Enamel Matrix Derivatives in Periodontal Regeneration: A Review

Dr Rohan Gupta
Assistant professor
Department of Periodontology and Oral Implantology
Rajasthan Dental College & Hospital, Jaipur

Dr Nidha Madan
PG student
Department of Conservative Dentistry & Endodontics
Mahatama Gandhi Dental College & Hospital, Jaipur

Introduction

Enamel matrix derivative proteins (EMD) are secreted by the Hertwig's epithelial root sheath (HERS) during tooth development and may be critical in the formation of cementum. These proteins share similar amino acid sequences between bovine, porcine and human species. Because of these inter-species similarities, EMD for dental use is sequestered from developing teeth of fetal pigs and is marketed by the Straumann Company as Emdogain gel. This gel is composed mainly of amelogenin, which makes up 90% of the enamel matrix derivative proteins and it is thought to be the key protein associated with cementogenesis during tooth formation. The remaining 10% of EMD is proline-rich non-amelogenins including among them: tuftelin, tuft protein, ameloblastin and amelin. The material is a viscous gel obtained by mixing 1 ml of a vehicle solution with a powder and applied with a syringe into the site.

Enamel matrix derivative (EMD) has been approved by the U.S. Food and Drug Administration for use in achieving periodontal regeneration in angular bony defects.

Literature Review

The freeze-dried protein extract is solubilized in a propylene glycol alginate carrier solution and applied to debrided, root-conditioned periodontal intrabony defects. Histologic evidence of periodontal regeneration has been shown in a human dehiscence model after application of enamel matrix derivative. However, human case reports have reported inconsistent histologic evidence of regeneration.

An examination of two specimens followed upto 12 months failed to show evidence of new attachment formation. Yukna et al (2000)[1] reported that periodontal regeneration was possible after the use of EMD, but on an inconsistent basis. In a 10-patient case series, evidence of regeneration was seen in three specimens, while new attachment (connective tissue attachment/adhesion only) was seen in three specimens, and the remaining four specimens exhibited healing with a long junctional epithelium.

These results may be supported by the findings of a recent in vivo study that reported that EMD was not an osteoinductive material, but rather an osteoconductive one. Most human clinical trials and case series of EMD have demonstrated significant improvements in probing measurements and radiographic evidence of bone fill. A recent systematic review has concluded that there is evidence supporting the use of EMD for periodontal osseous defects to improve Clinical attachment level (CAL) and reduce Probing Depth (PD), although long-term benefits have not been established. In a randomized, placebo-controlled, split-mouth trial design, 1- and 2-walled defects treated with enamel matrix derivative were compared to defects treated with a vehicle placebo over 3 years.

At the end of the trial, statistically significant reductions in probing depth (3.1 mm for test versus 2.3 mm for control) and attachment gain (2.2 mm for test versus 1.7 mm for control) were seen. In regard to radiographic evidence of bone gain at 3 years post-treatment, the mean gain for enamel matrix derivative-treated sites was 2.7 mm, or 36% of the initial bone loss, compared to unchanged bone levels on the control sites. The value of radiographic evidence of bone gain at 36 months in the test sites was equal to a mean 66% radiographic bone fill of the original defects treated. On the other hand, a recent case series reported that the positive clinical results obtained from the use of EMD in intrabony defects in 21 patients were not confirmed by the radiographic results obtained from standardized, computerized radiographs after 12 months of healing and did not reveal significant improvements. Similar results were also found at 36 months.

In vitro studies have shown the positive effect of EMD on proliferation of periodontal ligament cells, gingival fibroblasts, and cementoblasts. Consequently, EMD was applied to promote wound healing in a placebo-controlled, randomized study. EMD or a vehicle control was applied topically after root and soft tissue instrumentation. EMD-treated sites had less inflammation, less bleeding on probing, and less post-treatment discomfort. It appears that EMD offers some potential for regenerative therapy around natural teeth and represents a novel method for enhancing regeneration outcomes.

Heijl et al(1997)[3] have compared the use of enamel matrix derivatives with a placebo in 33 patients with 34 paired test and control sites, mostly one and two wall defects, followed for 3 years. They found a statistically significant radiographic bone gain of 2.6 mm.

Histologic evidence of new cementum formation with inserting collagen fibers on a previously periodontitis- affected root surface and the formation of new alveolar bone in human specimens have been demonstrated following EMD treatment (Mellonig, 1999)[4]. However, while in the study of Mellonig, healing had occurred with acellular cementum on the root surface, and the newly formed cementum in the study of Sculean et al. (2008)[5] which displayed a predominantly cellular character. The ability of EMD to produce regeneration has been confirmed in controlled animal experiments, following the treatment of intrabony, furcation and dehiscence defects (Hammarstrom et al, 1997; Araujo & Lindhe, 1998)[6,7].

Del Pizzo et al[8] assessed the ability of enamel matrix derivative (EMD) to improve root coverage with a coronally advanced flap (CAF) during a 2-year follow-up. Fifteen patients each with two single and similar bilateral Miller Class I or II gingival recessions (30 recessions) were selected. Each recession was randomly assigned to the test group (CAF+EMD) or the control

group (CAF only). Root coverage outcomes were similar in both groups and no statistically significant differences were found at all between them. Hence, the additional use of EMD to CAF is not justified for clinical benefits of root coverage, but as an attempt of achieving periodontal regeneration rather than repair.

Hoffmann et al[9] evaluated effects of patient factors on the outcome of regenerative treatment of buccal mandibular class II furcation defects. Fifty-one patients were recruited. In the intention-to-treat population 21 patients were allocated into the sequence left treatment with enamel matrix protein derivative (EMD) and right guided tissue regeneration (GTR) and 27 in the sequence left GTR and right EMD. Evaluated patient factors were: smoking, age, gender, hypertension and oral hygiene status. In patients 54 years of age and older, in males, in non-smokers and in patients with "poor" hygiene EMD-treated sites showed a significant higher mean reduction of the parameters d (age), b (gender, hygiene) a (smoking, hygiene) when compared with sites treated with GTR.[9]

Surgical Technique

The technique, as described by Mellonig[2], is as follows for Enamel Matrix Derivatives:

1. Raise a flap for regenerative purposes.
2. Remove all granulation tissue and tissue tags, exposing the underlying bone, and remove all root deposits by hand, ultrasonic scaling, or both.
3. Completely control bleeding within the defect.
4. Demineralize the root surface with citric acid pH 1, or preferably with 24% ethylen-ediaminetetracetic acid (EDTA Biora) pH 6.7 for 15 seconds. This removes the smear layer and facilitates adherence of the Emdogain.
5. Rinse the wound with saline and apply the gel to fully cover the exposed root surface. Avoid contamination with blood or saliva.
6. Close the wound with sutures. Perfect abutment of the flaps is necessary; if this cannot be obtained, correct the scalloping of the gingival margin or perform a slight osteoplasty. Although placement of the dressing is optional, it may protect the wound. Systemic antibiotic coverage for 10 to 21 days is recommended (Doxycycline, 100 mg daily).

Biological Properties

It appears to have significant roles in regeneration by the stimulation of the periodontal ligament (PDL), cementum, bone and vascular components.

Role in Periodontal Ligament Formation: In vitro studies have shown that EMD enhances proliferation of PDL cells. Other investigations revealed that cultured PDL cells exposed to EMD demonstrate increased attachment rate and metabolism. PDL cells exposed to EMD releases several growth factors such as transforming growth factor TGF, interleukin (IL-6) and platelet derived growth factor AB (PDGF-AB) all of which functions to recruit and differentiate mesenchymal cells for regeneration. Conversely, it inhibits epithelial cell growth. This inhibition may preferentially promote the proliferation of mesenchymal cells instead of epithelium by the PDL release of autocrine growth factors in a process mimicking natural root development.

Role in Cementogenesis: Secretion of EMD by the inner layer of the epithelial root sheath is required prior to cementum deposition. This regenerative process, modified through its application, results in cementum formation in both primates and humans.

Role in Osteogenesis: In vitro studies demonstrated an overall stimulatory effect of EMD on osteoblastic cells. Similar outcomes were noted in vivo in which the addition of EMD to demineralized freeze-dried bone allograft material (DFDBA) resulted in enhanced bone formation.

Role in Angiogenesis: The role of vascular ingrowth (angiogenesis) into healing periodontal sites is vital to the success of guided tissue regeneration procedures. In vitro wound studies investigating the effect of Emd have shown increased angiogenesis and improved healing properties after its application.

Role as an antimicrobial: A secondary property of EMD is the antimicrobial effect displayed in the in-vitro studies showing inhibition of periodontal pathogens such as Actinobacillus actinomycetemcomitans (Aa), Porphyromonas gingivalis (Pg) and Prevotella intermedia (Pi). Further investigation revealed this inhibition is due to the alginate carrier and not the proteins in Emd. More research is required in the in vivo model to substantiate this proposal.

Role as a Membrane: Periodontal membranes prevent the epithelial downgrowth into intrabony defects and allow the repopulation of the diseased root surface with undifferentiated cells from the surrounding bone and PDL. Because of its epithelium inhibitory properties, it may function as a periodontal membrane with varying degrees of clinical success.

Clinical Applications

Periodontal Defects: Emdogain was approved by the FDA for the topical application to diseased root surfaces to treat intrabony and furcation type of defects. The use of EMD in combination with flap debridement resulted in 2.4 mm of greater osseous fill compared to flap debridement alone. It can also be mixed with a graft material (autogenous or allograft) in the treatment of intrabony defects but there are no clinical studies that demonstrate the clinical significance of this combined therapy.

Periodontal Plastic Procedures Recession type defects treated with EMD (plus connective tissue grafts resulted in the histologic evidence of 1.87 mm of new bone and PDL over the previously diseased root surface. In a recent study, EMD plus a coronally positioned flap (CPF) compared to a connective tissue graft demonstrated similar clinical outcomes of 95.1% and 93.8% root coverage respectively. Even though the results clinically similar, the EMD plus coronally positioned flaps (CPF) eliminated the need for a donor site that is required for the connective tissue grafts.

It is supplied in a pre-filled, pre-mixed syringe that is available in two sizes - 0.7 ml for multiple defects and 0.3 ml for single defect sites. Each kit contains three syringes of EMD in addition to EDTA (24% ethylene-diaminetetraacetic acid) which functions as a root conditioner. Each syringe is intended for single use only. The kits must be maintained below 37 degree celcius during transport and must be refrigerated until use. It has a shelf life of 24 months; assuming proper refrigerated storage. After removal of all granulation tissue and calculus, the root surface is conditioned with EDTA gel for 2 minutes by gently burnishing with a cotton pellet. After removing the root conditioner with irrigation, EMD is applied to the root surfaces with a syringe. It is critical that no saliva or blood contaminate the root surface prior to its application. The gingival flaps are sutured following placement of appropriate graft material or membrane if indicated. Use of EMD in periodontal therapy in humans had no negative impact on periodontal wound healing. Serum samples of patients treated with this (in periodontal defects) demonstrated low immunogenic potential even after repeated applications. These results were confirmed in allergy prone patients indicating that its use in humans is safe. While possible transfer of viruses or other infectious agents such as prions among humans and animals is a valid concern, no disease transmission has been reported. Emdogain is a material recently available for general use as a periodontal regenerative product that is based on the concept of bioengineering. Further investigations are needed to elucidate the specific functions of the proteins. More clinical studies are needed comparing the efficacy of EMD with other treatment modalities presently available[10].

References

References are available on request at editor@healtalkht.com