A Clinical Comparison of a Bovine-Derived Xenograft Used Alone and in Combination With Enamel Matrix Derivative for the Treatment of Periodontal Osseous Defects in Humans

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Background: Enamel matrix protein derivative (EMD) and particulate anorganic cancellous bovine-derived bone xenograft (BDX) have both shown favorable clinical results in reducing intrabony periodontal defects as compared to open flap debridement alone. These materials have shown results comparable to those obtained with guided tissue regeneration. The primary aim of the present study was to evaluate the effectiveness of EMD combined with BDX as compared to BDX alone, with a secondary aim to compare the treatment outcomes of the 2 modalities.

Methods: Seventeen patients with paired intrabony defects and probing depths measuring ≥5 mm who were being treated for chronic periodontitis were selected for this controlled, blinded, split-mouth study. Following non-surgical periodontal therapy, sites were randomly selected to receive either a combination of EMD and BDX (test group) or BDX alone (positive control group). Baseline and 6-month surgical reentry measurements were taken by a calibrated examiner blinded to the treatment. A paired Student t test was utilized to evaluate differences between baseline and post-treatment and between the treatment groups.

Results: Favorable clinical outcomes for both hard and soft tissue measurements were achieved for both treatment groups when compared to baseline (P<0.001). There was no statistically significant difference for any of the measured clinical parameters. Probing depth reduction for the test group and control group was 4.2 ± 1.1 mm and 3.9 ± 1.3 mm, respectively (P>0.8). Mean gain in clinical attachment levels for the test and control groups was 3.8 ± 0.9 mm and 3.7 ± 1.5 mm, respectively (P>0.6). Hard tissue measurements obtained at surgical reentry were used to calculate the bone fill (BF) and percent bone fill (%BF). The BF was 3.2 ± 1.4 mm and 3.0 ± 1.2 mm (P>0.6), and the %BF was 63.3 ± 16.3% and 67.0 ± 19.0% (P>0.4) for the EMD+BDX and BDX groups, respectively.

Conclusions: In summary, both the particulate anorganic cancellous bovine-derived bone xenograft used alone and in combination with enamel matrix derivative are effective for the treatment of human intrabony periodontal lesions. J Periodontol 2002;73:423-432.

KEY WORDS
Periodontal regeneration; proteins, enamel matrix; enamel matrix derivative; grafts, bone; double-blind method; comparison studies; clinical trials, controlled.

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Regenerative periodontal procedures are one mode of therapy that attempts to restore the lost supporting structures of the dentition around a previously diseased root surface. In order to verify true periodontal regeneration, there must be histological evidence of new alveolar bone, periodontal ligament, and cementum attached to the root surface. Histological evidence is then supported with clinical studies that demonstrate significant improvement in clinical parameters. Evidence has shown that regeneration can be initiated through the use of guided tissue regeneration; autogenous bone; and demineralized freeze-dried bone allograft alone (DFDBA) or in combination with synthetic hydroxyapatite. The product is a deproteinized porous bovine allograft alone (DFDBA) or in combination with synthetic hydroxyapatite. It resembles human cancellous bone than DFDBA and has a smaller size, and calcium-to-phosphorus ratio more closely resemble that of human cancellous bone. The bone replacement graft provides for regeneration through conductive or inductive mechanisms by inductive or cell-stimulating mechanisms. The conductive graft acts as a scaffold to support new tissue growth and is eventually replaced by the host tissue. The inductive process involves the graft or growth factor stimulating the host tissues to regenerate lost structures.

The concept of combining materials for periodontal regeneration that is both inductive and conductive is intriguing. Particulate anorganic cancellous bovine-derived bone xenograft (BDX) has been used to successfully treat intrabony defects in humans with evidence of true periodontal regeneration. BDX undergoes a low heat (300°C) chemical extraction process that extracts the organic components, leaving the architecture of bone intact. The surface area, porosity, crystallite size, and calcium-to-phosphorus ratio more closely resemble human cancellous bone than DFDBA and synthetic hydroxyapatite. The product is a deproteinized porous bovine bone with a naturally occurring mineral phase and a 3-dimensional configuration that favors angiogenesis and bone formation. Some questions have developed as to the actual protein content of this material. A recent study was able to extract proteins from BDX particles which were intimately associated with and stabilized by the mineral phase. These proteins were shown to be osteoinductive when added to DFDBA and implanted into the calf muscles of nude mice. Western blot analysis suggested that these proteins may be transforming growth factor-beta (TGF-β) and bone morphogenetic protein (BMP). These proteins may assist BDX in having osteogenic effects. Regardless of the protein content and its effect on regeneration, extensive clinical and histological evidence exists for the use of BDX as a bone replacement graft in periodontal defects.

Enamel matrix derivative is derived from the developing tooth germ of fetal pigs. Its use is based on the principle that enamel matrix proteins play a crucial role in the development of the tooth, specifically, the cementum. EMD consists of 90% amelogenins, with the remaining 10% primarily proline-rich non-amelogenins, tuftelin, tuft protein, serum, ameloblastin, amelin, and salivary proteins. In vitro studies have established that EMD has the ability to enhance periodontal ligament (PDL) cell proliferation, as well as increase production of collagen and protein and promote mineralization. EMD had no significant effects on these parameters for epithelial cells. A more recent study found that enamel matrix proteins have a greater stimulatory effect for attachment of human periodontal ligament fibroblasts (HPLF) than human gingival fibroblasts (HGF), thus allowing the colonization of the root surface with the proper cell lines for periodontal regeneration. This study also found that EMD stimulates the expression of alkaline phosphatase and the release of TGF-β1 from both HPLF and HGF. This implies that EMD may influence HPLF to produce more cementum. The ability of EMD to stimulate both gingival and periodontal fibroblasts to increase production of TGF-β1, a multifactorial growth factor, provides additional evidence for its role in new bone formation. Another study found EMD to stimulate proliferation of osteoblast precursors and increase the differential activity of preexisting osteoblasts. These in vitro models provide a valuable rationale for the use of EMD by identifying some of the cellular effects and interactions that occur. Human and animal histological data have provided sound support for EMD’s role in the formation of cementum along with periodontal ligament and alveolar bone. Several studies report improvement in periodontal parameters following application of EMD to root surfaces in intrabony defects. EMD has proven to be superior to open flap debridement procedures and also shown favorable and comparable clinical outcomes to bioabsorbable and non-resorbable barriers used for guided tissue regeneration.

Since there is ample evidence of partial regeneration of structures lost to periodontal disease, periodontics is now searching for means of achieving even better results. It has been suggested that, due to the limited space-making potential of EMD, it could be added to a particulate graft to assist in maintaining the defect space. EMD and BDX are 2 materials that have been used alone in periodontal therapy and have provided proof of principle that true periodontal regeneration can occur. The purpose of the present study was to evaluate the effectiveness of EMD combined with BDX compared to BDX alone, with a secondary aim to compare the treatment outcomes of

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both modalities to baseline measurements. A separate study compares the effectiveness of EMD combined with BDX to the use of EMD alone.44

MATERIALS AND METHODS

Seventeen systemically healthy adults with no contraindications to periodontal therapy (6 males, 11 females; 3 smokers, 14 non-smokers) between the ages of 32 and 73 with moderate to severe chronic periodontitis were recruited to participate in this single-blind, randomized, controlled clinical trial. Inclusion criteria included 2 radiographic vertical defects measuring at least 3 mm on periapical film in 2 separate sites with periodontal probing depths ≥5 mm following initial therapy. Informed consent was obtained from each patient who agreed to participate in this investigation. The study protocol and the consent were approved by the Institutional Review Board.

All patients received initial therapy including full-mouth scaling and root planing with hand instruments and ultrasonic scalers. A minimum of 2 visits were utilized to complete initial therapy, with oral hygiene instructions and occlusal adjustment addressed when indicated. Approximately 4 to 6 weeks following the hygiene phase of therapy, all patients underwent a re-evaluation examination to assess periodontal changes. All patients were required to achieve a satisfactory O’Leary plaque index45 at the 20% level prior to progressing to the surgical phase.

Clinical parameters were obtained the day of surgery (baseline) by a calibrated examiner blinded to the treatment. Clinical measurements were made with a 15 mm University of North Carolina (UNC) probe and included both soft and hard tissue analysis. Soft tissue measurements included: 1) probing depth (PD), measured from the free gingival margin (FGM) to the base of the pocket (BP); 2) clinical attachment level (CAL), measured from the cemento-enameled junction (CEJ) to BP; and 3) recession, measured from the CEJ-FGM. Hard tissue measurements included: 1) CEJ to alveolar crest (AC); 2) CEJ to base of the defect (BD); and 3) AC-BD. If a permanent restorative margin was available, this was utilized in the same fashion as the CEJ.

The deepest point of each defect was selected as the site to be monitored. Surgical notes and clinical photographs were taken to further identify the surgical sites.

The 2 defects used were randomly assigned to either EMD and BDX or BDX alone by the toss of a coin. The patients were instructed to rinse with 0.12% chlorhexidine gluconate47 for 30 seconds prior to the procedure. Surgical sites were then anesthetized with 2% lidocaine with epinephrine 1:100,000. Intrasulcular incisions were utilized to reflect buccal and lingual full-thickness mucoperiosteal flaps. Debridement of granulation tissue and root surface deposits was accomplished with hand and ultrasonic instrumentation. Final inclusion in the study was based on the intrabony defect depth, AC-BD. Only those radiographic defects measuring ≥3 mm, confirmed surgically, were included in the study. Osseous defects were measured by the examiner blinded to the randomly assigned treatment. The osseous defects were classified by the number of osseous walls. Measurements were rounded to the nearest 1.0 mm by the examiners and recorded along with other surgical notes.

Following hard tissue measurements, the root surfaces were burnished with a cotton pellet soaked with 24% ethylene diamine tetraacidic acid (EDTA) gel (pH 6.7)46 for 2 minutes to remove the smear layer, detoxify the root surface, and expose collagen fibrils, since root conditioning may facilitate enamel matrix protein precipitation onto the root surface.46 The area was then irrigated with 0.9% sterile saline. The lyophilized EMD was reconstituted in a 1 ml propylene glycol alginate (PGA) 15 minutes prior to application. The sites receiving the combination therapy first had EMD applied to the cleansed root surface with the cannula of the carrying device at the most apical portion of the defect, expressing the material until it flowed out of the coronal portion of the defect. The BDX was hydrated with the remaining EMD. This combination of materials was then delivered into the defect. The sites receiving the BDX alone were treated in the same manner without the application of EMD. The soft tissue flaps were then repositioned with sutures** in modified vertical mattress and interrupted fashions. Following 5 minutes of pressure to the area for hemostasis and wound stability, a periodontal dressing†† was placed over the surgical area. Photographs were taken of the preoperative site, the debrided defect, defect fill, suture placement, postoperative healing, and reentry.

Patients were given written and oral explanations of the postoperative regimen. Patients were instructed to rinse twice daily with 0.12% chlorhexidine gluconate47 and to refrain from brushing and flossing in the area for 10 to 14 days. Analgesics were prescribed for postoperative discomfort, and doxycycline hyclate 100 mg†‡ at a dose of 200 mg the day of surgery and 100 mg per day for 10 days was used to prevent infection and aid in healing.47-51 Postoperative appointments were scheduled at 7 to 10 days, 1 month, 2 months, 4 months, and 6 months (reentry). Each appointment consisted of an evaluation of the healing tissues and oral hygiene instruction. At the 2- and 4-month visits, a professional prophylaxis was provided.

† Astra, Westminster, MA.
‡ PrefGel, Biora AB, Malmö, Sweden.
** Gore-Tex, W. L. Gore & Associates, Inc., Flagstaff, AZ.
†† Periocare, Pulpdent Co., Watertown, MA.
‡‡ Pfizer Inc., New York, NY.
At the 6-month appointment, a periodontal evaluation was completed, with all soft tissue measurements recorded by the examiner. The grafted areas were surgically reentered to evaluate and record hard tissue findings. If the residual defect measured ≥3 mm, the defect was retreated with the material originally utilized. If the defect was ≤3 mm, osseous recontouring was used to eliminate the defect and tissues were apically positioned. Periodontal flaps were sutured with 4-0 chromic gut in an interrupted fashion. Patients were evaluated 7 to 10 days postoperatively and then placed on a periodontal maintenance program.

**Statistical Analysis**

Power and sample size estimates were based on comparing 2 related means with a paired Student t test. Each patient had 2 treated sites and served as his/her own control. It was estimated that 16 patients would be sufficient to detect a difference by a paired Student t test at the P 0.05 level with a power of 0.85. Seventeen paired defects were treated in this study. A mean and standard deviation were determined for each clinical parameter in both groups. The baseline and 6-month values were compared for changes that occurred over time, i.e., probing depth reduction (PDR), clinical attachment level gain (ALG), gingival recession (REC), crestal resorption (CR), bone fill measured in mm (BF), percentage bone fill (%BF), and percentage defect resolution (%DR). The paired Student t test was utilized to evaluate differences between the treatment groups and to establish differences between baseline and reentry measurements.

**RESULTS**

All 17 patients returned for reentry evaluation. Clinical evaluation of postoperative healing revealed excellent soft tissue response to both treatment groups with no adverse complications seen or reported. During the 6-month period following treatment, all patients demonstrated plaque index scores similar to those prior to surgical therapy.

Tooth location and type, osseous wall defect, and treatment distribution are shown in Table 1. Overall, an analysis of sites based on maxillary versus mandibular, tooth type, and patient age and gender revealed no significant differences in any measured parameter. Smoking status was not analyzed because only 3 subjects had a positive smoking history.

There was no statistically significant difference between groups prior to treatment for PD, CAL, and surgical defect depth (AC-BD). The average initial PD, CAL, and defect depth were 7.1 mm, 7.5 mm, and 4.4 mm for those sites treated with BDX alone and 7.5 mm, 7.9 mm, and 5.0 mm for the combination therapy sites. Statistical analyses were carried out comparing all treated sites to baseline and comparing the 2 treatment modalities.

Postoperative probing depth and clinical attachment level were found to be significantly different when compared to preoperative measurements for both treatment groups, but there were no statistical differences between the 2 treatment groups (Table 2). Probing depth reduction (PDR) and clinical attachment level gain (ALG) were found to be statistically significant for both groups compared to baseline (P <0.001), but a comparison between the 2 treatments revealed no significant difference (Table 2). The PDR for the combination therapy was 4.2 ± 1.1 mm, while the BDX alone had a PDR of 3.9 ± 1.3 mm. The ALG for the combined group was 3.8 mm, and 3.7 mm for the BDX alone group. An evaluation of gingival recession that occurred after treatment revealed a mean increase in recession of 0.24 mm for the BDX group and 0.41 mm for the combined therapy, which was not statistically significant when compared to baseline or between the 2 treatments.

**Table 1.**

<table>
<thead>
<tr>
<th>Category</th>
<th>BDX (n = 17)</th>
<th>EMD + BDX (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxilla</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mandible</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Anterior teeth</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Premolars</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Molars</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>3 osseous walls</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>2 or 3 osseous walls</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

**Table 2.**

<table>
<thead>
<tr>
<th>Soft Tissue Response</th>
<th>BDX*</th>
<th>EMD + BDX*</th>
<th>t Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presurgical pockets</td>
<td>7.1 ± 1.0</td>
<td>7.5 ± 1.23</td>
<td>0.25</td>
<td></td>
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<tr>
<td>Postsurgical pockets†</td>
<td>3.2 ± 0.8</td>
<td>3.2 ± 0.8</td>
<td>0.80</td>
<td></td>
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<tr>
<td>Probing depth reduction</td>
<td>3.9 ± 1.3</td>
<td>4.2 ± 1.1</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Gingival recession</td>
<td>0.24 ± 0.6</td>
<td>0.41 ± 0.5</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Attachment level gain</td>
<td>3.7 ± 1.5</td>
<td>3.8 ± 0.9</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>

* Patient mean values for mm or percentage.

† Frequency of defect fill of at least 50% of original bony defect.
Evaluation of the hard tissue findings at baseline and at the reentry surgery showed both treatments had significantly improved the values of bone fill (BF), percentage bone fill (%BF), and percentage defect resolution (%DR) (Table 3). The amount of crestal resorption for both treatment groups was minimal, without any statistically significant difference between the 2 groups (0.60 mm for EMD + BDX and 0.70 mm for BDX alone). The mean bone fill in the experimental group was 3.2 mm, and for the control group, 3.0 mm. These values correspond to 63.3% and 67.0% bone fill, respectively. The percentage defect resolution for the experimental group was 75.1% and 84.6% for the control group, providing no statistically significant difference. A summary of soft and hard tissue values for sites treated with either modality was compared and showed no statistically significant difference between treatment types. Statistical analyses revealed similar favorable results for both treatment groups for hard and soft tissue measurements when compared to baseline.

**DISCUSSION**

This study compared enamel matrix derivative (EMD) combined with a particulate anorganic cancellous bovine-derived bone xenograft (BDX) to BDX alone in the treatment of human intrabony defects. The results of this study demonstrate that both treatment modalities provide improvements in hard and soft tissue measurements that are statistically and clinically significant when compared to baseline. Furthermore, statistical analysis of the data revealed no significant differences between the treatment groups.

Table 3.

**Hard Tissue Responses**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BDX*</th>
<th>EMD + BDX*</th>
<th>t Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original bone defect</td>
<td>4.4 ± 1.33</td>
<td>5.0 ± 1.7</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Amount defect fill</td>
<td>3.0 ± 1.2</td>
<td>3.2 ± 1.4</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Percent defect fill</td>
<td>67.0 ± 19.0</td>
<td>63.3 ± 16.3</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Crestal resorption</td>
<td>0.70 ± 0.5</td>
<td>0.60 ± 0.6</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Percent defect resolution</td>
<td>84.6 ± 14.4</td>
<td>75.1 ± 14.2</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

* Patient mean values for mm or percentage.

The treatment of intrabony defects with various grafting materials has provided a baseline for what can be achieved in reference to regenerative efforts to create bone fill. A review of the literature shows that a mean threshold of approximately 60% to 65% bone fill can be achieved. Quintero et al. and Mellonig demonstrated an average bone fill of 2.4 mm (65%) and 2.6 mm (65%), for defects treated with DFDBA. Other studies using DFDBA had bone gain of 1.9 mm (64%) and 2.2 mm (53%). Bone fill in the present study was 3.2 mm or 63.3% for sites treated with the combination of EMD and BDX, and 3.0 mm or 67.0% for sites treated with BDX alone. The results here compare favorably to earlier studies using DFDBA.

When evaluating our results, this study must be compared to others using BDX in the treatment of intrabony defects. Numerous studies have utilized BDX alone or in combination with collagen membranes and all reported improvements in clinical parameters. Richardson et al. compared BDX to DFDBA in human vertical intrabony defects and reported no statistical differences between treatment groups, although a trend towards BDX performing better than DFDBA was noted. Soft tissue measurements in this study were PDR = 3.0 mm and ALG = 3.6 mm. Surgical reentry showed BDX sites to have an increase in bone height of 3.0 mm and associated bone fill of...
56%. These parameters are comparable to the present study’s use of BDX alone in intrabony defects. Another surgical reentry study evaluated BDX in combination with a porcine-derived collagen membrane to treat intrabony defects. This study found the treatment outcomes to be significantly better when compared to the control sites receiving open flap debridement. The mean values for probing depth reduction were 3.6 mm; ALG 3.3 mm; and mean bone fill 3.8 mm. Studies by Cohen et al. and Brion, which relied on clinical and radiographic parameters to evaluate treatment outcome, found an increase in bone height of 2.6 mm and 3.12 mm, respectively. The soft and hard tissue results of our study for defects treated with BDX compare favorably to the previous studies with probing depth reduction of 3.9 mm, attachment level gain of 3.7 mm, bone fill of 3.0 mm, and percentage bone fill of 67.0%.

In vitro studies have identified favorable mechanisms initiated by EMD influencing periodontal wound healing. The clinical efficacy of EMD is well supported in the literature. The probing depth reduction in these studies ranged from 3.0 mm to 5.2 mm, and attachment level gains ranged from 1.7 to 4.6 mm. Most of these studies used radiographic analysis to assess bone fill, which ranged from 1.2 mm to 2.9 mm. In studies comparing EMD to guided tissue regeneration, EMD has provided similar favorable results. Histological studies have further confirmed that, not only does EMD have the potential of significantly improving soft tissue mea-
measurements, but it can also provide true periodontal regeneration consisting of cementum, periodontal ligament, and alveolar bone.\textsuperscript{15,16}

Although the idea of combining a bone graft with a biological modulator is not novel, the use of such a material has not been extensively studied in human intrabony defects caused by periodontal disease. Bowers and coworkers used osteogenin in combination with DFDBA to treat intrabony defects and compared the findings to the use of DFDBA alone.\textsuperscript{11} This study revealed no significant difference between the 2 groups; however, there was a trend towards the combination group showing more improvement. A multi-center trial compared a cell-binding protein (P-15) combined with an anorganic bovine-derived bone matrix (ABM) to ABM alone in the treatment of human intrabony defects.\textsuperscript{64} The results showed that statistically significantly greater defect fill was achieved with the ABM/P-15 (2.9 mm; 73%) versus the ABM alone (2.2 mm; 51%). Another study comparing ABM/P-15 demonstrated 2.8 mm (72%) defect fill.\textsuperscript{65} The combination of BDX and EMD in the current study resulted in a mean of 3.2 mm (63%) defect fill. When we assess the present study outcomes for bone fill and bone fill percentage, we see that both treatment groups compare favorably to those previously mentioned (Table 3). The difference between smokers and non-smokers was...
negligible. Since only 3 subjects were smokers, these data were not analyzed statistically.

Like the present study, Lekovic and coworkers66 used a split-mouth design combining EMD with BDX versus EMD alone to treat intrabony defects and surgical reentry at 6 months. The sites treated with the combination therapy resulted in a probing depth reduction of 3.43 mm, attachment level gain of 3.13 mm, and bone fill of 3.83 mm.66 Our study showed similar results: PDR of 4.2 mm, ALG of 3.8 mm, and BF of 3.2 mm.

It has recently been reported67 that a much larger sample size than ours is necessary to definitively show a statistically significant difference between 2 therapies. This observation was made after analyzing studies comparing 2 treatment modalities and finding that the inability to demonstrate a difference may be due to inadequate sample size. Gunsolley et al. reported that a sample size ranging from 64 to 137 per treatment group is needed to show a significant difference.67 A post-hoc power analysis done for our study showed that, in order to demonstrate statistical differences between the 2 treatment modalities for probing depth reduction, attachment level gain, and bone fill, approximately 128, 812, and 524 patients, respectively, would be needed. These are clearly unrealistic numbers for a clinical investigation.

It should be noted that there were other valuable outcomes from this study that are subject to empiricism, clinical judgment, and are difficult to quantify. First, it was noted that the handling characteristics of BDX were improved when combined with EMD. The consistency of the materials together provided a congealed gel-like graft that was easy to deliver to the intraoral site, easily packed into the defect, and demonstrated adhesion to the site once placed. Due to the fact that wound stability and defect space maintenance are desirable qualities for periodontal regeneration, the handling qualities of the combined materials may be of some benefit. It was also noted that the combination therapy demonstrated more rapid soft tissue healing during the immediate postoperative course in some cases. Furthermore, upon surgical reentry of the sites, it was noted that the consistency of the EMD + BDX sites appeared to be more bone-like with fewer bone particles evident. This may be due, in part, to biological responses triggered by the use of the enamel matrix proteins. These proteins have been shown to stimulate production of the growth factor TGF-β1 by mesenchymal cells in the wound site33,60 and to stimulate cells involved in bone metabolism and healing.35 Further studies are needed to better explain the mechanisms of biologic mediators like EMD and to substantiate the claim that EMD combined with BDX can provide true periodontal regeneration.

The results of this study provide evidence that EMD and BDX can be used for periodontal regenerative therapy without abnormal sequelae during postoperative healing. When evaluating all periodontal intrabony defects treated, soft tissue measurements recorded at baseline compared to those recorded at 6 months postoperatively demonstrated a statistically significant improvement regardless of treatment group, tooth type and location, age, and gender. In comparing sites treated with a combination of EMD and BDX versus BDX alone, no statistically significant difference was found. Furthermore, results reveal that the use of BDX alone in this treatment population is as effective as the use of EMD combined with BDX. With a greater knowledge and understanding of the biological effects that mediators such as EMD can produce, future outcomes in periodontal regeneration may reach new levels of success and predictability.

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