



British Society of  
Periodontology and  
Implant Dentistry

## 'BSP Systematic Review Prize 2020'

**TITLE:** Flapless non-surgical periodontal therapy with enamel matrix derivative: a systematic review

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**ABSTRACT:**

*Objectives:* This systematic review aimed to rigorously evaluate the available randomized controlled trials (RCTs) for conclusive evidence on efficacy of enamel matrix derivative (EMD) in improvement of treatment outcomes in flapless non-surgical periodontal therapy as an adjunct to scaling and root planing (SRP).

*Methods:* Systematic review was conducted in accordance with PRISMA guidelines. PubMed (MEDLINE), Cochrane Central Register of Trials (CENTRAL) and Embase electronic databases were searched along with hand searching of dental journals, up to September 2020. The focused question addressed was: What is the effectiveness of EMD as an adjunct to SRP on clinical and patient-centered treatment outcomes? Study selection criteria was: population: adult patients with periodontitis; intervention: flapless EMD application as an adjunct to SRP; comparison: SRP alone; outcome measures: studies were included if reporting at least one of the outcome measures viz., changes in clinical attachment level (CAL), periodontal pocket depth (PPD) and patient-centered treatment outcomes; study design: RCT. The titles and abstracts of all studies identified with literature searches were evaluated independently by two reviewers (KD and KLV) followed by full text evaluation. Articles fulfilling inclusion criteria were processed for data extraction regarding population, intervention, comparison outcome and study characteristics. Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) and GRADE approach were used to assess the risk of bias and quality of evidence, respectively, among the included RCTs.

*Results:* Three RCTs were selected after title and abstract screening followed by elimination of one of them as the control group was not SRP. The remaining two RCTs were included for data extraction. Due to heterogeneity (especially in terms of follow-up period) and few available trials, meta-analysis was not undertaken. The two included studies showed better improvements in PPD and CAL gain with EMD+SRP as compared to SRP alone at 3 months but significant improvement

only in PPD reduction was observed at 12 months with EMD+SRP treatment group in moderate periodontitis patients. The overall risk of bias was 'some concerns' and strength of evidence were rated as 'moderate'.

*Conclusions:* There is limited evidence available to show clinical efficacy of EMD in the flapless non-surgical periodontal therapy. Nevertheless, flapless EMD application as an adjunct to SRP appears as a promising treatment option for moderate periodontitis. The flapless EMD therapy also holds greater significance in the ongoing COVID-19 pandemic due to stress on use of non-aerosol generating periodontal procedures for patient treatment. Further robust RCTs are needed to evaluate the clinical effectiveness of flapless EMD therapy.

## **INTRODUCTION:**

EMD, since past 25 years, has been consistently demonstrated as a key regenerative protein capable of periodontal regeneration including new cementum, periodontal ligament and alveolar bone (Rojas et al. 2019). EMD is primarily composed of amelogenin besides enamelin, ameloblastin, amelotin, apin and proteinases (Graziani et al. 2014).

Scaling and root planing remain the cornerstone of periodontal therapy. EMD has been used extensively in periodontal surgical procedures for hard and soft tissue regeneration in intrabony defects, furcation defects and recession defects (Graziani et al. 2014; Rojas et al. 2019; Discepoli et al. 2019; Soares et al. 2020). Despite the evidence for significant clinical and radiographic improvements following the application of EMD, there have been concerns raised regarding the viscous nature of EMD which may hinder with flap collapse and space maintenance for periodontal regeneration (Polimeni et al. 2004, Siciliano et al. 2011). With the aim to enhance the clot stability and regenerative capacity of EMD, there have been clinical studies published evaluating the use of EMD as an adjunct to scaling and root planing in a flapless approach.

Therefore, the aim of the present systematic review was to rigorously evaluate the available RCTs for conclusive evidence on efficacy of EMD in improvement of treatment outcomes in flapless non-surgical periodontal therapy as an adjunct to SRP.

## **MATERIALS AND METHODS:**

### **Protocol development:**

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement was referred and used as a guide for quality reporting of this systematic review.

### **Focused question:**

In patients with periodontitis, what is the efficacy of EMD as an adjunct to SRP as compared to SRP alone in improvement of treatment outcomes in flapless non-surgical periodontal therapy?

### **Search strategy for identification of studies:**

The PubMed (MEDLINE) database of the U.S. National Library of Medicine, Cochrane Oral Health Group Specialized Trials Register (CENTRAL) database and EMBASE (Excerpta Medical Database by Elsevier) database were utilized as the electronic databases and a literature search was accomplished on articles from the inception of the respective database to 30<sup>th</sup> of September 2020, by using combination of various MeSH and free text words (Table 1). No restriction on the language and publication status of the articles was imposed. In addition, a hand search (up to September 2020) of the following journals was performed: *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research*, *Periodontology 2000*, *International Journal of Periodontics and Restorative Dentistry*, *Community Dentistry and Oral Epidemiology*, *Oral Diseases*, *Journal of Public Health Dentistry*, *International Dental Journal* and *International Journal of Dental Hygiene*. Additional studies were sought by searching the reference lists of identified trials and reviews.

### **Selection criteria for studies:**

In the first phase of study selection, the titles and abstracts of all identified publications were screened autonomously and in duplicate by two reviewers (K.D. and K.L.V.) to evaluate their eligibility for selection in this systematic review on the basis of predetermined inclusion and exclusion criteria.

Study selection criteria was:

- *Population*: adult patients with periodontitis (irrespective of case definition used)
- *Intervention*: flapless EMD application as an adjunct to SRP
- *Comparison*: SRP alone
- *Outcome measures*: studies were included if reporting at least one of the outcome measures viz., changes in CAL, PPD and patient-centered treatment outcomes
- *Study design*: RCT with blinded (masked) evaluation

Controlled clinical trials, open-label/open clinical trials, case series, uncontrolled studies, in-vitro studies, animal studies, review articles, articles published as abstract only, editorials, news and correspondence sections were excluded.

### **Quality of evidence and risk of bias assessment:**

The included articles were independently screened by the two reviewers (K.D. and K.L.V.) for risk of bias assessment and any disagreement was resolved by discussion. An overall estimation of plausible risk of bias was performed using the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). Risk of bias assessment was done using five domains: randomization process, deviations from the intended interventions, missing outcomes, measurement of the outcomes, and selection of the reported result. The risk of bias judgment (low, some concerns, or

high) was assigned to each domain or the entire study.

The quality of evidence was appraised for all the clinical outcomes separately, across the studies, according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. The quality of the body of evidence was assessed with reference to overall risk of bias of the included studies, directness of the evidence, consistency of the results, precision of the estimates and the risk of publication bias. The quality of the body of evidence was further classified into four categories i.e. high, moderate, low and very low.

#### **Data extraction:**

Data concerning the details of population, intervention, comparison, outcomes, and adverse events were independently extracted and summarized in evidence tables by the two reviewers (K.D. and K.L.V.), and questions were resolved by consensus.

#### **Data synthesis:**

Because of a limited number of selected studies and heterogeneity, which was evident especially in terms of follow-up period, meta-analysis was not performed.

### **RESULTS:**

#### **Study selection and description:**

The PubMed, Cochrane Central Register of Controlled Trials and EMBASE databases search provided 28, 12 and 23 hits, respectively (Figure 1). The hand searching, backward and forward snowballing did not reveal any additional article. Thus, the initial literature search resulted in a total of 63 articles. Of these, 60 articles were discarded after screening them based on their title and abstract, as they comprised of case reports, in-vitro studies, review articles, trials evaluating non-EMD assisted periodontal treatment and double publications. The remaining 3 articles (Aimetti et al. 2017; Graziani et al. 2019; Schallhorn et al. 2020) were selected for full text reading. After reading the full text of these 3 clinical trials, it was decided to exclude one (Aimetti et al. 2017) of them as the control group was not SRP. The 2 RCTs (Graziani et al. 2019; Schallhorn et al. 2020) evaluating the EMD as an adjunct to SRP using flapless approach, in comparison to SRP alone, fulfilled the inclusion criteria and were thus, selected for inclusion in the present systematic review. The study data was extracted from these trials including specific details about the interventions, populations, study methods, and outcomes of significance to the review question and specific objectives (Table 2).

#### **Quality of evidence and risk of bias assessment of selected studies:**

The RCT by Schallhorn et al. (2020) had 'some concerns' risk of bias (Table 3). It did not report blinding procedure and study outcomes were not reported at different study intervals. The RCT by

Graziani et al. (2019) had low risk of bias. The overall risk of bias was estimated to be 'some concerns' across all the RCTs.

The quality of evidence evaluated using GRADE approach was 'moderate' for both PPD and CAL outcomes following EMD as an adjunct to SRP compared to SRP in periodontitis patients (Table 4).

## **DISCUSSION:**

The two RCTs by Graziani et al. (2019) and Schallhorn et al. (2020) demonstrated moderate evidence for the efficacy of the flapless approach for EMD application as an adjunct to SRP for treatment of periodontitis patients. Thus, the results obtained with flapless EMD i.e. by avoiding any incision (as in non-surgical approach) must be interpreted with caution. Moreover, although the use of EMD following closed (non-surgical) instrumentation might maximize the natural regenerative potential of the residual intrabony defects by applying a biological mediator involved in cell differentiation processes in a blood clot-filled space, the regenerative potential of such a procedure is yet to be histologically established.

## **CONCLUSION:**

There is limited evidence available to show clinical efficacy of EMD in the flapless non-surgical periodontal therapy. Nevertheless, flapless EMD application as an adjunct to SRP appears as a promising treatment option for moderate periodontitis. The flapless EMD therapy also holds greater significance in the ongoing COVID-19 pandemic due to stress on use of non-aerosol generating periodontal procedures for patient treatment. Further robust RCTs are needed to evaluate the clinical effectiveness of flapless EMD therapy.

## **REFERENCES:**

Aimetti M, Ferrarotti F, Mariani GM, Romano F. A novel flapless approach versus minimally invasive surgery in periodontal regeneration with enamel matrix derivative proteins: a 24-month randomized controlled clinical trial. *Clin Oral Investig.* 2017 Jan;21(1):327-337.

Discepoli N, Mirra R, Ferrari M. Efficacy of Enamel Derivatives to Improve Keratinized Tissue as Adjunct to Coverage of Gingival Recessions: A Systematic Review and Meta-Analysis. *Materials (Basel).* 2019 Aug 30;12(17):2790.

Graziani F, Gennai S, Cei S, Ducci F, Discepoli N, Carmignani A, Tonetti M. Does enamel matrix derivative application provide additional clinical benefits in residual periodontal pockets associated with suprabony defects? A systematic review and meta-analysis of randomized clinical trials. *J Clin Periodontol.* 2014 Apr;41(4):377-86.

Graziani F, Gennai S, Petrini M, Bettini L, Tonetti M. Enamel matrix derivative stabilizes blood clot and improves clinical healing in deep pockets after flapless periodontal therapy: A Randomized Clinical Trial. *J Clin Periodontol.* 2019 Feb;46(2):231-240.

Polimeni G, Koo KT, Qahash M, Xiropaidis AV, Albandar JM, Wikesjö UM. Prognostic factors for alveolar regeneration: effect of a space-providing biomaterial on guided tissue regeneration. *J Clin Periodontol.* 2004 Sep;31(9):725-9.

Rojas MA, Marini L, Pilloni A, Sahrman P. Early wound healing outcomes after regenerative periodontal surgery with enamel matrix derivatives or guided tissue regeneration: a systematic review. *BMC Oral Health.* 2019 May 7;19(1):76.

Schallhorn RA, McClain PK, Benhamou V, Doobrow JH, Grandin HM, Kasaj A. Application of enamel matrix derivative in conjunction with non-surgical therapy for treatment of moderate to severe periodontitis: A 12-month, randomized prospective, multicenter study. *J Periodontol.* 2020 Sep 29. doi: 10.1002/JPER.19-0579.

Siciliano VI, Andreuccetti G, Siciliano AI, Blasi A, Sculean A, Salvi GE. Clinical outcomes after treatment of non-contained intrabony defects with enamel matrix derivative or guided tissue regeneration: a 12-month randomized controlled clinical trial. *J Periodontol.* 2011 Jan;82(1):62-71.

Soares DM, de Melo JGA, Barboza CAG, Alves RV. The use of enamel matrix derivative in the treatment of class II furcation defects: systematic review and meta-analysis. *Aust Dent J.* 2020 Sep 14. doi: 10.1111/adj.12794.

**Figure 1.** Flow-chart of the screening of the relevant publications.

**Table 1. Search terms for PubMed, Cochrane Oral Health Group Specialized Trials Register and EMBASE databases**

PubMed (MEDLINE) search	<p>1. SEARCH TERMS: (“emd” OR “emdogain” OR “enamel matrix derivative” OR “enamel matrix proteins”) AND (“flapless” OR “pocket depth” OR “clinical attachment level” OR “scaling” OR “root planing”)</p> <p>2. FILTERS: /</p>
EMBASE search	<p>1. SEARCH TERMS: (“emd” OR “emdogain” OR “enamel matrix derivative” OR “enamel matrix proteins”) AND (“flapless” OR “pocket depth” OR “clinical attachment level” OR “scaling” OR “root planing”)</p> <p>2. LIMITS: /</p>
COCHRANE search	SEARCH TERMS (each used individually): “emd”, “emdogain”, “enamel matrix derivative”, “enamel matrix proteins”, “flapless”, “pocket depth”, “clinical attachment level”, “scaling”, “root planing”
Data search date: 30 <sup>th</sup> September 2020	

**Table 2. Experimental characteristics of randomized controlled trials evaluating flapless enamel matrix derivative (n = 2)**

Study	Study design, Population and Evaluation period	Inclusion/exclusion criteria	Test group	Control group
Graziani et al. (2019)	<p>Study design: Double-blind, parallel, randomized controlled clinical trial</p> <p>Country: Italy</p> <p>Setting: University hospital</p> <p>Total patients: 38</p> <p>Patients discontinued and/or failed to follow-up: 0</p> <p>Test group: 19 patients</p> <p>Control group: 19 patients</p> <p>Evaluation period: 3 months</p>	<p>Included: proximal attachment loss of <math>\geq 3</math> mm in <math>\geq 2</math> non-adjacent teeth, bleeding on probing on at least 25% of total sites and documented radiographic bone loss. Excluded: (a) <math>&lt; 18</math> years and <math>&gt; 75</math> years of age, (b) pregnant or lactating females, (c) females using hormonal contraceptive methods, (d) reported diagnosis of any systemic illnesses including cardiovascular, renal and liver diseases, (e) any pharmacological treatment within 3 months before start of study, (f) smoking <math>&gt; 20</math> cigarettes/day and (g) periodontal treatment in previous 6 months.</p>	Flapless enamel matrix derivative application with scaling and root planing	Scaling and root planing
Schallhorn et al. (2020)	<p>Study design: blind (?), split mouth, randomized, prospective study</p> <p>Country: United States, Canada, and Germany</p> <p>Setting: clinic</p> <p>Total patients: 51</p> <p>Patients discontinued and/or failed to follow-up: 0</p> <p>Evaluation period: 12 months</p>	<p>Included: 1) patients voluntarily signed the informed consent form before any study related procedures, 2) male or female 18-85 years of age, 3) PPD 5 - 8mm in at least 2 pockets per contralateral quadrants in one arch, 4) no contraindications to periodontal therapy.</p> <p>Excluded: 1) patients unable or unwilling to provide informed consent, 2) uncontrolled systemic diseases, chronic high dose steroid therapy, bone metabolic disease, radiation or immuno-suppressive therapy, and infections at treatment sites, 3) heavy smoking (<math>&gt; 10</math> cigarettes per day or <math>&gt; 1</math> cigar per day) or smokeless tobacco use, 4) drug addiction or alcohol abuse, 5) current systemic antibiotic treatment or within 3 months prior to the study, 6) SRP or periodontal surgery within 6 months, 7) pregnancy, 8) necrotizing ulcerative periodontitis or periodontitis as a manifestation of systemic disease, 9) teeth with probing pocket depths <math>\geq 9</math> mm, furcation involvement, and/or mobility degree <math>&gt; 1</math>, 10) test and control sites on adjacent teeth in the two quadrants.</p>	Flapless enamel matrix derivative application with scaling and root planing	Scaling and root planing

**Table 3. Risk of bias assessment of included studies (n = 2) by Version 2 of the Cochrane risk-of-bias tool for randomized trials**

<i>Study</i>	<i>Randomization process</i>	<i>Deviations from the intended interventions</i>	<i>Missing outcomes</i>	<i>Measurement of the outcomes</i>	<i>Selection of the reported result</i>	<i>Estimated risk of bias across all studies</i>
Graziani <i>et al.</i> (2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Schallhorn <i>et al.</i> (2020)	Low risk	Some concerns	Low risk	Low risk	Low risk	

**Table 4. Quality of evidence (GRADE) of analyzed clinical treatment outcomes**

<i>Treatment outcome</i>	<i>Number of included randomized controlled trials assessing the outcome</i>	<i>Quality of evidence (GRADE) based on available study data from tables 2-3</i>
Pocket depth	2	⊕⊕⊕○ (Moderate)
Clinical attachment level	2	⊕⊕⊕○ (Moderate)