

Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects (Review)

Esposito M, Grusovin MG, Coulthard P, Worthington HV



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[Intervention Review]

Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Marco Esposito¹, Maria Gabriella Grusovin¹, Paul Coulthard¹, Helen V Worthington²

¹Department of Oral and Maxillofacial Surgery, School of Dentistry, The University of Manchester, Manchester, UK. ²Cochrane Oral Health Group, MANDEC, School of Dentistry, The University of Manchester, Manchester, UK

Contact address: Marco Esposito, Department of Oral and Maxillofacial Surgery, School of Dentistry, The University of Manchester, Higher Cambridge Street, Manchester, M15 6FH, UK. espositomarco@hotmail.com. marco.esposito@manchester.ac.uk. (Editorial group: Cochrane Oral Health Group.)

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ABSTRACT

Background

Periodontitis is a chronic infective disease of the gums caused by bacteria present in dental plaque. This condition induces the breakdown of the tooth supporting apparatus until teeth are lost. Surgery may be indicated to arrest disease progression and regenerate lost tissues. Several surgical techniques have been developed to regenerate periodontal tissues including guided tissue regeneration (GTR), bone grafting (BG) and the use of enamel matrix derivative (EMD). EMD is an extract of enamel matrix and contains amelogenins of various molecular weights. Amelogenins are involved in the formation of enamel and periodontal attachment formation during tooth development.

Objectives

To test whether EMD is effective, and to compare EMD versus GTR, and various BG procedures for the treatment of intrabony defects.

Search strategy

We searched the Cochrane Oral Health Group Trials Register, CENTRAL, MEDLINE and EMBASE. Several journals were hand-searched. No language restrictions were applied. Authors of randomised controlled trials (RCTs) identified, personal contacts and the manufacturer were contacted to identify unpublished trials. Most recent search: May 2005.

Selection criteria

RCTs on patients affected by periodontitis having intrabony defects of at least 3 mm treated with EMD compared with open flap debridement, GTR and various BG procedures with at least 1 year follow up. The outcome measures considered were: tooth loss, changes in probing attachment levels (PAL), pocket depths (PPD), gingival recessions (REC), bone levels from the bottom of the defects on intraoral radiographs, aesthetics and adverse events. The following time-points were to be evaluated: 1, 5 and 10 years.

Data collection and analysis

Screening of eligible studies, assessment of the methodological quality of the trials and data extraction were conducted in duplicate and independently by two authors. Results were expressed as random-effects models using mean differences for continuous outcomes and

risk ratios (RR) for dichotomous outcomes with 95% confidence intervals (CI). It was decided not to investigate heterogeneity, but a sensitivity analysis for the risk of bias of the trials was performed.

Main results

Ten trials were included out of 29 potentially eligible trials. No included trial presented data after 5 years of follow up, therefore all data refer to the 1-year time point. A meta-analysis including eight trials showed that EMD treated sites displayed statistically significant PAL improvements (mean difference 1.2 mm, 95% CI 0.7 to 1.7) and PPD reduction (0.8 mm, 95% CI 0.5 to 1.0) when compared to placebo or control treated sites, though a high degree of heterogeneity was found. Significantly more sites had < 2 mm PAL gain in the control group, with RR 0.48 (95% CI 0.29 to 0.80). Approximately six patients needed to be treated (NNT) to have one patient gaining 2 mm or more PAL over the control group, based on a prevalence in the control group of 35%. No differences in tooth loss or aesthetic appearance as judged by the patients were observed. When evaluating the only two trials at a low risk of bias in a sensitivity analysis, the effect size for PAL was 0.6 mm, which was less than 1.2 mm for the overall result. Comparing EMD with GTR (five trials), GTR showed a statistically significant increase of REC (0.4 mm) and significantly more postoperative complications. No trials were found comparing EMD with BG.

Authors' conclusions

One year after its application, EMD significantly improved PAL levels (1.2 mm) and PPD reduction (0.8 mm) when compared to a placebo or control, however, the high degree of heterogeneity observed among trials suggests that results have to be interpreted with great caution. In addition a sensitivity analyses indicated that the overall treatment effect might be overestimated. The actual clinical advantages of using EMD are unknown. With the exception of significantly more postoperative complications in the GTR group, there was no evidence of clinically important differences between GTR and EMD.

PLAIN LANGUAGE SUMMARY

Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Emdogain might have some advantages over other methods of regenerating the tissue supporting teeth lost by gum disease, such as less postoperative complications, but has not been shown to save more compromised teeth or that patients noticed any aesthetic improvement 1 year after its application.

Bacteria in plaque can cause gum disease (periodontitis) that breaks down tissue supporting teeth. Surgical cleaning tries to stop the disease to save loose teeth. Bone grafting, guided tissue regeneration and enamel matrix derivatives (such as Emdogain) aim to regenerate support tissues. Emdogain contains proteins (derived from developing pig teeth) believed to regenerate tooth attachment. The review found that adjunctive application of Emdogain regenerates a little more tissue than surgical cleaning alone, although it is unclear to which extent such improvement is noticeable since patients did not find any difference in the aesthetic results. Emdogain showed similar clinical results to guided tissue regeneration, but is simpler to use and determines less complications. It has not been compared with bone grafting. No serious adverse reactions to Emdogain were reported in trials.

BACKGROUND

Periodontitis is a chronic infective disease of the gums with severe forms affecting 10% to 30% of the adult population. Periodontitis rarely affects children and young adults but its prevalence increases steadily with advancing age. Periodontitis is caused by bacteria present in the dental plaque that induce an inflammatory response of the periodontal tissues. In susceptible individuals, this chronic inflammation will induce the breakdown of the periodontal ligament and the surrounding alveolar bone resulting in the formation of periodontal pockets around the roots. Such pockets constitute an ideal protected environment for bacteria and allow the proliferation of more aggressive anaerobic species. The symptoms of periodontitis are often underestimated and may include bleeding and recession of the gums. Painful periodontal abscesses may also form. At a more advanced stage teeth may drift and become increasingly mobile. The end result of the disease is tooth loss.

The treatment of periodontitis is cause-related. The role of the patient's home plaque control is crucial for the success of the therapy, since pockets can be recolonized by bacteria in a few weeks. Periodontal pockets and root surfaces have to be mechanically cleaned from bacteria (debridement). In the presence of deep pockets surgery may also be indicated to get access to the deepest parts of the pockets to properly clean them and to reduce the depth of the pockets (pocket elimination). The goal of this treatment approach is to stop the progression of periodontal disease. Following treatment, healing occurs by repair without the formation of new periodontal attachment (Bowers 1989a). One of the main concerns for many patients is that after periodontal treatment, the gum recession is increased and may cause aesthetic problems.

The ideal treatment would be to recover the periodontal tissues that have been lost (periodontal tissue regeneration). Several surgical techniques have been developed in an attempt to regenerate periodontal tissues including guided tissue regeneration (GTR), bone grafting (BG) and the use of enamel matrix derivative (EMD). All these treatments have been shown to have the potential to regenerate at least some periodontal attachment in humans (Bosshardt 2005; Bowers 1989b; Sculean 1999). With GTR a bio-compatible barrier (either resorbable or non-resorbable) is surgically positioned around the root to seal the bone defect and protect the blood clot. A Cochrane review (Needleman 1999) has shown that GTR is a little more effective than open flap debridement (1.1 mm in probing attachment levels (PAL) gain and 0.8 mm in probing pocket depths (PPD) reduction), however it was also observed that there was a marked variability of results (heterogeneity) with GTR among various randomised clinical trials. Grafting techniques may include autogenous bone grafting, demineralised freeze-dried bone allografts (DFDBA), animal derived graft materials (xenografts) and synthetic bone graft materials (alloplasts such as hydroxyapatite). The effectiveness of bone grafting for periodontal regeneration in intrabony defect was assessed in two sys-

tematic reviews (Reynolds 2003; Trombelli 2002). Both reviews showed improved probing attachment levels when grafts were used when compared to open flap debridement. However, in one review the gain varied considerably with respect to the different materials used (Trombelli 2002). The authors remarked that due to a significant heterogeneity in results between studies, general conclusions need to be drawn with caution (Trombelli 2002). The other review (Reynolds 2003) concluded that there were no differences in clinical outcome measures among various graft types. The results of both these reviews have to be carefully evaluated since the methodological standards were not similar, therefore further research is needed to confirm these findings. Both GTR and grafting procedures are based on the concept of selective exclusion of epithelial cells from colonizing the wound and space maintaining for the blood clot to regenerate the periodontal tissues. In addition, bone grafts may possess osteoinductive and osteoconductive properties.

Periodontal regeneration mediated by EMD is based on a different concept. It is believed that EMD used in periodontal lesions mimics the development of the tooth supporting apparatus during tooth formation (Hammarström 1997a). The enamel matrix is composed of a number of proteins, 90% of which are amelogenins. Such proteins are thought to induce the formation of the periodontal attachment during tooth formation. The only commercially available product using EMD is called Emdogain and is produced by Biora (Malmö, Sweden). The company has been incorporated into Straumann Biologics Division since 1 April 2004. Originally the product consisted of EMD and a vehicle solution (propylene glycol alginate) that had to be mixed before use. In order to save time and simplify the procedures a ready-to-use Emdogain gel was developed. A large multicentre randomised controlled trial (RCT) showed no differences between the original EMD and the new ready-to-use Emdogain gel formulation (Bratthall 2001). EMD is derived from the developing teeth germs of 6 month old piglets (Hammarström 1997b). Since EMD is a porcine-derived material, it might have the potential of stimulating immune reactions in humans. However, EMDs are quite similar among mammalian species (Brookes 1995), thus are less likely to be antigenic. Multiple exposures to EMD during periodontal therapy have been shown to be safe for the patient (Froum 2004; Heard 2000; Zetterström 1997). It is of interest to note that the vehicle solution (propylene glycol alginate abbreviated in PGA) of the EMD has significant antimicrobial effects on periodontal pathogens (Arweiler 2002; Sculean 2001c; Spahr 2002), however these authors interpreted their findings as Emdogain having antimicrobial properties.

Another issue was whether EMD could improve periodontal wound healing. Despite that EMD was not marketed or approved for non-surgical use, an RCT of 3 week duration suggested that EMD treated sites healed better than contralateral sites treated with the vehicle-control after non surgical root-planing and curettage (Wennström 2002). However, such findings were not con-

firmed by two non-placebo controlled RCTs using masked examiners for evaluating the early post-surgical healing events (Hagenaars 2004; Wachtel 2003). The different results of those trials may be partly explained in terms of different study design, therefore additional trials are needed to solve the issue.

Two RCTs compared the effect of postoperative antibiotics and no antibiotics in combination with EMD (Mombelli 2005; Sculean 2001d). Results were contradictory: while one study suggested no advantages in using postoperative antibiotics (Sculean 2001d), the other suggested that additional benefits may be expected using systemic antibiotics (Mombelli 2005), however patients of the latter trial were subjected to non-surgical interventions for which EMD is not marketed or approved.

Prior to the application of EMD, most authors 'condition' the root surface after mechanical debridement for gently removing the 'smear layer' (the residual of the debridement procedure). Various 'conditioning agents' have been used and the manufacturer of EMD produces one root conditioner called PrefGel composed of 24% ethylenediaminetetra-acetic acid (EDTA) at neutral pH. There is no evidence that this procedure is effective. Traditionally such root conditioners were used to chemically modify the root surface in order to stimulate periodontal regeneration. A systematic review (Mariotti 2003) failed to show the efficacy of such procedures.

EMD is also currently used in many other clinical situations such as the treatment of furcation defects of periodontally compromised teeth, recession, in combinations with GTR, BG, etc. A new recent application, for which EMD was not marketed or approved for, is to promote periodontal attachment regeneration around reimplanted traumatically avulsed teeth or reimplanted ankylotic teeth. However, contradictory results were reported (Filippi 2001; Filippi 2002; Schjøtt 2005).

In conclusion, there is conflicting evidence on the efficacy of EMD, and a comprehensive high-quality systematic review could be one way to investigate whether EMD is effective or not, and whether there are relevant clinical advantages for the patients in the treatment of intrabony defects.

After the publication of the first version of the present review, four different systematic reviews were published on the efficacy of EMD in the treatment of intrabony defects (Giannobile 2003; Kalpidis 2002; Trombelli 2002; Venezia 2004), reaching, in some cases, rather different conclusions. The present review has been criticised for not having included additional methodological criteria for the evaluation of equivalence trials (Tu 2005). The answer to this criticism is that we were not looking for equivalence between alternative methods for the treatment of intrabony defects but, as clearly stated in the objectives, we were looking for a difference.

OBJECTIVES

Primary

To test the null hypothesis of no difference in outcomes using EMD versus a placebo or not for the treatment of intrabony defects.

Secondary

To test the null hypothesis of no difference in outcomes between EMD versus guided tissue regeneration (GTR) for the treatment of intrabony defects.

To test the null hypothesis of no difference in outcomes between EMD versus various 'bone' grafting procedures (BG) for the treatment of intrabony defects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials (RCTs) testing the efficacy of EMD with at least 1 year follow up. The following time-points were to be evaluated: 1, 5 and 10 years.

Types of participants

Patients affected by chronic, aggressive, or early onset periodontitis with intrabony defects having an intrabony component of at least 3 mm to be treated. The depths of intrabony component could be assessed on intraoral radiographs, but intrasurgical measurements were preferred. Trials clearly including patients with shallower intrabony defects were excluded.

Types of interventions

(1) Interventions comparing the use of EMD versus a placebo or not. Both the test and the control sites have to undergo the same intervention, surgical or not, the only difference being the use of EMD for the treatment of intrabony defects.

(2) Interventions comparing the use of EMD versus GTR with barriers for the treatment of intrabony defects.

(3) Interventions comparing the use of EMD versus various types of BG, including animal-derived and synthetic bone, for the treatment of intrabony defects.

Trials describing the combined use of EMD, GTR, BG or other growth factors were not included in the present review.

Types of outcome measures

Primary

(1) Tooth loss

(2) Changes in probing attachment level (PAL)

- (3) Aesthetics (better, no change or worse according to patient opinion)
- (4) Postoperative complications (infection) and other adverse events.

Secondary

- (1) PAL gain < 2 mm (dichotomous outcome only for Emdogain versus control)
- (2) Changes in probing pocket depth (PPD)
- (3) Changes in gingival recession (REC)
- (4) Changes in bone level from the bottom of the defect (BD) in relation to cemento-enamel junction (CEJ) on intraoral radiographs taken with a parallel technique.

Search methods for identification of studies

For the identification of studies included or considered for this review we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE via OVID but revised appropriately for each database. The search strategy used a combination of controlled vocabulary and free text terms. See [Appendix 1](#).

Databases searched

The Cochrane Oral Health Group Trials Register (to May 2005)
 The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, Issue 2)
 MEDLINE (1966 to May 2005)
 EMBASE (1980 to May 2005)
 The most recent electronic search was carried out 18 May 2005.

Handsearching

We identified the following journals as being important to be handsearched for this review: *International Journal of Periodontics and Restorative Dentistry*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Periodontal Research*, *Journal of Periodontology*. For further information about the journals being handsearched consult the Cochrane Oral Health Group website www.ohg.cochrane.org. Where these journals had not already been searched as part of the Cochrane Journal Handsearching Programme, the journals were handsearched by one of the review authors.

Language

Non-English papers were included. The Cochrane Oral Health Group had non-English language trials translated.

Unpublished trials

The bibliographies of papers and review articles were checked for studies outside the handsearched journals. Authors of RCTs identified, personal contacts, the old and the new manufacturers were written to in an attempt to identify unpublished or ongoing trials.

Data collection and analysis

The titles and abstracts (when available) of all reports identified were scanned independently by two review authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained and was assessed independently by two authors to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third author was consulted. All studies meeting the inclusion criteria then underwent validity assessment and data were extracted. Studies rejected at this or subsequent stages were recorded in the table of excluded studies, and reasons for exclusion recorded.

Quality assessment

The quality assessment of the included trials was undertaken independently and in duplicate by two authors based on the content of the articles.

Three main quality criteria were examined:

- (1) Allocation concealment, recorded as:

- (A) Adequate
- (B) Unclear
- (C) Inadequate, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2 (section 6.3.). Allocation concealment was considered adequate if it was centralised (e.g. allocation by a central office unaware of subject characteristics); pharmacy-controlled randomisation; pre-numbered or coded identical containers which were administered serially to participants; on-site computer system combined with allocation kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled patient have been entered; sequentially numbered, sealed, opaque envelopes; and other approaches similar to those listed above, along with the reassurance that the person who generated the allocation scheme did not administer it. Some schemes may be innovative and not fit any of the approaches above, but still provide adequate concealment. Approaches to allocation concealment which were considered clearly inadequate included: alternation, use of case record numbers, dates of birth or day of the week, and any procedure that was entirely transparent before allocation, such as an open list of random numbers. Ideally the surgeon should have known the group allocation only after having elevated the flap and debrided the root surface. Those articles or authors stating that allocation concealment procedures were implemented but did not provide details on how this was accomplished, were coded as 'unclear'.

- (2) Outcome assessor blind to interventions (if applicable) as:

- (A) Yes
- (B) No
- (C) Unclear.
- (3) Completeness of follow up (is there a clear explanation for withdrawals and drop outs in each treatment group?) assessed as:
 - (A) Yes. In the case that clear explanations for drop outs are given, a further subjective evaluation of the risk of bias assessing the reasons for the drop out has to be made

(B) No.

After taking into account the additional information provided by the authors of the trials, studies were graded into the following categories.

(A) Low risk of bias (plausible bias unlikely to seriously alter the results) if all the three quality criteria were met.

(B) High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met. After modification from the *Cochrane Handbook for Systematic Reviews of Interventions*, section 6.7.

Data extraction

Data were extracted by two review authors independently using specially designed data extraction forms. Any disagreement was discussed and a third author consulted where necessary. Authors of the RCTs were contacted for clarification or missing information. Data were excluded until further clarification was available if agreement could not be reached.

For each trial the following data were recorded.

- Year of publication, country of origin, setting and source of study funding.
- Details of the participants including demographic characteristics and criteria for inclusion.
- Details on the study design (parallel group or split mouth).
- Details on the type of intervention.
- Details of the outcomes reported, including method of assessment and time intervals.

Data synthesis

For dichotomous outcomes, the estimate of effect of an intervention were expressed as risk ratios together with 95% confidence intervals. For continuous outcomes, mean differences and 95% confidence intervals were used to summarise the data for each group. The statistical unit was the patient and not the treated sites. Numbers needed to treat (NNT) were calculated for PAL gain < 2 mm.

Meta-analyses were done only with studies of similar comparisons reporting the same outcome measures. Risk ratios were combined for dichotomous data, and mean differences for continuous data, using random-effects models. Data from split-mouth and parallel group studies were combined using the procedures outlined in [Elbourne 2002](#). It was necessary to estimate the appropriate standard errors where these were not presented in the trial reports using the methods presented by [Follmann 1992](#). The generic inverse variance procedure in RevMan 4.2 was used to combine these two subgroups in the analyses.

The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity and the I^2 statistics, which describes the percentage total variation across studies that is due to heterogeneity rather than chance. However it was decided not to try to explain the heterogeneity. The motivation of this choice is

the following: in general subgroup analyses are exploratory investigations to generate hypotheses to be tested in future studies. The results from these are only tentative and need to be confirmed in studies designed specifically for this purpose. Unfortunately too much weight is often put on the results from subgroup analyses in this area, and too often such tentatively explanations are misused. We have therefore decided not to undertake any subgroup analyses apart from for study design, with subgroups for split-mouth and parallel group studies. Random-effects metaregression analysis was used to investigate whether the effect of study design (post hoc comparison) could explain heterogeneity for PAL, PPD and REC in the various comparisons.

Sensitivity analyses were undertaken to examine the effect size in PAL, PPD and REC, excluding trials at high risk of bias on the assessment of the overall estimates of effect. In addition, the effect of including unpublished literature on the review's findings was to be examined.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

See [Characteristics of included studies](#) table.

See [Characteristics of excluded studies](#) table.

Of the 29 potentially eligible trials, 10 were included in this review ([Francetti 2004](#); [Heijl 1997](#); [Okuda 2000](#); [Pontoriero 1999](#); [Rösing 2005](#); [Sanz 2004](#); [Silvestri 2000](#); [Silvestri 2003](#); [Tonetti 2002](#); [Zucchelli 2002](#)) and 19 trials ([Doertbudak 2000](#); [Eger 1998](#); [Francetti 2005](#); [Froum 2001](#); [Ghaffar 2001](#); [Hagenaars 2004](#); [Lombardo 2000](#); [Martinez 2001](#); [Martu 2000a](#); [Martu 2000b](#); [Minabe 2002](#); [Mombelli 2005](#); [Parashis 2004](#); [Sculean 1999](#); [Sculean 2001a](#); [Sculean 2001b](#); [Vandana 2004](#); [Wachtel 2003](#); [Windisch 2002](#)) were excluded for the following reasons: not RCT ([Doertbudak 2000](#); [Eger 1998](#); [Lombardo 2000](#); [Martu 2000a](#); [Martu 2000b](#); [Parashis 2004](#)), teeth extracted after 6 months ([Sculean 1999](#); [Windisch 2002](#)), insufficient data presented ([Ghaffar 2001](#); [Martinez 2001](#)), data in an inappropriate form ([Francetti 2005](#)), data presented in a way that we could not use ([Froum 2001](#); [Minabe 2002](#); [Wachtel 2003](#)), too short follow up ([Hagenaars 2004](#)) and included intrabony defects less than 3 mm deep ([Mombelli 2005](#); [Sculean 2001a](#); [Sculean 2001b](#); [Vandana 2004](#)).

Characteristics of the trial setting and investigators

Seven trials had a parallel group design ([Francetti 2004](#); [Pontoriero 1999](#); [Sanz 2004](#); [Silvestri 2000](#); [Silvestri 2003](#); [Tonetti 2002](#); [Zucchelli 2002](#)) and four studies were designed as split-mouth trials ([Heijl 1997](#); [Okuda 2000](#); [Pontoriero 1999](#); [Rösing 2005](#)). The comparisons made in one trial ([Pontoriero 1999](#)) were both

within patients and between patients. Five trials were conducted in Italy (Francetti 2004; Pontoriero 1999; Silvestri 2000; Silvestri 2003; Zucchelli 2002), one in Japan (Okuda 2000), one in Sweden (Heijl 1997), one in Norway (Rösing 2005), and two trials were conducted in several countries (Sanz 2004; Tonetti 2002). Six trials were multicentre (Heijl 1997; Sanz 2004; Silvestri 2000; Silvestri 2003; Tonetti 2002; Zucchelli 2002). Three trials were conducted in university dental clinics (Francetti 2004; Okuda 2000; Rösing 2005), five were conducted both in university dental clinics and private practices (Sanz 2004; Silvestri 2000; Silvestri 2003; Tonetti 2002; Zucchelli 2002), one study in a private practice (Pontoriero 1999) and one trial in a public specialist clinic of periodontology (Heijl 1997). Eight trials were funded or partially supported by manufacturers (Francetti 2004; Heijl 1997; Pontoriero 1999; Rösing 2005; Sanz 2004; Silvestri 2000; Silvestri 2003; Tonetti 2002), such information was explicit only in three trials (Heijl 1997; Sanz 2004; Tonetti 2002). Two trials were not supported by manufacturers (Okuda 2000; Zucchelli 2002).

In total 570 patients were treated in the 10 included trials.

Characteristics of the interventions

Eight trials (Francetti 2004; Heijl 1997; Okuda 2000; Pontoriero 1999; Rösing 2005; Silvestri 2000; Tonetti 2002; Zucchelli 2002) compared EMD versus control flap surgery. The surgical techniques for the control flaps were: the modified Widman flap in four trials (Heijl 1997; Okuda 2000; Pontoriero 1999; Silvestri 2000) whereas in the other four trials (Francetti 2004; Rösing 2005; Tonetti 2002; Zucchelli 2002) the simplified or the modified papilla preservation techniques were used. In four trials (Heijl 1997; Okuda 2000; Pontoriero 1999; Rösing 2005) a placebo (the propylene glycol alginate vehicle gel solution) was used in the control flaps.

Five trials (Pontoriero 1999; Sanz 2004; Silvestri 2000; Silvestri 2003; Zucchelli 2002) compared EMD versus guided tissue regeneration (GTR). In three trials non-resorbable barriers were used (Silvestri 2000; Silvestri 2003; Zucchelli 2002), in one trial resorbable barriers were used (Sanz 2004), and in one trial (Pontoriero 1999) both resorbable and non-resorbable barriers were used, however we used data only from the non-resorbable barrier group since defects shallower than 3 mm were included in the two groups in which resorbable barriers were used. Non-resorbable barriers were removed 6 weeks after their insertion with the exception of one trial (Pontoriero 1999) in which they were removed after 4 weeks. For one trial it is unclear when the barriers were removed (Sanz 2004). In one study connective tissue grafts were placed in six patients after barrier removal (Silvestri 2000). The following root-conditioning procedures before EMD application were implemented in all trials.

- 36% ortho-phosphoric acid for 15 seconds, also to the controls (Heijl 1997; Okuda 2000).
- 24% ethylenediaminetetra-acetic acid (EDTA) gel for 2 minutes only in the EMD treated sites (Francetti 2004;

Sanz 2004) and also to the open flap debridement control sites (Pontoriero 1999; Rösing 2005; Tonetti 2002; Zucchelli 2002) and the GTR sites (Silvestri 2003; Zucchelli 2002).

- 17% EDTA solution for 20 seconds only for the EMD group (Silvestri 2000).

The following postoperative systemic antibiotics and hygiene procedures were prescribed.

- Doxycycline (Vibramycin, Pfizer) 200 mg day 1 and 100 mg for 3 weeks; 0.2% chlorhexidine rinsing for 4 to 6 weeks and no mechanical cleaning in operated areas for 6 weeks (Heijl 1997).
- Amoxicillin 3 gram 1 hour before surgery; 0.12% chlorhexidine rinsing twice a day for 6 weeks (Pontoriero 1999).
- Cefaclor 750 mg per day for 5 days; 0.12% chlorhexidine rinsing three times a day for 6 weeks and no mechanical cleaning for the first postoperative week (Okuda 2000).
- Amoxicillin and clavulanic acid (Augmentin, Smith Klein Beecham) 2 grams per day for 6 days; 0.2% chlorhexidine rinsing twice a day for 8 weeks and no mechanical cleaning in operated areas for 2 months (Silvestri 2000; Silvestri 2003).
- Amoxicillin 500 mg three per day for 10 days; chlorhexidine rinsing twice a day for the initial healing period (Rösing 2005).
- In the published article the use of antibiotics was not mentioned but the authors informed us that antibiotics were used in five patients of the Emdogain group and seven control patients; 0.12% chlorhexidine rinsing twice a day for 4 weeks and gentle sweeping of operated areas with a postsurgical toothbrush starting from the third postoperative day without interdental cleaning for 4 weeks (Tonetti 2002).
- Amoxicillin and clavulanic acid (Augmentin, Smith Klein Beecham) 1 gram per day starting 1 day before surgery for 6 days thereafter; 0.2% chlorhexidine rinsing twice a day for 11 weeks without interdental cleaning in the operated areas (Zucchelli 2002).
- Amoxicillin and clavulanic acid (Augmentin, Smith Klein Beecham) 1 gram per day for 7 days; 0.2% chlorhexidine rinsing twice a day for 6 weeks without mechanical cleaning in the operated areas (Francetti 2004).
- In the published article the use of antibiotics was not mentioned but the authors informed us that amoxicillin 500 mg for 4 days was prescribed; 0.12% chlorhexidine rinsing twice a day for 4 weeks and gentle sweeping of operated areas with a postsurgical toothbrush starting

from the third postoperative day without interdental cleaning for 4 weeks (Sanz 2004).

Characteristics of outcome measures

After contacting the authors, postoperative complications (infection) were available for all trials.

Tooth loss was not described in one trial (Sanz 2004).

Changes in PAL and PPD were described in all trials.

PAL gain < 2 mm was described in five trials (Francetti 2004; Heijl 1997; Silvestri 2000; Tonetti 2002; Zucchelli 2002).

Four trials did not describe changes in REC (Francetti 2004; Heijl 1997; Rösing 2005; Silvestri 2003).

Bone level measurement from the bottom of the defect to the CEJ on intraoral radiographs taken with a paralleling technique were performed in four trials (Francetti 2004; Heijl 1997; Okuda 2000; Rösing 2005). Radiographic data from two studies were not used (Francetti 2004; Okuda 2000) because of data presented as per cent relative area of bone density and not as linear measurements (Okuda 2000) and for not having used a fixed reference mark to assess changes over time (Francetti 2004).

Aesthetics according to the patient's opinion was measured in one trial (Tonetti 2002).

Baseline characteristics

Specific exclusion criteria

- None in particular (Heijl 1997; Pontoriero 1999).
- Smokers (Okuda 2000; Silvestri 2000).
- Medium smokers, i.e. more than 10 cigarettes per day (Silvestri 2003).
- Heavy smokers, i.e. more than 20 cigarettes per day (Sanz 2004; Tonetti 2002; Zucchelli 2002).
- Any periodontal treatment in the previous 2 years (Okuda 2000).
- Any periodontal treatment in the previous 3 years (Francetti 2004).
- Antibiotics in the previous 6 months (Okuda 2000; Rösing 2005; Zucchelli 2002).
- Less than 2 mm of attached gingiva (Francetti 2004; Okuda 2000; Tonetti 2002).

In all trials defects did not extend into furcations and patients were selected because they were motivated and had good oral hygiene.

Presurgical treatments

- All patients treated with repeated mechanical debridement and some with antimicrobials and surgical interventions over long time periods (Heijl 1997).
- All patients treated with mechanical debridement and antiseptics and/or antibiotics when indicated (Tonetti 2002).
- All patients treated with mechanical debridement (Francetti 2004; Okuda 2000; Pontoriero 1999; Rösing

2005; Sanz 2004; Silvestri 2000; Silvestri 2003; Zucchelli 2002).

Characteristics of the defects

- PPD greater or equal to 6 mm and intrabony defects with a depth greater or equal to 4 mm (Francetti 2004; Heijl 1997; Okuda 2000; Silvestri 2000).
- PPD greater or equal to 6 mm and intrabony defects with a depth greater or equal to 3 mm (Pontoriero 1999).
- PPD greater or equal to 7 mm and intrabony defects with a depth greater or equal to 3 mm (Zucchelli 2002).
- Intrabony defects with a depth greater or equal to 3 mm (Rösing 2005; Sanz 2004; Tonetti 2002).
- Intrabony defects with a depth greater or equal to 4 mm (Silvestri 2003).

Baseline comparisons among groups

- No statistically significant differences among test and control groups for PAL, PPD and radiographic bone levels (Heijl 1997; Rösing 2005).
- No statistically significant differences among test and control groups for full mouth plaque score (FMPS), full mouth bleeding score (FMBS), PAL, PPD, REC and intrabony components (Okuda 2000; Pontoriero 1999; Sculean 2001a; Zucchelli 2002) and distribution of number of walls of the bony defects (Tonetti 2002) and smokers (Sanz 2004).
- No statistically significant differences among test and control groups for FMPS, PAL, PPD, REC and intrabony components (Sculean 2001b).
- No statistically significant differences among test and control groups for PAL, PPD, REC and intrabony components (Silvestri 2003).
- No statistically significant differences among test and control groups for intrabony components (Francetti 2004; Silvestri 2000).

Type of maintenance and frequency during the postoperative phase and the follow up of the trials

- Recall for professional tooth cleaning at week 2, 4, 6 and thereafter, depending on the level of plaque control, at 3, 6, 9 and 12 months or at 4, 8 and 12 months. At 1 year an individual recall program was decided and patients were recalled at least every 6 months (Heijl 1997).
- Recall every 15 days for professional tooth cleaning (Pontoriero 1999).
- Supragingival professional cleaning weekly for the first 6 weeks and thereafter prophylaxis once a month; 1 year (Okuda 2000).
- Supragingival professional cleaning weekly for the first 8 weeks and thereafter prophylaxis every 3 months; 1 year (Silvestri 2000; Silvestri 2003).

- Recall for professional tooth cleaning at week 1, 2, 3, 4, 6 and thereafter every 3 months; 1 year (Sanz 2004; Tonetti 2002).
- Recall for professional tooth cleaning once a month; 1 year (Francetti 2004; Zucchelli 2002).
- Recall for professional tooth cleaning once every 2 weeks for 8 weeks and thereafter every 3 months (Rösing 2005).

Duration of follow up

- Three years (Heijl 1997).
- Two years (Francetti 2004).
- One year (Okuda 2000; Pontoriero 1999; Rösing 2005; Sanz 2004; Silvestri 2000; Silvestri 2003; Tonetti 2002; Zucchelli 2002).

In the present review only 1 year data were used with the exception of one trial (Heijl 1997) for which 16-month data were used.

Risk of bias in included studies

The final assessment of the risk of bias after considering author's clarification is summarized in Additional Table 1.

Table 1. Results of quality assessment after correspondence with authors

Study	Allocation	Blinding of assessor	Withdrawals	Risk of bias
Heijl 1997	Adequate	Yes	Yes	A
Pontoriero 1999	Unclear	Yes	Yes	B
Okuda 2000	Unclear	Yes	Yes	B
Silvestri 2000	Inadequate	No	Yes	B
Tonetti 2002	Adequate	No	Yes	B
Zucchelli 2002	Unclear	Yes	Yes	B
Silvestri 2003	Unclear	No	Yes	B
Francetti 2004	Adequate	No	Yes	B
Sanz 2004	Adequate	No	No	B
Rösing 2005	Adequate	Yes	Yes	A

Allocation concealment

Three papers described clearly the procedure of allocation concealment (Heijl 1997; Rösing 2005; Sanz 2004). All the other trials were marked as unclear. All authors replied to our request for additional clarification. With three exceptions, they replied that allocation was concealed without providing any description of the concealment procedures. Thus all those trials were still scored as 'unclear' (Okuda 2000; Pontoriero 1999; Silvestri 2003; Zucchelli 2002), as additional information on the method of allocation concealment was not provided. The authors of two trials (Francetti 2004; Tonetti 2002) described the allocation concealment procedure which was then judged to be adequate. Allocation was not concealed and was scored as 'inadequate' for one trial (Silvestri 2000).

Blinding

Outcome assessors were considered to be blind in four cases (Heijl 1997; Okuda 2000; Rösing 2005; Zucchelli 2002), unclear in three cases (Pontoriero 1999; Silvestri 2000; Silvestri 2003) and not blinded in three cases (Francetti 2004; Sanz 2004; Tonetti 2002). After contacting the authors one trial was considered blind (Pontoriero 1999), and two were not (Silvestri 2000; Silvestri 2003).

Withdrawals

The reporting and explanation of withdrawals and drop outs were clear in eight trials (Francetti 2004; Heijl 1997; Okuda 2000; Rösing 2005; Silvestri 2000; Silvestri 2003; Tonetti 2002; Zucchelli 2002). After correspondence with authors all trials with only one exception (Sanz 2004) were considered to have clear explanations of withdrawals and drop outs.

Sample size

Sample size calculations studies were performed in four studies (Heijl 1997; Rösing 2005; Sanz 2004; Tonetti 2002). In one trial (Heijl 1997), the sample size was calculated to detect 1 mm difference (assuming standard deviation (SD) of 1 mm) of PAL and radiographic bone gain between test and control with a power (one minus beta) of at least 90% 8 months after surgery. For the other trial (Tonetti 2002), the size of the sample required to detect a true difference of 0.5 mm for PAL between test and control with 90% power and with an alpha error of 0.05 was 150 patients completing the trial. The third trial (Rösing 2005) was designed to have sufficient power to detect a 2 mm difference in PAL gain, adopting an alpha set at 0.05 and a power of 80%. It was calculated that a paired sample of nine individuals was sufficient. In those studies more patients than needed to detect the assumed differences completed the trials.

The fourth trial (Sanz 2004) was designed to have sufficient power to detect a true difference of 1 mm of PAL gain with alpha set at 0.05 and a power of 0.8. However the authors concluded that the

trial had insufficient power to detect potentially clinically relevant differences.

Agreement in methodological assessment

The percent agreement and kappa scores between the two raters on the published information were: 100%, 1.00 for allocation concealment; 100%, 1.00 for blinding of the outcome assessor and 100%, 1.00 for withdrawals.

The agreed quality of the included trials after having incorporated the information provided by the authors of the trials is summarized in Additional Table 1. Two trials were considered to be at low risk of bias (Heijl 1997; Rösing 2005), and the remaining trials at high risk of bias.

Effects of interventions

Data from parallel and split-mouth trials are analysed as separate subgroups, then combined using the generic inverse variance procedure in RevMan. No trial with a follow up of 5 years was included.

Emdogain (EMD) versus control/placebo at 1 year (Comparison 1, Outcomes 1.1 to 1.8)

Eight trials provided data for this comparison between EMD and control or placebo interventions (Francetti 2004; Heijl 1997; Okuda 2000; Pontoriero 1999; Rösing 2005; Silvestri 2000; Tonetti 2002; Zucchelli 2002), four of which were split-mouth placebo-controlled trials (Heijl 1997; Okuda 2000; Pontoriero 1999; Rösing 2005).

- Tooth loss: there were insufficient numbers of teeth lost to undertake an analysis of these. All teeth were extracted for prosthetic reasons. Four test teeth removed: two in Heijl 1997 and two in Rösing 2005 versus two control teeth removed in Heijl 1997.
- PAL: there were eight trials for this outcome measured as change from the baseline values. There was a significant gain in mean PAL for EMD compared with control sites with mean difference of 1.20 mm (95% CI 0.71 to 1.69, $\text{Chi}^2 = 33.41$, 7 df, $P < 0.0001$, $I^2 = 79\%$).
- Aesthetics: there was one trial reporting this (Tonetti 2002) and no statistically significant difference between EMD and control treatment was found.
- Complications and other adverse events: no particular adverse events or infection attributable to EMD were recorded in any of the trials with the exception of few problems attributable to the use of postoperative antibiotics. There were no differences in postoperative frequency of subjects reporting pain, intensity of pain recorded on a VAS scale, duration of pain, use of used analgesic tablets, edema, hematoma, wound dehiscence, and root sensitivity (Tonetti 2002).

- PAL gain < 2 mm: there were significantly more sites with less than 2 mm PAL gain in the control group RR 0.48 (95% CI 0.29 to 0.80; Chi² = 4.4, 4 df, P = 0.35, I² = 9.9%) (five trials). The number of patients needed to treat (NNT) in the control group to help one patient gain > 2 mm is 6 (95% CI 3 to 7) based on a prevalence of 35% of patient having < 2 mm gain in PAL. The NNT increases to 13 for a prevalence of 15%, and reduces to 3 with a prevalence of 60%.
- PPD: there were eight trials for this outcome measured as change from the baseline values. There was a significant reduction in PPD for EMD compared with control sites with mean difference of 0.77 mm (95% CI 0.54 to 1.00; Chi² = 24.56, 7 df, P = 0.0009, I² = 72%).
- REC: there was no statistically significant difference between the EMD and the control in REC (five trials).
- Radiographic bone level: there was no statistically significant difference between the EMD and the control for radiographic bone gain (two trials).

Heterogeneity

There was substantial heterogeneity for PAL (P < 0.0001; I² = 79%), PPD (P < 0.0009; I² = 72%) and REC (P = 0.04; I² = 60%), however we decided to only investigate this for study design, comparing split-mouth with parallel group studies between EMD and the control group. The results are given in Additional Table 2 and none of these were significant however there was a trend for PAL, with the split-mouth studies showing a lower effect (P = 0.08).

Table 2. Random-effects metaregression analysis of outcomes PAL, PPD, REC

Characteristic	Outcome	No. studies	Slope estimate (SE)	95% CI	Slope	P-value
Parallel versus split mouth	PAL	8	-0.95 (0.55)	(-2.02, 0.13)	Emdogain in parallel group trials has higher effect	0.08
Parallel versus split mouth	PPD	8	-0.94 (0.66)	(-2.24, 0.36)	Emdogain in parallel group trials has higher effect	0.16
Parallel versus split mouth	REC	5	-0.33 (0.38)	(-1.09, 0.41)	Emdogain in parallel group trials has higher effect	0.38

Sensitivity analysis

Only two studies were judged as of low risk of bias (Heijl 1997; Rösing 2005). From the sensitivity analysis the effect size for PAL was 0.56 mm (95% CI RE 0.14 to 0.98), which was less than 1.20 mm for the overall result, and for PPD was 0.58 mm compared with 0.77 mm of the overall result.

Emdogain (EMD) versus guided tissue regeneration (GTR) at 1 year (Comparison 2, Outcomes 2.1 to 2.6)

Five trials provided data for this comparison between EMD and GTR (Pontoriero 1999; Sanz 2004; Silvestri 2000; Silvestri 2003; Zucchelli 2002), none of which was a split-mouth trial. The comparison for another split-mouth trial (Pontoriero 1999) was between patients randomly allocated to the study groups, not using the split-mouth data.

- Tooth loss: there were no teeth lost in either group in any of these trials.
- PAL: there were no statistically significant differences for PAL (five trials).
- Aesthetics: no trial evaluated aesthetics.
- Complications and other adverse events: there was no statistically significant difference in postoperative infections (four trials). In the GTR group two abscesses and several barrier exposures occurred. However a further trial (Sanz 2004) reported postoperative complications without differentiating between minor complications (such as flap dehiscence) and more serious ones (such as abscesses). There were two (6%) complications in the Emdogain group compared to 32 (100%) in the GTR group, and this difference was statistically significant ($P < 0.001$), RR 0.06 (95% CI 0.02 to 0.24).
- PPD: there were five trials for this outcome and no statistically significant difference was found.
- REC: there were significant differences between EMD and GTR for change from baseline in REC (five trials), with a significant increase in recession for GTR with mean difference 0.39 mm (95% CI 0.13 to 0.66; $\text{Chi}^2 = 2.93$, 3 df, $P = 0.40$).
- Radiographic bone level: there were no trials evaluating this.

Emdogain versus bone grafting (BG)

No trial comparing the use of EMD alone to BG alone was identified.

It should be remembered that trials combining the use of EMD, GTR and BG as well as other regenerative procedures (e.g. BG plus GTR or EMD plus GTR) were not included in the present review.

DISCUSSION

The meta-analysis of eight trials showed that the use of EMD led to a statistically significant improvement in average PAL (1.2 mm) and PPD (0.8 mm) over control flap surgery when used in the treatment of intrabony defects after 1 year. However, the high degree of heterogeneity found ($I^2 = 79\%$ for PAL and $= 72\%$ for PPD) prevents us to assume average values as a demonstration of the extent of the difference between the therapies (mean values on the included trials varied from -0.15 to 3.3 mm for PAL gain; from -0.22 to 3.5 mm for PPD reduction). From the sensitivity analysis (i.e. a meta-analysis including only those trials at low risk of bias), the effect size for PAL was reduced to 0.56 mm and for PPD to 0.58 mm. This may indicate that the overall treatment effects of EMD is actually overestimated in the present meta-analysis, and may go some way to explain the heterogeneity.

The number needed to treat (NNT) was calculated to help clinicians understand how many patients would need to be treated with Emdogain to have one more patient gaining 2 mm or more PAL than would have done so in the control group. NNT depends on the prevalence of gaining less than 2 mm PAL in the control group. The mean prevalence was calculated across five studies and NNTs for a range of prevalences considered. For example the mean prevalence in the control group was 35% and the NNT was six, and this increased to 13 for a reduced prevalence of 15% and reduced to three for an increased prevalence of 60%.

Only one trial (Tonetti 2002) investigated patient centred outcomes and aesthetics as perceived by the patient themselves. After 1 year a general statistically significant improvement for patients centred outcomes was reported, however there were no statistically significant differences among the EMD and the control groups. The observation that both groups perceived an improvement in aesthetics despite that in reality some degree of gingival recession had occurred, emphasizes how the patient's judgement may be influenced simply by having received the therapy which they expected to improve their status (Hawthorne effect).

It is interesting to observe that in the multicentre trial in which a multivariate analysis was used to investigate whether the treating centre had an influence on PAL gain (Tonetti 2002), it was found that the centre effect (worse versus better) was statistically significant (-2.6 mm 0.6), while the overall treatment effect recalculated in the present review, was of 0.6 mm 0.2. There could be several explanations for instance the technique is extremely sensitive to the operators, the characteristics of the patients were different, the measurements were differently biased in the various centres, since outcomes assessors were not blinded, or a combination of the various explanations.

While the improvements in PAL and PPD levels are without any doubt positive findings, the real clinical utility of EMD may be debated. In particular, there is no evidence that more compromised teeth could be saved using EMD, that the amount of tissue

regeneration was clinically significant, or that patients preferred the EMD treatment for aesthetic reasons. It may be argued that only short-term follow-up studies on EMD are available, therefore it is unlikely that a difference in tooth loss could become apparent. Since the decision to remove a periodontally compromised tooth is generally driven by the dentist, it is imperative that the person who takes this decision is unaware of the precise nature of the treatment that the patient has received (i.e. EMD versus control flap surgery or EMD versus GTR). In fact, the knowledge of the type of therapy administered might influence the decision-making process of the dentist, who might systematically decide to remove more teeth from a certain patient group, according to personal belief, introducing bias in the results.

When comparing EMD with GTR (five trials), we found that GTR produced a statistically significant increase in REC (0.39 mm) after 1 year. This statistical difference may not be of clinical significance. No differences between EMD and GTR were found when comparing tooth loss or postoperative infections. While this is true from a statistical point of view, we have to stress that the only two postoperative abscesses occurred in the GTR group. We did not record as postoperative infections small dehiscences of the flaps over the barriers which were numerous in all studies. However in one additional trial, where all types of postoperative complications were added together (Sanz 2004), it was found that 100% of the sites treated with GTR had at least one complication versus only 6% of the sites treated with EMD. It is known that postoperative complications are common when using the GTR technique, but a 100% complication rate looks rather high. It could be hypothesized that the antibiotic coverage used (500 mg of Amoxicillin for 4 days) was insufficient to prevent infection of the barriers. No adverse reactions were reported for patients in the EMD or control groups with the exception of a few problems attributed to the use of antibiotics. While antibiotics may be useful when placing a barrier around teeth, they may not be necessary with EMD (Sculean 2001d), though this matter needs additional investigations in view of more recent findings (Mombelli 2005). It may also be useful to emphasize that the vehicle of EMD has shown antibacterial properties in vitro (Sculean 2001c; Spahr 2002). In addition, if non-resorbable barriers are used a second operation is needed for their removal. Taken together, all these aspects suggest that EMD might be a preferable choice over GTR.

It is unclear whether patients treated with EMD may benefit from postoperative antibiotics (Mombelli 2005; Sculean 2001d). Postoperative antibiotics were prescribed in all but one trial (Tonetti 2002). In that trial (Tonetti 2002) the operators were free to decide when to use systemic antibiotics. While the administration of antibiotics may be understandable for methodological reasons in trials comparing EMD with GTR, it may be considered whether it is appropriate to use antibiotics in those trials comparing EMD with flap surgery alone or even more to generalize the prescription of antibiotics in routine practice, since a generalized use of anti-

otics is associated with some risk.

We intentionally did not include RCTs describing the use of EMD in conjunction with other treatments such as GTR, BG, etc. This was done because we wanted to know whether EMD was effective, and whether there were some differences when compared to other regenerative techniques. This can only be done by reducing the number of confounding factors.

We noticed that the manufacturer suggests root-conditioning prior to the application of EMD and that in all the included RCTs this was done, however, the clinical efficacy of such a procedure has not been validated in any clinical trial.

With respect to the generalization of the findings of this review to a more general population, we have to be very cautious since treatments were administered, in many cases, by experienced clinicians, in some trials smokers were excluded and, moreover, very strict maintenance regimens were employed that are not generally used in routine clinical situations. In addition, the high degree of heterogeneity indicates that even within these 'optimal' conditions, the results of treatments were highly variable. Therefore, defining optimal patient selection, aspects of treatment delivery or maintenance is not possible from this review and this was not one of the aims.

AUTHORS' CONCLUSIONS

Implications for practice

One year after treatment, the application of EMD during surgery showed statistically significant improvements in PAL (1.2 mm) and PPD reduction (0.8 mm) when compared to a placebo or a control. However, the high degree of heterogeneity observed among trials, and the fact that trials judged to be at a lower risk of bias showed less benefit of the use of EMD, suggests that results have to be interpreted with great caution and that the overall PAL gain may represent an overestimation of the actual treatment effect. Approximately six patients needed to be treated with Emdogain to help one gain at least 2 mm of PAL. It is therefore the patient's and clinician's decision whether the clinical gain of periodontal attachment found in the present review is of clinical relevance.

No evidence of major differences between EMD and GTR could be found with the exception of slightly increased REC (0.4 mm) in GTR treated sites. EMD seems simpler to use, may not need antibiotic coverage and does not need a second surgical intervention (if compared with non-resorbable barriers). In addition, no postoperative infections or adverse events were observed with EMD versus two cases of infection (not statistically significant) and significantly more postoperative complications in the GTR group. Therefore if patients and clinicians decide to attempt a regeneration of the lost periodontal tissues, they have to consider risk-benefits and, when comparing EMD with GTR, the EMD treat-

ment might be preferable in light of the above issues. There are currently no trials comparing EMD versus BG to inform decision making.

Implications for research

The main implications for research are:

(1) The reporting and the design of trials could be improved. In particular, authors will find it useful to follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Moher 2001) (www.consort-statement.org/). Unit of analysis issues should be considered at the design stage of the trial. In particular more efforts should be made to blind outcome assessors to the treatment groups.

(2) More information is needed on whether Emdogain may actually save teeth with a questionable prognosis. In order to do so teeth with an expected poor prognosis should be included in the trials and should be followed for long periods, 5 years at least. In addition those responsible to take the decision whether to extract the teeth or not should not be aware of which type of therapy the teeth have received.

(3) It would also be important to evaluate whether patients perceive any aesthetic improvements after regenerative therapies or if they may have a preference for a given therapy, ideally in split-mouth

design trials.

(4) A question which has not been addressed yet is whether the use of root-conditioning is actually useful.

(5) The potential risks/benefits of using systemic antibiotics with EMD should be evaluated in larger trials.

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REFERENCES

References to studies included in this review

Francetti 2004 {published and unpublished data}

Francetti L, Del Fabbro M, Basso M, Testori R, Weinstein R. Enamel matrix proteins in the treatment of intra-bony defects. A prospective 24-month clinical trial. *Journal of Clinical Periodontology* 2004;**31**(1):52–9.

Heijl 1997 {published and unpublished data}

Heijl L, Heden G, Svardstrom G, Ostgren A. EMDOGAIN in the treatment of intrabony periodontal defects. *Journal of Dental Research* 1997;**76** (Special Abstract Issue 1):292.

* Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *Journal of Clinical Periodontology* 1997;**24**(9 Pt 2):705–14.

Okuda 2000 {published and unpublished data}

Okuda K, Miyazaki A, Momose M, Murata M, Yokoyama S, Yonezawa Y. Enamel matrix derivative (EMD) in the treatment of human intrabony periodontal osseous defects. *Journal of Periodontology* 2000;**71**:1913.

* Okuda K, Momose M, Miyazaki A, Murata M, Yokoyama S, Yonezawa Y, et al. Enamel matrix derivative in the treatment of human intrabony osseous defects. *Journal of Periodontology* 2000;**71**(12):1821–8.

Pontoriero 1999 {published and unpublished data}

Pontoriero R, Wennstrom J, Lindhe J. The use of barrier membranes and enamel matrix proteins in the treatment of angular bone defects. A prospective controlled clinical study. *Journal of Clinical Periodontology* 1999;**26**(12):833–40.

Rösing 2005 {published and unpublished data}

Rösing CK, Aass AM, Mavropoulos A, Gjermo P. Clinical and radiographic effects of enamel matrix derivative in the treatment of intrabony periodontal defects: a 12-month longitudinal placebo-controlled clinical trial in adult periodontitis patients. *Journal of Periodontology* 2005;**76**(1):129–33.

Sanz 2004 {published data only}

Sanz M, Tonetti M, Zabalegui I, Blanco J, Rebelo H, Sicilia A, et al. Treatment of intrabony defects with enamel matrix proteins. A multicentre practice-based study. Conference Proceedings of the Pan European Federation of the International Association for Dental Research. Newcastle: Pattinson and Sons, 2002:Abstract No 164.

* Sanz M, Tonetti MS, Zabalegui I, Sicilia A, Blanco J, Rebelo H, et al. Treatment of intrabony defects with enamel matrix proteins or barrier membranes. Results from a multicentre practice-based clinical trial. *Journal of Periodontology* 2004;**75**:726–33.

Silvestri 2000 {published and unpublished data}

Silvestri M, Ricci G, Rasperini G, Sartori S, Cattaneo V. Comparison of treatments of intrabony defects with enamel matrix deriva-

tive, guided tissue regeneration with a nonresorbable membrane and Widman modified flap. A pilot study. *Journal of Clinical Periodontology* 2000;**27**(8):603–10.

Silvestri 2003 {published and unpublished data}

* Silvestri M, Sartori S, Rasperini G, Ricci G, Rota C, Cattaneo V. Comparison of infrabony defects treated with enamel matrix derivative versus guided tissue regeneration with a non-resorbable membrane. *Journal of Clinical Periodontology* 2003;**30**(5):386–93.

Silvestri M, Sartori S, Rasperini G, Ricci G, Rota C, Cattaneo V. The treatment of infrabony defects. Clinical/statistical comparison in cases treated with enamel matrix derivative (Emdogain) versus GTR procedure and Widman modified flap. *Journal of Clinical Periodontology* 2001;**27** (Supplement 1 July):60.

Silvestri M, Sartori S, Rasperini G, Ricci G, Rota C, Cattaneo V. Treatment of infrabony defects with enamel matrix derivative (EMD) or non-resorbable membrane: a randomized controlled multicenter clinical trial. *Journal of Periodontology* 2002;**73**:1402.

Tonetti 2002 {published and unpublished data}

Tonetti MS, Fourmouis I, Suvan J, Cortellini P, Brägger U, Lang NP. Healing, post-operative morbidity and patient perception of outcomes following regenerative therapy of intrabony defects. *Journal of Clinical Periodontology* 2004;**31** (12):1092–8.

* Tonetti MS, Lang NP, Cortellini P, Suvan, JE, Adriaens P, Dubravec D, et al. Enamel matrix proteins in the regenerative therapy of deep intrabony defects. *Journal of Clinical Periodontology* 2002;**29**(4):317–25.

Zucchelli 2002 {published and unpublished data}

Zucchelli G, Bernardi F, Montebugnoli L, De M. Enamel matrix proteins and guided tissue regeneration with titanium-reinforced expanded polytetrafluoroethylene membranes in the treatment of infrabony defects: a comparative controlled clinical trial. *Journal of Periodontology* 2002;**73**(1):3–12.

References to studies excluded from this review

Doertbudak 2000 {published data only}

Doertbudak O, Durstberger G, Bernhart T, Haas R. Treatment of periodontal defects with an enamel matrix derivative (Emdogain). *Journal of Clinical Periodontology* 2000;**27** (Supplement 1 July):61.

Eger 1998 {published data only}

Eger T, Muller H-P. Periodontal regeneration in vertical bone defects with resorbable barriers and enamel-matrix proteins [Parodontale regeneration in vertikalen Knochendefekten mit resorbierbaren Membranen und Schmelz-matrix-proteinen]. *Deutsche Zahnärztliche Zeitschrift* 1998;**53**:590–4.

Francetti 2005 {published data only (unpublished sought but not used)}

Francetti L. A multicenter study to evaluate the clinical eligibility to periodontal treatment with enamel matrix derivative. Preliminary data. *Journal of Clinical Periodontology* 2000;**27** (Supplement 1 July):60.

* Francetti L, Carusi G, Caruso F, Guida L, Matarasso S, Sapelli P, et al. Evaluation of efficacy and eligibility of Emdogain in the treatment of intrabony defects. A 24-month randomized multicenter prospective clinical trial. *Journal of Periodontology* In press.

Froum 2001 {published data only (unpublished sought but not used)}

Froum SJ, Weinberg MA, Rosenberg E, Tarnow D. A comparative study utilizing open flap debridement with and without enamel ma-

trix derivative in the treatment of periodontal intrabony defects: a 12-month re-entry study. *Journal of Periodontology* 2001;**72**(1):25–34.

Ghaffar 2001 {published data only}

Ghaffar KA, Hosny MM, Garrett S. Enamel matrix proteins and biosorbable membranes in the treatment of early onset periodontitis. *Journal of Dental Education* 2001;**80** (January 2001 Special Issue AADR Abstracts):82.

Hagenaars 2004 {published and unpublished data}

Hagenaars S, Louwse PH, Timmerman MF, Van der Velden U, Van der Weijden GA. Soft-tissue wound healing following periodontal surgery and Emdogain application. *Journal of Clinical Periodontology* 2004;**31**(10):850–6.

Lombardo 2000 {published data only}

Lombardo G, Bernini R, Urbani G. Treatment of intrabony periodontal defects using enamel matrix derivative (EMDOGAIN). *Journal of Clinical Periodontology* 2000;**27** (Supplement 1 July):61.

Martinez 2001 {published data only}

Martinez GA, Rodriguez F, Sanz M. Efficacy of enamel matrix proteins derivative (EMDOGAIN) in intra-osseous defects. *Journal of Dental Research* 2001;**80**:1213.

Martu 2000a {published data only}

Martu S, Burlui V, Mocanu C, Forna N. Periodontal regeneration with enamel derivate proteins (Emdogain) - clinical evaluation. *Revista Medico-Chirurgicala a Societatii de Medici si Naturalisti din Iasi* 2000;**104**(4):147–51.

Martu 2000b {published data only}

Martu S, Burlui V, Forna N, Mocanu C. Preliminary account on the use of enamel matrix derivate (Emdogain) in intra-osseous defects. *Journal of Clinical Periodontology* 2000;**27** (Supplement 1 July):61.

Minabe 2002 {published data only}

Minabe M, Kodama T, Kogou T, Takeuchi K, Fushimi H, Sugiyama T, et al. A comparative study of combined treatment with a collagen membrane and enamel matrix proteins for the regeneration of intraosseous defects. *The International Journal of Periodontics and Restorative Dentistry* 2002;**22**(6):595–605.

Mombelli 2005 {published data only}

Mombelli A, Brochut P, Plagnat D, Casagni F, Giannopoulou C. Enamel matrix proteins and systemic antibiotics as adjuncts to non-surgical periodontal treatment: clinical effects. *Journal of Clinical Periodontology* 2005;**32**(3):225–30.

Parashis 2004 {published data only}

* Parashis A, Andronikaki-Faldami A, Tsiklakis K. Clinical and radiographic comparison of three regenerative procedures in the treatment of intrabony defects. *International Journal of Periodontics and Restorative Dentistry* 2004;**24**(1):81–90.

Parashis A, Andronikaki-Faldami A, Tsiklakis K. Comparison of three regenerative procedures in the treatment of intrabony defects: a clinical & radiographic study. *Journal of Clinical Periodontology* 2000;**27** (Supplement 1 July):29.

Sculean 1999 {published data only}

Sculean A, Donos N, Windisch P, Brex M, Gera I, Reich E, et al. Healing of human intrabony defects following treatment with enamel matrix proteins or guided tissue regeneration. *Journal of Periodontal Research* 1999;**34**(6):310–22.

Sculean 2001a {published and unpublished data}

Sculean A, Donos N, Blaes A, Lauer mann M, Reich E, Brex M. Comparison of enamel matrix proteins and bioabsorbable membranes in the treatment of intrabony periodontal defects. A split-mouth study. *Journal of Periodontology* 1999;**70**(3):255–62.

Sculean A, Donos N, Blaes A, Reich E, Brex M. Enamel matrix proteins (Emdogain) and guided tissue regeneration in the treatment of intrabony periodontal defects. A split-mouth clinical study. *Journal of Dental Research* 1998;**77** (June Special Abstract Issue B):924.

Sculean A, Donos N, Blaes A, Reich E, Brex M. Enamel matrix proteins and GTR in the treatment of intrabony defects. Three year results of a split-mouth study. *Journal of Clinical Periodontology* 2000;**27** (Supplement 1 July):62.

* Sculean A, Donos N, Miliuskaite A, Arweiler N, Brex M. Treatment of intrabony defects with enamel matrix proteins or bioabsorbable membranes. A 4-year follow-up split-mouth study. *Journal of Periodontology* 2001;**72**(12):1695–701.

Sculean 2001b {published and unpublished data}

Sculean A, Donos N, Schwarz F, Becker J, Brex M, Arweiler NB. Five-year results following treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. *Journal of Clinical Periodontology* 2004;**31**(7):545–9.

Sculean A, Windisch P, Blaes A, Gera I, Brex M, Donos N. Treatment of intrabony defects with enamel matrix proteins and GTR. *Journal of dental Research* 2000;**79** (Special Abstract Issue 1):171.

* Sculean A, Windisch P, Chiantella GC, Donos N, Brex M, Reich E. Treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. A prospective controlled clinical study. *Journal of Clinical Periodontology* 2001;**28**(5):397–403.

Vandana 2004 {published data only}

Vandana KL, Shah K, Prakash S. Clinical and radiographic evaluation of Emdogain as a regenerative material in the treatment of interproximal vertical defects in chronic and aggressive periodontitis patients. *The International Journal of Periodontics and Restorative Dentistry* 2004;**24**(2):185–91.

Wachtel 2003 {published data only}

Wachtel H, Schenk G, Böhm S, Weng D, Zuhr O, Hürzeler MB. Microsurgical access flap and enamel matrix derivative for the treatment of periodontal intrabony defects: a controlled clinical study. *Journal of Clinical Periodontology* 2003;**30**(6):496–504.

Windisch 2002 {published data only}

Windisch P, Sculean A, Klein F, Toth V, Gera I, Reich E, Eickholz P. Comparison of clinical, radiographic, and histometric measurements following treatment with guided tissue regeneration or enamel matrix proteins in human periodontal defects. *Journal of Periodontology* 2002;**73**(4):409–17.

References to ongoing studies**Grusovin** {published data only}

Grusovin MG, Worthington HV, Esposito M. The efficacy of Emdogain in the treatment of intrabony defects. A triple-blinded placebo-controlled randomized clinical trial. Ongoing.

Additional references**Arweiler 2002**

Arweiler NB, Ausschill TM, Donos N, Sculean A. Antibacterial effect of an enamel matrix protein derivative on in vivo dental biofilm vitality. *Clinical Oral Investigations* 2002;**6**(4):205–9.

Bosshardt 2005

Bosshardt DD, Sculean A, Windisch P, Pjetursson BE, Lang NP. Effects of enamel matrix proteins on tissue formation along the roots of human teeth. *Journal of Periodontal Research* 2005;**40**(2):158–67.

Bowers 1989a

Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, et al. Histologic evaluation of new attachment apparatus formation in humans. Part I. *Journal of Periodontology* 1989;**60**(12):664–74.

Bowers 1989b

Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, et al. Histologic evaluation of new attachment apparatus formation in humans. Part II. *Journal of Periodontology* 1989;**60**(12):675–82.

Bratthall 2001

Bratthall G, Lindberg P, Havemose-Poulsen A, Holmstrup P, Bay L, Soderholm G, et al. Comparison of ready-to-use Emdogain-gel and Emdogain in patients with chronic adult periodontitis. A multicenter clinical trial. *Journal of Clinical Periodontology* 2001;**28**(10):923–9.

Brookes 1995

Brookes SJ, Robinson C, Kirkham J, Bonass WA. Biochemistry and molecular biology of amelogenin proteins of developing dental enamel. *Archives of Oral Biology* 1995;**40**(1):1–14.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Filippi 2001

Filippi A, Pohl Y, von Arx T. Treatment of replacement resorption with Emdogain. Preliminary results after 10 months. *Dental Traumatology* 2001;**17**(3):134–8.

Filippi 2002

Filippi A, Pohl Y, von Arx T. Treatment of resorption with Emdogain. A prospective clinical study. *Dental Traumatology* 2002;**18**(3):138–43.

Follmann 1992

Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology* 1992;**45**:769–73.

Froum 2004

Froum S, Weinberg M, Novak J, Mailhot J, Mellonig J, Van Dyke T, et al. A multicenter study evaluating the sensitization potential of enamel matrix derivative after treatment of two intrabony defects. *Journal of Periodontology* 2004;**75**(7):1001–8.

Giannobile 2003

Giannobile WV, Somerman MJ. Growth and amelogenin-like factors in periodontal wound healing. A systematic review. *Annals of Periodontology* 2003;**8**(1):193–204.

Hammarström 1997a

Hammarström L. Enamel matrix, cementum development and regeneration. *Journal of Clinical Periodontology* 1997;**24**(9 Pt 2):658–68.

Hammarström 1997b

Hammarström L, Heijl L, Gestrelus S. Periodontal regeneration in a buccal dehiscence model in monkeys after application of enamel matrix proteins. *Journal of Clinical Periodontology* 1997;**24**(9 Pt 2):669–77.

Heard 2000

Heard RH, Mellonig JT, Brunsvold MA, Lasho DJ, Meffert RM, Cochran DL. Clinical evaluation of wound healing following multiple exposures to enamel matrix protein derivative in the treatment of intrabony periodontal defects. *Journal of Periodontology* 2000;**71**(11):1715–21.

Kalpidis 2002

Kalpidis CD, Ruben MP. Treatment of intrabony periodontal defects with enamel matrix derivative: a literature review. *Journal of Periodontology* 2002;**73**(1):1360–76.

Mariotti 2003

Mariotti A. Efficacy of chemical root surface modifiers in the treatment of periodontal disease. *Annals of Periodontology* 2003;**8**(1):205–26.

Moher 2001

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *The Lancet* 2001;**357**(9263):1191–4.

Needleman 1999

Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database of Systematic Reviews* 1999, Issue 3. [DOI: DOI: 10.1002/14651858.CD001724]

Needleman 2005

Needleman I, Tucker R, Giedrys-Leeper E, Worthington H. Guided tissue regeneration for periodontal intrabony defects - a Cochrane Systematic Review. *Periodontology 2000* 2005;**37**:106–23.

Reynolds 2003

Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL, Gunsolley JC. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. *Annals of Periodontology* 2003;**8**(1):227–65.

Schjøtt 2005

Schjøtt M, Andreasen JO. Emdogain does not prevent progressive root resorption after replantation of avulsed teeth: a clinical study. *Dental Traumatology* 2005;**21**(1):46–50.

Sculean 2001c

Sculean A, Auschill TM, Donos N, Brex M, Arweiler NB. Effect of an enamel matrix protein derivative (Emdogain) on ex vivo dental plaque vitality. *Journal of Clinical Periodontology* 2001;**28**(11):1074–8.

Sculean 2001d

Sculean A, Blaes A, Arweiler N, Reich E, Donos N, Brex M. The effect of postsurgical antibiotics on the healing of intrabony defects following treatment with enamel matrix proteins. *Journal of Periodontology* 2001;**72**(2):190–5.

Spahr 2002

Spahr A, Lyngstadaas SP, Boeckh C, Andersson C, Podbielski A, Haller B. Effect of the enamel matrix derivative Emdogain on the growth of periodontal pathogens in vitro. *Journal of Clinical Periodontology* 2002;**29**(1):62–72.

Trombelli 2002

Trombelli L, Heitz-Mayfield LJ, Needleman I, Moles D, Scabbia A. A systematic review of graft materials and biological agents for periodontal intraosseous defects. *Journal of Clinical Periodontology* 2002;**29** Suppl 3:117–35.

Tu 2005

Tu Y-K, Maddick I, Gilthorpe MS. Evaluating the quality of active-control equivalence trials in dental research. *Journal of Dental Research* 2005 (submitted).

Venezia 2004

Venezia E, Goldstein M, Boyan BD, Schwartz Z. The use of enamel matrix derivative in the treatment of periodontal defects: a literature review and meta-analysis. *Critical Reviews in Oral Biology and Medicine* 2004;**15**(6):382–402.

Wennström 2002

Wennström JL, Lindhe J. Some effects of enamel matrix proteins on wound healing in the dento-gingival region. *Journal of Clinical Periodontology* 2002;**29**(1):9–14.

Zetterström 1997

Zetterström O, Andersson C, Eriksson L, Fredriksson A, Friskopp J, Heden G, et al. Clinical safety of enamel matrix derivative (EMDOGAIN) in the treatment of periodontal defects. *Journal of Clinical Periodontology* 1997;**24**(9 Pt 2):697–704.

References to other published versions of this review**Esposito 2003**

Esposito M, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: DOI: 10.1002/14651858.CD003875]

Esposito 2004

Esposito M, Coulthard P, Thomsen P, Worthington HV. Enamel matrix derivative for periodontal tissue regeneration in treatment of intrabony defects: a Cochrane systematic review. *Journal of Dental Education* 2004;**68**(8):834–44.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Francetti 2004

Methods	2-year follow-up parallel group study including 2 groups with 24 patients in total. No drop outs at 1 year. Author informed us that the allocation to the intervention groups was concealed. During surgery, after debridement a sequentially numbered sealed opaque envelope containing the randomization code was opened.	
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with PPD greater or equal to 6 mm and intra-bony depth (IBD) greater or equal to 4 mm. 1-, 2- and 3-walls defects were included. Teeth with degree III mobility, necrotic, with incongruous reconstructions or under occlusal trauma were excluded. Patients should not have been treated for periodontitis in the last 3 years. Age ranging between 30 and 66; 11 males and 13 females recruited at one university dental clinic.	
Interventions	Emdogain versus flap surgery.	
Outcomes	FMPS (full mouth plaque score), FMBS (full mouth bleeding score). For experimental teeth only: PAL, PPD, IBD on standardized intraoral radiographs at baseline, 1- and 2-year. Tooth loss, postoperative infections and adverse events. Additional intrasurgical measurements were taken. 1-year data used.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Heijl 1997

Methods	3-year follow-up split-mouth study including 33 patients. Three drop outs at 16 months (tooth extractions in 2 cases and accident for 1 patient). It was reported in the paper "At the time of periodontal surgery, and only after the first surgical site was fully prepared, the envelope containing the randomization code was opened to expose treatment assignments".	
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with PPD greater or equal to 6 mm and IBD greater or equal to 4 mm. 1-, 2- and 3-wall defects were included. All patients had received systematic periodontal treatments (repeated debridement in some cases supplemented with antimicrobial and surgical treatment over long periods of time). Age ranging between 33 and 68; 7 males and 26 females recruited at 3 specialist clinics.	
Interventions	Emdogain versus flap surgery and placebo.	

Heijl 1997 (Continued)

Outcomes	FMPS and for experimental teeth only: BOP, PAL, PPD, IBD on standardized intraoral radiographs at baseline, 8-, 16-month and 3-years. Tooth loss, postoperative infections and adverse events. Additional intrasurgical measurements were taken. 1-year data used.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Okuda 2000

Methods	1-year follow-up split-mouth study including 16 patients. No drop outs at 1 year. Author informed us that allocation to intervention group was concealed, but did not explain how.	
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with PPD greater or equal to 6 mm and IBD greater or equal to 4 mm in presence of 2 mm of keratinized gingiva on the buccal aspect. Patients should not have been treated for periodontitis in the last 2 years. No antibiotics in the previous 6 months. Smokers were excluded. Age ranging between 45 and 67; 8 males and 8 females recruited at one university dental clinic.	
Interventions	Emdogain versus flap surgery and placebo.	
Outcomes	FMPS and FMBS. For experimental teeth only: vertical relative attachment gain, tooth mobility, PAL, PPD, REC, IBD on standardized intraoral radiographs measured as radiographic bone density at baseline and 1-year. Tooth loss, postoperative infections and adverse events. 1-year data used.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pontoriero 1999

Methods	1-year follow-up split-mouth study including 4 parallel arms with 40 patients in total. Only 2 parallel arms evaluated. No drop outs at 1 year. Author informed us that allocation to intervention group was concealed, but did not explain how.	
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Pontoriero 1999 (Continued)

Participants	Patients in good general health and motivated for good oral hygiene. Teeth with PPD greater or equal to 6 mm and IBD greater or equal to 3 mm. In 2 groups, however, defect shallower than 3 mm were included and therefore were excluded from the present review. Age ranging between 32-61; 15 males and 25 females recruited in one private practice.	
Interventions	Four split-mouth groups were included: (1) GTR with Guidor resorbable barriers versus flap surgery; (2) GTR with Resolut resorbable barriers versus flap surgery; (3) GTR with Gore-Tex non-resorbable barriers versus flap surgery; (4) Emdogain versus flap surgery and placebo. We analyzed only group (3) and (4) since in the other 2 groups defect shallower than 3 mm were included.	
Outcomes	FMPS, BOP and for experimental teeth only: PAL, PPD, REC at baseline and 1-year. Tooth loss and postoperative infections. Additional intrasurgical measurements were taken. 1-year data used.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rösing 2005

Methods	1-year follow-up split-mouth study including 16 patients. No drop outs at 1 year. Randomization of the site was decided with the flip of a coin after debridement of both sites and application of the EDTA solution.	
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with IBD greater or equal to 3 mm and wider than 2 mm on intraoral radiographs. Age ranging between 29-54; patients recruited in one University dental clinic.	
Interventions	Emdogain versus flap surgery and placebo.	
Outcomes	FMPS and FMBS For experimental teeth only: BOP, PAL, PPD, IBD on standardized intraoral radiographs at baseline, 6-month, and 1-year. Tooth loss, postoperative infections and adverse events. Additional intrasurgical measurements were taken. 1-year data used.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sanz 2004

Methods	1-year follow-up parallel group study including 2 groups with 72 patients in total. 5 drop outs for unknown reasons and from unspecified groups. In the paper it is reported that "Clinicians were not aware of treatment allocation until after root debridement."
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with IBD greater or equal to 3 mm in presence of 2 to 3 mm of keratinized gingiva on the buccal aspect. Heavy smokers (>20 cigarettes per day) were excluded. 1-, 2- and 3-walls defects were included. Age ranging between 43 to 61; females were 54.3% in the test and 53.1% in the control groups. Patients were recruited both from university dental clinics and private practices.
Interventions	Emdogain versus GTR with Resolut resorbable barriers.
Outcomes	FMPS and FMBS. For experimental teeth only: PAL, PPD, REC at baseline and 1-year. Postoperative infections. Additional intrasurgical measurements were taken. 1-year data used.
Notes	100% of postoperative complications (flap dehiscence, suppuration) in the GTR group versus 6% in the Emdogain group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Silvestri 2000

Methods	1-year follow up parallel-group study including 3 groups with 30 patients in total. No drop outs at 1 year. Author informed us that group allocation was not concealed
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with PPD greater or equal to 6 mm and IBD greater or equal to 4 mm. Smokers were excluded. Age ranging between 37 and 59; 11 males and 19 females recruited in one university dental clinic and several private practices.
Interventions	Emdogain versus GTR with Gore-Tex non-resorbable barriers versus flap surgery.
Outcomes	FMPS and FMBS. For experimental teeth only: PAL, PPD, REC at baseline and 1-year. Tooth loss and postoperative infections. 1-year data used.
Notes	

Risk of bias

Item	Authors' judgement	Description
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Silvestri 2000 (Continued)

Allocation concealment?	No	C - Inadequate
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Silvestri 2003

Methods	1-year follow up parallel-group study including 2 groups with 100 patients in total. Four drop outs at 1 year. Two patients (1 from each group) did not follow the postsurgical controls and 2 patients (1 from each group) did not show up at the 1-year examination for personal reasons. Author informed us that allocation to intervention group was concealed, but did not explain how.
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with PPD greater or equal to 6 mm and IBD greater or equal to 4 mm. Smokers (> 10 cigarettes per day) were excluded. 1-, 2- and 3-walls defects were included. Age ranging between 39 and 58; 45 males and 53 females recruited in one university dental clinic and several private practices.
Interventions	Emdogain versus GTR with Gore-Tex non-resorbable barriers.
Outcomes	FMPS and FMBS. For experimental teeth only: PAL, PPD, REC at baseline and 1-year. Tooth loss and postoperative infections. Additional intrasurgical measurements were taken. 1-year data used.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Tonetti 2002

Methods	1-year follow up parallel-group study including 2 groups with 172 patients in total. Six drop outs at 1 year. Three patients withdrew consent before surgery. Three patients (2 from the test and 1 from the control group) were unable to comply with the follow up for reasons independent from the treatments. Author informed us that the allocation to the intervention groups was concealed. During surgery, after debridement, a sealed opaque envelope containing the randomization code was opened.
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with IBD greater or equal to 3 mm in presence of 2 to 3 mm of keratinized gingiva on the buccal aspect. Heavy smokers (> 20 cigarettes per day) were excluded. 1-, 2- and 3-walls defects were included. Age ranging between 39 and 57; females were 54.2% in the test and 60.2% in the control groups. Patients were recruited both from university dental clinics and private practices.
Interventions	Emdogain versus flap surgery.

Tonetti 2002 (Continued)

Outcomes	FMPS and FMBS. For experimental teeth only: PAL, PPD, REC at baseline and 1-year. Tooth loss and postoperative infections. Additional intrasurgical measurements were taken. 1-year data used. Postoperative morbidity, patient satisfaction, aesthetics and several other patient-centred outcomes were evaluated.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Zucchelli 2002

Methods	1-year follow up parallel-group study including 3 groups with 90 patients in total. No drop outs at 1 year. Author informed us that allocation to intervention group was concealed, but did not explain how.	
Participants	Patients in good general health and motivated for good oral hygiene. Teeth with PPD greater or equal to 7 mm and IBD greater or equal to 3 mm. Heavy smokers (more than 20 cigarettes per day) were excluded. No antibiotics in the previous 6 months. Age ranging between 39 and 57; 30 males and 61 females. Patients were recruited from one university dental clinic and several private practices.	
Interventions	Emdogain versus GTR with Gore-Tex titanium-reinforced non-resorbable barriers versus flap surgery.	
Outcomes	FMPS and FMBS. For experimental teeth only: PAL, PPD, REC at baseline and 1-year. Tooth loss and postoperative infections. Additional intrasurgical measurements were taken. 1-year data used.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

FMBS = full mouth bleeding score
 FMPS = full mouth plaque score
 GTR = guided tissue regeneration
 IBD = intrabony depth
 PAL = probing attachment level
 PPD = probing pocket depth
 REC = gingival recession

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

Doertbudak 2000	Authors informed us that trial was a CCT.
Eger 1998	Not a RCT.
Francetti 2005	Multicentre study comparing Emdogain versus control, with data presented on site not patient basis. The authors have replied to a request for further information however have not supplied this.
Froum 2001	Trial comparing Emdogain versus control. This study was designed as a split-mouth study, and the data are presented for 53 defects in Emdogain group and 31 defects in control, in 23 subjects. The presentation of the data does not include an estimate of the standard error for the paired data and cannot therefore be included in the meta-analyses for this review. The authors have replied to a request for further information however they have not supplied the required standard errors, or variance estimates, despite repeated requests as suggested by one of the referees.
Ghaffar 2001	Insufficient data presented. Written to author and sponsor but no reply to letters.
Hagenaars 2004	Trial designed to evaluate the early postoperative phase (up to 8 weeks). Written to authors asking whether longer follow up was planned, but they replied that this was not their intention.
Lombardo 2000	Judged to be a CCT. No reply to letter.
Martinez 2001	Insufficient data presented. No reply to letter.
Martu 2000a	Judged to be a CCT. No reply to letter. Possibly same trial as Marthu 2000b.
Martu 2000b	Judged to be a CCT. No reply to letter. Possibly same trial as Marthu 2000a.
Minabe 2002	Parallel-group study with more than one site per patient treated in the EMD group. We are unable to extract data at a patient level. Authors did not respond to our request for further data.
Mombelli 2005	Included patients with less than 3 mm intrabony defect component.
Parashis 2004	Authors informed us that trial was a CCT.
Sculean 1999	6-month study designed so that teeth are extracted after 6 months. Unclear if this is the same study as Windisch 2002.
Sculean 2001a	Included patients with less than 3 mm intrabony defect component.
Sculean 2001b	Included patients with less than 3 mm intrabony defect component.
Vandana 2004	Unclear whether RCT or CCT. Authors replied it was a RCT. Trial excluded since the follow up was 9 months instead of 1 year and the intrabony components of some defect was less than 3 mm.

(Continued)

Wachtel 2003	Split-mouth study with more than one site per quadrant treated with one intervention. We were unable to extract simple 'paired data' for each patient and the authors did not respond to our request for further data.
Windisch 2002	6-month study designed so that teeth are extracted after 6 months. Unclear if this is the same study as Sculean 1999.

Characteristics of ongoing studies [ordered by study ID]

Grusovin

Trial name or title	The efficacy of Emdogain in the treatment of intrabony defects. A triple blind, placebo controlled randomized clinical trial.
Methods	
Participants	10 patients per group.
Interventions	Emdogain versus placebo (propylene glycol alginate)
Outcomes	Tooth loss; changes in probing attachment levels; changes in probing pocket depth, gingival recession, bone sounding, radiographic marginal bone changes on standardised intraoral radiographs, postoperative complications, side effects, patient evaluation of aesthetics.
Starting date	October 2004.
Contact information	Maria Gabriella Grusovin: gabri.grusovin@tiscali.it
Notes	

DATA AND ANALYSES

Comparison 1. Emdogain versus Control: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tooth Loss	8	418	risk ratio (Random, 95% CI)	Not estimable
1.1 Parallel group	4	270	risk ratio (Random, 95% CI)	Not estimable
1.2 Split mouth	4	148	risk ratio (Random, 95% CI)	Not estimable
2 PAL	8	412	mean difference (Random, 95% CI)	1.20 [0.71, 1.69]
2.1 Parallel group	4	270	mean difference (Random, 95% CI)	1.72 [0.81, 2.62]
2.2 Split mouth	4	142	mean difference (Random, 95% CI)	0.76 [0.48, 1.04]
3 PAL < 2 mm	5	332	risk ratio (Random, 95% CI)	0.48 [0.29, 0.80]
4 PPD	8	412	Mean difference (Fixed, 95% CI)	0.77 [0.54, 1.00]
4.1 Parallel group	4	270	Mean difference (Fixed, 95% CI)	0.86 [0.55, 1.17]
4.2 Split mouth	4	142	Mean difference (Fixed, 95% CI)	0.66 [0.31, 1.00]
5 REC	5	298	mean difference (Random, 95% CI)	0.04 [-0.32, 0.40]
5.1 Parallel group	3	246	mean difference (Random, 95% CI)	0.15 [-0.35, 0.66]
5.2 Split mouth	2	52	mean difference (Random, 95% CI)	-0.15 [-0.57, 0.26]
6 Marginal bone level	2	90	mean difference (Random, 95% CI)	1.08 [-0.72, 2.89]
6.1 Parallel group	0	0	mean difference (Random, 95% CI)	Not estimable
6.2 Split mouth	2	90	mean difference (Random, 95% CI)	1.08 [-0.72, 2.89]
7 Postoperative infection	7	388	risk ratio (Random, 95% CI)	Not estimable
7.1 Parallel group	4	270	risk ratio (Random, 95% CI)	Not estimable
7.2 Split mouth	3	118	risk ratio (Random, 95% CI)	Not estimable
8 Aesthetics	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 Parallel group	1		Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 2. Emdogain versus GTR: 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tooth loss	4	216	risk ratio (Random, 95% CI)	Not estimable
1.1 Parallel group	4	216	risk ratio (Random, 95% CI)	Not estimable
1.2 Split mouth	0	0	risk ratio (Random, 95% CI)	Not estimable
2 PAL	5	263	mean difference (Fixed, 95% CI)	-0.20 [-0.59, 0.20]
2.1 Parallel group	5	263	mean difference (Fixed, 95% CI)	-0.20 [-0.59, 0.20]
2.2 Split mouth	0	0	mean difference (Fixed, 95% CI)	Not estimable
3 PPD	5	263	mean difference (Random, 95% CI)	-0.49 [-1.23, 0.26]
3.1 Parallel group	5	263	mean difference (Random, 95% CI)	-0.49 [-1.23, 0.26]
3.2 Split mouth	0	0	mean difference (Random, 95% CI)	Not estimable
4 REC	4	167	mean difference (Random, 95% CI)	0.39 [0.13, 0.66]
4.1 Parallel group	4	167	mean difference (Random, 95% CI)	0.39 [0.13, 0.66]
4.2 Split mouth	0	0	mean difference (Random, 95% CI)	Not estimable
5 Postoperative infection	4	218	risk ratio (Random, 95% CI)	0.20 [0.01, 4.09]
5.1 Parallel group	4	218	risk ratio (Random, 95% CI)	0.20 [0.01, 4.09]

5.2 Split mouth	0	0	risk ratio (Random, 95% CI)	Not estimable
6 Postoperative complications	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.02, 0.25]
6.1 Parallel group	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.02, 0.25]

Analysis 1.1. Comparison 1 Emdogain versus Control: 1 year, Outcome 1 Tooth Loss.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

Outcome: 1 Tooth Loss

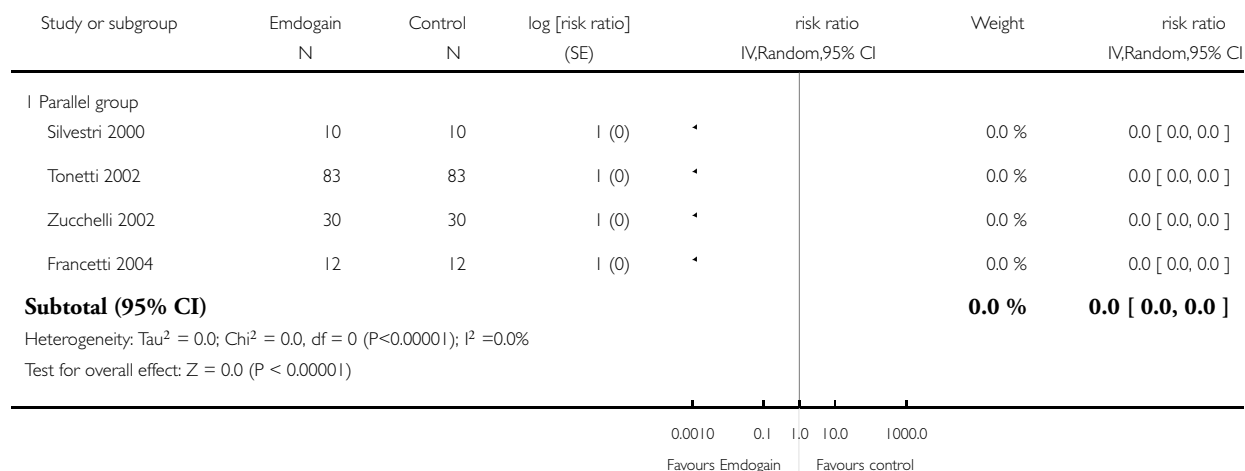
Study or subgroup	Emdogain N	Control N	log [risk ratio] (SE)	risk ratio IV,Random,95% CI	Weight	risk ratio IV,Random,95% CI
1 Parallel group						
Silvestri 2000	10	10	1 (0)	•	0.0 %	0.0 [0.0, 0.0]
Tonetti 2002	83	83	1 (0)	•	0.0 %	0.0 [0.0, 0.0]
Zucchelli 2002	30	30	1 (0)	•	0.0 %	0.0 [0.0, 0.0]
Francetti 2004	12	12	1 (0)	•	0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)					0.0 %	0.0 [0.0, 0.0]
Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, df = 0 (P<0.00001); I ² = 0.0%						
Test for overall effect: Z = 0.0 (P < 0.00001)						
2 Split mouth						
Heijl 1997	32	32	0 (0)	•	0.0 %	0.0 [0.0, 0.0]
Pontoriero 1999	16	16	0 (0)	•	0.0 %	0.0 [0.0, 0.0]
Okuda 2000	10	10	0 (0)	•	0.0 %	0.0 [0.0, 0.0]
Rsing 2005	16	16	0 (0)	•	0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)					0.0 %	0.0 [0.0, 0.0]
Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, df = 0 (P<0.00001); I ² = 0.0%						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Total (95% CI)					0.0 %	0.0 [0.0, 0.0]
Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, df = 0 (P<0.00001); I ² = 0.0%						
Test for overall effect: Z = 0.0 (P < 0.00001)						

0.0010 0.1 1.0 10.0 100.0
Favours Emdogain Favours control

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

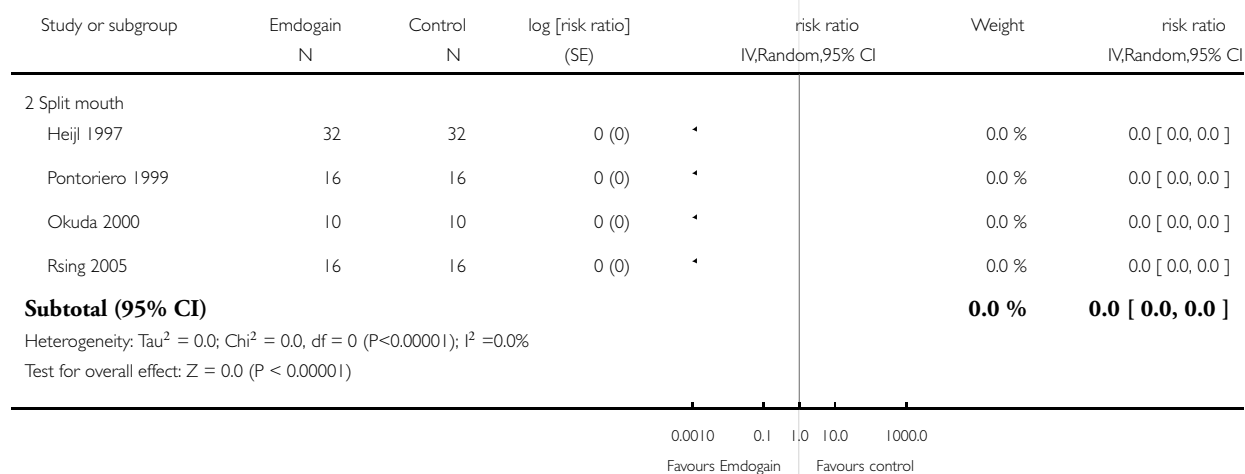
Outcome: 1 Tooth Loss



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

Outcome: 1 Tooth Loss

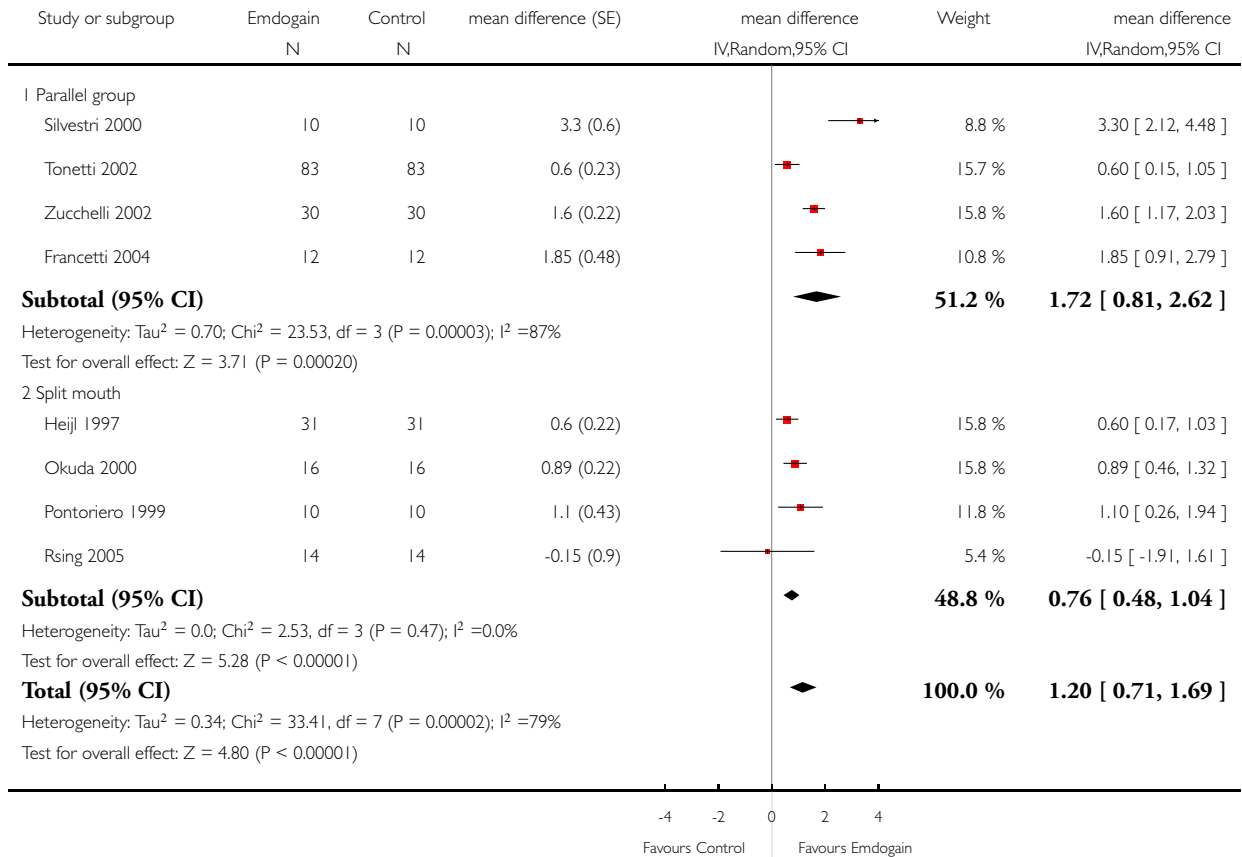


Analysis 1.2. Comparison 1 Emdogain versus Control: 1 year, Outcome 2 PAL.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

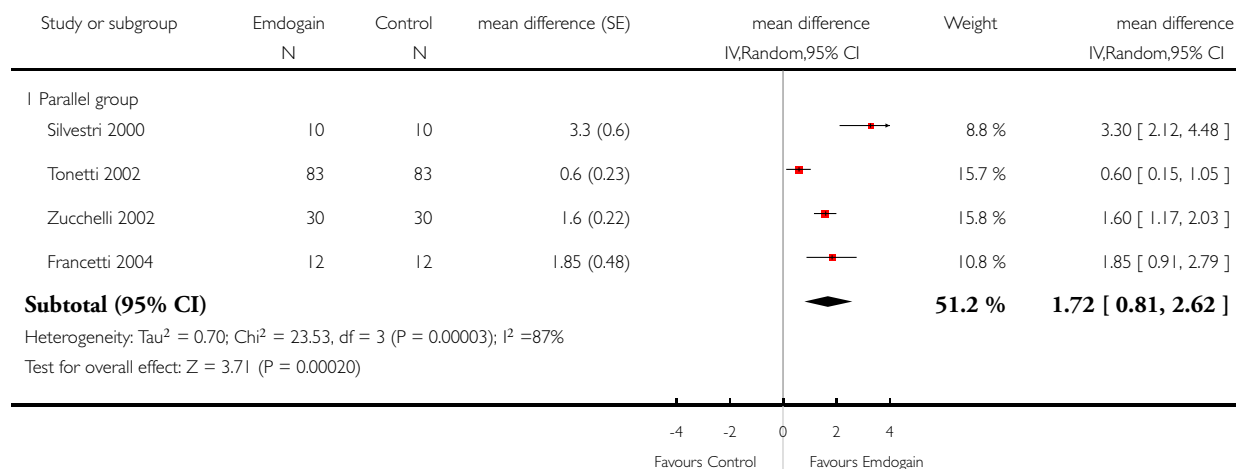
Outcome: 2 PAL



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

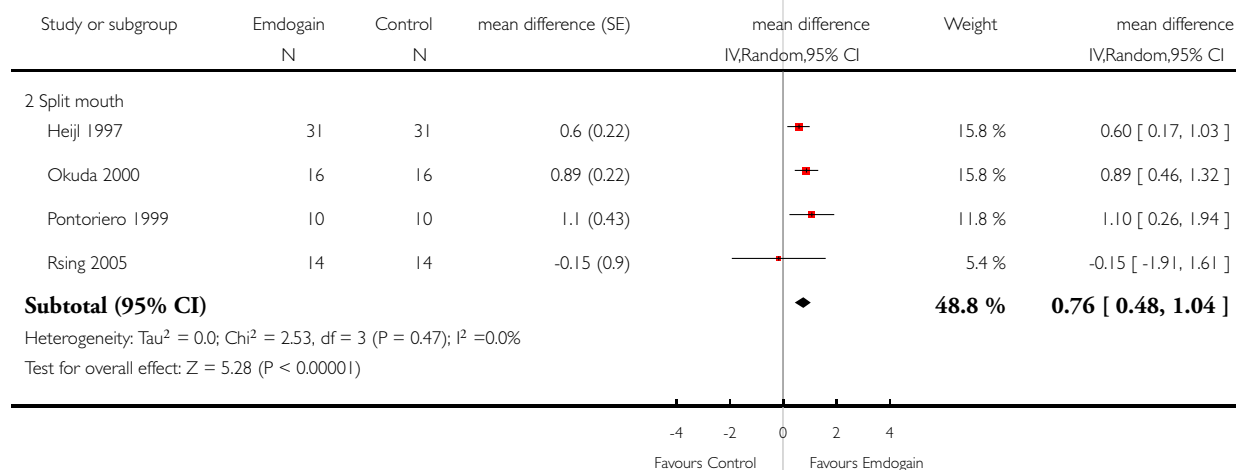
Outcome: 2 PAL



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

Outcome: 2 PAL

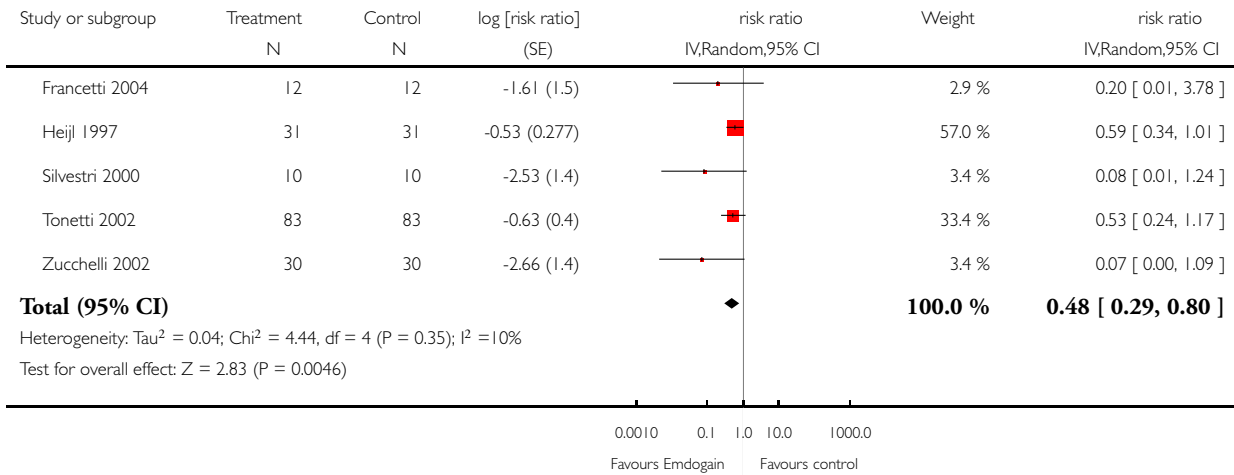


Analysis I.3. Comparison I Emdogain versus Control: 1 year, Outcome 3 PAL < 2 mm.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: I Emdogain versus Control: 1 year

Outcome: 3 PAL < 2 mm

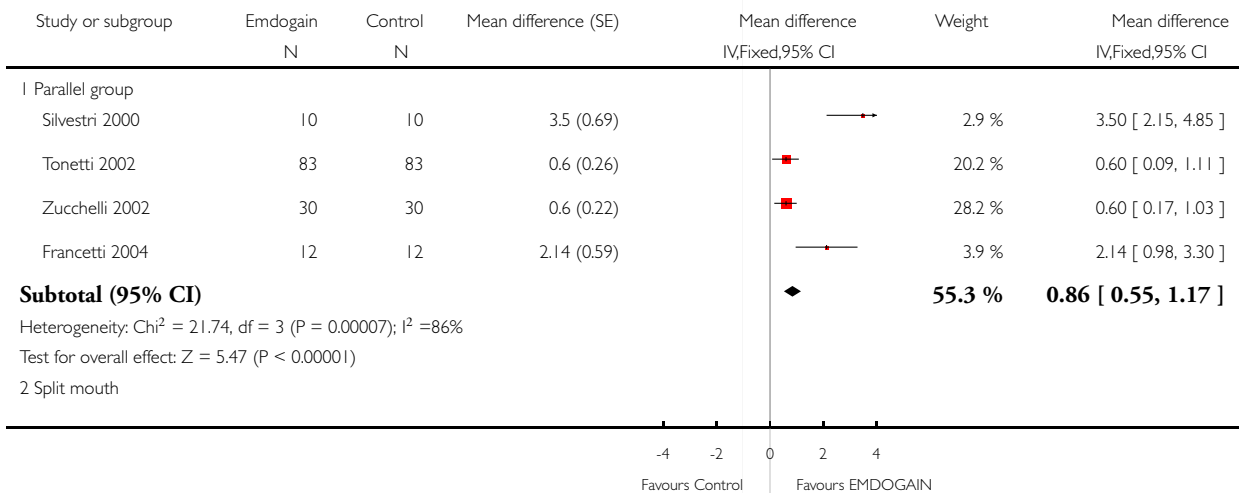


Analysis I.4. Comparison I Emdogain versus Control: 1 year, Outcome 4 PPD.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

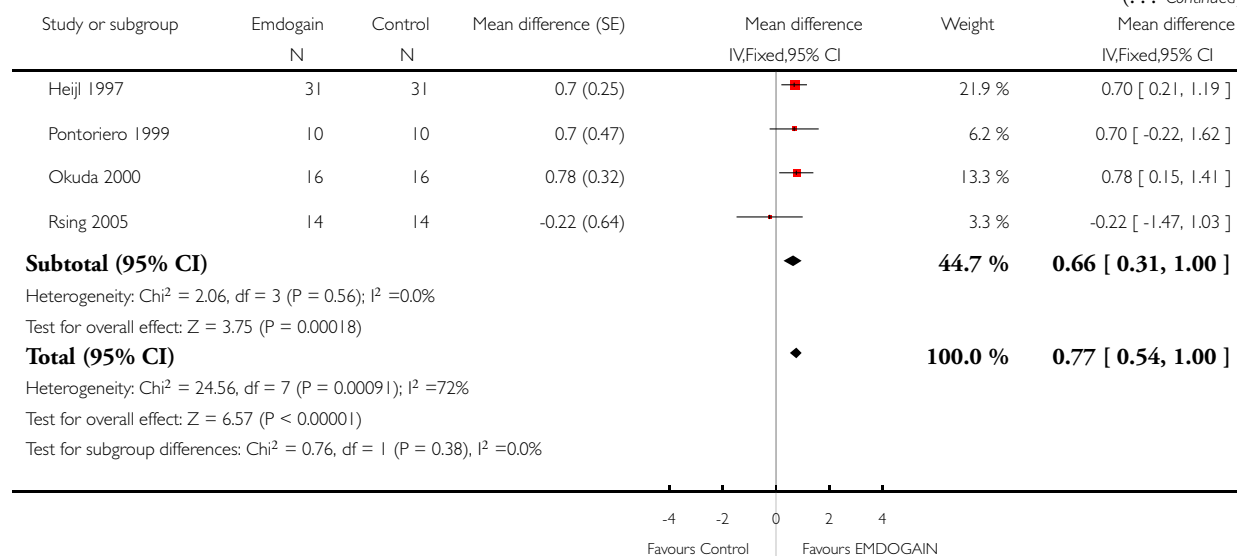
Comparison: I Emdogain versus Control: 1 year

Outcome: 4 PPD



(Continued ...)

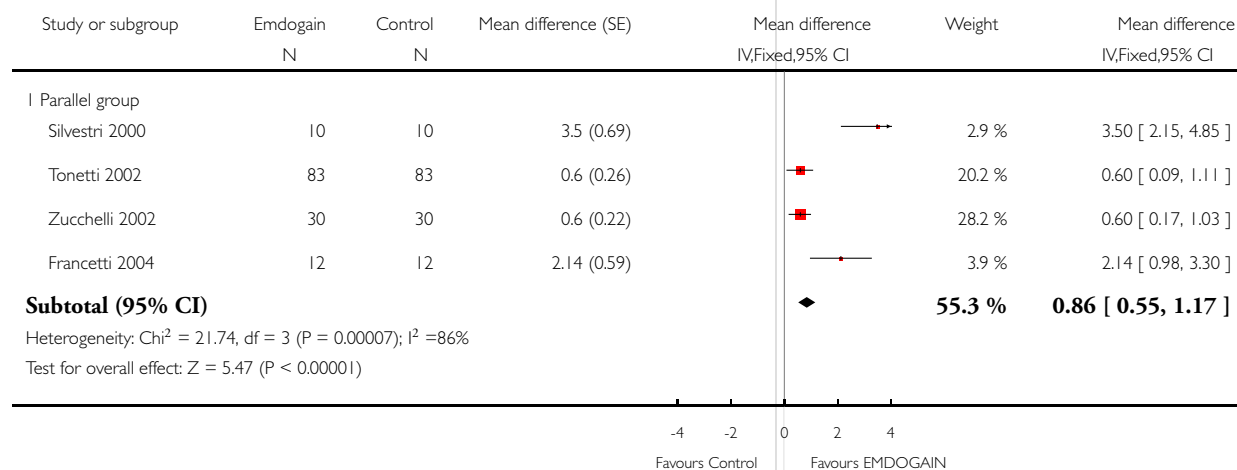
(... Continued)



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: I Emdogain versus Control: I year

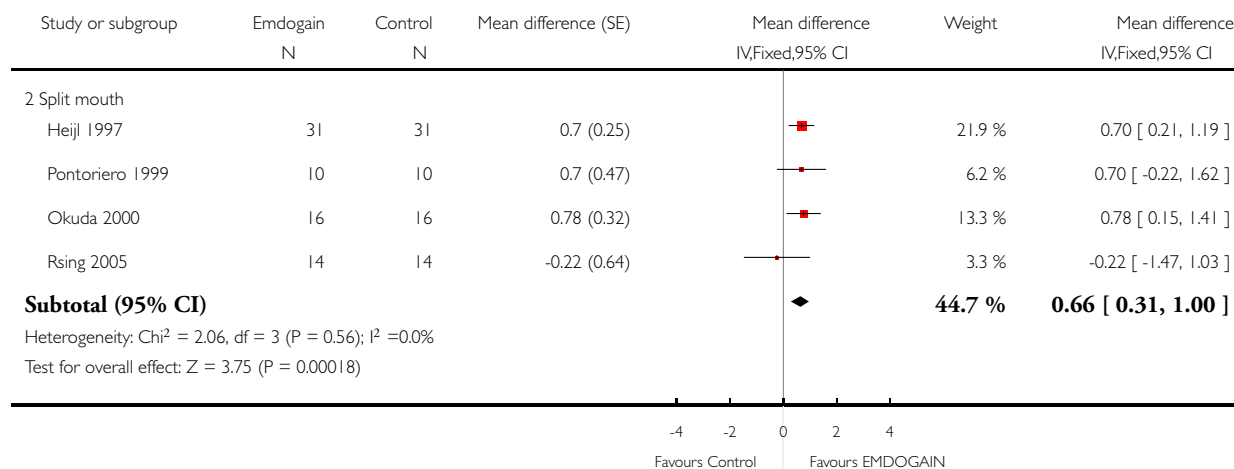
Outcome: 4 PPD



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: I Emdogain versus Control: 1 year

Outcome: 4 PPD

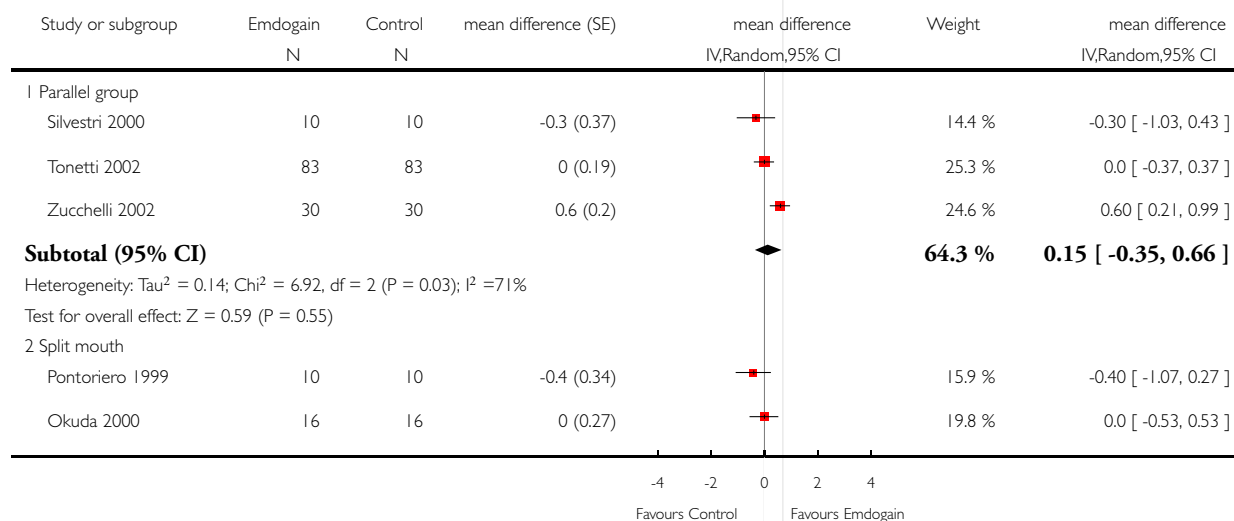


Analysis 1.5. Comparison I Emdogain versus Control: 1 year, Outcome 5 REC.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

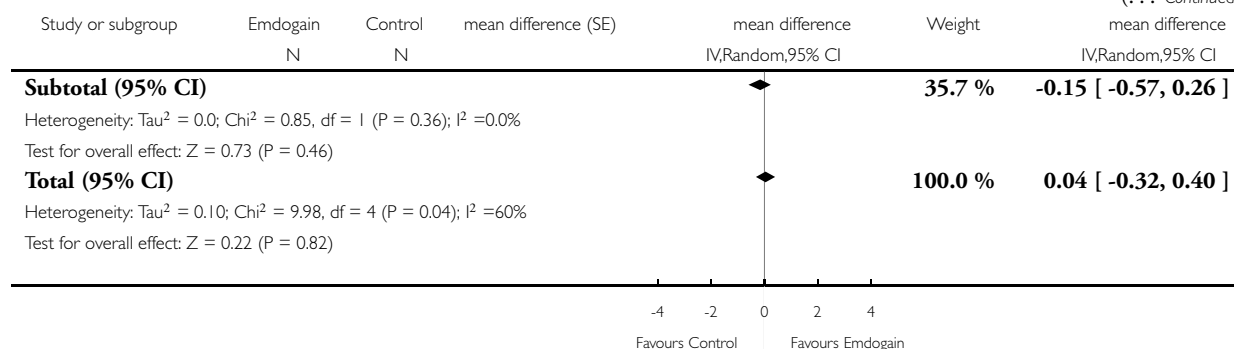
Comparison: I Emdogain versus Control: 1 year

Outcome: 5 REC



(Continued . . .)

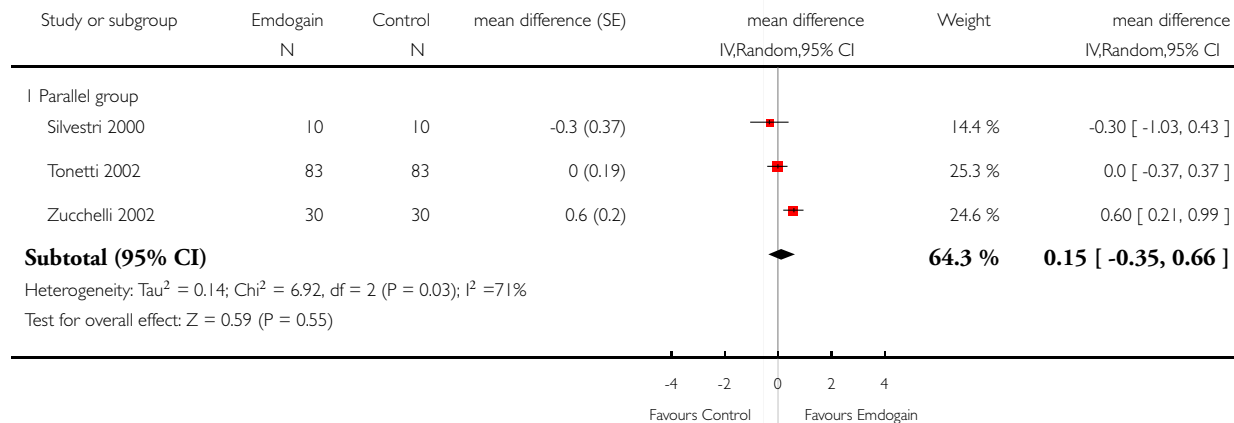
(... Continued)



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

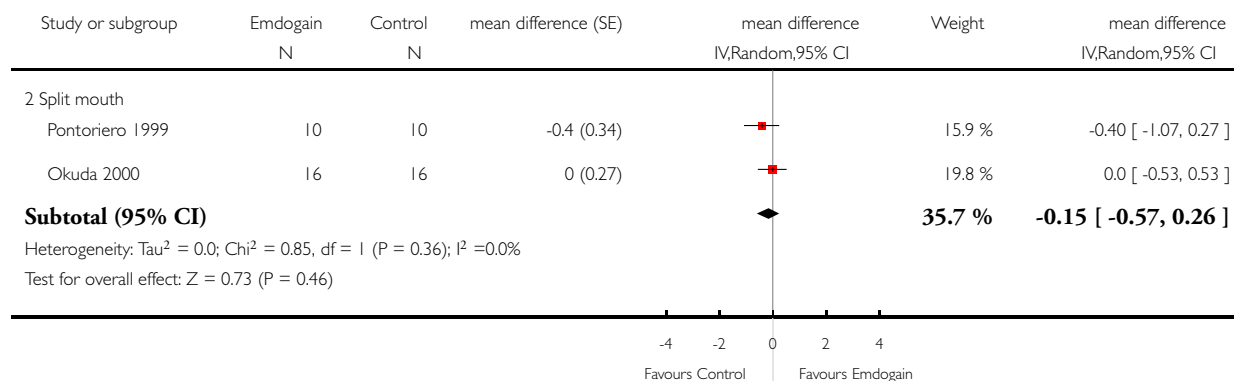
Outcome: 5 REC



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: I Emdogain versus Control: 1 year

Outcome: 5 REC

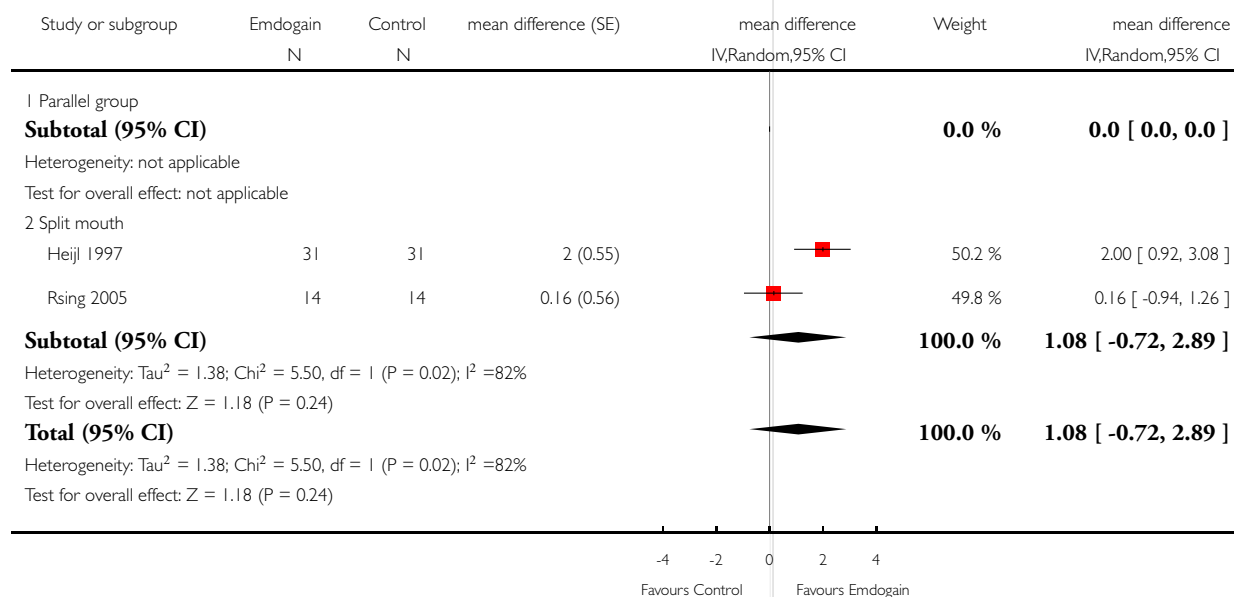


Analysis 1.6. Comparison I Emdogain versus Control: 1 year, Outcome 6 Marginal bone level.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: I Emdogain versus Control: 1 year

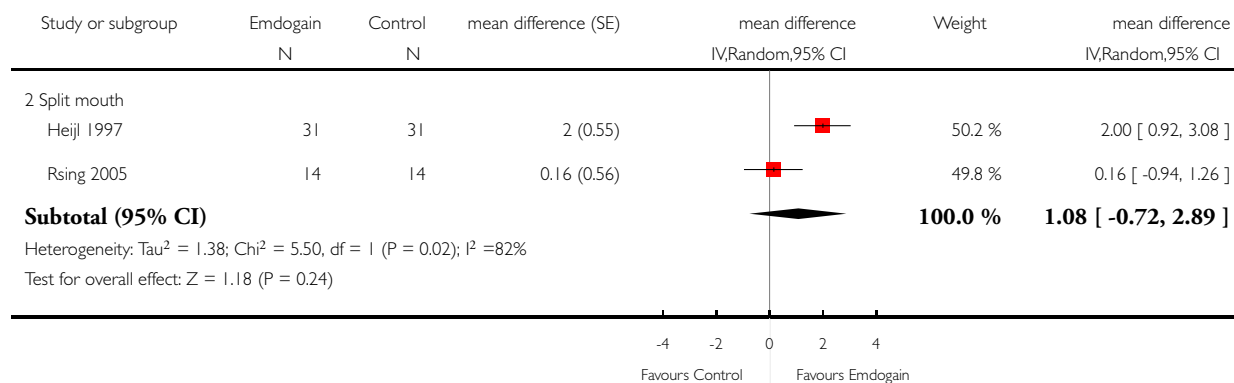
Outcome: 6 Marginal bone level



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

Outcome: 6 Marginal bone level

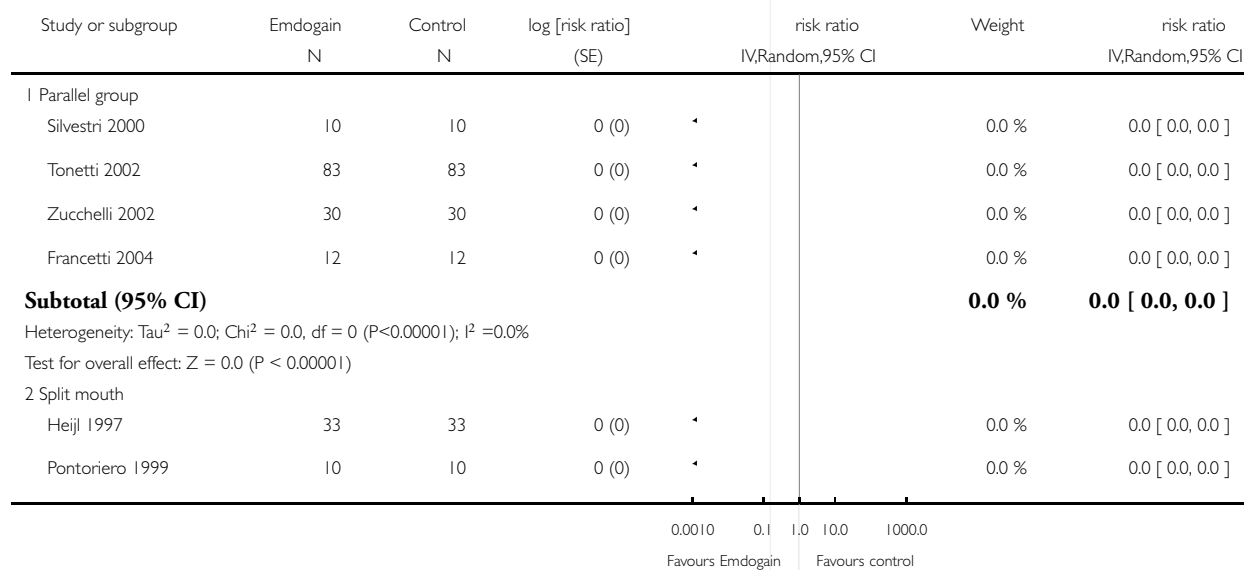


Analysis 1.7. Comparison 1 Emdogain versus Control: 1 year, Outcome 7 Postoperative infection.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

Outcome: 7 Postoperative infection



(Continued . . .)

(. . . Continued)

Study or subgroup	Emdogain N	Control N	log [risk ratio] (SE)	risk ratio IV,Random,95% CI	Weight	risk ratio IV,Random,95% CI
Okuda 2000	16	16	0 (0)		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)					0.0 %	0.0 [0.0, 0.0]
Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, df = 0 (P<0.00001); I ² =0.0%						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Total (95% CI)					0.0 %	0.0 [0.0, 0.0]
Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, df = 0 (P<0.00001); I ² =0.0%						
Test for overall effect: Z = 0.0 (P < 0.00001)						

0.0010 0.1 1.0 10.0 1000.0
Favours Emdogain Favours control

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

Outcome: 7 Postoperative infection

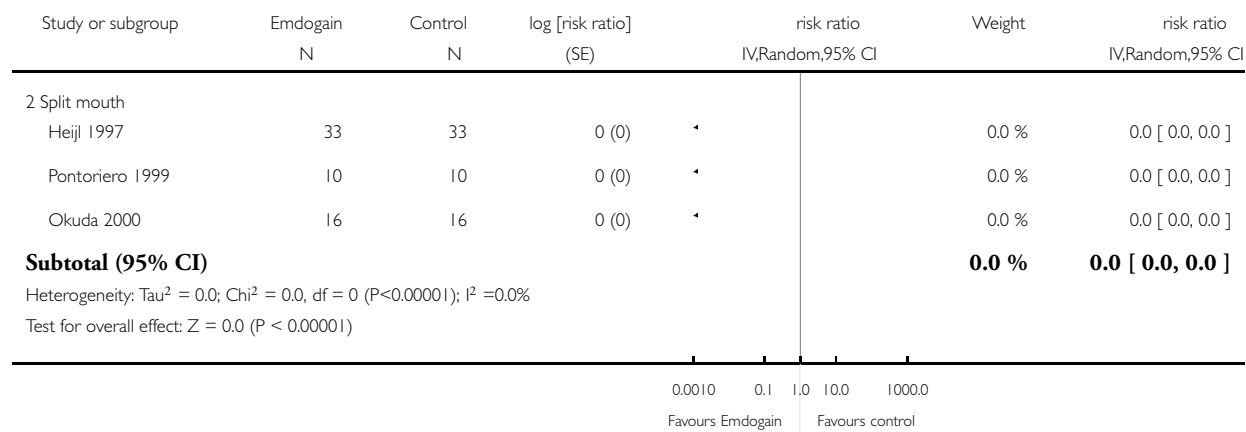
Study or subgroup	Emdogain N	Control N	log [risk ratio] (SE)	risk ratio IV,Random,95% CI	Weight	risk ratio IV,Random,95% CI
I Parallel group						
Silvestri 2000	10	10	0 (0)		0.0 %	0.0 [0.0, 0.0]
Tonetti 2002	83	83	0 (0)		0.0 %	0.0 [0.0, 0.0]
Zucchelli 2002	30	30	0 (0)		0.0 %	0.0 [0.0, 0.0]
Francetti 2004	12	12	0 (0)		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)					0.0 %	0.0 [0.0, 0.0]
Heterogeneity: Tau ² = 0.0; Chi ² = 0.0, df = 0 (P<0.00001); I ² =0.0%						
Test for overall effect: Z = 0.0 (P < 0.00001)						

0.0010 0.1 1.0 10.0 1000.0
Favours Emdogain Favours control

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: I Emdogain versus Control: 1 year

Outcome: 7 Postoperative infection

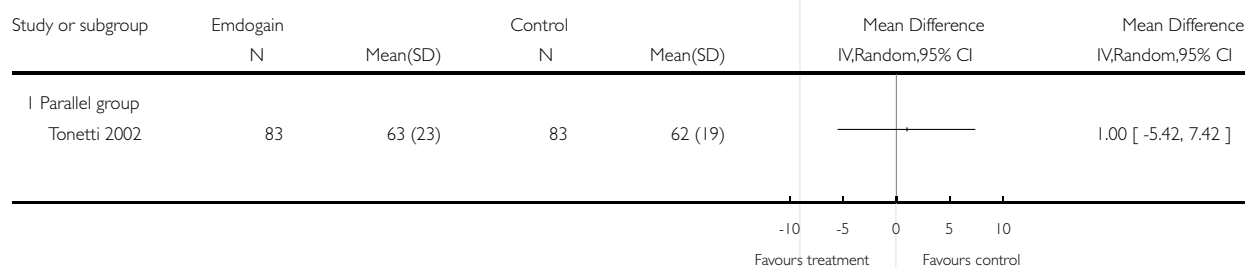


Analysis 1.8. Comparison I Emdogain versus Control: 1 year, Outcome 8 Aesthetics.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: I Emdogain versus Control: 1 year

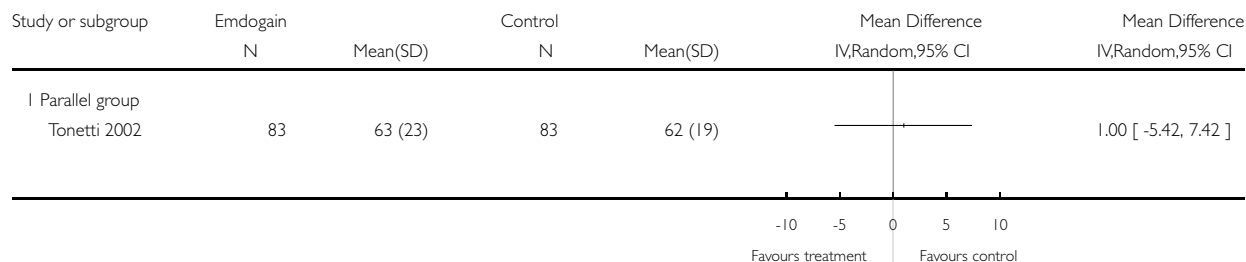
Outcome: 8 Aesthetics



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 1 Emdogain versus Control: 1 year

Outcome: 8 Aesthetics

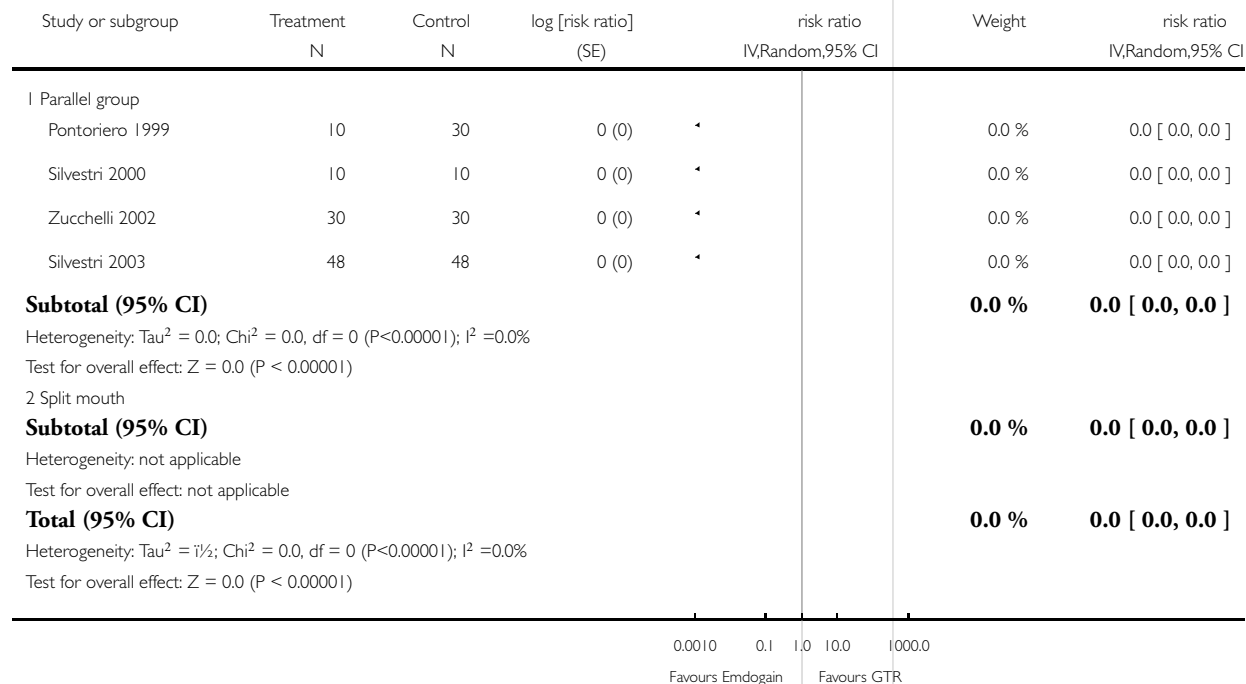


Analysis 2.1. Comparison 2 Emdogain versus GTR: 1 year, Outcome 1 Tooth loss.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

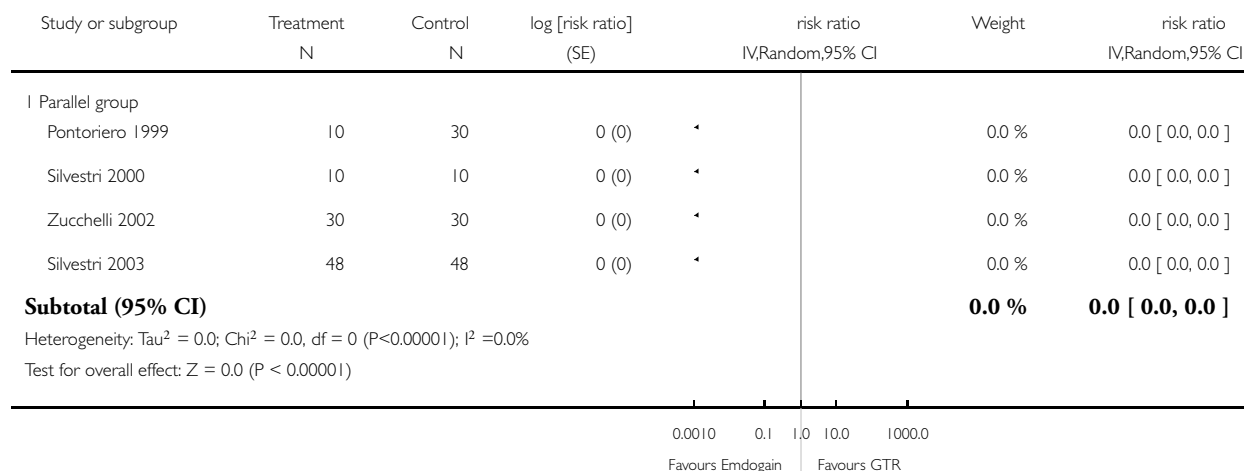
Outcome: 1 Tooth loss



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 1 Tooth loss

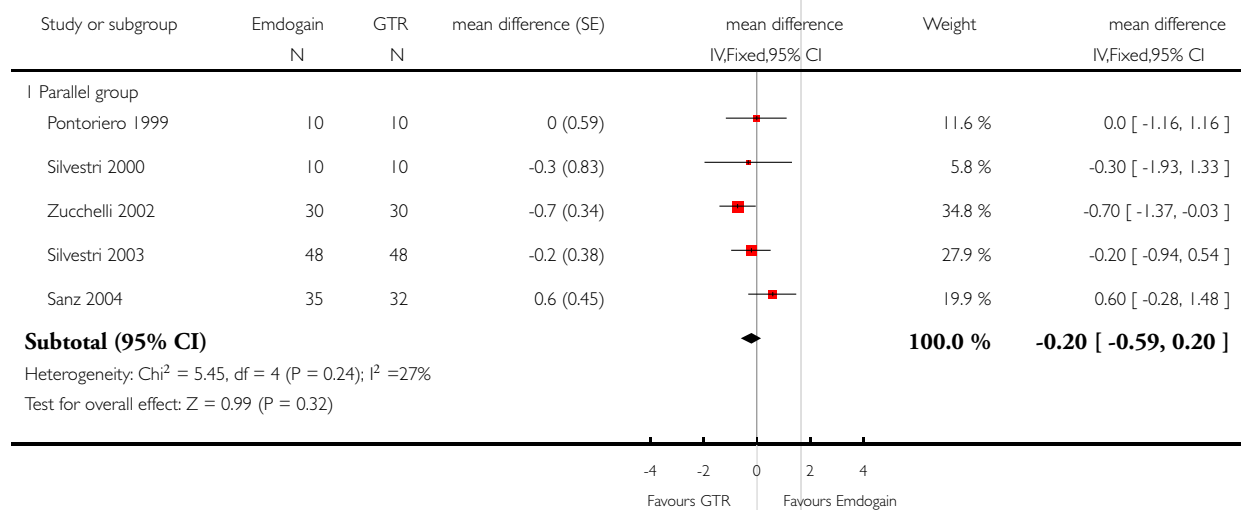


Analysis 2.2. Comparison 2 Emdogain versus GTR: 1 year, Outcome 2 PAL.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

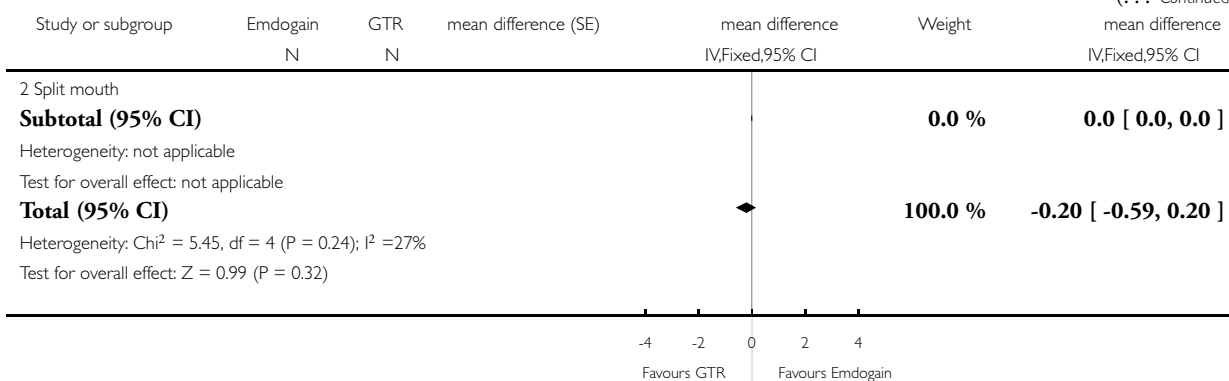
Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 2 PAL



(Continued ...)

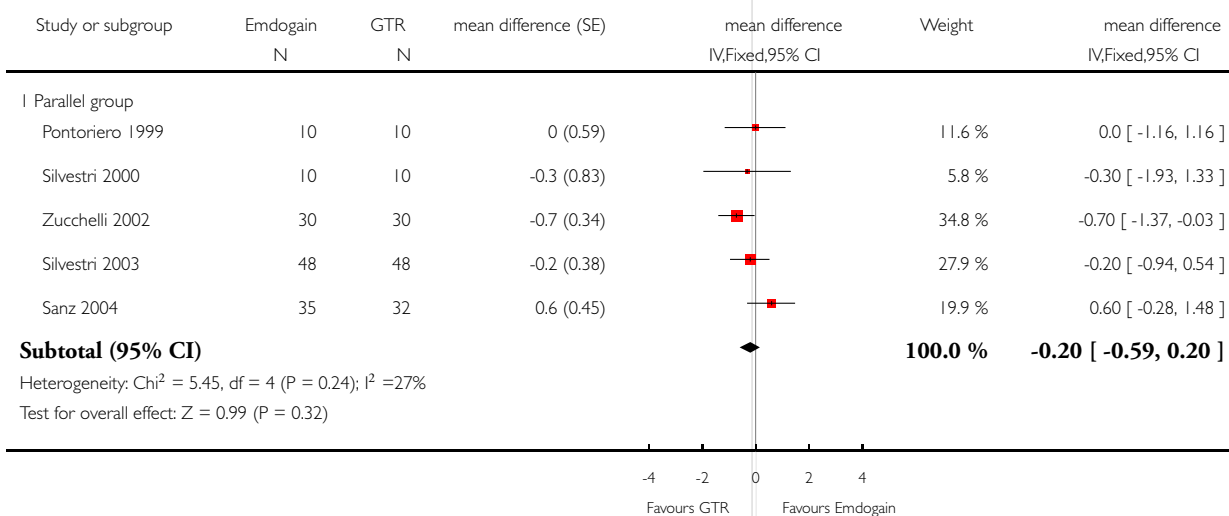
(... Continued)



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 2 PAL

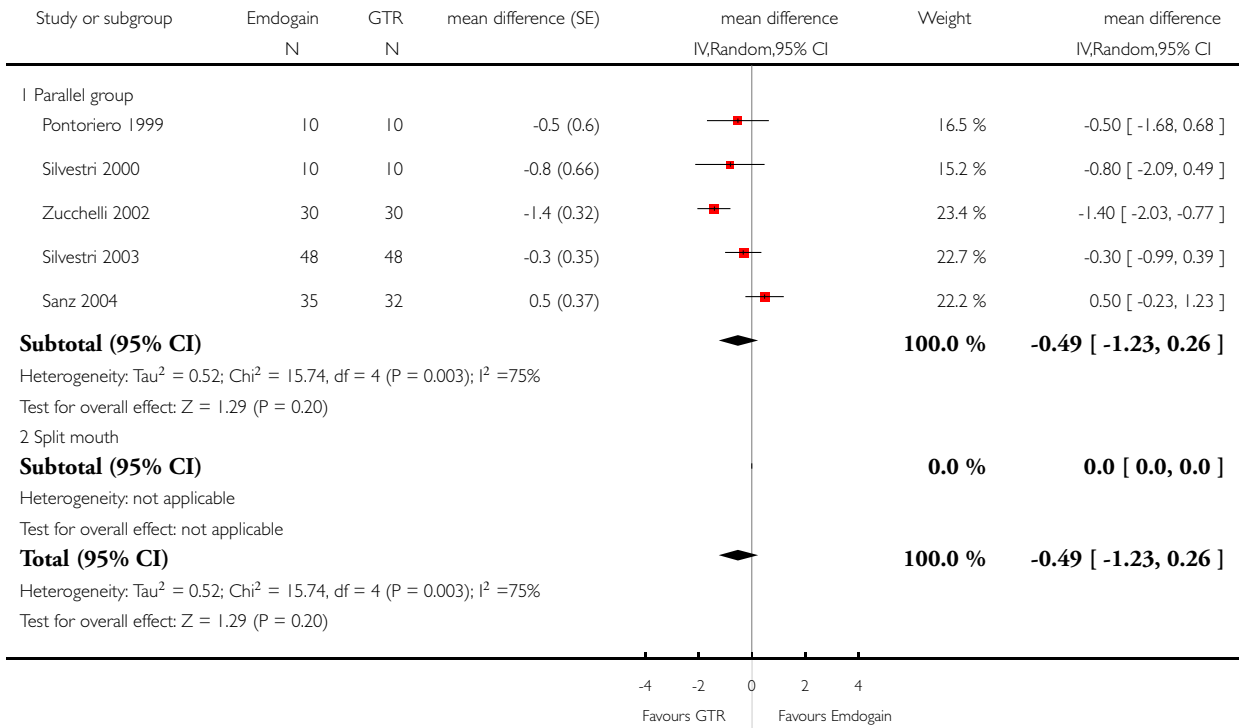


Analysis 2.3. Comparison 2 Emdogain versus GTR: 1 year, Outcome 3 PPD.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

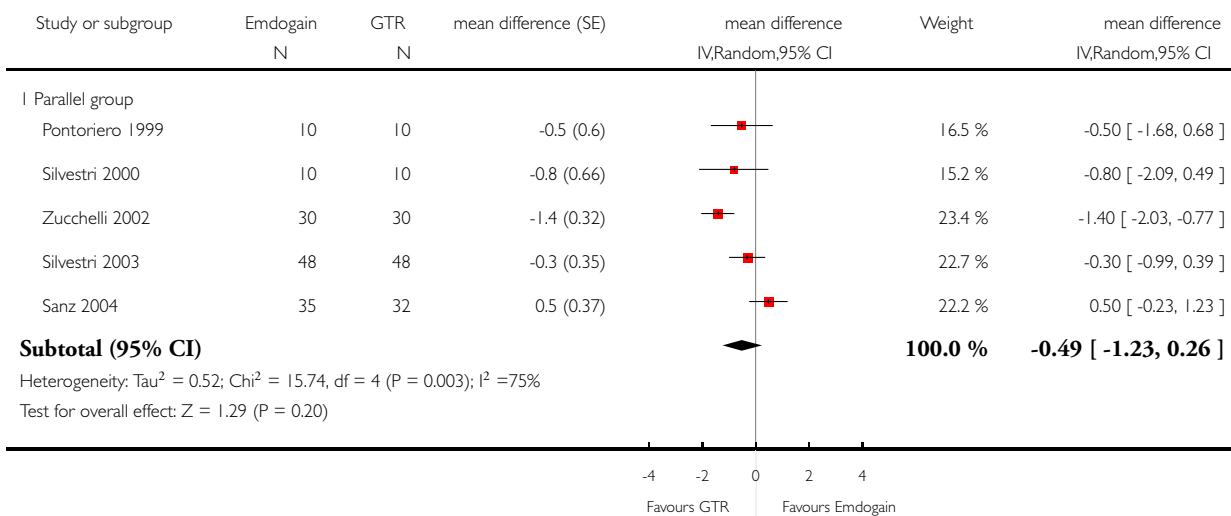
Outcome: 3 PPD



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 3 PPD

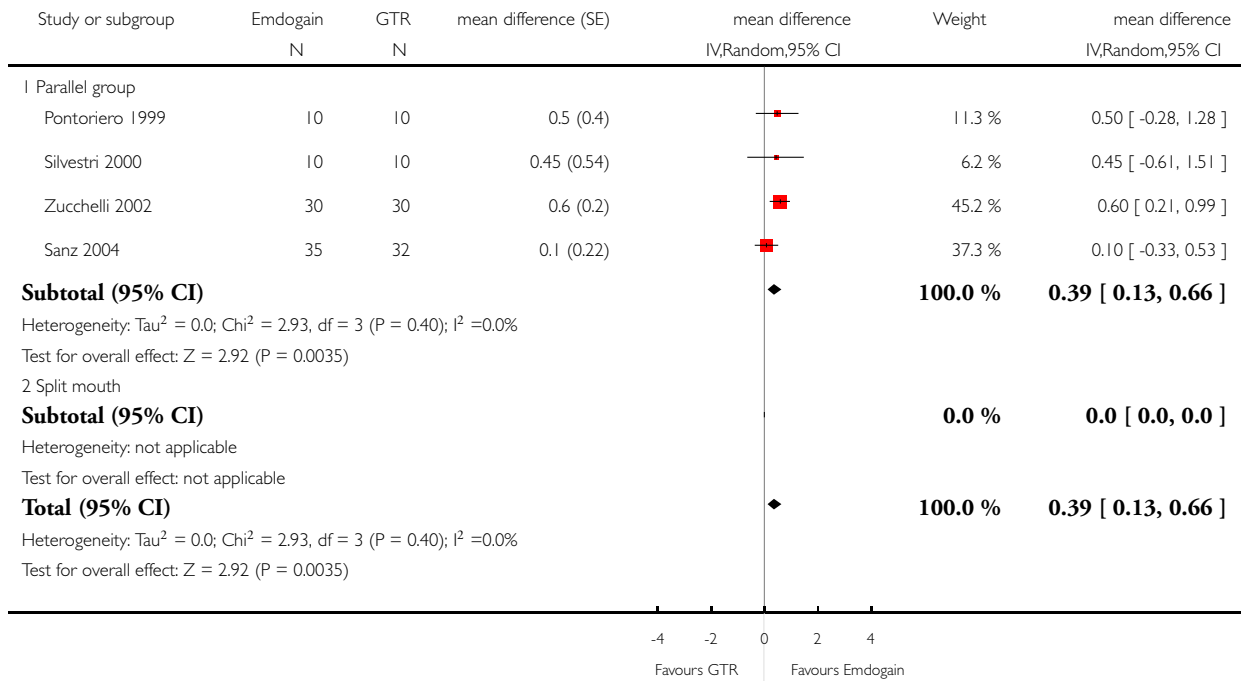


Analysis 2.4. Comparison 2 Emdogain versus GTR: 1 year, Outcome 4 REC.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

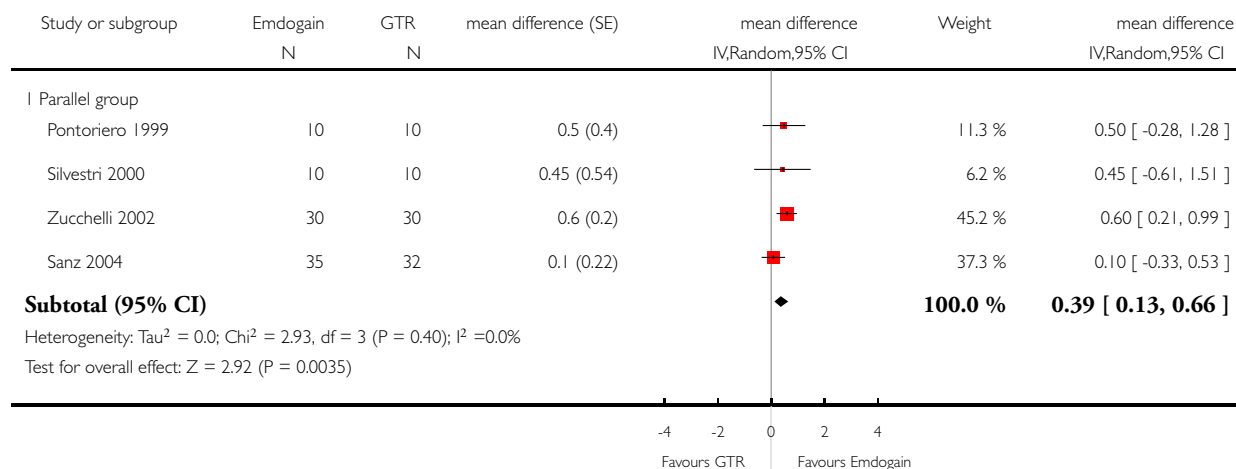
Outcome: 4 REC



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 4 REC

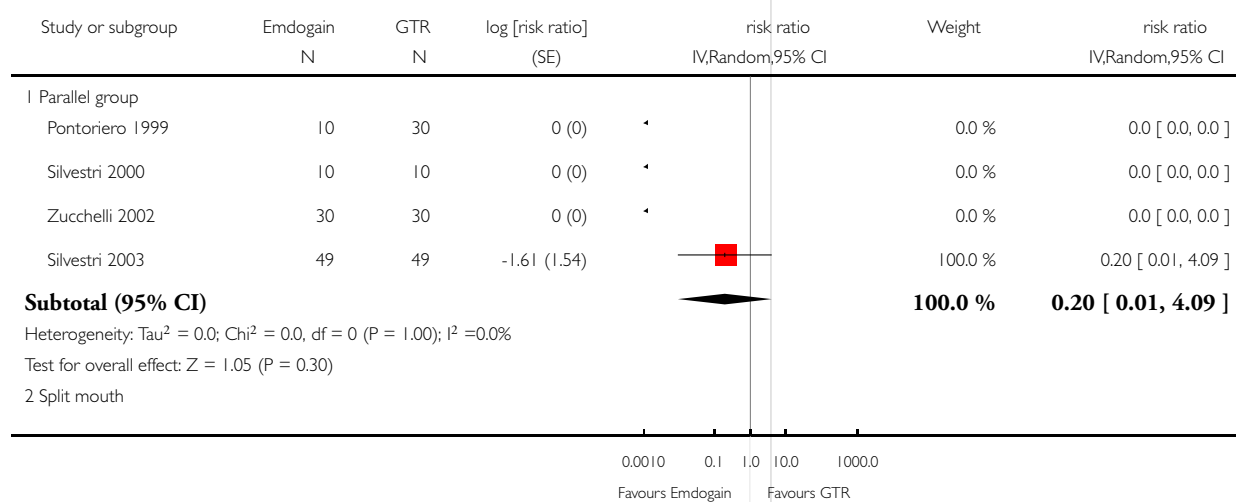


Analysis 2.5. Comparison 2 Emdogain versus GTR: 1 year, Outcome 5 Postoperative infection.

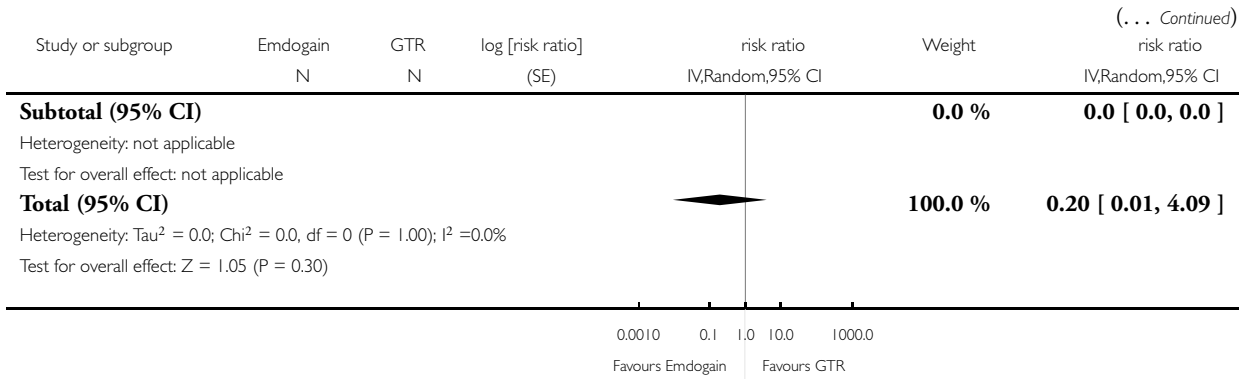
Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 5 Postoperative infection



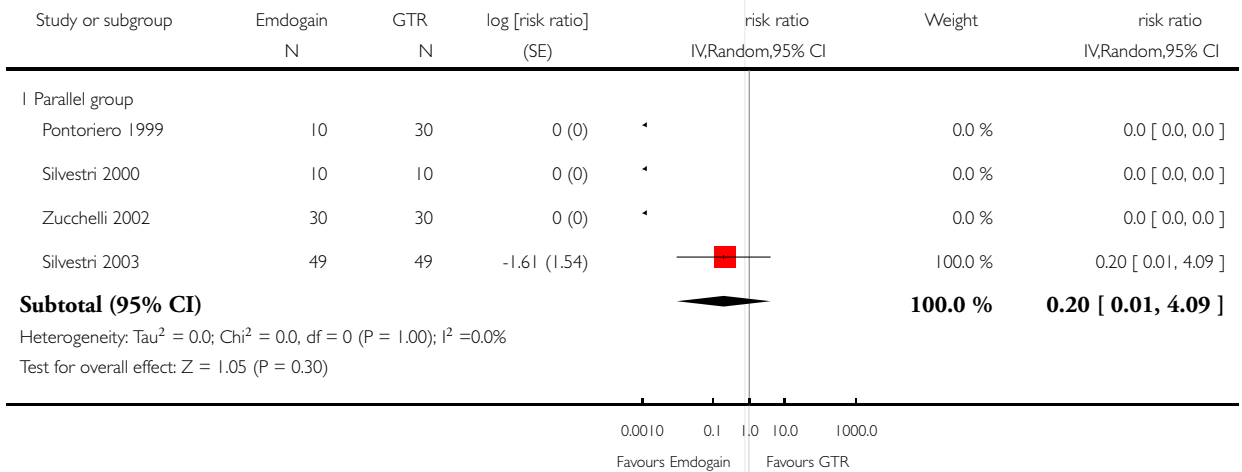
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Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 5 Postoperative infection

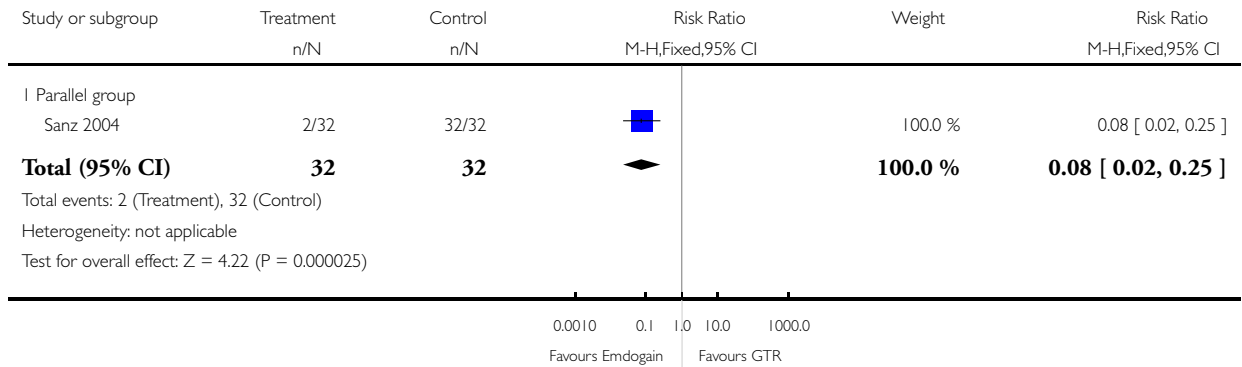


Analysis 2.6. Comparison 2 Emdogain versus GTR: 1 year, Outcome 6 Postoperative complications.

Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

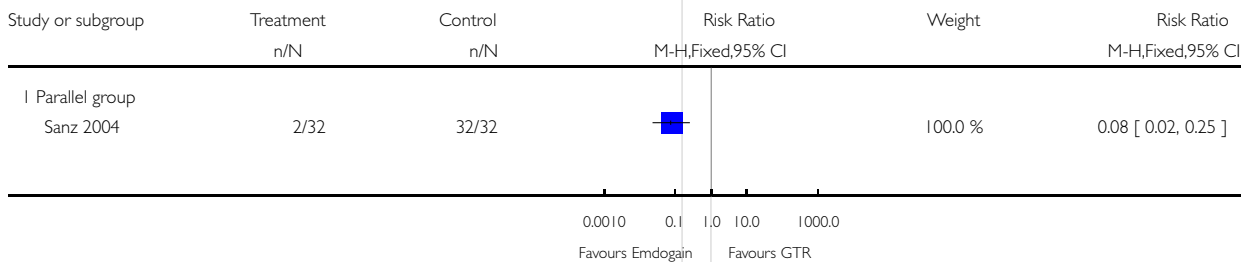
Outcome: 6 Postoperative complications



Review: Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects

Comparison: 2 Emdogain versus GTR: 1 year

Outcome: 6 Postoperative complications



APPENDICES

Appendix I. MEDLINE (OVID) search strategy

1. exp Periodontal Diseases/
2. periodont\$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3. intra bony defect\$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4. infra bony defect\$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5. intrabony defect\$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6. infrabony defect\$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7. or/1-6
8. Emdogain\$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
9. (enamel matrix derivative\$ or enamel matrix protein\$ or dental enamel protein\$ or (teeth and enamel protein\$) or (tooth and enamel protein\$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
10. or/8-9
11. 7 and 10

WHAT'S NEW

Last assessed as up-to-date: 4 August 2005.

20 June 2008	Amended	Converted to new review format.
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HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 2, 2003

5 August 2005	New citation required and major changes	Substantive amendment. Changes from the first version: Two additional trials were included, and two previously included studies were excluded, but no significant changes in the results and conclusions occurred. Numerous pending and new trials were excluded. Quality assessment was slightly simplified. Data from split-mouth trials were entered in the MetaView. Heterogeneity is now also assessed by I^2 . One additional post hoc subgroup analysis evaluating the effects of study design (parallel group versus split-mouth trials) was evaluated. Several previous post hoc subgroup analyses were excluded. Outcome endpoints are now measured at 1, 5 and 10 years. We have added the dichotomous outcome PAL < 2 mm, and calculated NNT.
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CONTRIBUTIONS OF AUTHORS

Conceiving, designing and co-ordinating the review (Marco Esposito (ME)).

Developing search strategy and undertaking searches (ME, Paul Coulthard (PC)).

Screening search results and retrieved papers against inclusion criteria (ME, Gabriella Grusovin (GG)).

Appraising quality (ME, PC, GG).

Extracting data from papers (ME, Helen Worthington (HW)).

Writing to authors for additional information (ME, HW, GG).

Data management for the review and entering data into RevMan (HW, ME).

Analysis and interpretation of data (HW, ME).

Writing the review (ME, HW).

Providing general advice on the review (PC, GG).

Performing previous work that was the foundation of current study (ME, HW, PC).

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- School of Dentistry, The University of Manchester, UK.

External sources

- Swedish Medical Research Council (9495), Sweden.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes from the protocol:

We investigated heterogeneity using post hoc factors found in the trial reports as follows: placebo or control group, antibiotics given, surgical technique used in control group, funded by manufacturer, depth of baseline intrabony defects, whether the trial was conducted in Italy or not.

We have added adverse effects to the list of outcomes, however none were found in the included trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Alveolar Bone Loss [surgery; * therapy]; Bone Regeneration; * Bone Transplantation; Dental Enamel Proteins [* therapeutic use]; * Guided Tissue Regeneration, Periodontal; Randomized Controlled Trials as Topic

MeSH check words

Humans