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Minimally invasive regenerative periodontal surgery - full papilla preservation: A literature review

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Literature review presented to the university Fernando Pessoa as part of the requirements for the obtention of Dental Medicine master's degree

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Resumo

Objetivo: O objetivo deste estudo foi descobrir se, entre pacientes com defeitos intrabônicos, as técnicas completas de preservação da papila melhoram os resultados clínicos e centrados no paciente em comparação às técnicas convencionais.

Materiais e Métodos: 11 ensaios clínicos randomizados foram avaliados nesta revisão de literatura. Os resultados primários foram profundidade de sondagem, nível de apego clínico e recessão. Os desfechos secundários foram os centrados no paciente. 319 locais em 313 pacientes foram tratados nos 11 artigos. 73 pacientes (25%) receberam uma abordagem completa de preservação da papila. 52,7% de todos os pacientes eram homens (165) e os estudos incluíram 5,5% de fumantes (16). Todos os pacientes foram diagnosticados com doença periodontal avançada.

Resultados: Todos os estudos mostraram redução da profundidade de sondagem, ganho de inserção clínica e aumento da recessão, em todas as diferentes técnicas. A redução média da DP foi de 4,33±1,50mm, o ganho médio da CAL foi de 3,81±1,53mm e o aumento médio da recessão foi de 0,22±0,80mm.

Conclusões: Dentro das limitações, esta revisão de literatura apontou uma leve tendência a melhores resultados nas técnicas de preservação total da papila em comparação com o grupo de papilas elevadas. De maneira mais ampla, há uma clara tendência de que cirurgias mais minimamente invasivas resultem em melhores resultados clínicos e centrados no paciente.

Palavras-chave: Periodontite, Defeito intrabono, Cirurgia minimamente invasiva, Preservação total das papilas, Regeneração

Abstract

Objective: The aim of this study was to find out if, among patients with intrabony defects, full papilla preservation techniques improve clinical and patient-centered outcomes as compared to conventional techniques.

Materials and Methods: 11 randomized control trials were assessed is this literature review. Primary outcomes were probing depth, clinical attachment level and recession. Secondary outcomes were patient-centered outcomes. 319 sites in 313 patients were treated in all 11 articles. 73 patients (25%) received a full papilla preservation approach. 52,7% of all patients were men (165) and the studies included 5,5% of smokers (16). All patients were diagnosed with advanced periodontal disease.

Results: All studies showed probing depth reduction, clinical attachment gain and recession increase, across all different techniques. Mean PD reduction was 4.33±1,50mm, mean CAL gain was 3,81±1,53mm and mean recession increase was 0,22±0,80mm.

Conclusion: Within the limitations, **t**his literature review pointed out a slight tendency towards better outcomes in full papilla preservation techniques compared to elevated papilla group. More broadly, there is a clear tendency where more minimally invasive surgeries result in better clinical and patient-centered outcomes.

Keywords: Periodontitis, Intrabony defect, Minimally invasive surgery, Full papilla preservation, Regeneration

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To all my friends in France.

Index

Attachment Index

Abbreviation list

CAL - Clinical Attachment Level

DBBX - Deproteinized Bovine Bone Xenograft

DFA - Double Flap Approach

DPSC - Dental Pulp Stem Cells

EMD - Enamel Matrix Derivative

EPP - Entire Papilla Preservation

Ha - Hydroxyapatite

MINST - Minimally Invasive Non-Surgical Technique

MIST - Minimally Invasive Surgical Technique

M-MIST - Modified Minimally Invasive Surgical Technique

MPPF - Modified Papilla Preservation Flap

NIPSA - Non-Incised Papilla Surgical Approach

PD - Probing Depth

PDBS - Porcine-Derived Bone Substitutes

PDGF - Recombinant human platelet-derived growth factor BB

PDGF+β-TCP - Recombinant human platelet-derived growth factor BB and β-tricalcium phosphate

PICO - Population, Intervention, Comparison, Outcomes

PRISMA - Preferred Reporting Items for Systematic review and Meta-Analyses

RCT - Randomized Clinical Trial

REC - Recession

SFA - Single Flap Approach

SPPF - Simplified Papilla Preservation Flap

VAS - Visual Analogue Scale

I. Introduction:

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions defined periodontitis as a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. Its primary features include the loss of periodontal tissue support, manifested through clinical attachment loss (CAL) and radiographically assessed alveolar bone loss, presence of periodontal pocketing and gingival bleeding (Papapanou *et al*., 2018).

Periodontitis is a multifactorial disease, influenced by general factors such as:

- Hereditary (Michalowicz *et al*., 1991; Michalowicz. 1994; Hodge & Michalowicz. 2001)
- Systemic disease (Albandar *et al*., 2018)
- Smoking (Leite *et al.*, 2018)
- Emotional disorder (Liu *et al*., 2018)

and local factors, for instance:

- Bacterial (Loe *et al.,* 1986., Baelum *et al.,* 1986)
- Occlusion forces and food impactation (Glickman *et al*., 1969; 1967)
- Plaque-retaining local elements and distance between adjacent root surfaces (Tal. 1984; Waerhaug. 1979 1, 2).

The main endpoints of periodontal therapy are to finish active periodontal treatment with bleeding on probing in < 30% of evaluated sites and probing depths ≤ 4mm (Matuliene *et al*., 2008; Loos *et al*., 2020). To achieve this therapeutic education of the patient with toothbrushing technique and counselling on control of risk factors such as smoking, medical status and stress are of paramount importance at the beginning of the treatment. Then non-surgical debridment of both supra and subgingival bacterial plaque and calculus is accomplished with periodontal scalling and root planning (SRP). After phase one therapy, periodontal revaluation is advocated (Segelnick & Weinberg. 2006). Non-surgical therapy is effective in adressing most of the shallow and moderately deep pockets - up to 5mm (Sanz-Sanchez *et al*., 2020). In more advanced periodontitis cases (grade III-IV), resective or regenerative surgical approaches are regularly required (Papapanou *et* *al.*, 2018).

Resective procedures are designed to reduce or eliminate periodontal pockets and create an acceptable bone architecture that will allow an effective oral hygiene and periodontal maintenance. Conventional non-surgical therapy and surgical resection techniques provide clinical attachment gain and probing depth reduction but mainly through the formation of a long junctional epithelium (Karring *et al.*, 1980). Regenerative and reconstructive procedures objective is to promote the new formation of cement, alveolar bone and periodontal ligament with the use of biomaterials and sophisticated surgical techniques. In their guidelines in 2001, The American Academy of Periodontology consider regenerative and reconstructive procedures as guided tissue regeneration, guided bone regeneration, soft tissue grafts, bone replacement grafts, root biomodification, ridge augmentation, ridge preservation, implant site development, and sinus grafting.

Defect morphology plays a major role in periodontal regenerative treatment. According to the classification of Goldman & Cohen (Goldman & Cohen. 1958), bone loss due to periodontitis can be divided in 3 main categories: Suprabony defects, Infrabony defects and Interradicular defects (Fig. 1). Suprabony defects are those where the base of the pocket is located coronal to the alveolar crest. Infrabony defects, on the other hand, are defined by the apical location of the base of the pocket with respect to the residual alveolar crest. Two types of infrabony defects can be recognized: intrabony defects and craters. Intrabony defects affects primarily one tooth, while in craters the defect affects two adjacent root surfaces to a similar extent. Intrabony defects can be defined on the basis of the number of residual alveolar bone walls missing: Three-wall, two-wall and one-wall defects (Fig. 2). Usually, intrabony defects present a more complex anatomy, consisting of a three-wall component in the apical portion of the defect, and two and/or one-wall components in the more superficial portions. Such defects are frequently referred to as combination defects (Goldman & Cohen. 1958).

Healing following regenerative treatment of intrabony defects is greatly influenced by defect morpholgy: The depth of the intrabony defect influence the amount of clinical attachment and bone gained: the deeper the defect, the greater the amount of clinical improvement (Ehmke *et al.*, 2003; Silvestri *et al.*, 2003; Tonetti *et al.*, 1996; 1993; Garrett *et al.*, 1988). Cortellini *et al.*, (1998) showed that both deep and shallow defects can express a regenerative potential up to the complete resolution of the intrabony defect, with deeper defect showing larger linear amounts of attachment gain than those obtained following the treatment of shallow defects.

The width of the defect, defined as the angle between the bony wall of the defect and the long axis of the tooth (Steffensen *et al*., 1989), can as well influence periodontal regeneration: wider is the defect, reduced is the clinical attachment level and bone gain (Cortellini *et al*., 1999; Tonetti *et al*., 1996; 1993; Garrett *et al*., 1988).

The number of residual bony walls is also correlated with the outcomes of various regenerative approaches (Schallhorn *et al*., 1988; Goldman *et al*., 1958). Articles that reviewed the impact of the number of residual bony walls on clinical attachment level highlighted the difference between several regenerative techniques: while non-resorbable barrieres, titanium renforced barrieres or combination techniques did not show any difference (Tonetti *et al*., 2004; 2004; 1996; 1993), bio-resorbable barrieres and amelogenines demonstrated a significant differences (Silvestri *et al*., 2003; Tonetti *et al*., 2002; Falk *et al*., 1997). More recently, it has been demonstrated that the reduced impact of the number of residual bony walls and of defect width on the outcomes using amelogenins in combination with a minimally invasive technique (Cortellini *et al*., 2009; 2008). The same articles illustrated the crucial importance of the stability of the flap to reduce the defect anatomy impact on the outcomes.

The mandatory conditions for successful regeneration include the presence of space for the formation of the blood clot at the interface between the flap and the root surface (Kim *et al*., 2004; Wikesjo *et al*., 2003; Tonetti *et al*., 1996; Cortellini *et al*., 1995; Sigurdsson *et al*., 1994; Haney *et al*., 1993), the stability of the blood clot to maintain continuity with the root surface, avoiding formation of a long junctional epithelium (Haney *et al*., 1993; Wikesjo & Nilveus. 1990; Hiatt *et al*., 1968; Linghorne *et al*., 1950) and the soft tissue protection of the treated area to avoid bacterial contamination (Sanz *et al*., 2005; DeSanctis *et al*., 1996; DeSanctis *et al*., 1996; Nowzari *et al*., 1995; Nowzari & Slots., 1994; Selvig *et al*., 1992).

While narrow defects provide space and stability for the blood clot (Linares *et al*., 2006; Tsitoura *et al*., 2004; Cortellini & Tonetti. 1999; Selvig *et al*., 1993; Schallhorn *et al*., 1970; Goldman & Cohen. 1958), wider defects need support to provide appropriate healing conditions (Tonetti *et al*., 2004; 2004; 2002; 1993; Falk *et al*., 1997). The support can be provided by barriers or bone grafts, which are able to support the soft tissues and stabilize the blood clot, or a combination of both approaches. It can also be provided by a more minimally invasive approach, that reduces flap extention and mobility (Cortellini & Tonetti. 2009; 2007; 2007; Cortellini *et al*., 2008).

Historically, the principle of guided tissue regeneration was the implementation of a barrier membrane that avoid epithelial and connective tissue cells to invade the root surface and the periodontal defect, letting the periodontal ligament cells and the alveolar bone repopulate the space (Hägi *et al*., 2014).

Takei *et al*., (1985) introduced the papilla preservation flap to prevent the immediate, partial or complete exfoliation of the graft materials. It was then modified by Cortellini *et al*., (1995) in order to achieve and maintain primary closure of the flap and to increase the ability to create space for periodontal regeneration. The modified papilla preservation technique allowed stable primary closure of the flap in the interdental space in 70% of the sites. Cortellini *et al*., (1995) showed in his study significantly greater amounts of attachment gain and less gingival recession compared with conventional guided tissue regeneration or flap surgery.

Later, Cortellini *et al*., (1999) proposed a simplified approach of the papilla preservation flap to treat narrower interdental spaces. This approach has shown the added benefits of using barrier membranes (Cortellini *et al*., 2001; Tonetti *et al*., 1998;), but also a variety of regenerative materials, such as amelogenins (Tonetti *et al*., 2002) and bone replacement grafts (Cortellini *et al*., 2008; Tonetti *et al*., 2004) in deep intrabony defects.

From then on, more patient centered surgeries have been suggested, with a minimally invasive approach. These minimally invasive surgeries aim to reduce surgical trauma, enhance post-operative outcomes and take greater account of patient-centered outcomes. They are based on horizontal or oblique incisions that provide better blood clot stability by reducing flap extention and mobility.

The minimally invasive surgery (MIS) has been proposed in 1995 with the aim to produce minimal wounds, minimal flap reflection, and gentle handling of soft and hard tissues in periodontal surgery. The salient difference between the minimally invasive approach and more traditional approaches for regeneration is in the use of much smaller incisions to gain surgical access and debride the periodontal defect before placing the bone graft and membrane. Data from case reports showed clinical improvements in terms of pocket depth reduction, attachment level gain, and minimal increase of recession after application of the MIS in different types of defects (Harrel *et al*., 2005; Harrel & Nunn. 2001; Harrel. 1999,).

The Minimally invasive surgical technique (MIST) was suggested to reduce surgical trauma, allow stable primary closure of the wound, increase flap and wound stability, reduce surgical chair time and minimize patient discomfort and side effects. It was specially designed to treat isolated intrabony defects and the defect-associated interdental papilla is accessed either with the simplified papilla preservation flap in narrow interdental spaces or the modified papilla preservation flap in large interdental spaces. (Cortellini & Tonetti. 2007)

The same authors proposed an enhancement of this technique, the modified minimally invasive surgical technique (M-MIST). It was designed to further reduce the surgical invasiveness, with three major objectives in mind: minimize the interdental tissue tendency to collapse, enhance the wound/soft tissue stability and reduce patient morbidity (Cortellini & Tonetti. 2009).

Trombelli *et al.*, (2007) submitted the single flap procedure in order to facilitate flap repositioning and suturing. The flap can easily be stabilized to the entire papilla, optimizing wound closure for primary intention healing. Moreover, by leaving a great volume of supracrestal soft tissues intact, accelerated reestablishment of the local vascular supply may occur. Wound stabilization and preservation of an intact interdental papilla may also contribute an enhanced preservation of the pre-existing gingival esthetics. The basic principle behind the SFA is the unilateral elevation of a limited mucoperiosteal flap to allow surgical access depending on the main, buccal or oral, extension of the intraosseous defect leaving adjoining gingival tissues intact (Trombelli *et al.*, 2010). SFA was designed in contrast with the Double flap approach (DFA), based on MPPF and SPPF, in which the papilla is raised both buccally and orally.

Recently, authors proposed to sustain the defect-associated papilla to enhance post-operative outcomes. The goal of these new approaches is to allow a better blood clot stabilization, mprove the wound healing process thanks to an intact gingival chamber, reduce chair-time procedure and thus, improve clinical and patient-centered outcomes. (Aslan *et al.*, 2019; Ribeiro *et al.*, 2012; Aimetti *et al.*, 2016)

Therefore, the present systematic review aimed to answer the following PICO question: Among patients with intrabony defects (Population), do full papilla preservation techniques (Intervention) improve clinical and patient-centered outcomes (Outcome) as compared to conventional techniques (Comparison)?

1. Materials and Methods:

i. Protocol development

A detailed review protocol was designed according to the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analyses) statement (Hutton *et al.*, 2015; Moher *et al.*, 2009).

ii. Population (P), Intervention (I), Comparison (C), Outcome (O) – PICO

Articles were included in this systematic review if they met the following inclusion criteria (PICOS):

- Type of Population (P): Patient older than 18 with advanced periodontal disease, in general good health, presenting with at least one deep intra-bony defect
- Type of Interventions (I): Any type of minimally invasive surgical or non-surgical approach alone or in combination with regenerative biomaterials.
- Comparisons (C): Any type of comparison between full papilla preservations techniques and more traditional techniques.
- Outcomes (O): Primary outcomes were changes in probing depth (PD), clinical attachment level (CAL) and gingival recession (REC). Secondary outcomes were Patient-centered Outcomes: Chair-time, Intra/Post-operative Discomfort, Intra/Post-operative Pain, Pain intensity, and Analgesic Consumption.

iii. Focused question

In the treatment of intrabony defects, do full papilla preservation techniques have better clinical and patient centered outcomes compared to conventional techniques ?

iv. Eligibility Criteria and study selection

Randomized control trials, whose objective was to analyze PD reduction, CAL gain and gingival recession were included. To be included, studies should have a minimum number of 10 patients and no limit regarding the time of follow-up was set. Systematic review, narrative review, animal studies and case reports were excluded.

v. Type of intervention and comparisons

To answer the PICO question, interventions in the first cluster included all full papilla preservation approaches, more specifically approaches without any papilla debridement, with or without any adjunctive therapies. The other cluster included minimally invasive surgeries raising the papilla, with or without any adjunctive therapies.

vi. Information sources and search

Electronic and manual literature searches were conducted independently by two authors (A.C & T.R.A.). Three electronic databases were used as sources in the search for studies satisfying the inclusion criteria: The National Library of Medicine (MEDLINE via PubMed), Cochrane Central Register of Controlled Trials and Scopus. These databases were searched for studies published until March 31th, 2020. Hand search of reference journals have been done in Journal of Periodontology, Journal of Periodontal Research, Journal of Clinical Periodontology, and International Journal of Periodontics and Restorative Dentistry).

vii. Search Strategy

The electronic search strategy included terms related to the intervention and used the following combination of keywords:
("intrabony defect" OR "periodontal regeneration" OR "Periodontal pocket" OR "periodontal healing" OR "Gingival recession") AND ("minimally invasive surgery" OR "papilla preservation technique" OR "minimally invasive periodontal surgery" OR "modified papilla preservation technique" OR "simplified papilla preservation technique" OR "single flap approach" OR "GTR" OR "full papilla preservation" OR "guided tissue regeneration" OR "amelogenin" OR "emdogain" OR "biomaterial" OR "aesthetic outcome")

viii. Screening methods

Two reviewers (A.C. and T.R.A.) screened independently the titles and abstracts. The same reviewers' selected full manuscripts of studies meeting the inclusion criteria, or those with insufficient data in the title and abstract to make a clear decision.

ix. Quality assessment (risk of bias in individual studies)

A quality assessment of the included RCTs was performed according to the Cochrane Collaboration risk of bias tool for randomized trials (Higgins *et al*., 2016). Seven main quality criteria were examined: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective outcome reporting (Table 3). Risk of bias in the included studies was categorized as below:

- Low risk of bias if all criteria were met (plausible bias unlikely to seriously alter the results).
- Unclear risk of bias if one or more criteria were partly met (plausible bias that raises some doubt about the results).
- High risk of bias if one or more criteria were not met (plausible bias that seriously weakens confidence in the results).

II. Development

1. Results

i. Study population

The mean age of the patients in the studies reviewed was 46,28 years old, with 313 patients in total (319 sites). 73 patients (25%) received a full papilla preservation approach. 52,7% of all patients were men (165) and the studies included 5,5% of smokers (16). All patients were diagnosed with advanced periodontal disease.

ii. Clinical studies and outcomes

Table 1 depicts the flow charts summarizing the results of the search. The search rendered 1509 results, with, after evaluating their titles and abstracts, resulted in 35 articles for full text analysis. After this analysis, 11 RCTs were included for data extraction. According to description by authors, nine main surgical approaches were considered after analysis of included studies: Minimally Invasive Surgical Technique (MIST), Double Flap Approach (DFA), Modified Minimally Invasive Surgical Technique (M-MIST), Single Flap Approach (SFA), Flapless and Entire Papilla Preservation (EPP). One non-surgical approach was also regarded: Minimally Invasive Non-Surgical Technique (MINST). Additionally, Enamel Matrix Derivated (EMD), Deproteinized Bovine Bone Xenograft (DBBX), dental pulp stem cells in collagen scaffolds (DPSC), Porcine-Derived Bone

Substitutes (PDBS), Recombinant human platelet-derived growth factor BB alone (PDGF) or in combination with β-tricalcium phosphate (PDGF+β-TCP), Hydroxyapatite (Ha) and collagen were used as regenerative tool alone or in possible combinations. Twenty different treatment combinations were assessed in the included articles, during six to sixty months. After analysis of each technique, two main groups of approaches were considered:

- Group 1 - Minimally invasive surgeries raising the papilla: MIST, DFA, M-MIST and SFA.
- Group 2 - Minimally invasive approaches with full papilla preservation: EPP, Flapless and MINST.

a) Probing depth reduction

All studies showed Probing depth reduction across all different techniques. Mean PD reduction was 4.33±1,50mm, with a minimum reduction of 3.4mm (Ferrarotti *et al.*, 2018) and a maximum reduction of 6,5mm (Aslan *et al.*, 2019). Mean PD reduction in full papilla preservation group was 4,93±1,55mm while, in elevated papilla group, mean PD reduction was 4,23±1,53mm.

b) Clinical attachment level

All studies showed clinical attachment level reduction across all different techniques. Mean CAL reduction was 3,81±1,53mm, with a minimum reduction of 2,58±1,13mm (Ribeiro *et al.*, 2012) and a maximum reduction of 6,33±2,5mm (Aslan *et al.*, 2019). Mean CAL reduction in full papilla preservation group was 4,55±1,59mm when in elevated papilla group mean CAL reduction was 3,65±1,55mm.

c) Recession increase

All studies showed increase in recession across different techniques. Mean REC increase was 0,22±0,80mm, with a minimum recession increase of 0,1±0,5mm (p>0,05) (Ribeiro *et al.*, 2012) and a maximum recession increase of 0,82±0,6mm (p=0,27) (Mishra *et al.*, 2013). In full papilla preservation group, mean recession increase was 0,19±0,61mm when in elevated papilla group recession increase was 0,23±0,86mm.

d) Secondary outcomes

Table 2 depicts flow chart synthetizing patient-centered outcomes. Only 5 RCTs measured patient centered outcomes in this literature review. 3 RCTs regarding full papilla preservation approaches, and 2 concerning elevated papilla techniques. 161 patients were assessed, from which 58 with full papilla approach and 103 with an elevated papilla technique. The parameters analyzed were: Chair-time, Intra/Post-operative Discomfort, Intra/Post-operative Pain, Pain intensity, and Analgesic Consumption.

Mean chair-time was 50,77±7,35min, with a minimum chair-time of 23,5±2,8min (Aimetti *et al.*, 2016) and a maximum chair-time of 65,4±10,14min (Aslan *et al.*, 2019). In full papilla preservation group, the mean chair-time was 43,77±7,29min. In elevated papilla group, mean chair-time was 56,26±7,40min.

Discomfort and Pain were analyzed through different parameters: number of patient that felt Intra/Post-operative Discomfort and Pain, Pain intensity measured with a visual analogue scale (VAS) and Analgesic Consumption in tablets.

Two articles measured the number of patient that felt Intra/Post-operative Discomfort and Pain. (Aslan *et al.*, 2019; Cortellini *et al.*, 2011) In full papilla preservation group, 3 out of 30 (10%) patients felt intra/post-operative discomfort and 2 out of 30 (6,7%) patients felt intra/post-operative pain. In elevated papilla group, 9 out of 45 (20%) patients felt intra/post-operative discomfort and none felt pain.

All articles measured pain intensity with a 100mm VAS. Four articles measured post-operative pain, with a mean VAS score of 9,45±8,02mm (Aslan *et al.*, 2019; Aimetti *et al.*, 2016; Schincaglia *et al.*, 2015; Ribeiro *et al.*, 2011). Mean VAS score in full papilla preservation group was 7,49±9,01mm while mean VAS score in elevated papilla group was 11,56±9,46mm. Three articles measured 1-week pain, with a mean VAS score of 10,30±7,82mm. (Aimetti *et al.*, 2016; Schincaglia *et al.*, 2015; Cortellini *et al.*, 2011) Only Aimetti *et al.*, (2016) measured 1-week pain in full papilla preservation group (11±17mm). In elevated papilla group, mean VAS score was 10,19±14,79mm.

In term of analgesic consumption, three studies gave Ibuprofen 600mg (Aslan *et al.*, 2019; Schincaglia *et al.*, 2015; Cortellini *et al.*, 2011) and one Paracetamol 750mg (Ribeiro *et al.*, 2011). Mean analgesic consumption was 1,62±4,18 tablets, with a minimum analgesic consumption of 0,3±0,6 tablets (Cortellini *et al.*, 2011) and maximum of 8,69±11,6 tablets (Schincaglia *et al.*, 2015). In full papilla preservation group, mean consumption was 0,64±0,76 tablets while in elevated papilla group, mean consumption was 2,12±5,11 tablets.

2. **Discussion**

i. Main findings

a) Primary outcome

The main objectives of evaluating less invasive techniques is to achieve better outcomes, reduce per-operative and post-operative patient morbidity and maintain gingival aesthetics (Harrel *et al*., 2005; Hunter *et al*., 1993). Only two articles compared directly elevated papilla and preserved papilla approaches. In Aimetti *et al*., (2016), they assessed the effectiveness of EMD in combination with flapless or flap procedure. Both therapeutic modalities yielded similar PD reduction, CAL gain and REC increase at 24 months, with a mean PD reduction of 3.6 ± 1.0 mm, CAL gain of 3,2±1,1mm and REC increase of 0,4±0,7mm in flapless group and 3.7 ± 0.6mm, 3,6±0,9mm and 0,1±0,5mm in the MIST group. The results of this study showed that both approaches may lead to substantial clinical improvements which were maintained over a period of 24 months. These findings were consistent with those of Ribeiro *et al*. (2012), who observed a mean PD reduction of 3.5±0.9mm, a mean CAL gain of 2.9±1.2mm and a mean REC increase of 0,59±0,60mm at MIST sites compared to 3.1±0.7mm, 2.6±1.1mm and 0,58±0,83mm, respectively, at MINST sites. Despite a slight increase in REC in both studies, it was not statistically significant.

Aslan *et al*., (2019) compared the clinical efficacy of the entire papilla preservation technique (EPP) alone and in combination with EMD plus bovine derived bone substitutes. The amount of CAL gain (6.3±2.5 mm) and PD reduction (6.5±2.65 mm) observed in the EPP EMD + BS and in the EPP alone (CAL gain of 5.83 ± 1.12 mm and PD reduction of 6.2±1.33 mm) resulted in similar outcomes. Average REC increase from baseline to 1 year was clinically and statistically not significant in both groups (Test: -0,2±0,25mm, Control: -0,36±0,54mm), and no statistically significant differences were found between groups.

These three studies pointed out a tendency towards better outcomes in full papilla preservation group compared to elevated papilla group: in full preservation group, we noticed a mean PD reduction of 4,93±1,21mm, a CAL gain of 4,55±1,47mm and a REC increase of 0,19±0,57mm compared to a PD reduction of 4,23±1,43mm, CAL gain of 3,65±1,47mm and REC increase of 0,23±0,82mm in elevated papilla group. (Ferrarotti *et* *al*., 2018; Ghezzi *et al*., 2016; Schincaglia *et al*., 2015; Mishra *et al*., 2013; Trombelli *et al*., 2012; 2010; Cortellini *et al*., 2011; Ribeiro *et al*., 2011)

In addition, in Aslan *et al*., (2019), the 1-year clinical outcomes demonstrate that EPP with and without regenerative biomaterials is similarly effective in the treatment of isolated intrabony defects. These results were similar to other RCTs where flap design was based on preservation of the interdental papilla by elevation of a buccal flap. (Mishra *et al*., 2013; Cortellini *et al*., 2011; Trombelli *et al*., 2010). In all four studies, the lack of an adjunctive clinical benefit was consistent despite the different biomaterials utilized. These results can be explained by the more conservative approaches implemented in these studies, in which a more stable and less invasive flap improves blood clot formation and stabilization, enhancing regeneration.

b) Secondary outcome

Chair-time analysis shows the important time-gain with certain full papilla preservation techniques, where fewer or no incisions were made: In Aimetti *et al*., (2016) study, mean chair-time was 23,5±2,8min for Flapless group where SFA surgery lasted 54,9±7,1min. In Ribeiro *et al*., (2011), MINST procedures lasted 29,15±4,3min where MIST surgeries lasted 60,71±9,41min. Besides much shorter and less invasive surgeries, a slight reduction in intra/post-operative discomfort and pain was measured in full papilla preservation group (VAS: 7,49±9,01mm) compared to elevated papilla group (VAS: 11,56±9,46mm). In Schincaglia *et al*., (2015) significantly lower values of pain were observed in SFA group compared to DFA group at day 1, day 2 and day 6. In addition, significantly lower analgesics were consumed in SFA group compared to DFA group during 2 weeks post-operation. These results appear to be encouraging for less invasive approaches, although further research is needed.

ii. Agreements and disagreements

a) Primary outcome

In their systematic review, Barbato *et al*., (2020) explored the efficacy of different minimally invasive surgical (MIS) and non-surgical (MINST) approaches for the treatment of intra-bony defect. They used a network meta-analysis to rank the treatment efficacy and found that the groups M-MIST/SFA and M-MIST/SFA+EMD showed higher probabilities to be the best treatment compared to other techniques reviewed. More generally, their analysis showed superior results in terms of CAL gain for studies using more minimally invasive techniques such as elevating the flap only at buccal/palatal side, with or without a regenerative tool applied. These results confirm the tendency observed in this literature review, where better clinical outcomes are measured when applying a more minimally invasive approach. Besides these results, MINST showed the lowest probability to be the best treatment. These results seem to confirm the benefits of proper root debridement in intrabony treatment but need further investigation.

Other articles support the tendency of greater clinical outcomes using a full papilla approach: A previous prospective study applying the EPP (Aslan *et al*., 2017) showed improved results compared to those found in elevated papilla group in this study. With the non-incised papilla surgical approach (NIPSA), Moreno Rodriguez *et al*., (2019, 2018) suggested an apical approach, without tissue incision or disinsertion at papilla level or marginal tissues. Their studies showed greater PD reduction, CAL gain and REC management compared to the results of elevated papilla approaches in this study. In Moreno Rodriguez *et al*., (2019), they measured a significative reduction in REC when the NIPSA was applied in combination with EMD and DBBX. This can be explained by the apically positioned flap, that allow the creation of space provision by pushing the inter-proximal supra-alveolar soft tissue coronally and by preserving the architecture of the interproximal and marginal tissues. The unaltered supra-alveolar soft tissue acts as a dome protecting the blood clot, enhancing wound stability and supports mechanical traumas during early healing.

b) Secondary outcome

In Cortellini *et al*., (2012) literature review, the reported outcomes indicate that postoperative discomfort and pain apparently are influenced by the type of surgical approach: The number of subjects reporting postoperative interference with daily activities, discomfort and pain as well as pain intensity and consumption of pain killers was similar in the 2 papilla preservation flap studies, much reduced in the MIST study and very limited or none in the M-MIST study. A shorter chair-time and a more minimally invasive surgery seem to lead to better patient-centered outcomes such as pain and discomfort (Cortellini & Tonetti. 2011; Cortellini *et al*., 2007; Tonetti *et al*., 2004; Cortellini *et al*., 2001). These results acknowledge the slight tendency we observed in the studies included in this literature review: where minimally invasive approaches lead to better patient-centered outcomes.

iii. Limitations

The main limitation of this review is that only two articles compared directly elevated papilla and preserved papilla approaches. In addition, there is a lack of RCTs comparing promising new techniques such as the EPP and NIPSA.

Despite the effort of some of the articles reviewed, this literature review depicts the lack of studies evaluating patient-centered outcomes and more generally the lack of standardization for analyzing such outcomes.

III. Conclusion

Within the limitations of the study, we pointed out a tendency towards better outcomes in full papilla preservation group compared to elevated papilla group, and more broadly, going further in minimally invasive techniques seems to enhance clinical and patient-centered outcomes. When focusing on regenerative biomaterials, applying less invasive approaches may limit their benefits - elevating papilla at only buccal or palatal sites and full papilla preservation techniques enable blood clot formation and stabilization and thus probably allowing a better regeneration, regardless of the regenerative biomaterial.

Finally, more well designed randomized, controlled, properly blinded, clinical trials are needed to validate these tendencies.

IV. Bibliography

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V. Attachments

1. Table 1: PICO

Study (year)	Study design	N Patients (m/f age) Smoking Status	Test Groupe	Control Groupe	Number of Applications sites	Drop-Outs (N)	Follow-up (Month)	Clinical Outcomes									
								Probing Depth (mm)			Clinical Attachment Level (mm)			Recession (mm)			Primary Wound Closure (%)
								Baseline	Re-Evaluation	Difference	Baseline	Re-Evaluation	Difference	Baseline	Re-Evaluation	Difference	
Aslan *et al.*, (2019)	RCT	15 (10/5, 44,93) 0 Smokers	EPP+EMD+DBBX	/	15	0	12	9,33±2,87	2,83±0,74	6,5±2,65	11,66±3,45	5,36±1,85	6,33±2,5	2,33±1,23	2,53±1,36	-0,2±0,25 (p=0,14)	100
		15 (8/7, 43,93) 0 Smokers	/	EPP	15			9,26±1,65	3,06±0,79	6,2±1,33	11,4±2,17	5,56±1,74	5,83±1,12	2,13±1,12	2,5±1,4	-0,36±0,54 (p=0,14)	
Aimetti *et al.*, (2016)	RCT	30 (18/12, 43,25) 0 Smokers	Flapless	/	15	0	24	7.5 ± 0.9	3,9±0,9	3,6±0,1	9,4±2,0	6,2±2,3	3,2±1,1	1,9±1,8	2,3±2,6	-0,4±0,7 (p>0,05)	100
			/	SFA/M-MIST+EMD	15			7,3±0,8	3,6±0,9	3,7±0,6	9,0±1,7	5,4±1,6	3,6±0,9	1,7±1,2	1,8±1,0	-0,1±0,5 (p>0,05)	
Ribeiro *et al.*, (2012)	RCT	13 (4/9, 45,31) 0 Smokers	MINST	/	13	2	12	6,35±0,92	3,15±0,66	3,19±0,71	11,25±2,11	8,67±1,79	2,58±1,13	4,96±1,66	5,55±1,30	-0,58±0,83 (p>0,05)	/

		14 (6/8, 45,43) 0 Smokers	/	MIST	14			7,07±1,13	3,57±0,76	3,50±0,87	10,73±1,56	7,93±1,52	2,80±1,14	3,74±1,09	4,32±1,34	-0,59±0,60 (p>0,05)	
Cortellini *et al.*, (2011)	RCT	45 (24/21, 49,9) 5 Smokers	M-MIST+EMD	/	15	0	12	7,8±0,9	3,4±0,6	4,4±1,2	9,9±1,3	5,7±1,7	4,1±1,2	2,1±1,4	2,3±1,4	-0,3±0,5 (p<0,02)	100
			M-MIST+EMD+DBBX	/	15	0		7,3±1,2	3,3±0,6	4,0±1,3	10,1±2,4	6,4±2,4	3,7±1,3	2,9±1,8	3,1±2,1	-0,3±0,7 (p>0,05)	92,7
			/	M-MIST	15	0		7,5±1,6	3,1±0,6	4,4±1,6	9,6±2,0	5,5±1,6	4,1±1,4	2,1±1,4	2,4±1,4	-0,3±0,6 (p>0,05)	100
Mishra *et al.*, (2013)	RCT	24 (12/12) 0 Smokers	M-MIST+PDGF	/	14	1	6	7,73 ± 1,19	/	4,18±0,60	7,36 ± 1,28	/	3,00±0,89	0,18 ± 0,40	/	-0,82±0,60 (p=0,27)	/
			/	M-MIST	14	1		7,64 ± 0,67	/	3,82±0,87	6,91 ± 0,70	/	2,64±0,67	0 ± 0,0	/	-0,55±0,52 (p=0,27)	/
Schincaglia *et al.*, (2015)	RCT	15 (9/6, 50,1) 3 Smokers	SFA+PDGF+β-TCP	/	15	0	6	8,7±2	4,5±1,6	4,1±1,7	9,7±2,5	5,7±2,6	4,0±1,9	1,1±1,3	1,2±1,5	-0,1±0,7 (p=0,618)	80
		14 (9/5, 46,7) 0 Smokers	/	DFA+PDGF+β-TCP	14			7,7±1,5	4,1±1,2	3,6±1,1	8,5±1,6	5,2±1,6	3,2±1,4	0,8±1,3	1,2±1,6	-0,4±1,3 (p=0,618)	53,4

Trombelli *et al.*, (2012)	RCT	14 (10/4, 55,1) 1 Smoker	SFA	/	14	0	6	8,7±1,7	3,5±0,8	5,2±1,6	9,4±2,1	4,9±1,6	4,5±1,1	0,7±0,8	1,4±1,2	-0,7±0,8 (p=0,06)	92,8
		14 (7/7, 42,9) 5 Smokers	/	DFA	14			7,4±1,2	3,5±0,9	3,9±1,1	8,4±1,7	4,9±1,8	3,4±1,4	0,9±1,0	1,4±1,7	-0,5±1,1 (p=0,110)	85,7
Trombelli *et al.*, (2010)	RCT	12 (9/3, 45,6) 2 Smokers	SFA+HA+GTR	/	12	0	6	9,1±2,6	3,8±1,3	5,3±2,4	11,4±2,4	6,4±1,7	4,7±2,5	2,1±1,7	2,5±1,3	-0,4±1,4 (p=0,318)	57,5
		12 (8/4, 56,3) 0 Smokers	/	SFA	12			8,5±1,8	3,3±0,6	5,3±1,5	9,2±2,4	4,8±1,5	4,4±1,5	0,7±0,9	1,5±1,1	-0,8±0,8 (p=0,005)	100
Ribeiro *et al.*, (2011)	RCT	14 (5/9, 48,14)	MIST+EMD	/	14	1	6	7.09±1.70	3.53±1.12	3.56±2.07	12.23±2.03	9.21±2.46	3.02±1.94	5.28±1.90	5.74±1.88	-0.46±0.87	/
		15 (5/10, 45,53)	/	MIST	15	0		7.12±1.10	3.57±0.81	3.55±0.88	11.03±1.91	8.21±1.74	2.82±1.19	3.93±1.46	4.47±1.52	-0.54±0.58	/
Ferrarotti *et al.*, (2018)	RCT	29 (13/14, 50,7) 0 Smokers	MIST+DPSC	/	15	0	12	8.3±1.2	3.4±0.9	4.9±1.4	10.0 ± 1.6	5.5 ± 1.1	4.5 ± 1.9	1.7 ± 1.2	2.1 ± 1.3	-0.4 ± 1.1 (p>0,05)	100
			/	MIST+Collagen	14			7.9±1.3	4,5±1,0	3.4±1.7	9.4 ± 1.5	6.5 ± 1.2	2.9 ± 2.2	1.5 ± 0.8	2.0 ± 1.2	-0.5 ± 0.9	100

																(p>0,05)	
Ghezzi *et al.*, (2016)	RCT	10 (5/5, 56)	MIST+EMD+DBBX	/	10	0	12	8.2±1.30	3.3±0.48	4.9±1.20	9.2 ± 1.90	4.8 ± 1.40	4.4 ± 1.17	1.0 ± 1.10	1.5 ± 1.18	-0.5 ± 0.85 (p=0,09)	100
		10 (4/6, 52,9)	/	MIST+DBBX+GTR	10			7.8±2.40	3.1±0.57	4.7±2.36	8.5 ± 2.20	4.5 ± 1.27	4.0 ± 1.82	0.7 ± 0.67	1.4 ± 1.07	-0.7 ± 0.95 (p=0,045)	100

DBBX: Deproteinized Bovine Bone Xenograft; DFA: Double Flap Approach; DFDBA: Demineralized freeze-dried humain bone allograft; DPSC: Dental pulp stem cells in collagen scaffold; EMD: Enamel Matrix Derivative; EPP: Entire Papillae Preservation Technique; GTR: Guided Tissue Regeneration; HA: Hydroxyapatite; MIST: Minimally Invasive Surgical Technique; M-MIST: Modified Minimally Invasive Surgical Technique; MINST: Minimally Invasive Non-Surgical Technique; PDGF: Recombinant human platelet derived growth factor; PDGF+β-TCP: Recombinant human platelet-derived growth factor BB plus β - tricalcium phosphate; SFA: Single Flap Approach.

2. Table 2: Patient-centered outcomes

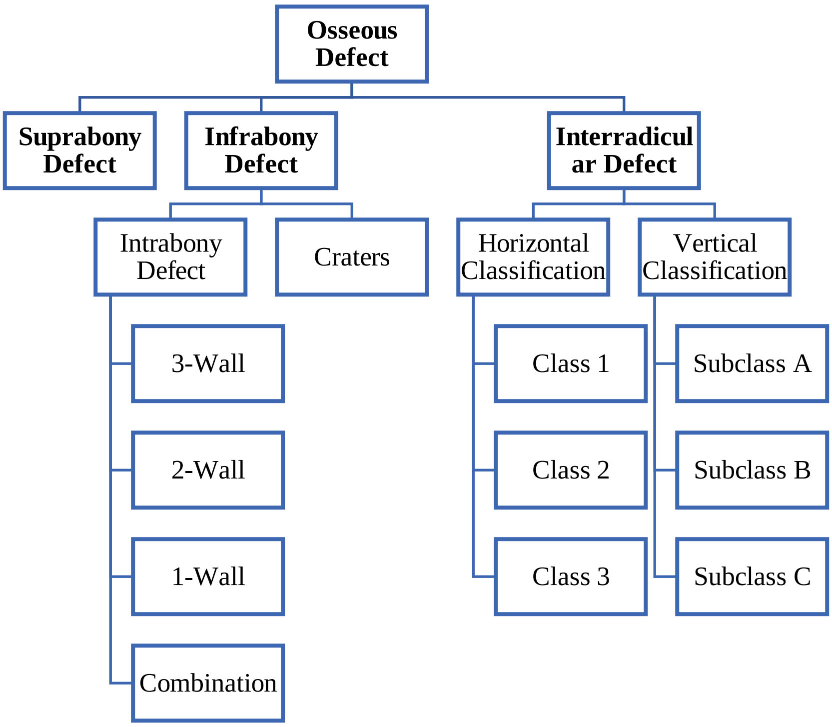
Articles	Study design	N Patients (m/f age) Smoking Status	Test Groupe	Control Groupe	Number of Applications sites	Drop-Outs (N)	Follow-up (Month)	Patient-Centered Outcomes					
								Chair-Time (Min)	Intra/Post-Operative Discomfort (n=Patient)	Intra/Post-Operative Pain (n=Patient)	Pain Intensity (VAS)		Analgesic (Tablets)
											Intra/Post-Operative	1 week	
Aslan et al., (2019)	RCT	15 (10/5, 44,93) 0 Smokers	EPP+EMD+DBBX	/	15	0	12	65,4±10,94	2	1	9,33±9,03	/	0,87±0,74
		15 (8/7, 43,93) 0 Smokers	/	EPP	15			55,07±7,86	1	1	8,33±9,38	/	0,73±0,88
Aimetti et al., (2016)	RCT	30 (18/12, 43,25) 0 Smokers	Flapless	/	15	0	24	23,5±2,8	/	/	9 ±11	11 ±17	/
			/	SFA/M-MIST+EMD	15			54,9±7,1			6 ±9	8 ±11	
Ribeiro et al.,(2011)	RCT	13 (4/9, 45,31) 0 Smokers	MINST	/	13	2	12	29,15±4,3	/	/	3,8±6,3	/	0,31±0,63
		14 (6/8, 45,43) 0 Smokers	/	MIST	14			60,71±9,41			4,8±8,9		0,40±0,74
Cortellini et al., (2011)	RCT	45 (24/21, 49,9) 5 Smokers	M-MIST+EMD	/	15	0	12	54,2±7,4	2	0	/	11,5±0,7	0,3±0,6
			M-MIST+EMD+DBBX	/	15	0		58,9±6,2	4	0		12,3±3,1	0,5±1
			/	M-MIST	15	0		52,9±6,6	3	0		10,7±2,1	0,4±0,7
Schincaglia et al., (2015)	RCT	15 (9/6, 50,1) 3 Smokers	SFA+PDGF+β-TCP	/	15	0	6	/	/	/	28	17	2,73±5,04 (2 week total)
		14 (9/5, 46,7) 0 Smokers	/	DFA+PDGF+β-TCP	14						5	1	8,69±11,6 (2 week total)

DBBX: Deproteinized Bovine Bone Xenograft; DFA: Double Flap Approach; EMD: Enamel Matrix Derivative; EPP: Entire Papillae Preservation Technique; PDGF+β-TCP: Recombinant human platelet-derived growth factor BB plus β - tricalcium phosphate; MIST: Minimally Invasive Surgical Technique; M-MIST: Modified Minimally Invasive Surgical Technique; MINST: Minimally Invasive Non-Surgical Technique; SFA: Single Flap Approach.

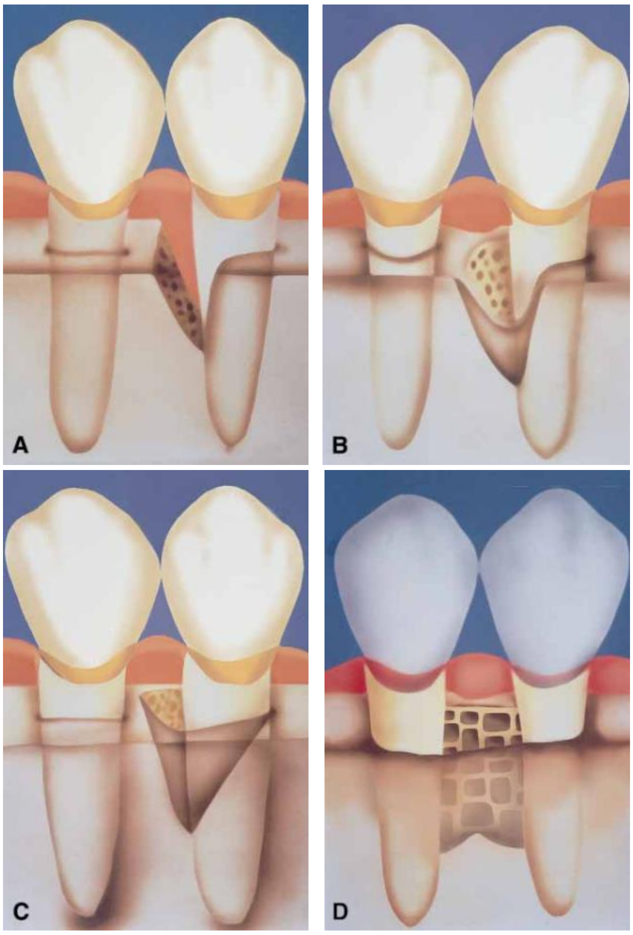
3. **Table 3: Cochrane**

	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome data	Selective Reporting	Other Bias
Aslan *et al.*, 2019	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Aimetti *et al.*, 2016	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ribeiro *et al.*, 2011	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Cortellini *et al.*, 2011	Low Risk	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk
Mishra *et al.*, 2013	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk
Schincaglia *et al.*, 2015	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk
Trombelli *et al.*, 2012	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Unclear Risk
Trombelli *et al.*, 2010	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
Ribeiro *et al.*, 2011	Low Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ferrarotti *et al.*, 2018	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ghezzi *et al.*, 2016	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk

4. **Figure 1: Classification of periodontal osseous defect**



5. **Figure 2: Intrabony Defect**



A. One-wall intrabony defect.

B. Two-wall intra- bony defect.

C. Three-wall intrabony defect.

D. Interproximal crater.