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Efficacy of Enamel Matrix Proteins in Periodontal Regeneration of Intraosseous Defects: An Umbrella Review

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ABSTRACT

Periodontitis is a chronic inflammatory disease that affects the supporting tissues of the teeth. When periodontal disease progress, it is common to find intrabony defects, one of the alternatives for its treatment is the use of enamel-matrix derivative proteins. The present umbrella review aimed to assess the effectiveness of enamel-matrix derivative proteins in periodontal regenerative treatment of intrabony defects. A review of systematic reviews published between January 2000 and March 2019 in indexed journals was performed. The qualitative evaluation was conducted using the AMSTAR-2 guide. Data analysis was purely qualitative. Nine (9) systematic reviews with meta-analysis were selected. An average reduction in PPD of 4,10mm and an average increase of 3,32mm in CAL were observed, showing statistically significant differences supporting the intervention with EMD in comparison with open flap debridement (OFD). Differences found between the included articles were statistically significant, showing better outcomes for the treatment with EMD combined with periodontal therapy. However, these results should be carefully interpreted because of the methodological variability between studies.

Keywords

Periodontics, Enamel matrix proteins, Intrabony periodontal defects, Periodontal regeneration (Mesh).

Introduction

Periodontitis is a chronic inflammatory disease, it affects tissues that support and surround the teeth [1], despite its multifactorial etiology, dental biofilm is considered a necessary although not sufficient cause for its development and progression [2]. When periodontal disease progresses, it is common to find intrabony defects, which can generate difficulties in the non-surgical treatment of the condition [3]. Intrabony defects can be classified according to the number of remaining bony walls, and it has been shown that their anatomy may affect periodontal therapy success [4,5]. Intrabony defects with 3 remaining walls do not show spontaneous resolution, but it is easier in these cases to stabilize the material compared to defects with 1 and 2 walls, in which factors that promote bone healing are decreased [6-8].

One goal of periodontal therapy is to regenerate support structures that may be affected because of the natural course of the disease. To achieve said objective, literature has proposed many procedures, among which are bone grafts, guided tissue regeneration, the use of enamel matrix derivatives (EMD) and even, associations between these procedures [10-12].

A widely proposed technique is enamel matrix derivative proteins (EMDp). These proteins have been used in recent decades for regenerative treatment of periodontal intrabony defects, furcation involvements and in root coverage procedures [2]. Some authors have proposed the use of EMDp alone or in combination with bone grafts, pursuing to achieve a synergistic effect of both materials.

Regenerative periodontal treatment mediated by EMDp founds its plausibility in a concept that differs from conventional regeneration; it bases its foundation on the reproduction, during periodontal lesions, of the development of dental support structures

just as it occurs throughout tooth formation. Proteins compose the enamel matrix, 90% are amelogenins, which induce periodontium development during tooth constitution [13].

Enamel matrix derivative proteins promote cell proliferation, expression of growth factors, of cytokines, and extracellular matrix; it has been shown that they can also allow the mineralization of periodontal ligament while generating apoptosis of epithelial cells. On the other hand, bone grafts can improve the osteoinductive potential and act as an osteoconductive scaffold, increasing the action of EMDp [14,15].

Different systematic reviews with and without Meta-analyzes of randomized controlled clinical trials have been conducted to assess the use of EMDp by comparing it with placebos, conventional periodontal therapy and other regenerative alternatives. However, up to this date there is no one review that summarizes the reported information from these studies. The aim of this umbrella review is to evaluate the effectiveness of EMDp in the periodontal regenerative treatment of intrabony defects.

Materials and Methods

PICO question and inclusion criteria

A research question based on the PICO (Patient, intervention, control, outcome) method was developed: In patients with intrabony defects, what is the efficacy of enamel matrix derivative proteins for the regenerative treatment?

The inclusion criteria for the research articles were:

- Systematic reviews with or without meta-analysis of Randomized Controlled Trials (RCT)
- Research articles assessing EMDp in the regeneration of intrabony defects
- Research articles assessing Pocket Probing Depth (PPD) and Clinical Attachment Level (CAL) before and after regenerative therapy
- Research articles published in English or Spanish
- Research articles published between 2000 and 2019

Search strategy and information retrieval:

Authors conducted the information research and retrieval procedures on Medline and Google Scholar, aiming to include studies published in high-impact journals. The search strategy used was: (((enamel matrix proteins) OR (emdogaim)) NOT (soft tissue)) Sorted by: Best MatchFilters: Review; Systematic Reviews; Publication date from 2000/01/01 to 2019/03/19, using Boolean operators and different filters to avoid publications that did not match the inclusion criteria, and that had not only evaluated soft tissue management in root coverage procedures. In addition, through manual search no eligible additional article was found.

Quality assessment

Two calibrated reviewers (RM, SF) assessed the quality of selected studies using the AMSTAR tool, which through a 16-item checklist allows to evaluate methodological quality of each study in its different components. It assigned each item a value of 1 if it complied with, and 0 if it did not, was not clear or did not apply.

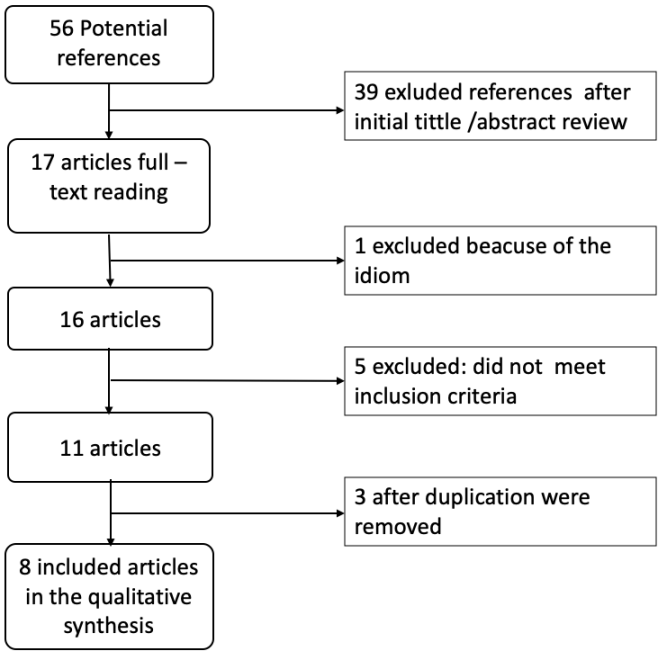
Review	AMSTAR-2 Score
Trombelli et al. 2002	11/16
Esposito et al. 2004	9/16
Esposito et al. 2009	12/16
Koop et al. 2012	11/16
Li et al. 2012	12/16
Zanatta et al. 2013	10/16
Matarasso et al. 2015	14/16
Liu et al. 2017	12/16

Table 1: Quality assesment.

Table 1 shows quality evaluation of the included articles.

Analysis of data:

All data were qualitatively extracted and analyzed to be presented narratively by the two reviewers.



Results

Figure 1 presents the articles collecting process for this review. Search strategy yielded 56 studies, after analyzing titles and abstracts 39 were excluded because they did not match the inclusion criteria. Out of the remaining 17, 1 was excluded because it was published in a language other than English and Spanish (Mandarin). After reading full texts, 5 articles were excluded since they assessed suprabony defects, furcation lesions, soft tissue regeneration, or because they presented results in non-clinical parameters, 3 articles were also excluded because of duplication (Table 2). Finally, 8 systematic reviews were selected for the qualitative analysis (Table 3).

The selected articles focused on the treatment of intrabony defects by using enamel matrix derivative proteins as regenerative material. In 2002, Trombelli et al. evaluated the existing evidence on the effect of biological agents and biomaterials for periodontal treatment, including EMD in combination with conventional surgical periodontal therapy to treat intrabony defects, they

Excluded Articles	
Authors	**Reason**
Esposito et al. 2003[24]	Duplication (presents a more up-to-date review)
Esposito et al. 2005[25]	Duplication (presents a more up-to-date review)
Palmer at al. 2008[26]	results are not expressed in the parameters indicated by the inclusion criteria
Li et al. 2009[27]	Article published in mandarin
Rathe et al. 2009[28]	It presents histometric results, does not assess clinical parameters
Graziani et al.2014[29]	Review based on studies performed on suprabony effects
Kao et al.2015[30]	Review that assessed mostly case series
Wu et al. 2017[31]	Included studies that did not restrict the assessment to intrabony periodontal defects
Troiano et al. 2017[32]	Studies where EDM was always used in combination with other material

Table 2: Excluded items.

Author	Objectives	Analysis method	Evaluated parameters	EMD findings
Trombelli et al. 2002 [16]	To determine the adjunct effect of biomaterials and biological agents with OFD in the treatment of deep intraosseous defects	Meta analysis	CAL - PPD	PPD: 4.22 CAL: 3.31
Esposito et al. 2004 [17]	Test the null hypothesis that there are no differences in rtg between EMD and OFD; EMD AND GTR; EMD AND BG	Qualitative	CAL- PPD-REC	PD: 4.17 CAL: 3.29
Esposito et al. 2009 [18]	Test if the EMD is effective and compare it with GTR and BG for the treatment of intraosseous defects	Meta analysis	CAL -PPD-REC	PD: 4.20 CAL: 3.16
Koop et al 2012 [19]	Answer the question of whether the additional use of EMD in different periodontal treatments is more effective compared to the control or other treatments	Meta analysis	CAL-PPD	PD: 4.10 CAL: 3.27
Li et al. 2012 [20]	To compare the clinical results of EMD used alone and in combination with BG in intraosseous defects.	Meta analysis	CAL-PPD.REC	PD: 3.72 CAL: 3.02
Zanatta et al. 2013 [21]	Test the null hypothesis that there were no differences between the 12-24 month follow-up studies	Meta analysis	CAL-PPD	PD: 3.82 CAL: 3.32
Matarasso et al. 2015 [22]	To assess the clinical efficacy of periodontal regeneration cx using a combination of EMD + BG and EMD alone.	Meta analysis	PD- CAL	PD: 4.17 CAL: 3.4
Liu et al. 2017 [23]	To explore whether graft use (alloplastic) + EMD is better compared to EMD alone in the regeneration of intra-bone defects	Meta analysis	PD-CAL	PD: 4.09 CAL: 3.30

Table 3: Characteristics of the studies.

	Esposito et al. 2004 [17]	Esposito et al. 2009 [18]	Li et al. 2012 [20]	Koop et al. 2012 [19]	Liu et al. 2017 [23]	Zanatta et al. 2013 [21]	Matarasso et al. 2015 [22]	Trombelli et al. 2002 [16]
ZETTERSTROM 1997 [33]								
HEIJL 1997 [34]								
PONTORIERO 1999 [35]								
OKUDA 2000 [36]								
SILVESTRI 2000 [37]								
SCULEAN 2001 [38]								
SCULEAN 2001 [39]								
FROUM 2001 [40]								
PIETRUSKA 2001 [41]								
TONETTI 2002 [42]								
ZUCHELLI 2002 [43]								
SILVESTRI 2003 [44]								
ZUCHELLI 2003 [45]								
WATCHEL 2003 [46]								
FRANCETII 2004 [47]								
SANZ 2004 [48]								
ROSING 2005 [49]								
SCULEAN 2005 [50]								
FRANCETTI 2005 [51]								
MOMBELLI 2005 [52]								
BOKAN 2006 [53]								
SCULEAN 2006 [54]								
GUIDA 2007 [55]								

SCULEAN 2007 [56]								
CREA 2008 [57]								
SCULEAN 2008 [58]								
GRUSOVIN 2009 [59]								
LEKNES 2009 [60]								
FICKL 2009 [61]								
YILMAZ 2010 [62]								
CHAMBRONE 2010 [63]								
MEYLE 2011 [64]								
CORTELINI 2011 [65]								
PIETRUSKA 2012 [66]								
DE LEONARDIS 2013 [67]								
BHUTDA 2013 [68]								
HOFFMANN 2016 [69]								

Table 4: Randomized controled clinical trials included

reported as a result an average decrease in PPD of 4.22 mm and an average increase in CAL of 3.31 mm. Both parameters showed statistically significant differences favoring the group treated with biological agents [16].

In 2004, Esposito et al. included 10 randomized controlled clinical trials (6 with parallel design and 4 with split-mouth design) in a systematic review comparing the use of EMDp against guided tissue regeneration (GTR) and open flap surgery (OFS). Their outcomes showed that by using EMD a decrease of 4.17mm in PPD was achieved, along with an increase of 3.29mm in CAL. The authors reported that EMD is more effective to treat intrabony defects when compared to placebo, but slightly less effective in comparison with GTR [17].

The same group of researchers reviewed again in 2009 randomized clinical trials regarding EMD use in intrabony defects, improving like this their previous research. However, results were similar to those obtained back then [18].

A systematic review of randomized controlled clinical trials with at least 1 year of follow-up was conducted in 2012 by Koop et al., it included 20 articles that compared the use of EMD in intrabony defects against other regenerative techniques. Authors reported an average decrease in PPD of 4.10 mm and a 3.27 mm increase in CAL; however, these measurements were not statistically significant when compared to other regenerative techniques [19].
Li et al. in 2012, reviewed clinical results of treatment with EMD alone and compared it to its use in combination with bone grafts, and although they found that PPD decreased by 3.72 mm, and CAL increased by 3.02 mm, it was stated that EMD + bone grafts showed only a slight improvement in regenerative treatment compared to EMD alone, and such difference was not statistically significant [20].

In a systematic review in 2013, Zanatta et al. evaluated the long-term effect of EMD in the treatment of intrabony defects, reporting a decrease in PPD of 3.82 mm and a CAL increase of 3.32 mm [21].

Matarasso et al. in 2015 assessed randomized controlled clinical trials comparing the effect of EMD alone vs. EMD + bone grafts to treat intrabony defects, their results showed a decrease of 4.17 mm in PPD and a 3.4 mm increase in CAL [22].

In 2017, Liu et al. carried out a systematic review, assessing the effectiveness of EMD for intrabony defects treatment, reporting that PPD decreased by 4.09 mm and CAL increased by 3.30 mm [23].

Discussion

Table 4 shows the comparison of controlled clinical trials included on each review, which comprises 52 studies conducted between 1997 and 2016 that compared effectiveness of EMD in the treatment of intrabony defects against different therapeutic alternatives, ranging from the conventional periodontal therapy, to the use of additional bone grafts. Results were reported parting from the clinical changes in PPD and CAL, and they showed a positive effect of EMD, since a reduction of approximately 4.06 mm in PPD, and an increase in CAL of 3.25 mm on average were found. However, it is worth mention that these studies were developed in different contexts, with variable sample sizes and with treatment protocols that commonly differed from one another. Therefore, its comparison should be carried out with caution.

Out of 8 selected studies, 2 compared the use of EMD alone VS EMD + bone grafts. Matarasso et al., in 2012, included 2 clinical trials divulged after the publication of Liu et al. that same year. However, the results presented were very similar [22-23].

All the involved reviews that compared EMD VS surgical periodontal therapy showed statistically significant results favoring EMD; on the other hand, when EMD was compared to GTR, the differences not only lacked statistical significance, but additionally slightly favored GTR in all the assessed parameters.

Quality parameters of each review were evaluated through the AMSTAR-2 guide. It stated a general flaw in systematic reviews as they did not specify financing sources for the selected studies, which may allow to suspect potential conflicts of commercial

interest. Regarding the development of a research question, only Matarasso et al. were explicit about using the PICO method.

Conclusion

This umbrella review represents the first one that analyzes the effect of EDM in treating intrabony defects. Although differences found between the studies were statically significant, supporting EDM in combination with periodontal therapy, the methods used by each study varied, and in many of them, convenience sampling was used. It is recommended to realize randomized controlled trials with probabilistic sampling before EMD can be justified as a therapeutic alternative.

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