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Research Article

Treatment of Intrabony Defects with Enamel Matrix Derivative Proteins Using Minimally Invasive Surgical Approaches to Papilla Preservation: A Systematic Review with Metanalysis

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Abstract

Background: To investigate the clinical performance of minimally invasive surgical approaches for interdental tissue preservation in association with enamel matrix derivatives in the treatment of intraosseous defects.

Materials and Methods: A systematic literature review was carried out (PROSPERO: CRD42020135131) through research, extraction and analysis of data in duplicate, according to the PICOS strategy. The Ovid MEDLINE databases were consulted; Ovid EMBASE; Open Gray and in the *journals Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research and Journal of Dental Research*, the search covered an unlimited period until May 2019, following the guide PRISMA. For assessment was used Cochrane Collaboration's risk

Results: Eight randomized controlled trials reporting 557 subjects and 698 defects were identified. Among in techniques for preserving interdental tissues, there were no differences between them. However, in the meta-analysis obtained by the studies, the results were superior in clinical gain of insertion in favor of the test group [n = 119; MD = 0.92; 95%; IC (0.35; 1.50); p = 0.002 I^2 78%], with these results statistically significant

Conclusions: the open flap debridement technique using interdental tissue preservation approaches in association with EMD promote slightly superior clinical results in insertion gain

Clinical Relevance: Assist the professional in their clinical practice in treatment of periodontal defects with minimally surgical approaches and furthermore, demonstrate the possibility and the benefits of using the biomaterials like the enamel derivative proteins in the regeneration these periodontal defects.

Keywords: Dental Enamel Proteins; Minimally Invasive Surgical Procedures; Clinical trial

Introduction

Periodontal disease is a chronic infectious disease that results in inflammation in the supporting tissues of the teeth, leading to apical migration of the junctional epithelium and bone loss, with subgingival biofilm being the main etiologic agent. From this point view, the main approach to its therapy is to disorganize and disperse the biofilm through mechanical debridement and, in some situations, with chemical substances [1]. However, in sites affected by the progression of periodontal disease, with destruction of the support apparatus and formation of intraosseous defects, there is the possibility of surgical technical approaches aimed at periodontal regeneration of these sequelae, forming new tissues that were previously lost (periodontal ligament, cementum) root and alveolar bone [2-5]. In the treatment of intraosseous defects, surgical decontamination of this and the root surface involved, can restore periodontal health, when an adequate control of biofilm is achieved. However, several surgical techniques and materials have been developed in order to improve clinical results, and to treat intraosseous

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defects conservativel[6].Minimally invasive surgery is a term that describes the use of smaller and more accurate surgical procedures that are possible through the use of enlargement instruments. The purpose of using this approach in regenerative periodontal surgery is to preserve interdental tissues, which will result in better wound healing, blood clot stability and improvement in periodontal clinical parameters [7-9].

Among the materials used for periodontal regeneration, Enamel Matrix Derivative (EMD) stand out for playing an important role in cementogenesis and mimicking the events that occur during root development, in addition to being able to stimulate various cellular activities, resulting in better postoperative results. Thus, being able to regenerate the periodontal apparatus in cases where bone loss occurred with the application of EMD has been the objective of several studies [6-8]. One of the indications for the use of EMD is in the treatment of intraosseous defects. And its use has been evaluated in humans with clinical results showing to be significantly better than just open flap debridement [3,4].

Despite the publication of several systematic reviews demonstrating that the use of EMD [10-13], can be a viable alternative to enhance clinical results in the treatment of intraobony defects, there is still no systematic review that evaluates the clinical performance of surgical approaches to preserve interdental tissues in association with EMD in the treatment of these defects, associated with a comparison between the follow- up times.

Therefore, the objective of this study was to conduct a systematic review to investigate the clinical performance of surgical approaches that preserve interdental tissues, in association with enamel matrix derivative in the treatment of intrabony defects.

Material and Methods

A detailed research protocol was designed according to PRISMA [14] and registered with PROSPERO under number CRD42020135131. The focused question was: “What is the clinical effect of using Open Flap Debridment (OFD) associated with EMD, in terms of clinical gain of insertion, compared to OFD not associated with EMD in the treatment of intraosseous defects?

This question was elaborated according to the PICOS strategy, an acronym used to formulate well-defined research strategies [15] which “P” is the patient with intraosseous defects, “I” means the intervention with open flap debridement in association with the EMD, “C the comparison group that was open flap debridement not associated with the EMD, “O” the result was the clinical gain of insertion and “S” means the type of study, which were randomized clinical trials.

Criteria for the Studies Considered for this Review Types of Studies

The study included Randomized Controlled Clinical Trials (RCTs) with a minimum of 10 participants treated for each group or as a sample [5]. Studies in split or parallel mouth with two or more arms were also considered.

The studies, which were included, reported the average clinical gain of insertion, after the regenerative procedures in intraosseous defects. The reduction in probing depth, increased gingival recession and bone gain were present in secondary evaluations. The studies had a minimum follow-up of 6 months. The studies were carried out in humans who received periodontal regenerative therapy to treat intraosseous defects of 1.2 or 3 walls.

Exclusively radiographic studies were excluded, with predominantly morphological, histological data, teeth with furcation defects, teeth with grade 3 mobility and supraconse defects.

Types of Participants

Adult individuals (>18 years) who received regenerative surgical treatment of intrabony defects through Open Flap Debridement (OFD) were selected, with a surgical technique that preserved interdental tissues associated with the use of EMD, with a minimum follow-up period of 6 months. Study participants were systemically and periodically healthy.

The study patients underwent non-surgical treatment of periodontal disease and had at least one intraosseous defect of one, two or three walls, involving the interproximal region of the affected tooth, with low bleeding at probing ≤ 20%, accompanied by for at least six months.

The depth of the radiographic intraosseous defect was considered as the vertical distance in millimeters between the alveolar bone crest and the defect base or the distance between the JCE and the defect base. And the width of the bone defect, in turn, was considered as the distance between the alveolar bone crest and the root surface or the distance between the JCE and the alveolar bone crest [16]. Measures of bone defects were calculated based on periapical digital radiographic examinations or computed tomography scans.

Types of Interventions

A. Patients received periodontal surgical treatment using the following therapeutic approachOFD, through the Modified Papilla Preservation Technique (MPPT) [17]; Simplified Papilla Preservation Flap (SPPF) [18], which encompass the Minimally Invasive Surgical Technique (MIST) [19], + EMD compared to DRA not associated with EMD

B. OFD, through the Papilla Preservation Flap (PPF) [20]; Modified Minimally Invasive Surgical Technique (M-MIST) [9,21] + EMD, compared to OFD, not associated with EMD

Studied Clinical Outcomes

Changes in the Clinical Attachment Level (CAL) were considered as the primary outcome for this review. As secondary outcomes, descriptions regarding postoperative

morbidity, regarding pain or discomfort, presence of edema, hematoma, suppuration, flap dehiscence and presence of granulation tissue were considered. The following clinical- periodontal parameters were also considered.

a. Probing depth;

b. Bone gain / fill percentage;

c. Gingival recession.

d. Bleeding rate on probing

Research Methods for Locating Studies

The search for studies was carried out in the databases Ovid MEDLINE, Ovid EMBASE and Scopus using combinations of the terms MESH, EMTREE and keywords. In addition, the bibliographies of all included articles and relevant revisions to the sub-

ject were selected for possible analysis. The search covered an unlimited period until May 2019. The OpenGray platform for unpublished works (gray literature), in addition to banks of university theses and dissertations, as well as Google Scholar were researched, in an attempt to minimize the risk of publication bias. Databases from five dental journals - *Journal of Periodontology, Periodontology 2000. Journal of Clinical Periodontology, Journal of Periodontal Research and Journal of Dental Research* were also searched. In addition, the clinical trials, controlled trial database sites were consulted, in search of the registration of completed or ongoing controlled clinical trials. In addition, when necessary, the authors of the studies were contacted to provide the missing data in the evaluated article.

Selection of Studies

The research was carried out in three phases, by two reviewers (EB and LM), duplicated, with the results evaluated independently, in order to test the sensitivity and specificity of the search. Any disagreement between the two researchers was resolved with a discussion and in the absence of consensus, a third reviewer was consulted (BV). The initial research stage represented the calibration period between the reviewers, referring to the data collection instruments

The subsequent stage, the research itself, was divided into three stages. The first one, the analysis of the titles, was carried out to eliminate the materials that would not fulfill the norms established by the inclusion criteria of the research protocol. The second step was the evaluation of the abstracts of the studies initially selected. It was the studies in terms of research characteristics, that is, the characteristics of populations, interventions, results, design, quality and results. In addition, this step was used to determine the similarity of the studies for a possible meta-analysis assessment based on the type of study, characteristic of the population, intervention, primary and secondary outcomes, previously established in the protocol, eliminating studies not corresponding to them.

Data Extraction

A data extraction form was designed specifically for this study and was used to record details of the selected articles. The completion of the form was carried out by the two researchers independently. The data collected from the studies were based on important questions for the research, such as: characteristics of the population, the intervention, the results and the type of study. These records allowed for a more detailed analysis of the data at a later stage of the systematic review.

Evaluation of the Quality of Studies

The quality assessment of all included studies was conducted independently by two reviewers (EB and LM) using the RTC risk of bias tool (Appendix B), prepared in accordance with the Cochrane manual [22]. Each study was judged as low, high or uncertain risk of bias based on five domains: Generation of random sequence, concealment of allocation, blinding of participants and researchers, blinding of evaluators, incomplete outcome data, selective reporting and other sources of bias. The judgment of each item involved answering a question, with answers 'Yes' indicating low risk of bias, 'No' indicating high risk of bias and 'Not clear' indicating lack of information or uncertainty about the potential for bias.

Summary of the Data

The data for each study was collected in tables and grouped according to the study design, with the assistance of the Review Manager (RevMan). The descriptive analysis was initially carried out to determine the amount of data, also checking the variations of the third stage, the analysis of the full texts, was carried out using the data extraction form (appendix A) that verified the study's eligibility based on the established inclusion and exclusion criteria. In addition, the form was also used to assess the methodological quality of the study and extract the most detailed data on its characteristics and results obtained. The studies, which were excluded after the complete reading, had the reason for their exclusion registered, in order to be mentioned in results of the review.

Summary Measures

The Mean Difference (DM) with 95% Confidence Interval (CI) was used for the analysis of dichotomous and continuous data, respectively. Heterogeneity was assessed using the Cochran Q test and I^2 statistics (I^2 <40%: low heterogeneity; $I^2 \geq 40\%$: high heterogeneity) [22]. A fixed-effect model was used in studies that showed low statistical and random heterogeneity for those with high heterogeneity. The inverse of variance method was used to combine data for continuous outcomes, while Mantel-Haenszel was used to combine dichotomous outcomes. The computer program (ReVMan [Computer program]. Version [5.3]. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) was used for the meta-analysis calculations. A p-value less than 0.

Additional Analysis

The Kappa value for agreement between reviewers was 0.81 in title analysis, 0.76 in summary analysis and 0.79 in reading the full text, showing good agreement between the reviewers.

Results

Selection of Studies

Altogether, 11,092 titles were found, through the search in electronic databases, carried out in a duplicate and independent way by the authors. The search details are described in the PRISMA flow chart (Figure 1). After removing the duplicates, 7,773 titles remained for analysis. In all, 38 articles were selected to read the full text. After this stage, 27 articles were excluded for different reasons (Table 1), thus leaving 11 publications. However, since 3 studies had the same population[24-25,41], as a result, it was considered the most complete publication of these studies. Therefore, only 8 studies were considered for statistical analysis and eligible for data extraction (Tables 2,3 and 4).

Table 1: Studies excluded.

Studies	Reason for Exclusion
Cortellini et al.; Harrel et al.; Milauskaite et al.; [Cortellini, Tonetti; Froum et al.]; Fujinami et al.; Saito et al.; Seshima et al.; Farina et al.	Case series
Chambrone et al.; Aimetti et al.; Mironet al.; Tonetti et al.; Okuda et al.; Mârţu et al.; Sculean et al.; Pietruska et al.	Do not report the use of techniques that preserveinterdental tissues
Aimetti et al.; Moreno et al.	Used PDME in both groups
Grusovin, Esposito.	Used grade III mobility teeth
Rosing et al.	Does not report the average clinical gain of insertion

Source: The author

Table 2: Population characteristics and interventions in the included studies.

	Characteristics of the Study and Population					Intervention and Comparison Characteristics		
Studies: author / Year / location	**Types of**	**Participants**	**Characteristics of the defects**	**Follow up (Months)**	**1. Characteristics of the test**	**Type of intervention (number of patients)**	**Orientation and Care**	**Periodontal Support**
		1. Number (N°F, N°M)	1. Number of teeth		2. Number of centers	1. Test group	1. Preoperative	
		2. Age (Year)	2. Type of teeth		3. Financing source	2. Control group	2. Posoperative	
		3. Dropouts Placement of recruitment	3. Number of defects (test / control)					
		4. Smoking (frequency)	4. Types of defects (1, 2, 3 walls and combined)					
Tonetti et al. (2002), (2004), Belgium, Germany, Greece, Italy, The Netherlands, Switzerland, USA.	RCT	1.169 (95F, 71M).	1. Not reported.	12	1. Parallel group.	1.OFD + SPPF / MPPT	1. Not reported.	Weekly (one month), quarterly
		2.48 ± 9 years.	2. Not reported.		2. Multicentric.	+ EMD (83).	2. 600 mg ibuprofen or 500 mg acetaminophen. after. 0.12% chlorhexidine.	
		3. 3	3. 83/83		3. University and industry.	2. OFD + SPP / MPP (83).		
		4. University (2) and private practice (10).	4. Combined (1-2-3).				Modified oral hygiene procedures (4 weeks).	
		5. Included (<20 cigarettes / day).						
Zucchelli et al. (2002), Italy.	RCT	1.90 (49F, 41M)	1. 9	12	1. Parallel group.	1.OFD + SPPF	1. Amoxicillin plus clavulanic acid 1g / day (1 day before).	Monthly(1 y).
	(3-arm)	2.48.2 ± 7.4 (30-61)	2. 40 incisors, 28 cuspids, 12 bicuspids, 10 molars. 52 maxillary.		2 Unicentric.	+ EMD (30).	2. Amoxicillin plus clavulanic acid 1g / day (7 days). 0.2% solution of chlorhexidine digluconate. Professional tooth clean(11 weeks).	
		3. 0	3. 30/30		3. Not reported.	2. OFD + SPP (30).		
		4. Not clear.	4. Not reported.					
		5. Included (<20 cigarettes / day).						
Wachtel et al. (2003), 41 Fickl et al. (2009), Germany.	RCT	1. 19 (13F, 6M).	1. Not reported.	12	1. Split-mouth.	1.OFD + MPPT	1. Not reported.	Not reported.
		2. 46.1 (28-63).	2. Not reported.		2. Unicentric.	+ EMD (19).	2. 0.2% solution of chlorhexidine digluconate (2x daily, 4 postoperative weeks). Mechanical oral hygiene not allowed (four weeks).	
		3. Not reported.	3. 70.		3. University and self.	2. OF D + MPP (1 9).		
		4. Treatment center.	4. Not reported					
		5. Included (<10 cigarettes / day).						
Francetti et al. (2004), (2005), Italy.	RCT	1. 153 (87F, 66M).	1. Not reported.	24	1. Parallel group.	1. OFD + SPPF	1. Not reported.	12 and 24 months.
		2. 44 ± 8.2 (30-70).	2. Not reported.		2. Multicentric.	+ EMD (83).	2. Mechanical oral hygiene avoided (6 weeks). 0.12% solution of chlorhexidine digluconate.	
		3. 43.	3. 108/87.		3. Industry.	2. OFD + SPP (70).		
		4. University and private practice (11) and treatment centers.	4. Not reported.				3. Amoxycillin + clavulanic acid 1 g. Nimesulide 100 mg.	
		5. Included (10/15 cigarettes / day).						

Cortellini and Tonetti (2011), Italy.	RCT	1. 45 (21F, 24M).	1. 45.	12	1. Parallel group.	1. OFD + M-MIST	1. Not reported.	3-months recall system (1 y).
	(3-arm)	2. Control: 48.9 ± 7.9 (34-59); Test: 47.2 ± 8.5 (34-64).	2. Not reported.		2. Unicentric.	+ EMD (15).	2. 600 mg ibuprofen or 500 mg acetaminophen. 0.12% chlorhexidine. No interdental cleaning (one month). Weekly prophylaxis (6 weeks).	
		3. Not reported.	3. 45.		3. Organization and research group.	2. OFD + M-MIST (15).		
		4. Not clear.	4. Combined (1-2-3).					
		5. Included (≤10cigarettes / day).						
Ribeiro et al. (2011), Brazil.	RCT	1.30 (19F, 11M)	1. Not reported.	6	1. Parallel group.	1.OFD + MIST	1.4 mg dexamethasone (1 hour before);	15 days (1 month). Monthly (6 month).
		2. 47.10 ± 6.89.	2. Not reported.		2. Unicentric.	+ EMD (15).	2. Paracetamol (every 6 hours for 2 days) 0.12% chlorhexidine. Mechanical oral hygiene not allowed (10 days).	
		3. 1.	3. 1.15 (not reported).		3. Organization.	2.OFD + MIST (15).		
		4. University. 5.Not included.	4. Not Reported					
		5. Not included.						
Bhutda and Deo (2013), India.	RCT	1. 36 (21F, 15M).	1. 15.	60	1. Split-mouth.	1. OFD + FPP	1. Not reported.	15 days (2 months) Monthly (1 y). 6 months (4 y).
		2.40.66 ± 2.96 (37-45)	2. 3 (lower PM) and 12 (lower M), both groups.		2. Unicentric.	+ EMD (15).	2. Amoxicillin 500 mg. Ibuprofen 400 mg. 0.12% chlorhexidine digluconate.	
		3. Not reported.	3. 15 Both groups.		3. Not Clear.	2. OFD + FPP (15).		
		4. University.	4. 2,3, combined.					
		5. Not included.						
Leonardis and Paolantonio (2013) Italy.	RCT	1. 36 (21F, 15M)	1. 36.	24	1. Split-mouth.	1.OFD + SPPF / MPPT	1. Not reported.	Weekly (6 weeks). 3-Month.
	(3-arm)	2. 45.3 ± 5.9 (30-68)	2. Not Reported		2. Unicent	+ EMD (34).	2. Amoxicillin + clavulonate potassium. 400 mg oral ibuprofen.0.12% chlorhexidine gluconate.	
		3. 2	3. 72 (36 each group).		3. University and self.	2. OFD + SPP / MPP 34).		
		4. Private practice.	4. 1, 2 and combined (1-2).					
		5. Not included						

RCT: Randomized Clinical Trial; OFD: Open Flap Debridement; SPPF: Simplified Papilla Preservation Flap; MPPT: Modified Papilla Preservation; FPP: Papilla Preservation Flap; M-MIST: Modified Minimally Invasive Surgical Technique; EMD: Enamel Matrix Derivative PDME
Source: The author

Study Characteristics

The 8 studies [23-30] was included in this review, resulted in randomized controlled trials. Three studies [25,26,30] were designed with the split mouth design, while the others were performed with parallel and simultaneous groups. The follow-up period reported in the publications ranged from 6 to 60 months. Author, year of publication, study design, comparison, types of defects, evaluation methods and follow-up period for the included studies are shown in tables 1,2 and 3.

Population Characteristics

The characteristics of the population of the studies included in this review are summarized in Table 1. In two studies [23,27] the place of recruitment is unclear, in three studies [24,27,30] a study was developed in Italy [25] was developed in Germany. One study [29] was developed in Brazil, one study [26] was developed in India and one study was multicenter [28]. The age among participants in the included studies ranged between 28 and 70 years. 3 studies did not include smoking patients [26,29,30], 3 studies used antibiotic therapy after the procedures [23,24,30].

Table 3: Results characteristics.

Studies: author / Year / location	CAL gain (mm)	PPD (mm)	GR (mm)	Bone Gain (%)	BP (%)	Postoperative morbidity (test /control)	Analyze Statistic
	1. Test group	1. ction instrument	1. Test group	1. Definition	1. Definition	1. Pain	
	2. Control group	2. Test group	2. Control group	2. Test group	2. Test group	2. Edema	
		3. Control group		3. Control group	3. Control group	3. Suppuration	
						4. Dehiscence of the flap	
						5. Granulation tissue	
Tonetti et al. (2002), 2004	1. 3.1 ± 1.5.	1. Pressure sensitive manual periodontal probe at 0.3N.	1. Not reported.	1. Not reported.	1. FMBS (dichotomously).	1. (VAS; 28 ± 20/31 ± 23).	Unbalances (test and control, randomization): unpaired t-test (continuous variables) and the chi square test (categorical variables). Dependent variables: linear models using the SAS GLM procedure. Frequency distributions: Mantel-Hansel chi-square test.
Belgium, Germany, Greece, Italy, The Netherlands, Switzerland, USA	2. 2.5 ± 1.5.	2. 8 ± 1.5 (BL) / Not report.		2. Not reported.	2. 13 ± 6 (BL) / 10 ± 8 (1y).	2. Only be detected by intraoral examination.	
		3. 7.7 ± 1.5 (BL) / Not report.	2. Not reported.	3. Not reported.	3. 13 ± 6 (BL) / 11 ± 7 (1y).	3. Never observed.	
						4. Limited to the interdental incision line.	
						5. Not clear.	
Zucchelli et al. (2002)	1. 4.2 ± 0.9.	1. Pressure sensitive manual periodontal probe at 0.3N.	1. 0.8 ± 0.8 (BL) /1.7±0.9(1y).	1. Not reported.	1. FMBS (dichotomously).	1. Not rated.	General linear models (CALG, PPDR, \ IGR, INFRA, FMBR), if p <0.05, Bonferroni t test (multiple comparison). One way. ANOVA: differences: clinical parameters at 1 year.
	2. 2.6 ± 0.8.	2. 9.2 ± 1.0 (BL) / 4.0 ± 0.7 (1y).	2. 1.1 ± 0.9 (BL) /3.1±0.9(1y).	2. Not rated.	2. 10.4 ± 1.1 (BL) /9.4 ± 1.1 (1y).	2. Not rated.	
		3. 8.9 ± 0.9 (BL) / 4.4 ± 0.8 (1y).		3. Not rated.	3. 10.2 ± 2.2 (BL) /9.8±1.8 4. (1y).	3. Not rated.	
						4. Not rated.	
Wachtel et al. (2003) 4 Fickl et al. (2009) Germany.	1. 3.7 ± 0.4 (1y);	1. Pressure sensitive manual periodontal probe at 0.2N.	1. Not reported.	1. Not reported.	1. Bleeding on probing to the base of the pocket (BOP).	1. Not rated.	The means for test and control sites calculated (every patient): two-tailed t-tests for paired comparisons. To correct for multiple testing.
	2. 1.7 ± 0.3 (1y).	2. Not reported	2. Not reported.	2. Not rated.	2. 26 (BL); 6 (6m); 0 (1y).	2. Not rated.	
		3. Not reported		3. Not rated.	3.29 (BL); 29 (6m); 37 (1y).	3. Not rated.	
						4. EHI (%): 11/4; 9/3.	
						5. Not rated.	
Francetti et al. (2004), (2005) Italy.	1. 3.41 (1y); 3.51 (2y);	1. Periodontal probe. (PCP-UNC 15).	1. 1.16 (BL) /1.95 (1y) /1.68 (2y).	1. Ratio between gain and the baseline value.	FMBS (dichotomously).	1. Not rated.	Two-way analysis (variance): differences BL and 12- and 24-month. The unpaired Student t test to compare two groups.
	2. 1.96 (1y); 2.51 (2y);	2. 8.06 ± 2.0 (BL) /4.06=1.94 (1y) / 4.04 ± 1.85 (2y).	2. 0.93 (BL) /1.85 (1y) /1.80 (2y).	2. 53.7 (1y) /55.2 (2y).	.Not reported.	2. Not rated.	
		3. 7.11 ± 1.3 (BL) /4.11±1.55 (1y) / 3.60 ± 1.56 (2y).		3. 35.4 (1y) /45.7 (2y).	.Not reported.	3. Not rated.	

				4. Not report-ed.		4. Not rated.	
						5. Not rated.	
	1. 4.1 ± 1.2 (1y);	1. Pressure sensitive manual periodontal probe at 0.3N.	1. 2.1 ± 1.4 (BL) / 2.3 ± 1.4 (1y).	1. (X-ray Bone Gain) / X-ray INFRA x 100.	.FMBS (dichoto-mously).	1. 11, 5 ± 0, 7/10, 7 ± 2, 1 (VAS).	Comparisons BL and 1y: paired Student-test (α= 0.05). Comparisons among the experimental groups at BL and at 1 y: ANOVA.
	2. 4.1 ± 1.4 (1y);	2. 7,8 ± 0,9 (BL) / 3, 4 ± 0,6 (1y).	2. 2.1 ± 1.4 (BL) / 2.4 ± 1.4 (1y).	2. 71 ± 18 (1y)	.0, 4 ± 3.4 (BL) / 5.7 ± 3.0 (1y).	2. Not edema.	
		3. 7.5 ± 1, 6 (BL) / 3, 1 ± 0.6 (1y).		3. 77 ± 19 (1y)	.10, 3 ± 4.4 (BL) / 7.0 ± 5.2 1y).	3. Not rated.	
						4. Not rated.	
						5. Not rated.	
Ribeiro et al. (2011) Brazil.	1. 3.02 ± 1.94 (6m) §	1. Periodontal probe§.	1. 5.28 ± 1.90 (BL) / 5.74 ± 1.88 (6m).	1. Not rated.	.FMBS (dichoto-mously).	1. Not rated.	Homogeneity (baseline) :(ANOVA). Intra- and intergroup differences (clinical and radiographic): ANOVA and the Tukey test. Intragroup differences: Friedman test. Intergroup differences (FMBS): Mann-Whitney U test.
	2. 2.82 ± 1.19 (6m) §	2. 7.09 ± 1.70 (BL) /3.53=1.12 6m).	2. 3.93 ± 1.46 (BL) / 4.47 ± 1.52 (6m).	2. Not rated.	.11.99 ± 4.56 (BL) /7.65 ± 3.16.	2. Not rated.	
		3. 7.12 ± 1.10 (BL) / 3.57 ± 0.81 6m).		3. Not report-ed.	.9.33 ± 5.39 (BL) /6.15±3.63.	3. Not rated.	
						4. Not rated.	
						5. Not rated.	
Bhutda and Deo (2013) India	1. 3.96 ± 0.44 (1y) / 3.18 ± 0.87	1. Computerized constant pressure	1. 0.84 ± 0.17 (BL) / 0.16 ± 0.09 (1y) 0.66 ± 0.01 (5y).	1. Not report-ed.	.Mulhemann (1977).	1. Not rated.	The Student Paired t-test: homogeneity(test and control, BL). Difference between BL and 5 y (within group): paired t-test.
	2. 2.05 ± 0.78 (1y) / 1.60 ± 0.54	2. 7.24 ± 1.11 (BL) (5y). /3.12=0.87(1y) 3.40 ± 0.57 (5y). 3.6.82 ± 0.48 (BL) /4.60;0.93(1y) 4.90 ± 0.53 (5y).	2. 0.50 ± 0.85 (BL) / 0.17 ± 0.11 (1y) 0.32 ± 0.52 (5y).	2. 66.66 ± 7.8 (5y).	.Not clear. ¥	2. Not rated.	
				3. 31.71 ± 4.1 (5y).	.Not clear. ¥	3. Not rated.	
						4. Not rated.	
						5. Not rated.	
Leonardis and Paolan-tonio (2013) Italy.	1. 2.73 ± 0.64 (1y); 2.95 ± 0.74 (2y).	1. Periodontal probe.	1. 0.51 ± 0.39 (BL) /1.29=0.61(1y)	1. Not report-ed.	1. FMBS (dichoto-mously).	1. Not rated.	Shapiro-Wilk test and Q – Q normality plots: normality. Levene test and Q – Q normality plots: equality of variance. Balancing of experimental groups by age and sex was tested by one-way analysis of variance (ANOVA) and χ2 analysis. FMBS: one-way ANOVA. Friedman test and a Bonferroni-corrected Wilcoxon test (PD, CAL, and GR).
	2. 1.54 ± 0.64 (1y); 1.40 ± 1.13 (2y).	2. 8.73 ± 1.03 (BL) / 5.22 ± 1.00 1.32 ± 0.57 (2y). 1y).	2. 0.60 ± 0.5 6 (B L) /1.6 4=0. 60(1y) 1.61 ± 0.47 (2y).	2. Not report-ed.	2. Data not shown.	2. Not rated.	
		3. 97 ± 1.14 (2y)		3. Not re po rted.	3. Data not shown.	3. Not rated.	
		4. 8.70 ± 1.03 (BL) / 6.11 ± 1.35 (1y) 6.33 ± 1.83 (2y)		4. Not report-ed.		4. 3 (OFD) / 2 (EMD).	
						5. Not rated.	

Table 4: Mean percent clinical attachment level gain (CALG), Probing pocket depth (PPDR) and increase gengival recession (IGR).

Study	Outcomes				
	Follow up (month)	Intervention	CALG (mm)	PPDR (mm)	IGR (mm)
Tonetti et al. (2002), (2004)	12	OFD+SPPF/MPPT+EMD	3.1±1.5	3.9±1.7	0.8±1.2
		OFD+SPPF/MPPT	2.5±1.5	3.3±1.7	0.8±1.2
Zucchelli et al. (2002)	12	OFD+SPPF+EMD	4.2±0.9	5.1±0.7	1.0±0.5
		OFD+SPPF	2.6±0.8	4.5±1.0	1.9±0.8
Wachtel et al. (2003)	12	OFD+MPPT+EMD	3.7±0.4	4.2±0.3	0.5±0.2
Fickl et al. (2009)		OFD+MPPT	1.7 ±0.3	2.4±0.3	0.7±0.2
Francetti et al. (2004), (2005)**	24	OFD+SPPF+EMD	3.51	4.02	-
		OFD+SPPF	2.51	3.51	-
Cortellini e Tonetti (2011)	12	OFD+M-MIST+EMD	4,1±1.2	4.4±1.2	0.3±0.5
		OFD+M-MIST	4,1±1.4	4.4±1.6	0.3±0.6
Ribeiro et al. (2011)	6	OFD+MIST+EMD	3.02 ±1.9	3.56±2.0	0.46±0.8
		OFD+MIST	2.82±1.1	3.55±0.8	0.54±0.5
Bhutda e Deo (2013)	60	OFD+PPF+EMD	3.18 ±0,87	3.84±1.50	0.66±0.1
		OFD+PPF	1.60 ±0,54	1.92±0.35	0.32±0.5
Leonardis e Paolantonio (2013)	12	OFD+SPPF/MPPT+EMD	2.73±0.64	3.51±0.58	0.77±0.37
		OFD+SPPF/MPPT	1.54±0.64	2.58±0.55	1.04±0.25

Source: The author

In 4 studies [23,28,29,30] there were reports of losses after the interventions. These, for the most part, were justified as the patient's refusal to continue the study, change of address, difficulty in contact and involvement by serious illness. No study has reported problems with healing or adverse events resulting from interventions.

Evaluation of the Effects of Interventions

A total of 698 intraosseous defects in 557 patients were included in this review. The 8 studies included can be divided into 5 groups according to the therapeutic approach studied: 1) studies that used the OFD + SPPF / MPPT + EMD surgery technique compared to OFD + SPPF / MPPT alone [28,30]. 2) studies that used the OFD + SPPF + EMD technique compared to OFD + SPP alone [23,24]. 3) Studies that used the OFD + MPPT + EMD technique compared to OFD + MPPT alone [25], 4) Studies that used the OFD + M-MIST + EMD technique compared to OFD + M-MIST alone [27], 5) Studies that used the OFD technique + MIST + EMD compared to OFD + MIST alone [29] and 6) Studies that used the OFD + FPP + EMD technique compared to OFD + FPP alone [26].

OFD + SPPF / MPPT + EMD versus OFD + SPPF / MPPT

Two studies [28,30] compared the treatment of intraosseous defects using the OFD + SPPF / MPPT + EMD test group and the OFD + SPPF / MPPT control group. In the study by Tonetti *et al* [28] the follow-up time was 12 months and that of Leonardis e Paolantonio [30] was 24 months. In the study by Tonetti et al. [28] smoking patients were included and the study by Leonardis e Paolantonio [30] was a split-mouth clinical trial. Both used defects of 1,2 or 3 walls. It is important to highlight that the studies included in this group mentioned that they used two surgical techniques SPPF or MPPT in the treatment of intraosseous defects, the choice for one or the other was due to the width of the defect. Regarding the clinical gain of insertion, in the study [28] the test group had an average of 3.1± 1.5mm and 2.5 ± 1.5mm in the control group at 12 months of follow-up. In the study [30], the test group showed 2.73 ± 0.64mm at 12 months of follow-up and 2.95 ± 0.74mm at 24 months, and in the control group the results were 1.54 ± 0.64mm at 12 months and 1.40 ± 1.13 mm at 24 months. Both studies showed clinical gain of insertion after 12 and 24 months of treatment compared to the baseline data, also showing superior results with statistically significant differences for the test group compared to the control group. In relation to the reduction of the drilling depth. In the test group, the studies obtained similar results. 3.9 ± 1.7mm in the study [28] and 3.51 ± 0.58mm in the study [30] after 12 months of follow-up. In the control group, there was a greater difference, 3.3 ± 1.7mm in the study [28] and 2.58 ± 0.55mm in [30] after 12 months of follow-up. In both studies [28,30], the results were statistically significant compared to the data in the baseline and with the test group with superior results. In relation to the increase in gingival recession in both studies and in both groups, the averages ranged from 0.77mm to 1.4mm.

OFD + SPPF + EMD versus SPPF + EMD

Two studies [23,24] evaluated the treatment of intraosseous defects using OFD + SPPF + EMD in the test group, compared to SPP in the control group. In the study by Zucchelli *et al* [23] the clinical follow-up was 12 months and in the study by Francetti *et al* [24] it was 12 and 24 months. Both studies included smoking patients and bone defects of 1.2 or 3 walls. Regarding the clinical gain of insertion, the study Zucchelli et al [23] observed a percentage of 4, 2± 0.9mm in the test group and 2.6 ± 0.8 in the control group, on the other hand, in the study Francetti et al [24] only the simple mean gain of insertion was reported, which was 3.41mm in the test group and 2.51 mm in the control group. Both studies [23,24] the results were superior and statistically significant in 12 and 24 months compared to the data in the baseline, and the test group obtained superior and statistically significant results compared to the control group in the periods of 12 and 24 months. In relation to the reduction in the depth of sounding, the study [23] showed an average of 5.1 ± 0.7 mm in the test group and 4.5 ± 1.0 in the control group. The study [24] showed an average of 4.02 mm in the test group and 3.51 mm in the control group. In both groups of the two studies [23,24], better results were obtained compared to baseline. With the test group showing better results compared to the control in the 12-month period, and these were statistically significant. Both studies [23,24] showed an increase in gingival recession in both groups. In the study [24], the percentage of bone gain after the procedures was also reported, with percentage values of 53.7% after one year and 55.2 after 2 years in the test group and 35.4% after one year and 45 after two years in

the control group. The results of both groups were superior to those of the baseline after 24 months, but there were no statistically significant differences between the groups. In the study [24], the percentage of bone gain after the procedures was also reported, with percentage values of 53.7% after one year and 55.2 after 2 years in the test group and 35.4% after one year and 45 after two years in the control group. The results of both groups were superior to those of the baseline after 24 months, but there were no statistically significant differences between the groups. In the study [24], the percentage of bone gain after the procedures was also reported, with percentage values of 53.7% after one year and 55.2 after 2 years in the test group and 35.4% after one year and 45 after two years in the control group. The results of both groups were superior to those of the baseline after 24 months, but there were no statistically significant differences between the groups.

OFD + MPP + EMD versus OFD + MPP

Only one study Fickl *et al* [25], used in the treatment of intraosseous defects OFD + MPPT + EMD in the test group and OFD + MPPT in the control group. It was a split- mouth study with a 12-month clinical follow-up. Smoking patients were included in the study and defects of 1.2 or 3 walls. Regarding the clinical gain of insertion, an average of 3.7 ± 0.4 mm and 1.7 ± 0.3 mm in the control group was observed in the test group, both groups showed statistically significant results after 6 and 12 months compared to baseline, however the clinical gain of insertion was higher in the test group. In evaluating the depth reduction of the probe, the study showed a value of 4.2 ± 0.3 in the test group and 2.4 ± 0.3 mm in the control group. In both groups, the results showed a reduction in the probing depth after 6 and 12 months compared to baseline and statistically significant differences were found. The reduction in the drilling depth in the test group showed superior results compared to the control group. Regarding the increase in gingival recession, both groups showed an increase in recession 6 and 12 months after the procedure, however, there were no statistically significant differences between the groups. Both groups showed significant bone filling after 6 and 12 months, with the test group showing superior results compared to the control group. Regarding the increase in gingival recession, both groups showed an increase in recession 6 and 12 months after the procedure, however, there were no statistically significant differences between the groups. Both groups showed significant bone filling after 6 and 12 months, with the test group showing superior results compared to the control group. Regarding the increase in gingival recession, both groups showed an increase in recession 6 and 12 months after the procedure, however, there were no statistically significant differences between the groups. Both groups showed significant bone filling after 6 and 12 months, with the test group showing superior results compared to the control group.

OFD + M-MIST + EMD versus OFD + M-MIST

Only one study Cortellini and Tonetti *et al* [27] used this approach in the treatment of intraosseous defects. Clinical follow-up was 12 months. The study included smoking patients and defects of 1.2 or 3 walls were used. Regarding the clinical gain of insertion, in the test group a value of 4.1 ± 1.2 mm and 4.1 ± 1.4 in the control group were presented, observing similar results in both groups, with no significant differences between groups. With regard to the reduction of the depth of sounding, the study showed values of 4.4 ± 1.2 mm in the test group and 4.4 ± 1.6 in the control group, observing similar results between the groups. Regarding the increase in gingival recession, the study showed no statistically significant difference between the test and control groups. The mean bone gain after the procedures was also evaluated, showing values of 71 ± 18 in the test group and 77 ± 19 in the control group, this average was calculated using a pre-established formula: X ray bone gain / X ray INFRA x 100 [27]. The differences between the groups in relation to the percentage of bone gain, were not statistically significant. Regarding the patient's perception of postoperative pain, the study evaluated using the VAS scale, with results of 11.5 ± 0.7 in the test group and 10.7 ± 2.1 in the control group. No patient reported postoperative edema were not statistically significant. Regarding the patient's perception of postoperative pain, the study evaluated using the VAS scale, with results of 11.5 ± 0.7 in the test group and 10.7 ± 2.1 in the control group. No patient reported postoperative edema were not statistically significant. Regarding the patient's perception of postoperative pain, the study evaluated using the VAS scale, with results of 11.5 ± 0.7 in the test group and 10.7 ± 2.1 in the control group. No patient reported postoperative edema.

OFD+MIST+EMD versus OFD+MIST

Only one study Ribeiro *et al*. [29] reported the approach using OFD + MIST + EMD in the test group and OFD + MIST in the control group. Clinical follow-up was 6 months and smoking patients were not included. The mean clinical gain of insertion was 3.02 ± 1.9 mm in the test group and 2.82 ± 1.1 mm in the control group, showing statistically significant differences in both groups compared to baseline data, and these differences were greater in the test group, however the results were not statistically significant between groups. The probing depth reduction was observed with average values of 3.56 ± 2.0 in the test group and 3.55 ± 0.8mm in the control group, showing statistically significant differences compared to baseline, but without statistically significant differences between groups. In relation to the increase in gingival recession, values of 0.46 ± 0.8 mm were observed in the test group and 0.54 ± 0.5 mm in the control group, which did not show statistically significant differences between the groups.

OFD+FPP+EMD versus OFD+FPP

Only one study by Bhutda *et al*. [26], used this therapeutic approach. This study was divided mouth with a clinical follow-up of 60 months. Defects of 2 or 3 walls were included, and smoking patients were excluded. Regarding the mean clinical gain of insertion, values of 3.96 ± 0.44 mm were observed in the test group and 2.05 ± 0.78 mm in the control group after 1 year, and 4.90 ± 1.21 mm in the test group and 5, 72 ± 1.09mm in the control group after 5 years, these results were statistically significant in both the test and control groups when compared to the baseline data. With regard to the reduction of depth of sounding, the averages observed were 3.40 ± 0.5 mm in the test group and 4.90 ± 0.5 mm in the control group after 5 years. After the 5-year period, the test group showed significantly higher results than the control group in the mean reduction in the depth of sounding. The increase in gingival recession was also assessed in the study and averages of 0.66 ± 0.1 mm in the test group and 0.32 ± 0.5 mm in the control group were observed. The percentage of bone gain from defects was calculated after 5 years of the procedures, and the results showed a percentage of 66.66 ± 7.8% in the test group and 31.71 ± 4.1% in the control group. There was a statistically significant difference when comparing the test group and the control group, observing a greater bone gain in the test group. The percentage of bone gain from

defects was calculated after 5 years of the procedures, and the results showed a percentage of 66.66 ± 7.8% in the test group and 31.71 ± 4.1% in the control group. There was a statistically significant difference when comparing the test group and the control group, observing a greater bone gain in the test group. The percentage of bone gain from defects was calculated after 5 years of the procedures, and the results showed a percentage of 66.66 ± 7.8% in the test group and 31.71 ± 4.1% in the control group. There was a statistically significant difference when comparing the test group and the control group, observing a greater bone gain in the test group.

Quantitative Analysis

Due to the methodological heterogeneity and variability of the evaluation periods and incomplete reporting of the data, it was considered appropriate to perform a meta-analysis for data on bone gain and patient-centered outcomes. The statistical combination of results was performed for the outcomes clinical attachment gain, reduction of probing depth and increase of gingival recession with data from studies [29,30] that used the same technique and surgical approach (OFD + SSPF / MMPT + EMD and OFD + SSPF / MMPT) with 1 year of follow-up.

There was a statistically significant difference in the assessment of clinical attachment gain [n=119; MD=0.92; 95%; CI (0.35; 1.50); p=0.002] I^2 78% in favor of the test group, with a high heterogeneity of studies in this parameter (Graph 3). A statistically significant difference was also observed in the outcome reduction of probing depth [n=119; MD=0.86; 95%; CI (0.63, 1.10); p=0.0001] I^2 20%, in favor of the control group (Graph 4). There was a statistically significant difference in the outcome of increased gingival recession [n=119; MD= -0.23; 95%; IC (- 0.37, -0.10); p=0.0008] I^2 45% in favor of the control group (Graph 5).

Qualitative Analysis of the Studies Included in the Review

The assessment of the risk of bias is summarized in graphics 1 and 2. In order to hide the allocation, the risk of bias was considered unclear in 6 studies [23-26,28,29]. For blinding the participants, the risk of bias was considered unclear in three studies [26-28]. For risk of detection bias, three studies were deemed unclear [26,28].

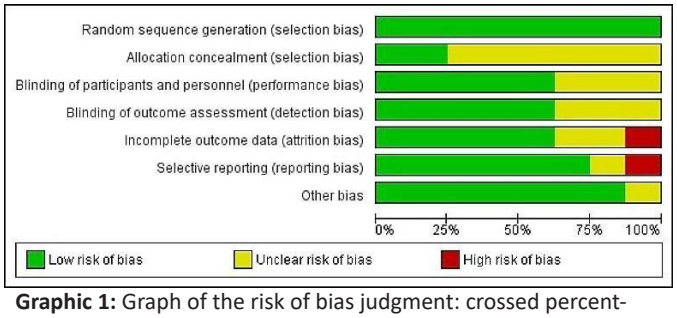
For incomplete outcome data, the risk of bias was considered unclear in one study [26] and high risk in one study [24]. For the risk of selective reporting bias, a study [24] reported in two publications was considered to be high risk.

Only one study [30] was considered low risk of bias in all categories.

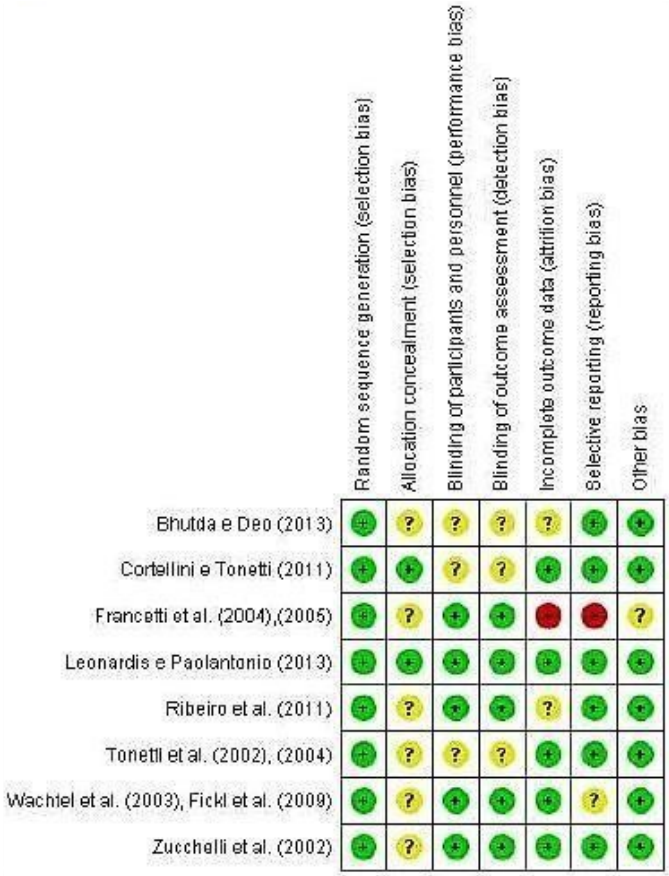
Graphics (1,2)

Meta Analysis Graphics

Graphics (3,4,5)



Graphic 1: Graph of the risk of bias judgment: crossed percentages of all included studies.



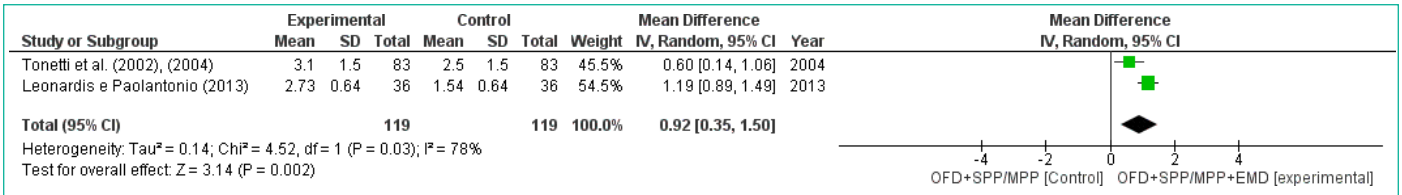
Graphic 2: Summary of judgment for each item of risk of bias in the included studies.
Source: The author

Discussion

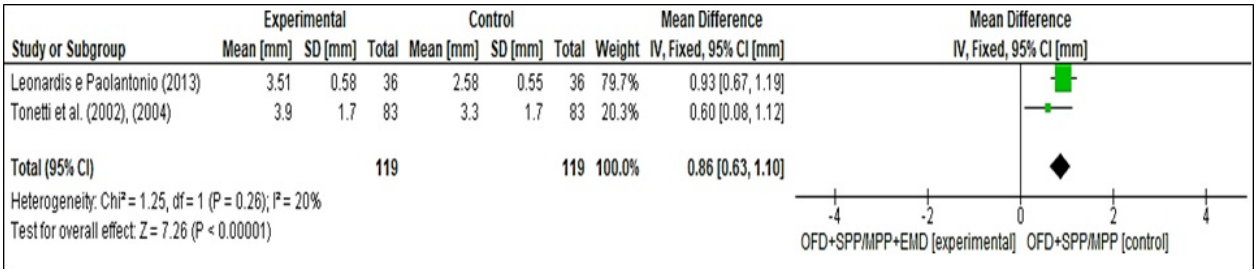
This systematic review was designed to assess the clinical performance of the minimally invasive surgical approach to preserve interdental tissues in association with proteins derived from the enamel matrix, compared to that same approach without PDME, in the treatment of intraosseous defects. In general, the evidence collected suggests that only surgical access with the use of minimally invasive techniques of preservation of the papilla, can lead to satisfactory clinical results in terms of clinical gain of insertion, reduction of probing depth and radiographic bone filling, as this This approach aims at better wound healing, surgical clot stability and provides a stable space for regeneration [26,27].

However, the use of PDME associated with minimally invasive approaches to preserve interdental tissues, can lead to an optimization of these clinical results, since PDME promote periodontal regeneration through the formation of periodontal ligament, root cement and alveolar bone, in addition to favoring the tissue healing process. Six studies from this review showed that the association of PDME, produced better clinical results in 12 months [23-25,27,28,30], however, only two studies [27,29] showed that PDME did not promote additional benefits.

So much so that in the study [29] the clinical follow-up was only 6 months, and it is known that studies that show an advantage with the association of PDME, the clinical follow-up is at least 12 months, so it is interesting to have longer clinical follow-ups, to be able to more accurately assess the long-term benefit of PDME. A meta-analysis by Zanatta *et al* [31]. evaluated the effect of PDME compared to open flap surgery over a 12-month period; results were demonstrated for clinical gain of insertion and reduction in probing depth consistently favorable to the PDME group.



Graphic 3: Forest Plot of the comparation between OFD+SPPF/MPPT+EMD and OFD+SPPF/MPPT for the clinical Attachment gain, after 1 year of the intervention (random model).
Source: The author



Graphic 4: Forest plot of the the comparation between OFD + SPPF / MPPT + EMD and OFD + SPPF / MPPT for the outcome reduction in Probing depth , after 1 year of the intervention (fixed model).
Source: The author

However, a high heterogeneity was observed in the outcome, reduction of the depth of probe and clinical gain of insertion, in the follow-up period of less than 12 months. And these results are in line with two other systematic reviews of the subject [5,17]. However, in the meta-analysis by Zanatta et al [31], there were analyzes by subgroups, considering the time of follow-up, suggesting that the magnitude of the differences between the use of PDME and OFD decreases considerably over time. Thus, it can be assumed that in some sites treated with PDME, the formation of long junctional epithelium occurred after using the PDME and, therefore, presented a healing pattern similar to that of the control groups. In addition, the factor would justify the results of greater clinical gain in the first 12 months

Unlike these systematic reviews, this study used open flap decontamination as a control group only with surgical techniques that preserved interdental tissues. It is known that from a clinical point of view, better results of clinical insertion gain are achieved through this approach when compared to conventional approaches, and this leads to better wound healing patterns, with greater clot stability in the interproximal area, favoring healing of the intraosseous defect. In a systematic review by Graziani *et al* [32], the treatment of intraosseous defects over a period of 12 months, treated with conservative periodontal surgery, was evaluated has showed significant improvement in periodontal clinical parameters and it was pointed out that clinical performance may vary according to the type of surgical flap used.

In addition, the authors suggested that further studies should be carried out with the comparison group using minimally invasive techniques for preserving the papilla, which according to some studies[25-28] promote better healing and stabilization of the clot in the wound, these Advantages are critical to successful regenerative treatment.

Studies [33-35] suggest better results when using papilla preservation flaps associated with PDME. And it can be argued that, given the lack of adverse effects reported with the papilla preservation flaps, they may represent the best available technique to gain access to intraosseous defects. And with the association of PDME, these results can be enhanced, since they have properties to stimulate various cellular reactions, which promote less inflammatory activities and accelerate healing.

Only two studies [27,28] evaluated the patient's perception of pain and level of satisfaction after treatment of intraosseous defects with interdental tissue preservation technique and PDME. In both studies, the results indicated that the adverse events of postoperative discomfort / pain, edema and flap dehiscence were lower in patients who used PDME. And in relation to the patient's satisfaction level after one year of the procedure, in both studies, the patients reported high levels of satisfaction with the results, mainly due to the possibility of preserving the tooth, on the other hand, as significant disadvantages were mentioned the needs of frequent follow-ups.

Within the minimally invasive surgical approaches for preserving interdental tissues, there are several techniques, which are used in surgical access to intraosseous defects. This systematic review divided them into groups to assess the occurrence of differences in the clinical gain of insertion between them and to compare them with the association of enamel matrix proteins in the treatment of these defects. Six studies [23-25,28-30] used the MIST approach that can be subdivided into SPPF and MMPT according to the width of the interdental space.

Five of them [23-25,38,30] demonstrated favorable clinical results when the PDME were associated with the MIST technique, with averages of clinical insertion gain ranging from 2.95mm to 4.92mm. On the other hand, in these studies, when the defects were not associated with PDME, the gain was slightly smaller, varying from 1.40mm to 2.6mm, this over a period of 12 to 24 months. Only the study by Ribeiro *et al*. [29], showed no differences between the groups, reporting that the improvements in clinical parameters are similar. However, despite the study being well designed, clinical follow- up was 3 to 6 months, which is considered short for a more accurate assessment of the benefit of PDME. It was possible to perform a meta-analysis in relation to the clinical gain of insertion after 1 year with two studies [28,30] that used OFD + SPPF / MPPT + EMD in comparison with OFD + SPPF / MPPT, the results [n = 119; MD = 0.92; 95%; IC (0.35; 1.50); p = 0.002] I^2 78%, showed greater gain in insertion in the test group, the differences being statistically significant, presenting results similar to the study by Zanatta *et al* [31].with values 1.19 mm (CI95% 0.77 -1.60) favorable to PDME, with one year of follow- up and 1.11 mm (CI95% 0.84 - 1.48) with two years of follow-up.

In the meta-analyzes [17-19], similar results were found, since the mean clinical gain of insertion and reduction of the depth of probing were slightly higher than the group that used PDME, however it is suggested that, despite the PDME being an excellent alternative in the treatment of intraosseous defects, there is a variability in the results presented, with minor differences between groups of studies with low risk of bias and studies with greater clinical follow-up. In view of this, it should be discussed whether its use will actually make a greater contribution compared to retail decontamination. Cortellini *et al*. [27] used a less invasive variation of the MIST approach, the M-MIST and their results were similar to those of Riberio *et al* [29], however with a superior clinical follow-up. And these data suggest that the intraosseous defects treated with M- MIST with or without the association of PDME, resulted in significant improvements in clinical and radiographic parameters. The study by Bhutda *et al* [26] was the one with the longest clinical follow-up time, 5 years, and used the conventional papilla preservation flap. The study revealed that treatment with PDME resulted in significant improvements in clinical gain of insertion, reduction of the probing depth and filling of the bone defect in all follow-up periods (1 and 5 years). These results are in accordance with a study by Heden *et al.* [33] which demonstrated an average insertion gain of 4.3 mm in the period of 1 year and 5.3 mm in the period of 5 years, respectively, demonstrating an excellent maintenance of the results obtained in the long term.

Evidence has shown that the topography of the intraosseous defect is directly related to its regenerative potential. Defects of three walls are more easily regenerated when compared to defects of a wall, due to the presence of a greater number of bone walls and, consequently, a greater number of cell sources capable of differentiating into cementoblasts, osteoblasts and fibroblasts of the periodontal ligament. In addition, the vertical and horizontal components of the defects have an influence on their regenerative potential.

Deeper defects compete with more favorable prognosis, and angles less than 45° formed between the root surface and bone wall show greater predictability in relation to regeneration than larger defects [4,23,34]. From this aspect, differences in the topography of defects, can characterize a risk of bias and can also explain a variability in the results, since this systematic review included studies that treated defects with 1, 2 or 3 walls. Five studies included smoking patients [23-25,27,28]. Smoking has been shown to be an important risk factor for periodontitis. The response to periodontal therapy is worse in smokers than in non-smokers. Regarding the treatment of intraosseous defects, these studies showed that non-smoking patients obtained greater gains in clinical insertion than smokers. The criteria for smokers were (<10 or <20 cigarettes per day), which may be an explanation for the high heterogeneity between studies, also considering a risk of bias. This makes it difficult to draw conclusions about smoking as an influencing factor in regeneration with PDME.

A possible variability in the results can be explained by the fact that three studies [23,26,30] used antibiotics. However, the beneficial effect of antibiotics in the postoperative period has not been demonstrated. Thus, it is likely that the prescription of antibiotics in the postoperative period did not have a great effect on the results. Studies [35-38] demonstrate that the antimicrobial properties of Emdogain's vehicle: Propylene glycol alginate, can contribute to optimize the regeneration.

The results related to the clinical gain of insertion and the reduction of the probing depth were consistently favorable to the treatment with the PDME. However, when the magnitude of these differences is discussed, you can see advantages that do not exceed 1.58 mm for the parameters evaluated in studies with follow-up periods of more than 24 months. Therefore, one can question the clinical relevance of these differences in the magnitude of the effect, since the assessment of the heterogeneity of the clinical insertion gain shows differences in relation to the follow-up time, in which studies with a follow- up period of more than two years shows little variability in the results, already. Studies with shorter follow-up periods these differences tend to be greater [38-40].

Additional studies are needed comparing surgical approaches to preserve interdental tissues with the use of PDME, with more rigorous methodologies and follow- up times longer than 12 months, since there are still few studies with this proposal, so that, it is possible to reach more accurate conclusions of the additional clinical benefit that this approach can bring in comparison to conventional flap debridement and other regenerative materials.

Another perspective that should be taken into account is in relation to the risk of publication bias, since studies that do not present significant differences between the groups tested, tend not to be published, because, although PDME is an excellent alternative in periodontal regenerative therapy, published studies should be carefully evaluated due to bias, since studies with lower risk of bias, the results are similar between groups with PDME or without PDME.

Conclusions

Even considering the limited available evidence, the results found suggest that the treatment of intraosseous defects using the open flap debridement technique using minimally invasive approaches to preserve interdental tissues in association with proteins derived from the enamel matrix promote slightly clinical results higher in insertion gain when compared to open flap debridement without association of proteins derived from the enamel matrix.

No differences were found between the groups regarding the degree of postoperative morbidity of patients, suggesting that only the use of a conservative surgical approach to preserve interdental tissues is sufficient for good postoperative healing. Although the evidence is scarce in the literature regarding this outcome.

Regarding the follow-up time, the use of PDME showed clinical results slightly superior in clinical gain of insertion period of 12 months after the intervention, in the periods of 24 months or more, this difference between groups tends to fall, showing similar results and more stable between groups.

Author Statements

Author Contributions

All authors made substantial contribution to the conception and design of the manuscript. E.F.B and L.M.L.O performed the literature search and interpretation of the data. All authors drafted the work and revised it critically for important intellectual content. All authors agree to be accountable for all aspects of the study design and its content. All authors approved the final submitted version.

Conflict of Interest

The authors have declared that they have no conflict of interest.

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Ethical Approval

This article does not contain any study with human or animal participants done by any of the authors.

Informed Consent

For this type of study, formal consent is not necessary.

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