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Clinical Report

Treatment of Periodontal Defects with Enamel Matrix Derivative: Clinical Evaluation at Early Healing Stages

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Abstract

The aim of this retrospective clinical study was to evaluate the treatment of intrabony periodontal defects with enamel matrix derivative (EMD) during the early stages of healing. Sixteen patients aged 38–77 years with a clinical diagnosis of chronic periodontitis were subjected to data analysis. A total of 25 teeth with various osseous defects received regenerative therapy with EMD, and were followed for a minimum of 6 months. Post-operative healing was uneventful in the majority of cases. Treatment of the intrabony defects with EMD led to a statistically significant improvement in the mean value of probing depth at 3 months compared with that at baseline (p<0.001). Mean values of attachment gain at 3 and 6 months were of clinical significance: 3.6±1.8 mm and 3.2±1.5 mm, respectively. Reduction in probing depth was achieved with minimal recession of gingival margin and was sustained over a time course of 6 months. A progressive increase in radiopacity, suggestive of initial signs of bone-fill, was observed by 6 months. In summary, the results suggest that treatment of intrabony defect with EMD induces favorable periodontal healing with a high level of predictability.

Key words: Periodontal regeneration—Periodontitis—Enamel matrix derivative (EMD)—Intrabony defects

Introduction

Periodontitis, one of the most common infectious diseases in humans, is characterized by gingival inflammation, as well as loss of connective tissue and alveolar bone, which eventually leads to tooth exfoliation. In recent years, a number of new treatment procedures have been introduced in attempts to regenerate lost periodontal tissues. An attractive way of promoting periodontal regeneration is to try to mimic the events that took place during the
development of the periodontal tissues. One such example is treatment with an enamel matrix derivative (EMD). EMD represents an extracellular matrix derivative that seems to control and promote periodontal regeneration. EMD is derived from porcine tooth buds and is available in a commercial formulation (Emdogain® Gel, Biora AB, Malmö, Sweden). This product is composed primarily of acidic extracted amelogenins in an aqueous viscous solution of propylene glycol alginate. The activities of EMD on epithelial cells suggest a potential desirable inhibitory effect on epithelial downgrowth during the early regenerative stages.

Since its introduction, extensive research regarding EMD has been carried out. EMD has demonstrated the ability to encourage periodontal regeneration in both animal studies and clinical trials. The clinical significance of EMD therapy, however, is still under debate, and its scientific base has yet to be firmly established. While it is imperative to evaluate the efficacy of a treatment modality in longitudinal studies, it is equally important to understand the healing process during early periods. It is assumed that EMD has an effect on the critical steps of periodontal wound healing that occur during the early healing phase.

In our teaching hospital, surgical treatment with EMD has been the treatment of choice for patients requesting periodontal regenerative therapy. In the practice of evidence based medicine, it is important to integrate individual clinical expertise with the best available external clinical evidence from systematic research. Toward this end, it is necessary to evaluate the clinical outcomes in one’s own practice setting.

The aim of the present study was to evaluate the clinical outcomes of periodontal regenerative surgery with EMD during the early stages of healing.

Methods

1. Subjects

The study participants were selected from a patient population at Suidobashi Hospital, Tokyo Dental College, with clinical diagnosis of moderate to advanced chronic periodontitis. Written informed consent was obtained from all patients. The following criteria were used for inclusion and data analysis in the present study: 1) no serious systemic complications or history of allergies; 2) periodontal pockets with a probing depth (PD) of ≥6 mm; 3) osseous defects estimated to be at least 4 mm deep and 2 mm wide (largest width). A total of 16 patients (12 women and 4 men) with a mean age of 56.7 years (range; 38 to 77) were subjected to data analysis.

2. Initial periodontal therapy

After systemic and oral assessments, a periodontal treatment plan was formulated for each patient. Initial periodontal therapy consisting mainly of oral hygiene instructions, full-mouth scaling and root planing, and occlusal adjustment (if trauma from occlusion was present) was performed by three clinicians.

3. Clinical parameters

At least 4 weeks after the initial therapy, re-evaluation was performed. The following baseline clinical parameters were recorded prior to the surgery. PD was measured using a Williams probe with a force of 0.25 N by the examiner and rounded up to the nearest millimeter. Clinical attachment level (CAL) was measured from the cemento-enamel junction to the apical depth of periodontal probe penetration. PD, CAL and gingival recession were registered at six sites. Tooth mobility was recorded using Miller’s index. The presence or absence of supragingival dental plaque was recorded by the Plaque Control Record (PCR) of O’Leary et al.

Postoperative re-evaluations were performed at 3 and 6 months after surgery.

4. Radiographic examination

Intraoral radiographs were obtained with a paralleling cone technique. Subjective evaluation was used to detect potential changes in radiographical images.
5. Periodontal regenerative therapy

An individualized treatment plan, with alternatives, was presented to the patient. Informed consent to the proposed surgical intervention was obtained from each patient. If other dental pathologies or conditions were present, they were treated prior to or concurrently with the regenerative therapy. Surgical interventions were implemented between January 2008 and June 2009. Interventions ranged from localized to quadrant surgery, with at least one tooth in the quadrant having intrabony defects matching the above-mentioned criteria. Regenerative therapy with EMD was performed by the standard procedure as described previously. Briefly, a full-thickness periodontal flap (papilla preservation technique) was employed to gain access to the root surface for scaling and root planing. In localized procedures, a vertical releasing incision was made on the buccal aspect, at least one tooth distant from the lesion. Following debridement, sites were acid-etched with 36% ortho-phosphoric acid for 15 seconds in order to remove smear layers. After the sites were thoroughly rinsed with sterile saline, 0.3 ml or 0.7 ml EMD solution (Emdogain® Gel) was applied, in accordance with the manufacturer’s instructions. No attempt was made to use bone graft or other supplementary modalities. The flaps were immediately replaced and sutured with monofilament, non-resorbable sutures. Either modified vertical mattress or interrupted sutures were used to obtain complete closure of the interdental soft tissues. Postoperative instructions were subsequently given to the patients. Patients received an oral antibiotic (typically 300 mg/d cefdinir) and a non-steroidal anti-inflammatory drug for 3 to 5 days. They were advised to use a mouth rinse twice daily. The sutures were removed after 10 to 14 days. After suture removal, patient plaque control with the roll brushing technique utilizing an ultra-soft toothbrush was resumed at the surgically treated sites.

Any adverse reactions or patient perceptions (i.e., pain, bleeding, or swelling, as obtained by interview) during the first week postsurgery were assessed and recorded.

6. Supportive periodontal therapy

Meticulous supragingival professional tooth cleaning was also performed biweekly for the first 6 weeks postsurgery. Thereafter, patients were recalled once a month. They received supportive periodontal therapy, consisting mainly of oral hygiene instruction and professional plaque control.

7. Data management and statistical analysis

The deepest site of the defect was used for evaluating the clinical changes in the primary outcome variables PD and CAL. For statistical analysis of the quantitative data, a software package (InStat version 3.10 for Windows, GraphPad Software, La Jolla, CA, USA) was used. p-values less than 0.01 were considered statistically significant.

Results

None of the patients showed any healing complications with the initial periodontal therapy. During the initial therapy, an effort was made to obtain an optimal level of oral hygiene by patient self-care, as well as professional care.

A total of 25 sites (18 molars, 3 premolars, 4 canines) in 16 patients received regenerative therapy with EMD and were followed up for at least 6 months. The mean PD of the sites at baseline was $7.3 \pm 1.6$ mm, and the defect type included 1 to 3-wall intrabony defects (1-wall: 3 sites, 2–3-wall: 22 sites). The majority of defects treated demonstrated good flap closure during the first and second postoperative week. Examples of the patients’ perceptions of healing during the first week postoperatively are listed in Table 1. The frequency of no perceived pain or swelling was 52%. Post-operative healing, thereafter, was uneventful in the vast majority of patients.

A statistically significant improvement in mean PD was already observed at 3 months postsurgery (Fig. 1). Mean PD reductions in the recorded sites at 3 and 6 months
were 4.4 ± 1.4 mm (range 3 to 8 mm) and 4.2 ± 1.2 mm (range 3 to 7 mm), respectively. The reduction in PD was maintained during the 6 months observation period, with no significant change.

A statistically significant change in CAL was also observed at 3 months postsurgery (Fig. 2). Mean CAL gains in the recorded sites at 3 and 6 months were 3.6 ± 1.8 mm (range 0 to 7 mm) and 3.2 ± 1.5 mm (range 0 to 7 mm), respectively. The CAL gain was maintained during the 6 months observation period, with no significant change. Table 2 shows the frequency distribution of CAL gains at 6 months. Twelve sites demonstrated a CAL gain of 2 to 3 mm and 7 sites a gain of 4 to 5 mm. No significant correlation was found between the baseline PD and CAL gain at 6 months (r = 0.4388, p = 0.0282, by Spearman rank correlation). The reduction in PD was achieved with minimal recession of the gingival margin (Fig. 3).

There was no significant change in tooth mobility during the observation period (Fig. 4), although it was typical to find a transient increase in mobility immediately after surgery. When the relationship between the baseline tooth mobility and CAL gain was assessed, no significant difference in CAL gain was found between teeth without mobility and teeth

<table>
<thead>
<tr>
<th>Perceptions</th>
<th>Prevalence (% surgery events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No remarkable distress</td>
<td>52</td>
</tr>
<tr>
<td>Minor pain</td>
<td>20</td>
</tr>
<tr>
<td>Minor swelling</td>
<td>8</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>8</td>
</tr>
<tr>
<td>Sore spot in gum</td>
<td>16</td>
</tr>
</tbody>
</table>

* Frequencies do not add up to 100% as multiple answers were allowed.

<table>
<thead>
<tr>
<th>CAL gain (mm)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>16</td>
</tr>
<tr>
<td>2–3</td>
<td>48</td>
</tr>
<tr>
<td>4–5</td>
<td>28</td>
</tr>
<tr>
<td>≥6</td>
<td>8</td>
</tr>
</tbody>
</table>

**Fig. 1** Change in PD (mean ± SD). n = 25 *p < 0.001, Friedman test with Dunn post test

**Fig. 2** Change in CAL (mean ± SD). n = 25 *p < 0.01, Friedman test with Dunn post test

**Fig. 3** Contribution of gingival recession and clinical attachment gain in reduction of PD.

**Fig. 4** Change in tooth mobility (mean ± SD). n = 25
with mobility (≥1, Miller index, p = 0.2249, Mann-Whitney U test).

No apparent adverse reactions were recorded as a result of multiple applications of EMD within the same patient. The clinical and radiographic appearances of representative cases are shown in Figs. 5 and 6.

**Discussion**

In the present study, periodontal surgery with EMD resulted in significant PD reductions and CAL gains at treated sites during the early healing period. Although it is generally recommended to wait for 6 months before taking any clinical measurements after EMD treatment, we performed careful probing (0.25 N) to assess soft tissue healing at early stages. An improvement in PD was detected as early as 3 months postoperatively. The observed improvement in PD at 6 months (approximately 4.3 mm; 59% of the baseline PD) was in accordance with the results from a multi-center study of 956 cases in Japan. The mean CAL gain at 6 months was of clinical significance (3.4 mm; 40% of the baseline attachment level). A meta analysis of clinical studies on the management of angular osseous defects with EMD revealed a PD reduction of 4.0 mm (50% of the baseline PD) and CAL gain of 3.2 mm (33% of the original attachment level) for a total of 317 lesions during an observation period ranging from 6 to 12 months.
months. In their international multi-center study, Tonetti et al.\textsuperscript{21} reported a mean CAL gain of 3.1 mm at 1 year. Previous study by our group evaluated the long-term clinical outcomes of treatment with EMD in a private practice setting\textsuperscript{17}. The mean CAL gain at 6 months was 3.6 mm, which was significantly greater than that (2.2 mm) observed in our study on guided tissue regeneration utilizing bioresorbable membrane\textsuperscript{26}. The results of the present study were comparable to those of earlier studies reporting the efficacy of EMD therapy.

In this study, 8 teeth showed mobility at 6 months postoperatively. During the 6 months observation period, no significant change in tooth mobility was observed (Fig. 4). Moreover, no significant difference in CAL gain was found in relation to tooth mobility. It has been suggested that mobile teeth are at greater risk of future attachment loss when compared to teeth without mobility\textsuperscript{23}. Although it is not clear if this is the case for teeth with regenerative therapy, more attention should be paid to mobile teeth during the maintenance period.

It was typical to find a slight improvement in radiopacity at as early as 3 months postoperatively (Fig. 5c). Signs of possible bone-fill were generally more apparent at 6 months. Sculean et al.\textsuperscript{19} reported the formation of new attachment at 6 months following EMD treatment of advanced intrabony lesions. In their study using histological analysis in humans, the formation of new attachment was not always followed by bone regeneration, although the newly formed cementum was predominantly of a cellular character. Heijl et al.\textsuperscript{7} reported that distinct radiographical bone-fill was observed as early as 5 months after surgery with EMD, and further bone gain may be expected for as long as 3 years. Radiographic imaging provides evidence for bone-fill rather than true regeneration, and the present report is based solely on clinical cases, with no histological evidence. However, based on the theoretical basis of this procedure and the cumulative evidence presented by many studies, it seems sound to assume that the results do demonstrate initial signs of regeneration.

In the present study, wound healing immediately following EMD application appeared to be favorable, with few adverse events, as judged by patient perceptions as well as clini-
cal observations. EMD may influence soft-tissue healing, which may cause better post-operative patient perceptions, in addition to its capability of promoting periodontal regeneration. Lack of pain, improved healing of the soft tissues and limited inflammation of the operated areas have been common clinical observations following EMD therapy. Ozcelik et al. reported that patient perceptions on the immediate post-operative period were significantly better in the non-surgery and surgery with EMD groups when compared with the surgery group. On the other hand, Zetterström et al. and Hagenaars et al. reported no differences in post-surgical healing and patient perceptions, between surgeries with EMD and flap operations. Further controlled studies are needed in order to clarify whether application of EMD induces an added healing effect on soft tissues during the early postoperative period.

While the majority of cases in the present study demonstrated clinically favorable healing, it is noteworthy that 4 sites (16%) demonstrated a CAL gain of less than 2 mm. In particular, a case of tooth #37, which had poor prognosis, exhibited a particularly unfavorable outcome by 6 months. The CAL gain once confirmed at 3 months was subsequently lost, showing a PD of 7 mm at 6 months. The wide and deep 1-wall intrabony defect, which extended to the root apex, was likely to be the main cause for the poor outcome in this tooth. An occlusal overload without canine guidance might have contributed as well. These findings call for even more careful judgment based on the prognosis.

With regard to possible sensitization to EMD, Froum et al. reported a lack of clinical adverse reactions following separate applications of EMD in the same individual. The results from our study also support this, since no adverse reactions were observed in patients after multiple applications of EMD.

Like all research, the methods used in this study warrant some consideration. Since the size of the patient sample was small, no attempts were made to differentiate location of surgical sites or defect types in the data analysis. Type of osseous defect has been shown to be important determinant in EMD treatment. Since this was not a prospective case-controlled study, no control (flap surgery only or with placebo) data were available. Furthermore, a standardized reproducible method or computer-assisted subtraction was not utilized for analysis of intraoral radiographs. The evaluation of subgingival microflora was not performed in the patients in the present study. The effect of subgingival microflora on EMD treatment is another area that needs to be investigated.

In summary, results presented in this report, of a 3 to 6 month observation period, demonstrate that periodontal surgery with EMD results in a clinically relevant reduction in PD and a gain in attachment with early signs of bone-fill. Within the limitation of the present study, treatment of intrabony defect with EMD appears to be capable of inducing favorable periodontal healing with a high level of predictability.

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