REVIEW ARTICLE

ENAMEL MATRIX PROTEIN AND PERIODONTAL REGENERATION

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Abstract

Therapeutic approaches to periodontal regeneration in the past have utilized bone replacement grafts, growth factors, barrier membranes or combinations of these approaches. More recently, enamel extracellular matrix proteins have been introduced to stimulate periodontal regeneration. This article attempts to enlighten its readers with the role of enamel matrix protein in periodontal regeneration.

Key Words Enamel matrix protein; Emdogain; Intrabony defect; Regeneration

INTRODUCTION

Recently biomodification of the root surface with enamel matrix proteins (EMP) during surgery and following demineralization with EDTA has been introduced. It is believed that the application of EMP (amelogenins) might promote periodontal regeneration as it would mimic events that took place during the development of the periodontal tissues.[1] This view is based on the finding that the cells of the Hertwigs epithelial root sheath deposit EMP on the root surface prior to cementum formation and that these proteins are the initiating factor for the formation of acellular cementum.

The commercially available product Emdogain ®, (Fig. 1) approved by the U.S. Food and Drug Administration (USFDA) is a purified acid extract of porcine origin and contains enamel matrix derivatives (EMD). The material is available in a viscous gel form and consists of enamel-derived proteins from tooth buds in a polypropylene liquid. One ml of the vehicle solution is mixed with a powder and then delivered by a syringe to the defect site. Ninety percent of the EMP is formed by amelogenin while the rest is composed of proline rich non-amelogenins, tuftelin, tuft protein, serum proteins, ameloblastin and amelin.[1]

ROLE IN PERIODONTAL LIGAMENT FORMATION

In vitro studies have shown that Emdogain enhances proliferation of PDL cells. Other investigations revealed that cultured PDL cells exposed to Emdogain demonstrate increased attachment rate and metabolism.[2] PDL cells exposed to Emdogain release several growth factors such as transforming growth factor (TGF-1), interleukin (IL-6) and platelet derived growth factor AB (PDGF-AB) all of which function to recruit and differentiate mesenchymal cells for regeneration.[2] Conversely, Emdogain inhibits epithelial cell growth. This inhibition may preferentially promote the proliferation of mesenchymal cells instead of epithelium by the PDL release of autocrine growth

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Fig. 1 Emdogain ®

factors in a process mimicking natural root development.[2]

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 the application of Emdogain, results in cementum formation in both primates and humans.[3]

ROLE IN OSTEOGENESIS

In vitro studies demonstrated an overall stimulatory effect of Emdogain on osteoblastic cells. Similar outcomes were noted in vivo in which the addition of Emdogain to demineralized freeze-dried bone allograft material (DFDBA), resulted in enhanced bone formation.[4]

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 Emdogain have shown increased angiogenesis and improved healing properties after its application.[5]

ROLE AS AN ANTIMICROBIAL

A secondary property of Emdogain is the antimicrobial effect displayed in the in vitro studies showing inhibition of periodontal pathogens such as Actinobacillusactinomycetemcomitans, Porphyromonasgingivalis and Prevotella intermedia. Further investigation revealed this inhibition is due to the alginate carrier and not the proteins in Emdogain.[6] 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, Emdogain may function as a periodontal membrane with varying degrees of clinical success.[7]

METHOD OF USAGE:

The technique of using enamel protein derivative has been described by Mellonig (1999) as follows:[8]

After raising a flap for reconstructive purposes (either a papilla preservation flap or a conventional flap), all granulation tissues and tissue tags from the area are removed to expose the underlying bone. All root irritants are removed by hand scaling or ultrasonic scaling or both. Hemostasis is achieved. Root surface demineralization is done with citric acid (pH of 1) or preferably with 24% EDTA (pH of 6.7) for 15 seconds. This removes the smear layer and facilitates adherence of Emdogain. The area is rinsed with saline and EMP available in gel form is applied over the exposed root surface completely. Contamination with blood or saliva should be avoided. The wound is closed, sutures placed and periodontal dressing given. Perfect adaptation of the flaps is a must and if not achieved a little osteoplasty may be performed. Doxycycline, 100mg daily for 10-21days is advised.

REVIEW OF LITERATURE

In a series of case reports, Heden(2000) reported 4–4.5 mm gain of clinical attachment and about 70% bone fill in intrabony defects after treatment with EMD.[9] In a multicenter clinical study comprising of 33 subjects with 34 paired intrabony defects, EMD resulted in a larger amount of probing attachment level (PAL) gain (2.2 mm) and statistically significantly more bone gain (2.6 mm) than open-flap debridement when evaluated after 36 months.[10]

In another split-mouth clinical trial of 23 patients by Froum et al. (2001) a probing pocket depth (PPD) reduction of 4.9 mm, a PAL gain of 4.3 mm and a bone gain of 3.8 mm (evaluated by re-entry surgery) were observed after EMD application in 53 intrabony defects. These values were statistically significant when compared to results obtained by flap surgery (2.2 mm, 2.7 mm and 1.5 mm respectively in 31 defects).[11]

Tonetti et al.(2002) compared the clinical outcomes of simplified papilla preservation flap (SPPF) with or without the application of EMP in a total of 83 test and 83 control subjects with similar baseline periodontal conditions and defect types and concluded that the test defects showed significantly more clinical attachment level (CAL) gain than the controls (3.1 ± 1.5 mm and 2.5 ± 1.5 mm respectively).[12]

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Filippi et al (2002) showed that Emdogain might play a role in reducing external root resorption following avulsion and subsequent re-implantation. In a prospective study, trauma induced ankylosed teeth treated with application of Emdoga in prior to re-implantation showed reduced rate of external root resorption compared to teeth that did not receive its application.[13]

Cochran et al.(2003) in a study in monkeys showed that the combined application of EMD and autogenous bone grafts may improve periodontal regeneration in periodontal defects compared to flap surgery alone.[14]

In a recent study, Emdogain 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 were clinically similar, the Emdogain plus coronally positioned flaps (CPF) eliminated the need for a donor site that is required for the connective tissue grafts.[15]

Pontorieroet al. compared EMD application with GTR with both resorbable and non-resorbable membranes in intrabony defects. After 12 months, there were no significant differences among the groups and EMD application resulted in a PPD reduction of 4.4 mm and a PAL gain of 2.9 mm, while the corresponding values from the membrane-treated sites (both GTR groups combined) were 4.5 mm and 3.1 mm respectively.[16] Similar results were reported by other investigators also.[7,17]

Jepsen et al (2004) compared EMP, Emdogain with GTR therapy in 45 paired mandibular molars with Degree II (Hamp) furcation involvement. After 14 months, there was a mean reduction in the open horizontal furcation depth of 2.8 mm for EMP sites as compared to 1.8 mm for GTR treated sites. Completely closed furcation defects were 8/45 for EMP and 3/45 for GTR. It was concluded that though both treatment modalities resulted in significant clinical improvement, EMP provided greater reduction of furcation depths, a smaller incidence of post-operative pain or swelling and less gingival recession.[18]

In a case cohort study, Cortellini and Tonetti (2007) indicated that a minimally invasive surgical technique combined with EMD in the regenerative treatment of isolated intrabony defects resulted in excellent clinical improvements while limiting patient morbidity.[19] Sculean et al (2008) reported at the end of their 10 year study, positive results in intrabony defects treated with EMD.[20]

Kuru et al (2009) demonstrated in two cases the possibility of treating human buccal recessions with EMD plus a laterally sliding flap, with predictable root coverage and clinical attachment gain.[21]

SO DOES EMD IMPROVE THE OUTCOME OF PERIODONTAL REGENERATION?

Though several studies highlight the beneficial role of EMP/EMD in periodontal regeneration, there are studies to the contrary. Araùjoet al. (2003) in a study in dogs noted that re-implanted roots that had been extracted and deprived of vital cementoblasts and subsequently treated with EMD failed to prevent ankylosis and root resorption.[22] Another study in vitro by Chong et al. (2006) has also failed to confirm that EMD has any significant effect on periodontal ligament cell proliferation.[23] Grusovin et al (2009) attempting regeneration in deep and wide intrabony defects, found no additional clinical benefits of using Emdogain in comparison with a placebo (Emdogain carrier alone).[24] Aroca et al (2010) showed that EMD did not enhance clinical outcome in the treatment of a class III recession-type defect when used with a modified tunnel/connective tissue graft technique compared with the modified tunnel/connective tissue graft technique alone.[25] The additional use of EMD combined with a subepithelial connective tissue graft procedure does not produce a beneficial clinical outcome in terms of root coverage was reported by Rasperini et al (2011).[26]

CONCLUSION

Application of enamel matrix proteins in the form of Emdogain has set a modern standard for periodontal regeneration therapy. Despite the lack of clarity regarding its beneficial effects, clinicians employ EMP as root surface biomodifiers in regenerative surgeries to condition the root surfaces and to make the exposed root surface biologically compatible with a healthy periodontium.Further studies are needed in order to clarify definitively the possible advantage of combination therapy using EMD and bone grafts/bone substitutes.

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