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

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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 handsearched. No language restrictions were applied. Authors of randomized controlled trials (RCTs) identified, personal contacts and the manufacturer were contacted to identify unpublished trials. Most recent search: February 2009. 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: Thirteen trials were included out of 35 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 nine trials showed that EMD treated sites displayed statistically significant PAL improvements (mean difference 1.1 mm, 95% CI 0.61 to 1.55) and PPD reduction (0.9 mm, 95% CI 0.44 to 1.31) 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 0.53 (95% CI 0.34 to 0.82). Approximately nine 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 25%. No differences in tooth loss or aesthetic appearance as judged by the patients were observed. When evaluating only trials at a low risk of bias in a sensitivity analysis (four trials), the effect size for PAL was 0.62 mm (95% CI 0.28 to 0.96), which was less than 1.1 mm for the overall result. Comparing EMD with GTR (five trials), GTR showed statistically significant more postoperative complications (three trials, RR 0.12, 95% CI 0.02 to 0.85) and more REC (0.4 mm 95% CI 0.15 to 0.66). The only trial comparing EMD with a bioactive ceramic filler found statistically significant more REC (-1.60 mm, 95% CI -2.74 to -0.46) at the EMD treated sites.

Authors' conclusions: One year after its application, EMD significantly improved PAL levels (1.1 mm) and PPD reduction (0.9 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 analysis 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. Bone substitutes may be associated with less REC than 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 about 1 mm 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. Bone substitutes may induce less gum retraction than Emdogain. No serious adverse reactions to Emdogain were reported in trials.

COMMENTARY

Periodontitis results in soft and hard tissue destruction around teeth. Once the inflammatory aspect of the disease has been controlled, the ultimate goal of periodontal therapy is the regeneration of the destroyed tissues. Current regenerative techniques are aimed at the treatment of intrabony and furcation defects. Intrabony defects are defined by the apical location of the base of the defect in relation to the residual alveolar crest, in contrast to suprabony defects whose base is located at the crest. Intrabony defects can further be classified as one-wall, two-wall or three-wall defects, according to the number of residual alveolar bone walls surrounding the tooth surface.

Several clinical techniques have been developed in order to promote periodontal regeneration, including guided tissue regeneration (GTR), the use of bone grafts, and the use of biologically active agents. Enamel matrix derivative (EMD) (Emdogain-Straumann, Basel, Switzerland) is the most

widely studied commercially available bioactive agent. It is derived from the tooth pouches of unerupted porcine teeth and is composed of amelogenins and enzyme components. The biological rationale for the use of EMD is to recapitulate developmental mechanisms whereby enamel matrix proteins are proposed to play a critical role in stimulating cementogenesis. EMD is relatively easy to use because it is administered in a gel carrier and does not require the delicate handling and adaptation associated with membranes used for GTR. However, because it is a gel, it also has the negative characteristic of being non-supportive and hence its use is generally limited to self supporting two and three wall periodontal defects.

The aim of this systematic review was to assess the effectiveness of EMD in the treatment of intrabony periodontal defects. The study inclusion criteria were limited to randomized controlled clinical trials (RCTs) of at least one year follow-up which investigated the treatment of intrabony periodontal defects of at least 3 mm. EMD was compared to either a control (open flap surgical debridement (OFD) – 9 trials), GTR (six trials) or the use of a bone grafting material (one trial). Both parallel group (nine trials) and split mouth (five trials) trial designs were included. The control surgical treatment included a modified Widman flap design (five trials) and papilla preservation flap designs (four trials). A placebo carrier gel without the active EMD ingredient was used in five trials. In the GTR treatment group, most of the trials utilized a non resorbable membrane, with only one trial using a resorbable membrane. The trial which compared EMD with a bone graft used a bone substitute material made of granulated ceramic (BioGlass, US Biomaterials, Alachua, FL, USA). A variety of root conditioning procedures were employed before EMD application, and a variety of postoperative regimes were implemented.

The primary outcome measures that were assessed were tooth loss, changes in probing attachment level (PAL), aesthetics and postoperative complications. Secondary outcome measures included PAL gain <2 mm, as well as changes in probing pocket depth (PPD), gingival recession (REC) and bone level from the base of the defect.

This systematic review is an update of a previous review conducted in 2005.¹ Eight suitable studies were identified in the previous review, with an additional five studies being included in this review. Only one year follow-up data were available. When compared to the control (OFD), statistically significant improvements in the EMD treated sites were found in average PAL gain (1.1 mm) and PPD reduction (0.9 mm). Furthermore, there were fewer sites that failed to gain 2 mm of attachment in the EMD compared to the OFD groups. It is important to note that there was extensive heterogeneity in the reported outcomes, which indicates that the clinical procedure can be unpredictable.

There were no differences in the ultimate treatment outcome of tooth retention, largely because very few teeth were lost following either the control or EMD treatment, which is understandable considering the short follow-up period of one year. In the absence of tooth loss data, if the gain of a minimum of 2 mm of attachment is considered to be a 'de facto' measure of the success of the treatment and taking into account that OFD achieves this outcome in 3 of 4 treated sites, a 'need to treat' analysis indicated that a practitioner would need to treat 9 sites with EMD instead of OFD in order to achieve one additional site with PAL gain of 2 mm. However, it should be noted that this type of analysis is very dependent on the criteria for 'success' and the likelihood of the control achieving this outcome. For example, if the criteria for 'success' is set at 1 mm of PAL gain, then the control treatment (OFD) would achieve this in most cases, and the number of sites that would need to be treated with EMD to obtain one additional site with PAL gain of 1 mm would greatly increase. Although the choice of 2 mm PAL gain as a measure of treatment success is a relatively arbitrary one, this analysis does challenge the cost effectiveness of using EMD in combination with OFD. Nevertheless, any cost effectiveness decision ultimately needs to consider the strategic value of a given tooth, as well as the costs involved with an alternative treatment option.

In terms of the reliability of data obtained from the studies included in this review, it is important to note that, when the authors classified the included studies as having a 'high' (5 studies) or 'low' (4

studies) bias potential, the treatment effect in terms of PAL gain was decreased when only the low bias studies were analysed (from 1.11 mm to 0.6 mm). This means that the overall effect reported in this review on the basis of the complete set of 13 studies may be overestimated.

When compared to GTR (5 trials), EMD had similar results in most parameters, although it was superior in terms of having fewer postoperative complications and resulting in statistically lower recession. When compared with the bone graft, EMD again performed similarly, with the only exception being that there was more recession in the EMD group. However, this finding must be interpreted with caution, as only one trial containing 16 patients compared EMD with a bone grafting procedure.

Overall, this is a comprehensive review which uses stringent inclusion criteria to assess the effect of EMD on the regeneration of intrabony periodontal defects. It should be noted that trials combining the use EMD with GTR and/or bone grafts were not included in this systematic review. However, EMD is often used in conjunction with other regenerative procedures, especially in the management of non-supportive defects. Furthermore, none of the studies reported in this review had 5-year data so only 1-year data were included. However, it is noteworthy that long-term (10 year) data are available showing that the outcomes of EMD can be maintained over long periods, but this particular study² did not meet the criteria for inclusion in this review.

One issue that is not considered in this review is that there are known patient, site, tooth and surgical technique related issues that impact on the success of regenerative techniques.

Furthermore, in most part, the studies included in this review were undertaken by experienced clinicians under optimal conditions. Therefore, if one considers that the results were still very variable, then great caution must be used in generalizing these outcomes to one's own practice.

Given the unpredictability of treatment outcomes using EMD, it should be used judiciously with case selection likely to be of critical importance.

In summary, it can be concluded that EMD has the potential to improve clinical measures of periodontal status to a similar extent as GTR which is widely considered to be the 'gold standard' technique in periodontal regeneration. However, EMD has fewer postoperative complications and less recession, and is generally considered easier to use. Similar to the findings using GTR, the treatment outcomes are variable and both techniques can be considered to be unpredictable. Furthermore, it is unclear whether EMD leads to the ultimate treatment goal of preventing tooth loss, and only long-term studies (minimum 5-year duration) will be able to address this issue.

REFERENCES

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