Evidence-Based Dentistry

Enamel Matrix Derivative for Periodontal Tissue Regeneration in Treatment of Intrabony Defects: A Cochrane Systematic Review


Abstract: We reviewed the literature on the efficacy of enamel matrix derivative (EMD) in comparison with open flap debridement, guided tissue regeneration (GTR), and bone grafting for the treatment of intrabony defects. We searched four major electronic databases for randomized controlled trials (RCTs) with at least one year of follow-up. Several journals were handsearched with no language restrictions. Outcome measures were: tooth loss, changes in probing attachment levels (PAL), pocket depths (PPD), gingival recessions (REC), marginal bone levels on intraoral radiographs, and postoperative infections. Screening of eligible RCTs, assessment of the methodological quality, and data extraction were conducted in duplicate. No difference in tooth loss was observed. A meta-analysis (eight trials) showed that EMD-treated sites displayed statistically significant PAL improvements (mean difference 1.3 mm) and PPD reduction (1 mm) when compared to flap surgery. When EMD was compared to GTR (six trials), GTR showed a statistically significant reduction of PPD (0.6 mm) and increase of REC (0.5 mm). No difference in postoperative infections was observed. No trials compared EMD with bone grafts alone. EMD is able to significantly improve PAL levels and PPD reduction when compared to flap surgery; however, there is no evidence that more teeth could be saved. There was no evidence of important differences between EMD and GTR.

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This invited review is based on a Cochrane systematic review entitled “Enamel matrix derivative (Emdogain®) for periodontal tissue regeneration in intrabony defects,” published in The Cochrane Library (see www.CochraneLibrary.net for information). Cochrane systematic reviews are regularly updated to include new research and in response to comments and criticisms from readers. If you wish to comment on this review, please send your comments to Marco Esposito. The Cochrane Library should be consulted for the most recent version of the review. The results of a Cochrane review can be interpreted differently, depending on people’s perspectives and circumstances. Please consider the conclusions presented carefully. They are the opinions of review authors and are not necessarily shared by the Cochrane Collaboration. This review has been supported by the Faculty of Odontology, the Sahlgrenska Academy at Göteborg University, Sweden; the University Dental Hospital of Manchester, UK; the Swedish Medical Research Council (9495); and the Hjelmar Svensson Foundation, Sweden. Conflicts of interest: none.

Key words: dental enamel proteins, periodontal disease, literature review

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The goal of the treatment of periodontitis is to stop the progression of the disease. Following treatment, healing usually occurs by repair without the formation of new periodontal attachment.1 One of the main concerns for many patients is that after periodontal treatment, gingival recession is increased and may cause aesthetic problems. The ideal treatment is to recover (i.e., regenerate) the periodontal tissues that have been destroyed by disease. Several surgical techniques have been developed in the attempt to regenerate periodontal tissues including guided tissue regeneration (GTR), bone grafting (BG), and the use of enamel matrix derivative (EMD) proteins. All these treatments have
been shown to have the potential to regenerate at least some periodontal attachment in humans.²,³ With GTR, a biocompatible barrier (either resorbable or nonresorbable) is surgically positioned around the root to seal the bone defect and protect the blood clot. A Cochrane review⁴ has shown that GTR is a little more effective than open flap debridement; however, it was also observed that there was a marked variability of results with GTR among various randomized controlled trials (RCTs). Grafting techniques may include autogenous bone grafting, demineralized 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 a systematic review.⁵ That review showed improved probing attachment levels for some biomaterials when compared to open flap debridement. However, the gain varied considerably with respect to the different materials used. The authors remarked that due to a significant heterogeneity in results between studies, general conclusions should be drawn with caution. Both GTR and grafting procedures are based on the concept of selective exclusion of epithelial cells from colonizing the wound and maintaining 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.⁶ The enamel matrix is composed of a number of proteins, 90 percent 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®, which is produced by Biora (Malmö, Sweden). The company has been incorporated into Straumann Biologics Division as of April 1, 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 multicenter RCT showed no differences between the original EMD and the new ready-to-use Emdogain gel formulation.⁷ EMD is derived from the developing teeth germs of six-month-old piglets.⁸ Since Emdogain is a porcine-derived material, it might have the potential of stimulating immune reactions in humans. However, EMD are quite similar among mammalian species and, consequently, less likely to be antigenic. Multiple exposures to EMD during periodontal therapy have been shown to be safe for the patient.¹⁰,¹¹ It is of interest to note that the vehicle solution (propylene glycol alginate) of the EMD has significant antimicrobial effects on periodontal pathogens.¹²,¹³ An additional RCT compared the effect of postoperative antibiotics and no antibiotics in combination with EMD. That study suggested no advantages in using postoperative antibiotics.¹⁴

The objectives of this systematic review were:

1) To test the null hypothesis of no difference in periodontal tissue “regeneration” between surgery with EMD versus open flap debridement for the treatment of intrabony defects.
2) To test the null hypothesis of no difference in periodontal tissue regeneration between surgery with EMD versus GTR for the treatment of intrabony defects.
3) To test the null hypothesis of no difference in periodontal tissue regeneration between surgery with EMD versus various “bone” grafting procedures (BG) for the treatment of intrabony defects.

### Materials and Methods

#### Criteria for Considering Studies in This Review

Only RCTs that employed EMD with at least a one year follow-up were considered in this review. The subjects of these RCTs should be affected by periodontitis and should have intrabony defects. Interventions comparing the use of EMD versus open flap debridement, versus GTR procedures, or versus various types of bone graft procedures, including animal-derived and synthetic bone, for the treatment of intrabony defects were of interest. Trials describing the combined used of EMD, GTR, bone grafting, or other growth factors were not included in the present review.

The outcome measures of interest were:

1) Tooth loss,
2) Changes in probing attachment level (PAL),
3) Changes in probing pocket depth (PPD),
4) Changes in gingival recession (REC),
5) Changes in marginal bone level on intraoral radiographs taken with a parallel technique,
6) Postoperative complications (infection),
7) Aesthetics (better, no change, or worse according to patient opinion), and
8) Adverse events.

Search Strategy for Identification of Studies

For the identification of studies to be 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 as shown in Table 1.

We searched the following electronic databases: the Cochrane Oral Health Group’s Trials Register (to January 2003); Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2002); MEDLINE (1966 to January 2003); and EMBASE (1980 to January 2003). The most recent electronic search was carried out on January 8, 2003.

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, and Journal of Periodontology. For further information and the updated list of the journals being handsearched by the Cochrane collaboration in the field of dentistry, please consult the Cochrane Oral Health Group website at www.cochrane-oral.man.ac.uk. Where these journals had not already been searched as part of the Cochrane Journal Handsearching Programme, the journals were handsearched by one of the present authors (hereafter referred to as “reviewers”).

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

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

Methods of the Review

The titles and abstracts (when available) of all reports identified were scanned independently by two reviewers. 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 reviewers to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third reviewer was consulted. All studies meeting the inclusion criteria then underwent validity assessment, and data were extracted. The reasons for rejecting the study at this or subsequent stages were recorded.

Quality assessment. The quality assessment of the included trials was undertaken independently and in duplicate by two reviewers based on the content of the articles. Three main quality criteria were assessed:
1) Allocation concealment, recorded as:
   a) Adequate
   b) Unclear
   c) Inadequate
2) Interventions blind to assessor (if applicable) as:
   a) Yes
   b) No
   c) Unclear
3) Completeness of follow-up (is there a clear explanation for withdrawals and dropouts in each treatment group?) assessed as:
   a) None
   b) Yes
   c) No

After taking into account the additional information provided by the authors of the trials, studies

<table>
<thead>
<tr>
<th>Table 1. Search strategy developed for MEDLINE via OVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Explode PERIODONTAL-DISEASES</td>
</tr>
<tr>
<td>2 periodont$</td>
</tr>
<tr>
<td>3 “intra bony defect$”</td>
</tr>
<tr>
<td>4 “infra bony defect$”</td>
</tr>
<tr>
<td>5 OR/1-4</td>
</tr>
<tr>
<td>6 Emdogain$</td>
</tr>
<tr>
<td>7 “enamel matrix derivative$”</td>
</tr>
<tr>
<td>8 “enamel matrix protein$”</td>
</tr>
<tr>
<td>9 “dental enamel protein$”</td>
</tr>
<tr>
<td>10 (teeth AND (“enamel protein$”))</td>
</tr>
<tr>
<td>11 (tooth AND (“enamel protein$”))</td>
</tr>
<tr>
<td>12 OR/6-11</td>
</tr>
<tr>
<td>13 (5 and 12)</td>
</tr>
</tbody>
</table>
were graded into three categories: A) low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met; B) moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were partly met (when authors responded that they had made some attempts to conceal the allocation of patients, to blind the assessors, or to give an explanation for withdrawals, but these attempts were not judged to be ideal, these criteria were categorized as “partly”); and C) high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met as described in the Cochrane Reviewers’ Handbook 6.7. (See Table 2.)

Data extraction. Data were extracted by two reviewers independently using specially designed data extraction forms. Any disagreement was discussed and a third reviewer consulted where necessary. Authors of 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; and
- details of the outcomes reported, including method of assessment and time intervals.

Data synthesis. For dichotomous outcomes, the estimates of effect of an intervention were expressed as relative risks together with 95 percent confidence intervals. For continuous outcomes, mean differences and 95 percent confidence intervals were used to summarize the data for each group.

Clinical heterogeneity was assessed by examining the types of participants, interventions, and outcomes in each study with a planned subgroup analysis for a maintenance regimen over three months compared with maintenance at more frequent intervals. Meta-analyses were done only with studies of similar comparisons reporting the same outcome measures. Relative risks were combined for dichotomous data and weighted mean differences for continuous data, using random effects models. 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 any heterogeneity was investigated.

Data from split mouth and parallel group studies were combined using the procedures outlined by Elbourne et al. It was necessary to estimate the appropriate standard errors where these were not presented in the trial reports using the methods presented by Follmann et al. Sensitivity analyses were undertaken to examine the effect of concealed randomization and outcome assessor’s being blind 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.

Description of Studies

Of the seventeen eligible trials, ten were included in this review, and seven trials were excluded for the following reasons: not RCTs, teeth extracted after six months, data in an inappropriate form, and data presented in a way we could not use.

Six trials had a parallel design, and four studies were designed as split mouth trials. In one trial, comparisons were undertaken both within patients and between patients. Five trials were conducted in Italy, two in Germany, one in Japan, one in Sweden, and one trial was conducted in several countries. Five trials were multi-center. Four trials were conducted in university dental clinics, four were conducted in both university dental clinics and private practices, one study in a private practice, and one trial in a public specialist clinic of periodontology. Six trials were funded or partially supported by manufacturers, but such information was explicit in only two trials. Four trials were not supported by manufacturers.

In total, 577 patients were enrolled in the ten included trials.

Eight trials compared Emdogain versus control flap surgery. The surgical techniques for the control flaps were the modified Widman flap in four trials, whereas in the other three trials the simplified or the modified papilla preservation techniques were used and in one trial coronally advanced flaps were used. In three trials, a placebo (the propylene glycol alginate vehicle gel solution) was used in the control flaps.

Six trials compared Emdogain versus GTR. In three trials nonresorbable barriers were used, in two trials resorbable barriers were
used,\textsuperscript{21,22} and in one trial\textsuperscript{18} both resorbable and nonresorbable barriers were used. Nonresorbable barriers were removed six weeks after their insertion with the exception of one trial\textsuperscript{18} in which they were removed after four weeks. In one study, connective tissue grafts were placed in six patients after barrier removal.\textsuperscript{20}

The following root-conditioning procedures before EMD application were implemented in all trials:

- 36 percent Ortho-phosphoric acid for fifteen seconds in treated sites and controls,\textsuperscript{17,19}
- 24 percent Ethylenediaminetetra-acetic acid (EDTA) gel for two minutes only in EMD treated sites,\textsuperscript{21,22,26} also at the open flap debridement sites,\textsuperscript{18,23,24} and at the GTR sites,\textsuperscript{24,25} and
- 17 percent EDTA solution for twenty seconds.\textsuperscript{20}

The following postoperative systemic antibiotics and hygiene procedures were prescribed:

- Doxycycline (Vibramycin, Pfizer) 200 mg day one and 100 mg for three weeks; 0.2 percent chlorhexidine rinsing for four to six weeks; and no mechanical cleaning in operated areas for six weeks.\textsuperscript{17}
- Amoxicillin 3 gram one hour before surgery; 0.12 percent chlorhexidine rinsing twice a day for six weeks.\textsuperscript{18}
- Cefaclor 750 mg per day for five days; 0.12 percent chlorhexidine rinsing three times a day for six weeks; and no mechanical cleaning for the first postoperative week.\textsuperscript{19}
- Amoxicillin and clavulanic acid (Augmentin, Smith Klein Beecham) 2 grams per day for six days; 0.2 percent chlorhexidine rinsing twice a day for eight weeks; and no mechanical cleaning in operated areas for two months.\textsuperscript{20,25}
- Amoxicillin 375 mg and metronidazole 275 mg three times a day for seven days; 0.2 percent chlorhexidine rinsing twice a day; and no mechanical cleaning in the operated areas for six weeks.\textsuperscript{21}
- Amoxicillin 500 mg three per day for ten days; 0.2 percent chlorhexidine rinsing twice a day; and no mechanical cleaning in the operated areas for six weeks.\textsuperscript{22}
- No antibiotics; 0.12 percent chlorhexidine rinsing twice a day for four weeks; and gentle sweeping of operated areas with a postsurgical toothbrush without interdental cleaning for four weeks.\textsuperscript{23}
- Amoxicillin and clavulanic acid (Augmentin, Smith Klein Beecham) one gram per day starting one day before surgery and for six days thereafter; 0.2 percent chlorhexidine rinsing twice a day for eleven weeks without interdental cleaning in the operated areas.\textsuperscript{24}
- Amoxicillin and clavulanic acid (Augmentin, Smith Klein Beecham) 1 gram per day for seven days; 0.2 percent chlorhexidine rinsing twice a day for six weeks without mechanical cleaning in the operated areas.\textsuperscript{26}

Characteristics of Outcome Measures

After contacting the authors, we found that tooth loss and postoperative complications (infection) were available for all trials. Changes in PAL and PPD were described in all trials. Three trials did not describe changes in REC;\textsuperscript{17,25,26} however, these can be easily estimated by subtracting PPD from PAL. Marginal bone level measurement on intraoral radiographs taken with a paralleling technique were performed in three trials.\textsuperscript{17,19,26} The radiographic data from two studies\textsuperscript{20,25} were not used because the data were presented as percent relative area of bone density and not as linear measurements\textsuperscript{17} and for not employing a fixed reference mark to assess changes over time.\textsuperscript{26} Aesthetic parameters were not measured in any of the trials.

Baseline Characteristics of the Included Trials

Specific exclusion criteria:

- None in particular\textsuperscript{17,18}
- Smokers\textsuperscript{19,20}
- Medium smokers, defined as more than ten cigarettes per day\textsuperscript{25}
- Heavy smokers, defined as more than twenty cigarettes per day\textsuperscript{23,24}
- Any periodontal treatment in the previous two\textsuperscript{19,22} or three years\textsuperscript{26}
- Antibiotics in the previous six months\textsuperscript{19,21,22,24}
- Less than 2 mm of attached gingiva\textsuperscript{19,23}

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.\textsuperscript{17}
- All patients treated with mechanical debridement and antiseptics when indicated.\textsuperscript{23}
• All patients treated with mechanical debridement.18-22,24-26

Characteristics of the defects:
• PPD $\geq 6$ mm and intrabony defects with a depth $\geq 4$ mm17,19,20,26
• PPD $\geq 6$ mm and intrabony defects with a depth $\geq 3$ mm18
• PPD $\geq 7$ mm and intrabony defects with a depth $\geq 3$ mm24
• PPD $\geq 6$ mm21,22
• Intrabony defects with a depth $\geq 3$ mm23
• Intrabony defects with a depth $\geq 4$ mm25

Baseline comparisons among groups:
• No statistically significant differences among test and control groups for PAL, PPD, and radiographic bone levels.17
• 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 components18,19,21,24 and distribution of number of walls of the bone defects.23
• No statistically significant differences among test and control groups for FMPS, PAL, PPD, REC, and intrabony components.22
• No statistically significant differences among test and control groups for FMPS, PAL, PPD, REC, and intrabony components.25
• No statistically significant differences among test and control groups for intrabony components.26
• A statistically significant difference of the intrabony components was present among the various groups,20 i.e., the group treated with the modified Widman flap had the shallowest mean intrabony component (4.6 mm); for the group treated with GBR, it was 5.2 mm; and the group treated with EMD had the deepest mean (5.9 mm) intrabony component.

Type of maintenance and length of the follow-up:
• Recall for professional tooth cleaning at week two, four, six, and thereafter, depending on the level of plaque control, at three, six, nine, and twelve months or at four, eight, and twelve months. At one year, an individual recall program was developed, and patients were recalled at least every six months; three years.17
• Recall every fifteen days for professional tooth cleaning; one year.18

Methodological Quality of Included Studies

Allocation concealment. Only one paper clearly described the procedure of allocation concealment.17 All the other trials were marked as unclear. However, all authors provided the requested information; thus, concealment allocation procedures were scored as adequate for five trials,17,18,23,24,26 partially adequate for four trials,19,21,22,25 and inadequate for one trial20 as presented in Table 2.

Blinding. Outcome assessors were scored as blind in five cases,17,19,21,22,24 unclear in three cases,18,20,25 and not blinded in two cases.23,26 After contacting the authors, we considered one trial to be blind18 and two were not.20,25

Withdrawals. The reporting and explanation of withdrawals and dropouts were clear in eight trials. After correspondence with the authors, all trials were considered to have clear explanations of withdrawals and dropouts.

Sample size. Sample size calculations were performed in only two studies.17,23 In one trial,17 the sample size was calculated to detect one mm difference (assuming one mm of standard deviation, SD) of PAL and radiographic bone gain between test and control with a power (one minus beta) of at least 90 percent eight months after surgery. For the other trial,23 the size of the sample required to detect a true difference of 0.5 mm for PAL between test and con-
control with 90 percent power and with an alpha error of 0.05 was 150 patients completing the trial. In both studies more patients than needed to detect the assumed differences completed the trials.

Agreement in methodological assessment. The percent agreement and kappa scores between the two raters on the published information were: 100 percent, 1.00 for allocation concealment; 100 percent, 1.00 for blinding of the outcome assessor; and 80 percent, 0.71 for withdrawals.

The agreed quality of the included trials after having incorporated the information provided by the authors is summarized in Table 2.

Table 2. Results of quality assessment after correspondence with authors

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding of Assessor</th>
<th>Withdrawals</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heijl et al. 1997&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>A</td>
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<tr>
<td>Pontoriero et al. 1999&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>A</td>
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<tr>
<td>Okuda et al. 2000&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Silvestri et al. 2000&lt;sup&gt;20&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>C</td>
</tr>
<tr>
<td>Sculean et al. 2001&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Sculean et al. 2001&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Partly</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Tonetti et al. 2002&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes</td>
<td>B</td>
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<tr>
<td>Zucchelli et al. 2002&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>A</td>
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<tr>
<td>Silvestri et al. 2003&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Partly</td>
<td>No</td>
<td>Yes</td>
<td>C</td>
</tr>
<tr>
<td>Francetti et al. 2004&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Yes</td>
<td>Partly</td>
<td>Yes</td>
<td>B</td>
</tr>
</tbody>
</table>

Results

The data and the pooled results from the meta-analyses are given in Tables 3 to 6. No adverse events attributable to EMD or control flap surgery were recorded, with the exception of a few problems attributable to the use of postoperative antibiotics. In the GTR treated group, two infections of the barriers and several barrier exposures occurred.

Emdogain (EMD) Versus Control/Placebo

Eight trials provided data for this comparison between Emdogain and control or placebo interventions. There were insufficient numbers of teeth lost (all four teeth extracted, two in the control group and two in the test group, were extracted for prosthetic reasons<sup>17</sup>) to undertake an analysis of Emdogain versus control or placebo interventions. There were significant differences between Emdogain and the control for the three outcomes measured as change from the baseline values: PAL (eight trials; Table 3), PPD (eight trials; Table 4); and radiographic marginal bone levels (one trial). There was a significant gain in mean PAL for Emdogain compared with control sites with a weighted mean difference (WMD) of 1.31 mm (95 percent confidence interval, CI: 0.84 to 1.78, chi-square=32.9, 7df, p<0.001) and a significant reduction in PPD with WMD of 0.96 mm (95 percent CI: 0.50 to 1.41; chi-square=23.0, 7df, p=0.002). The high levels of heterogeneity found in these meta-analyses will be considered later in this section. The significant increase in marginal bone levels favoring Emdogain was based on only one trial with WMD of 2.0 mm (95 percent CI: 0.88 to 3.12). There was no statistically significant difference in REC between Emdogain and the control (six trials) with WMD 0.16 (95 percent CI: -0.23 to 0.55). No postoperative infections or other adverse events were reported.

Emdogain (EMD) Versus Guided Tissue Regeneration (GTR)

Six trials provided data for this comparison between Emdogain and GTR. There were no teeth lost in either group in any of these trials. There were significant differences between Emdogain and GTR for two outcomes measured as change from the baseline values: PPD (six trials; Table 5) and REC (five trials; Table 6). There was a significantly greater reduction in PPD for GTR with WMD of 0.58 mm (95 percent CI: 0.08 to 1.07; chi-square=8.9, 5 df, p=0.11). There was also a significant increase in REC for GTR with WMD of 0.47 mm (95 percent CI: 0.17, 0.76; chi-square=1.5, 4 df, p=0.82). There were no statistically significant differences for PAL (six trials) and post-operative infections (one trial).
### Table 3. Comparison between Emdogain and control/placebo for changes in probing attachment levels (PAL)

<table>
<thead>
<tr>
<th>Study</th>
<th>Split</th>
<th>Emdogain n mean (SD)</th>
<th>Control n mean (SD)</th>
<th>Difference n mean (SE)</th>
<th>95 percent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sculean et al. 2001*</td>
<td>P</td>
<td>14 3.4 (1.5)</td>
<td>14 1.7 (1.5)</td>
<td>1.70 (0.57)</td>
<td>(0.54, 2.87)</td>
</tr>
<tr>
<td>Tonetti et al. 2002*</td>
<td>P</td>
<td>83 3.1 (1.5)</td>
<td>83 2.5 (1.5)</td>
<td>0.60 (0.23)</td>
<td>(0.14, 1.06)</td>
</tr>
<tr>
<td>Pontoriero et al. 1999*</td>
<td>S</td>
<td>1.1 (0.43)</td>
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<td></td>
<td>(0.12, 2.08)</td>
</tr>
<tr>
<td>Zucchelli et al. 2002*</td>
<td>P</td>
<td>30 4.2 (0.9)</td>
<td>30 2.6 (0.8)</td>
<td>1.6 (0.22)</td>
<td>(1.16, 2.04)</td>
</tr>
<tr>
<td>Francetti et al. 2004*</td>
<td>P</td>
<td>12 4.14 (1.35)</td>
<td>12 2.29 (0.95)</td>
<td>1.85 (0.48)</td>
<td>(0.86, 2.84)</td>
</tr>
<tr>
<td>Okuda et al. 2000*</td>
<td>S</td>
<td>16 1.72 (1.07)*</td>
<td>16 0.83 (0.86)</td>
<td>0.89 (0.22)</td>
<td>(0.42, 1.36)</td>
</tr>
<tr>
<td>Heijl et al. 1997*</td>
<td>S</td>
<td>31 2.3 (1.6)*</td>
<td>31 1.7 (1.2)</td>
<td>0.6 (0.22)</td>
<td>(0.15, 1.05)</td>
</tr>
<tr>
<td>Silvestri et al. 2000*</td>
<td>P</td>
<td>10 4.5 (1.58)</td>
<td>10 1.20 (1.03)</td>
<td>3.30 (0.60)</td>
<td>(2.05, 4.55)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td></td>
<td></td>
<td>1.31</td>
<td>(0.84, 1.78)</td>
</tr>
</tbody>
</table>

*p-value = 0.00125, ^p-value<0.01

### Table 4. Comparison between Emdogain and control/placebo for changes in probing pocket depth (PPD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Split</th>
<th>Emdogain n mean (SD)</th>
<th>Control n mean (SD)</th>
<th>Difference n mean (SE)</th>
<th>95 percent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sculean et al. 2001*</td>
<td>P</td>
<td>14 4.1 (1.7)</td>
<td>14 3.7 (1.4)</td>
<td>0.40 (0.59)</td>
<td>(-0.81, 1.61)</td>
</tr>
<tr>
<td>Tonetti et al. 2002*</td>
<td>P</td>
<td>83 3.9 (1.7)</td>
<td>83 3.3 (1.7)</td>
<td>0.60 (0.26)</td>
<td>(0.08, 1.12)</td>
</tr>
<tr>
<td>Pontoriero et al. 1999*</td>
<td>S</td>
<td>0.7 (0.47)</td>
<td></td>
<td></td>
<td>(-0.37, 1.77)</td>
</tr>
<tr>
<td>Zucchelli et al. 2002*</td>
<td>P</td>
<td>30 5.1 (0.7)</td>
<td>30 4.5 (1.0)</td>
<td>0.60 (0.22)</td>
<td>(1.15, 1.05)</td>
</tr>
<tr>
<td>Francetti et al. 2004*</td>
<td>P</td>
<td>12 4.71 (1.60)</td>
<td>12 2.57 (1.27)</td>
<td>2.14 (0.59)</td>
<td>(0.92, 3.36)</td>
</tr>
<tr>
<td>Okuda et al. 2000*</td>
<td>S</td>
<td>16 3.0 (0.97)*</td>
<td>16 2.22 (0.81)</td>
<td>0.78 (0.32)</td>
<td>(0.09, 1.46)</td>
</tr>
<tr>
<td>Heijl et al. 1997*</td>
<td>S</td>
<td>31 3.3 (1.4)*</td>
<td>31 2.6 (1.2)</td>
<td>0.70 (0.25)</td>
<td>(0.19, 1.21)</td>
</tr>
<tr>
<td>Silvestri et al. 2000*</td>
<td>P</td>
<td>10 4.9 (1.79)</td>
<td>10 1.40 (1.26)</td>
<td>3.5 (0.69)</td>
<td>(2.05, 4.95)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
<td>(0.50, 1.41)</td>
</tr>
</tbody>
</table>

*p-value = 0.0262, ^p-value<0.01

### Table 5. Comparison between Emdogain and GTR for changes in probing pocket depth (PPD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Split</th>
<th>EMD n mean (SD)</th>
<th>GTR n mean (SD)</th>
<th>Difference n mean (SE)</th>
<th>95 percent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontoriero et al. 1999*</td>
<td>P</td>
<td>10 4.2 (1.3)</td>
<td>30 4.5 (1.7)</td>
<td>-0.30 (0.59)</td>
<td>(-1.49, 0.89)</td>
</tr>
<tr>
<td>Silvestri et al. 2000*</td>
<td>P</td>
<td>10 4.9 (1.79)</td>
<td>10 5.7 (1.06)</td>
<td>-0.80 (0.66)</td>
<td>(-2.18, 0.58)</td>
</tr>
<tr>
<td>Sculean et al. 2001*</td>
<td>S</td>
<td>14 4.1 (1.7)</td>
<td>14 4.2 (1.9)</td>
<td>-0.10 (0.68)</td>
<td>(-1.50, 1.30)</td>
</tr>
<tr>
<td>Sculean et al. 2001*</td>
<td>P</td>
<td>30 5.1 (0.7)</td>
<td>30 6.5 (1.6)</td>
<td>-1.40 (0.32)</td>
<td>(-2.04, -0.76)</td>
</tr>
<tr>
<td>Zucchelli et al. 2002*</td>
<td>P</td>
<td>48 5.3 (1.9)</td>
<td>48 5.6 (1.5)</td>
<td>-0.30 (0.35)</td>
<td>(-0.99, 0.39)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td></td>
<td></td>
<td>-0.58</td>
<td>(-1.07, -0.08)</td>
</tr>
</tbody>
</table>

*p-value = 0.028; ^p-value<0.01

### Table 6. Comparison of Emdogain and GTR for changes in gingival recession (REC)

<table>
<thead>
<tr>
<th>Study</th>
<th>Split</th>
<th>EMD n mean (SD)</th>
<th>GTR n mean (SD)</th>
<th>Difference n mean (SE)</th>
<th>95 percent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pontoriero et al. 1999*</td>
<td>P</td>
<td>10 1.3 (0.9)</td>
<td>30 1.4 (1.0)</td>
<td>0.10 (0.36)</td>
<td>(-0.82, 0.62)</td>
</tr>
<tr>
<td>Silvestri et al. 2000*</td>
<td>P</td>
<td>10 -0.5 (0.97)</td>
<td>10 -0.95 (1.40)</td>
<td>0.45 (0.54)</td>
<td>(-0.68, 1.58)</td>
</tr>
<tr>
<td>Sculean et al. 2001*</td>
<td>S</td>
<td>14 -0.7 (0.8)</td>
<td>14 -1.1 (1.4)</td>
<td>0.40 (0.43)</td>
<td>(-0.49, 1.29)</td>
</tr>
<tr>
<td>Zucchelli et al. 2002*</td>
<td>P</td>
<td>30 -1.0 (0.5)</td>
<td>30 -1.6 (1.0)</td>
<td>0.60 (0.20)</td>
<td>(-3.01, -2.19)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
<td>(0.17, 0.76)</td>
</tr>
</tbody>
</table>

*p-value = 0.0028; ^p-value<0.01

*greater increase from baseline for GTR
Emdogain (EMD) Versus “Bone” Grafting (BG)

No trial comparing the use of EMD alone to bone grafting procedures alone was identified. It should be noted that trials combining the use of EMD, GTR, and bone grafting as well as other regenerative procedures (e.g., bone grafting plus GTR or EMD plus GTR) were not included in the present review.

Heterogeneity

Random effects meta regression analysis was used to investigate whether the following factors explained the heterogeneity in the comparisons between Emdogain and control/placebo for PAL, PPD, and REC:

- placebo or control group
- antibiotics given (yes or no)
- surgical technique used in control group (traditional modified Widman flap or new papilla preservation flaps)
- funded by manufacturer (yes or no)
- risk of bias (low versus medium or high)
- baseline depth of intrabony defects (<5 mm or ≥5 mm)
- where trial conducted (Italy or elsewhere).

Only one of random effects meta regressions was significant, where manufacturer-funded studies found less gingival recessions (REC) than the unfunded studies (six studies, slope estimate (SE) 0.67 (0.29) (95 percent CI: 0.10 to 1.24), p=0.02). Apart from this we are unable to explain the heterogeneity found between the studies. A planned subgroup for periodontal maintenance was not possible as all studies were categorized as providing very high levels of maintenance. We were also unable to consider the effect of unpublished results as we were unable to find any unpublished studies that had not been submitted for publication.

Discussion

The meta-analysis of eight trials showed that the use of Emdogain led to a statistically significant improvement in average PAL (1.3 mm) and PPD (1 mm) over control flap surgery when used in the treatment of intrabony defects. However, we found a high degree of heterogeneity in the included trials that could not be explained by the different qualities of the trials involved, the use of antibiotics, the different surgical techniques used in the control flap procedure, the use of a placebo (the vehicle gel) in the control sites, the initial depth of the intrabony defects, or whether the trial was conducted in Italy or elsewhere. The only exception was funding from the manufacturer, where studies funded by the manufacturer had lower levels of gingival recession than unfunded trials. Because multiple comparisons were made, this could be a spurious finding (i.e., we used a p-value of 0.05, so on average one in twenty comparisons, 5 percent, will be “significant”). However, the trial that showed the highest mean value of PAL gain for the EMD group (3.2 mm) had, at baseline, a deeper mean intrabony component than the open flap debridement group (5.9 mm versus 4.6 mm) and this trial was judged to be at a high risk of bias.

While the improvements in PAL and PPD levels are without any doubt positive findings, the real clinical utility of Emdogain may be debated. In particular, there is no evidence that more compromised teeth could be saved using Emdogain or that the amount of tissue regeneration was clinically significant. It may be argued that we have assessed only short-term follow-up studies (one year). On the other hand, the number of long-term trials is still small, and it may be assumed that the effect of Emdogain should be seen one year after its administration when the area has properly healed. Longer follow-up periods may provide results that reflect the quality of maintenance more than the effect of Emdogain.

When comparing Emdogain with GTR (six trials), we found that GTR produced a statistically significant reduction of PPD (0.6 mm), which was due to an increase in REC (0.5 mm). This statistical difference may not be of clinical significance. No differences between Emdogain 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 infections occurred in the GTR group. We did not record as postoperative infections small dehiscences of the flaps over the barriers that were numerous in all studies. No adverse reactions were reported for the other 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 Emdogain. It may also be useful to emphasize that the vehicle of Emdogain has shown antibacterial properties in vitro. In addition, if nonresorbable barriers are used, a second operation is needed for their removal. Taken together, all of these aspects
may suggest that Emdogain might be a preferable choice.

We intentionally did not include RCTs describing the use of Emdogain in combination with other treatments such as GTR, bone grafts, etc. This was done because we wanted to know whether Emdogain was superior to flap surgery and to other regenerative techniques, and 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 Emdogain and that in all RCTs this was done; however, the clinical efficacy of such a procedure has not been validated in clinical trials.

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 by very experienced clinicians and in some trials smokers were excluded; moreover, very strict maintenance regimens were employed that are not generally used in routine clinical situations. In addition, the heterogeneity indicates that even within these “optimal” conditions, the results of treatments are highly variable and the data do not explain the variability. Therefore, defining optimal patient selection, aspects of treatment delivery, or maintenance is not yet possible.

Conclusions

One year after treatment, EMD showed statistically significant improvements in PAL (1.3 mm) and PPD reduction (1 mm) in comparison with flap surgery. However, the actual clinical advantages might be questioned since there is not yet evidence that more teeth can be saved using EMD.

No evidence of major differences between EMD and GTR could be found with the exception of slightly more PPD reduction (0.6 mm) due to increased REC (0.5 mm) in GTR treated sites. On the other hand, EMD seems simpler to use, may not need antibiotic coverage, and does not need a second surgical intervention (if compared with nonresorbable barriers). In addition, no postoperative infections or adverse events were observed with EMD versus two cases of infection (not statistically significant) in the GTR group.

No RCT was identified testing the efficacy of surgery with EMD versus various “bone” grafting procedures alone for the treatment of intrabony defects.

The main implication for research is that 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 (www.consort-statement.org/). A question that has not yet been addressed with proper clinical trials is whether the use of root-conditioning is actually useful.

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REFERENCES