recession coverage showed only superior results in KT gain (1.25 mm) for CAF combined with CTG. This was shown in only one RCT. There was a high degree of heterogeneity between studies observed among trials for EMD compared with a control in intrabony defects and EMD in combination with CAF compared with CAF alone for the treatment of recessions. The lesser benefit of EMD in studies judged to be at low risk of bias for CAL gain and PD reduction in intrabony defects and no significant effect for RecRed and CAL gain in the treatment of recessions suggest that the effect of EMD should be interpreted with great caution and that the results could be an overestimation of the actual treatment effect.

ACKNOWLEDGMENT

The authors report no conflict of interest related to this study.

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Submitted May 3, 2011; accepted for publication September 9, 2011.