Matteo Scali

Comparison between Entire Papilla Preservation and Modified minimally invasive technique in periodontal regeneration - Systematic review

Universidade Fernando Pessoa

Faculdade de Ciências da Saúde

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Dissertation presented to University Fernando Pessoa

as part of the requirements for the the degree of

Master in Dental Medicine

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Matteo Scali

RESUMO

Objetivo: Comparar a *modified minimally invasive surgical technique* e a *entire papilla preservation* em termos de resultados clínicos, tais como o nível de inserção clínica, recessão gengival, profundidade de sondagem e níveis de sangramento em na regeneração periodontal de defeitos intraósseos.

Métodos: Foi realizada uma pesquisa electrónica através das bases de dados *Pubmed* (220), *B-On* (5127), *Scielo* (2) *Cochrane Library* (258) de 2003 a 2023. A seleção dos estudos e a sua eligibilidade foi direcionada através da leitura do título, *asbtract*, e leitura integral do artigo de acordo com o diagrama PRISMA. A avaliação de risco de viés foi realizada utilizando a ferramenta *Joanna Briggs Institute critical appraisal* mostrando que todos os artigos apresentaram boa qualidade. Foram incluídos, estudos clínicos, estudos clínicos comparativos, estudos clínicos caso-controle, estudos clínicos controlados e randomizados, com idioma em inglês, estudos em humanos que apresentem tempo de acompanhamento mínimo de 6 meses.

Resultados: De acordo com os critérios de inclusão e exclusão aplicados à pesquisa, dos 5.607 estudos, 6 foram considerados elegíveis. Esses artigos foram escortinados por forma em tentar encontrar a resposta para objetivo deste trabalho.

Conclusões: A *entire papilla preservation* é apontada na literatura como uma das melhores técnicas de regeneração periodontal, face aos resultados mais elevados e seguros, apresentando menor comorbidade. Contudo existe a necessidade de analisar as técnicas regenerativas e das suas vantagens, através da elaboração de estudos clínicos com amostras mais elevadas, tempos de *follow-up* mais longos e com protocolos mais rigorosos e padronizados.

Palavras-chave: Preservação total da papila; retalho cirúrgico; proteínas derivadas da matriz de esmalte; regeneração tecidular guiada; defeito intraósseo.

ABSTRACT

Objective: To compare the modified minimally invasive surgical technique and the entire papilla preservation in terms of clinical results such as clinical attachment level, gingival recession, probing pocket depth and full-mouth bleeding scores in the periodontal regeneration of intraosseous defects.

Methods: An electronic search was carried out through the databeses Pubmed (220), B-on (5127), Scielo (2) Cochrane (258) from 2003 to 2023. The selection of studies and their eligibility was directed by reading the title, abstract, and full text according to the PRISMA diagram. The risk of bias assessment was carried out using the Joanna Briggs Institute, critical appraisal tool, showing that all articles were of good quality. Clinical studies, clinical trials, comparative studies, control clinical trials, randomized control trials in English, and humans study sample with a 6 months minimum follow-up were included.

Results: According to the inclusion and exclusion criteria applied to the research, of the 5607 studies 6 were found eligible. These articles then were evaluated and studied to find the answer to the aim of this work, try to understand which one of the microsurgical techniques in comparison led to better outcomes.

Conclusions: The entire papilla preservation is highlighted in the literature as one of the best periodontal regeneration techniques, given the highest and safest results, with less comorbility. However, there is a need to analyze regenerative techniques and their advantages, through the development of clinical studies with larger samples, longer follow-up period and more rigorous and standardized protocols.

Keywords: *Entire papilla preservation; Surgical flaps; Enamel-matrix-proteins; Guided tissue regeneration; Intrabony defect.*

DEDICATION

“To see the world, things dangerous to come to, to see behind walls, draw closer, to find each other and to feel”

James Thurber

ACKNOWLEDGMENT

A mia madre il mio amore più grande

A mio padre il mio maestro di vita e l'uomo che voglio diventare

A Chiarulla la mia migliore amica e la mia voce della ragione

A Francy il mio binomio, non ci sono abbastanza pagine e abbastanza inchiostro su questa terra per descrivere il tuo appoggio e il bene che provo per te

A mio zio Sergio che mi ha mostrato la via

Ai miei nonni, ai miei zii e ai miei cugini che mi hanno sempre fatto sentire il loro affetto, supporto e il loro orgoglio

Ai Davide che mi hanno indicato come essere più maturo

A tutti i miei compagni di questo viaggio specialmente Francesca Ster Simone Raffaele Lorenzo e Rosita

E agli amici di una vita che ad ogni mio ritorno mi hanno fatto sentire sempre a casa

Alla mia terra che mi ha cresciuto e che mi è mancata terribilmente

E alla terra che mi ha adottato, che mi ha reso uomo e poi Dottore

Al dr Filipe de Castro per la guida, il supporto e le consulte alle 4 di notte

E infine alla vita che mi ha dato quest'opportunità

SORTE

Il Figlio preferito di Dio

““Sono il re di Salem,” gli aveva detto il vecchio.

“Perché mai un re parla con un pastore?” domandò il ragazzo, pieno di vergogna e di stupore.

“Per varie ragioni. Ma diciamo che la più importante è che tu sei stato capace di realizzare la tua Leggenda Personale.”

Il ragazzo non sapeva neppure che cosa fosse la Leggenda Personale.

“È quello che hai sempre desiderato fare. Tutti, all’inizio della gioventù, sanno qual è la propria leggenda personale. In quel periodo della vita tutto è chiaro, tutto è possibile, e gli uomini non hanno paura di sognare e di desiderare tutto quello che vorrebbero veder fare nella vita. Ma poi, a mano a mano che il tempo passa, una misteriosa forza comincia a tentare di dimostrare come sia impossibile realizzare la Leggenda Personale.”

Le parole del vecchio non avevano molto senso per il ragazzo, che tuttavia voleva sapere quali fossero quelle “forze misteriose”: la figlia del commerciante sarebbe rimasta a bocca aperta.

“Sono le forze che sembrano negative, ma che in realtà ti insegnano a realizzare la tua Leggenda Personale. Preparano il tuo spirito e la tua volontà. Perché esiste una grande verità su questo pianeta: chiunque tu sia o qualunque cosa tu faccia, quando desideri una cosa con volontà, è perché questo desiderio è nato nell’anima dell’Universo. Quella cosa rappresenta la tua missione sulla Terra.”

“Anche se si tratta soltanto di viaggiare? O di sposare la figlia di un commerciante di tessuti?”

“Oppure di cercare un tesoro. L’Anima del Mondo è alimentata dalla felicità degli uomini. O dall’infelicità, dall’invidia, dalla gelosia. Realizzare la propria Leggenda Personale è il solo dovere degli uomini. Tutto è una sola cosa. E quando tu desideri qualcosa, tutto l’Universo cospira affinché tu realizzi il tuo desiderio.”“

”Il ragazzo si rivolse allora alla Mano che aveva scritto Tutto. Ma, invece di rivolgerle la parola, tacque, sentendo che anche l’universo si manteneva in silenzio.

La forza dell’Amore sprizzò dal suo cuore e il ragazzo cominciò a pregare. Era una preghiera che non aveva mai recitato prima, perché si trattava di una preghiera senza parole e in cui non si chiedeva nulla. Lui non stava ringraziando perché le pecore avevano trovato un pascolo, né stava implorando per vendere più cristalli, né stava chiedendo che la donna incontrata

attendesse il suo ritorno. Nel silenzio che ne seguì, il ragazzo capì che il deserto, il vento e anche il sole cercavano i segnali che quella Mano aveva scritto, nel tentativo di ritrovare il proprio cammino e di capire quanto fosse scritto su un semplice smeraldo. Sapeva che quei segnali erano sparpagliati sulla Terra e nello Spazio, che apparentemente non avevano alcun motivo o significato e che né i deserti, né i venti, né i soli, e neppure gli uomini sapevano perché mai fossero stati creati. Ma quella Mano aveva un motivo per tutto: solo lei poteva operare miracoli, poteva trasformare gli oceani in deserti, e gli uomini in vento. Perché soltanto lei capiva che un disegno superiore spingeva l'Universo a un punto in cui i sei giorni della creazione si sarebbero trasformati nella Grande Opera.

E il ragazzo si immerse nell'Anima del Mondo: si rese conto di come essa facesse parte dell'Anima di Dio e di come l'Anima di Dio fosse la sua stessa anima. E, in quel momento, fu consapevole che anch'egli avrebbe potuto compiere miracoli."

"Maktub"

L'Alchimista - Paolo Coelho

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INDEX OF ABBREVIATIONS AND ACRONYMS

BMDX	*bone mineral derived xenograph*
BS	*bovine-derived bone substitutes*
CAL	*clinical attachment level*
CAL-G	*gain in attachment level*
CEJ-AC	*cementoenamel junction to alveolar crest*
CEJ-BD	*cementoenamel junction to base of the defect*
DD	*defect depth*
EMD	*enamel matrix derivative*
EPP	*entire papilla preservation*
FMBS	*full-mouth bleeding scores*
JBI	*Joanna Briggs Institute*
LBG	*linear bone growth*
MIST	*minimally invasive surgical technique*
M-MIST	*modified minimally invasive surgical technique*
p	*significance (intergroup)*
p'	*significance (intragroup)*
PD	*probing depth*
PD-R	*probing depth reduction*
PICO	*Population, Intervention, Comparison, Outcome*

PPD	*probing pocket depth*
REC	*recession of the gingival margin*
rhPDGF-BB	*recombinant human platelet derived growth factor*
SFA	***s**ingle-flap approach*

I. INTRODUCTION

When both the local and systemic conditions are favorable, regeneration is a healing outcome that can take place. The local conditions for periodontal regeneration include the availability of space for the formation of a blood clot at the interface between the root surface and the flap, the stability of the blood clot to maintain a continuity with the root surface preventing the formation of a long junctional epithelium, and the protection of soft tissue from bacterial contamination (Cortellini e Tonetti, 2011).

In the past 30 years, the evolution of periodontal regeneration therapy has been reflected mainly in two ways. First, the planning and execution of surgical procedures, in particular minimally invasive surgery, have been explored. Second, there has been significant advancement in regeneration materials, such as demineralized freeze-dried bone allograft, spongy bone with collagen (Bio-Oss Collagen), enamel matrix derivative (EMD) and recombinant human platelet-derived growth factor BB (rhPDGF-BB), which provide more benefits than conventional flap debridement in terms of improving clinical attachment and reducing the probing depth of the affected teeth. On the other hand, common issues, like early wound failure and the consequent regenerating area, barrier membrane and embedded material exposure, have adversely impacted its clinical outcomes of periodontal regeneration surgery (Nevins *et al.*, 2005; Sali e George, 2016; Aslan, Buduneli e Cortellini, 2017a; Li *et al.*, 2017; Takeda *et al.*, 2018; Zhang *et al.*, 2020).

To address this issue numerous periodontal surgical designs and techniques have been put forth and continuously worked upon. Harrel and Ress in 1995, proposed applying minimally invasive surgery to periodontal surgical treatment, whose main principles were small incision, small flap and minimization of damage to both the soft and hard tissues (Harrel e Rees, 1995). Then the papilla preservation techniques were proposed by Cortellini, Prato e Tonetti in 1995 and 1999, in order to maintain interdental soft tissues as thoroughly as possible and to separate the surgical site from the oral environment. In light of this, the idea of minimally invasive surgery was suggested and gradually improved upon in order to further increase the surgical effect (Cortellini, Prato e Tonetti, 1995, 1999).

In order to address periodontal intrabony defects and promote more periodontal tissue regeneration, Cortellini and Tonetti then introduced a minimally invasive surgical technique

(MIST) in 2007. This method was originated in order to decrease postoperative distress, operative time, and surgical trauma. In 2009, Cortellini and Tonetti further designed a modified minimally invasive surgical technique (M-MIST) (Cortellini e Tonetti, 2007a, 2007b, 2009; Zhang *et al.*, 2020).

The surgical procedure of this technique requires a small interdental incision in which is elevated only a buccal triangular flap, leaving the papilla in place, attached to the root of the crest-associated tooth with its supracrestal fibers. The operation excludes the palatal or lingual tissues. The aim of this approach was to decrease even more the surgical invasiveness, keeping in mind these other objectives: ensure an improved part of the blood supply at the level of the crest and the papilla; improve the flap/wound/soft tissue stability; ensure tighter primary wound closure still maintaining space for regeneration; lessen patient morbidity by lowering the risk of bacterial infection; and finally minimize the interdental tissue tendency to collapse. (Cortellini e Tonetti, 2009, 2011).

The incision of the interdental papilla can offer an unobstructed view of interdental defects, unfortunately, it improves as well the risk of biomaterial exposure and postoperative flap dehiscence which are two major short-term postoperative problems in the early soft tissue healing stage. The membrane exposure and lack of primary closure might happen in 60% to 80% of the treated sites, in particular when membranes and bone materials were used to fill the defects (Pei, 2021).

The rate of primary wound closure and uneventful early healing phase has been impacted positively due to the widespread application of microsurgical procedures.

The implementation of microsurgery has increased the interest in the use of minimally invasive surgical approaches without palatal papilla elevation or with papilla elevation in an effort to improve even more wound stability and primary closure of the flap reducing the risk of early wound failure. The vascular integrity of the interdental tissues may be compromised by all of the aforementioned procedures since they all involve an incision of the interdental papilla associated with the defect. The entire papilla preservation (EPP) is an innovative surgical technique that has been created for the regenerative treatment of isolated deep intrabony defects (Cortellini e Tonetti, 2001, 2007a, 2007b, 2009; Trombelli *et al.*, 2009; Aslan, Buduneli e Cortellini, 2017b, 2020).

The main objective of this technique is to maintain the complete integrity of the interdental

papilla that is linked with the lesion by providing a tunnel-like undermining incision. The integrity of the papilla is of paramount importance because it establishes an intact gingival chamber that enhances the wound healing process and more importantly stabilizes the blood clot, also preserving soft tissue profile and papilla integrity are the keys to decreasing complications, especially in the esthetic area. Then EPP necessitates a small buccal vertical releasing incision on the buccal side of the adjacent tooth that extends just past the mucogingival line in order to enable appropriate access for debridement (Aslan, Buduneli e Cortellini, 2017a; Pei, 2021).

The goal of this systematic review is to explore the clinical outcomes of the two microsurgical approaches: the modified minimally invasive surgical technique (M-MIST) and the entire papilla preservation (EPP). In specific to understand the differences of the clinical results of clinical attachment level (CAL), recession of the gingival margin (REC), probing pocket depth (PPD) and full-mouth bleeding scores (FMBS) in the periodontal regeneration of intraosseous defects. Both the techniques have been developed for the same main reason, to further reduce surgical invasiveness in the treatment of isolated vertical intrabony defects, to prevent wound failure and subsequent exposure of the biomaterials, hence the aim is to demonstrate which of the two can be considered the more patient-friendly, conservative, painless, uneventful technique.

II MATERIALS AND METHODS

2.1. Plan of Study

The clinical question formulated for the continuation of this systematic review was based on the PICO strategy (Population, Intervention, Comparison, Outcome).

Table 1. PICO strategy (Population, Intervention, Comparison, Outcome)

Population	Patients with periodontal intraosseous defects
Intervention	Periodontal regeneration of intraosseous defects
Comparison	Comparison between EPP and M-MIST techniques in periodontal regeneration of intraosseous defects
Outcome	Evaluation of the clinical results of CAL, REC, PDD et FMBS in the periodontal regeneration of intraosseous defects through the analyzed techniques: EPP and M-MIST

Population: Patients with periodontal intraosseous defects; Intervention: Periodontal regeneration of intraosseous defects; Comparison: Comparison between EPP and M-MIST techniques in periodontal regeneration of intraosseous defects; Outcome: Evaluation of the clinical results of clinical attachment level (CAL), recession of the gingival margin (REC), probing pocket depth (PPD) and full-mouth bleeding scores (FMBS) in the periodontal regeneration of intraosseous defects through the analyzed techniques: EPP and M-MIST

2.2. Search strategy

The systematic research started the 17 January 2023 and terminated 5 days after, identifying 5607 records using four databases: Pubmed (220), B-on (5127), Scielo (2) Cochrane (258). The chosen keywords were ((((entire papilla preservation) AND (surgical flaps)) AND (enamel-

matrix-proteins)) OR (guided tissue regeneration)) AND (intrabony defect).

2.3. Eligibility

For the selection of studies, the following inclusion criteria were considered:

- Type of Study: Case reports, Clinical trials, Comparative Studies, Control Clinical trials, Randomized control trials
- Studies published between January 2003 and January 2023
- Studies realized in human
- Studies in English
- Studies with a follow-up of minimum 6 months

For the selection of studies, the following exclusion criteria were considered:

- Studies without the modified minimally invasive surgical technique (M-MIST) and the entire papilla preservation (EPP)
- Studies published before 2003
- Studies realized in vitro, in animals or secondary
- Studies not in English
- Studies with a follow-up under 6 months

2.4. Prisma

The flow diagram shows the flow of information through the different phases of a systematic review. It maps out the number of records identified, which ones were included and which ones were excluded, and the reasons for their exclusions.

2.5. Article selection and extraction of information

The analysis was carried out independently by 2 reviewers, (M.S.) and (F.P.), and in case of disagreement regarding the selection of the articles to include, they were resolved by consensus. The results obtained were discussed by integrating the inclusion/exclusion criteria, by analyzing each article to be included in this review, by the title, abstract and by reading the full text of the article.

2.6. Risk of bias

The methodological quality of the studies was assessed using a risk of bias tool of the Joanna Briggs Institute (JBI) for analysis of bias in clinical trials to determine the extent to which a Study has addressed the possibility of bias in its design, conduct and analysis.

Case Reports Critical Appraisal Tool

1. Were patient's demographic characteristics clearly described?

Does the case report clearly describe patient's age, sex, race, medical history, diagnosis, prognosis, previous treatments, past and current diagnostic test results, and medications? The setting and context may also be described.

2. Was the patient's history clearly described and presented as a timeline?

A good case report will clearly describe the history of the patient, their medical, family and psychosocial history including relevant genetic information, as well as relevant past interventions and their outcomes (Gagnier *et al.*, 2013).

3. Was the current clinical condition of the patient on presentation clearly described?

The current clinical condition of the patient should be described in detail including the uniqueness of the condition/disease, symptoms, frequency and severity. The case report should also be able to present whether differential diagnoses was considered.

4. Were diagnostic tests or methods and the results clearly described?

A reader of the case report should be provided sufficient information to understand how the

patient was assessed. It is important that all appropriate tests are ordered to confirm a diagnosis and therefore the case report should provide a clear description of various diagnostic tests used (whether a gold standard or alternative diagnostic tests). Photographs or illustrations of diagnostic procedures, radiographs, or treatment procedures are usually presented when appropriate to convey a clear message to readers.

5. Was the intervention(s) or treatment procedure(s) clearly described?

It is important to clearly describe treatment or intervention procedures as other clinicians will be reading the paper and therefore may enable clear understanding of the treatment protocol. The report should describe the treatment/intervention protocol in detail; for e.g., in pharmacological management of dental anxiety - the type of drug, route of administration, drug dosage and frequency, and any side effects.

6. Was the post-intervention clinical condition clearly described?

A good case report should clearly describe the clinical condition post-intervention in terms of the presence or lack thereof symptoms. The outcomes of management/treatment when presented as images or figures would help in conveying the information to the reader/clinician.

7. Were adverse events (harms) or unanticipated events identified and described?

With any treatment/intervention/drug, there are bound to be some adverse events and, in some cases, they may be severe. It is important that adverse events are clearly documented and described, particularly when a new or unique condition is being treated or when a new drug or treatment is used. In addition, unanticipated events, if any that may yield new or useful information should be identified and clearly described.

8. Does the case report provide takeaway lessons?

Case reports should summarize key lessons learned from a case in terms of the background of the condition/disease and clinical practice guidance for clinicians when presented with similar cases.

The risks of bias in the final studies were categorized as below:

YES) Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.

UNCLEAR) Unclear risk of bias " plausible bias" data raises some doubt about the results) if one or more criteria were partly met.

NO) High risk of bias (plausible bias that seriously weakens confidence in the results) if honor more criteria were not met.

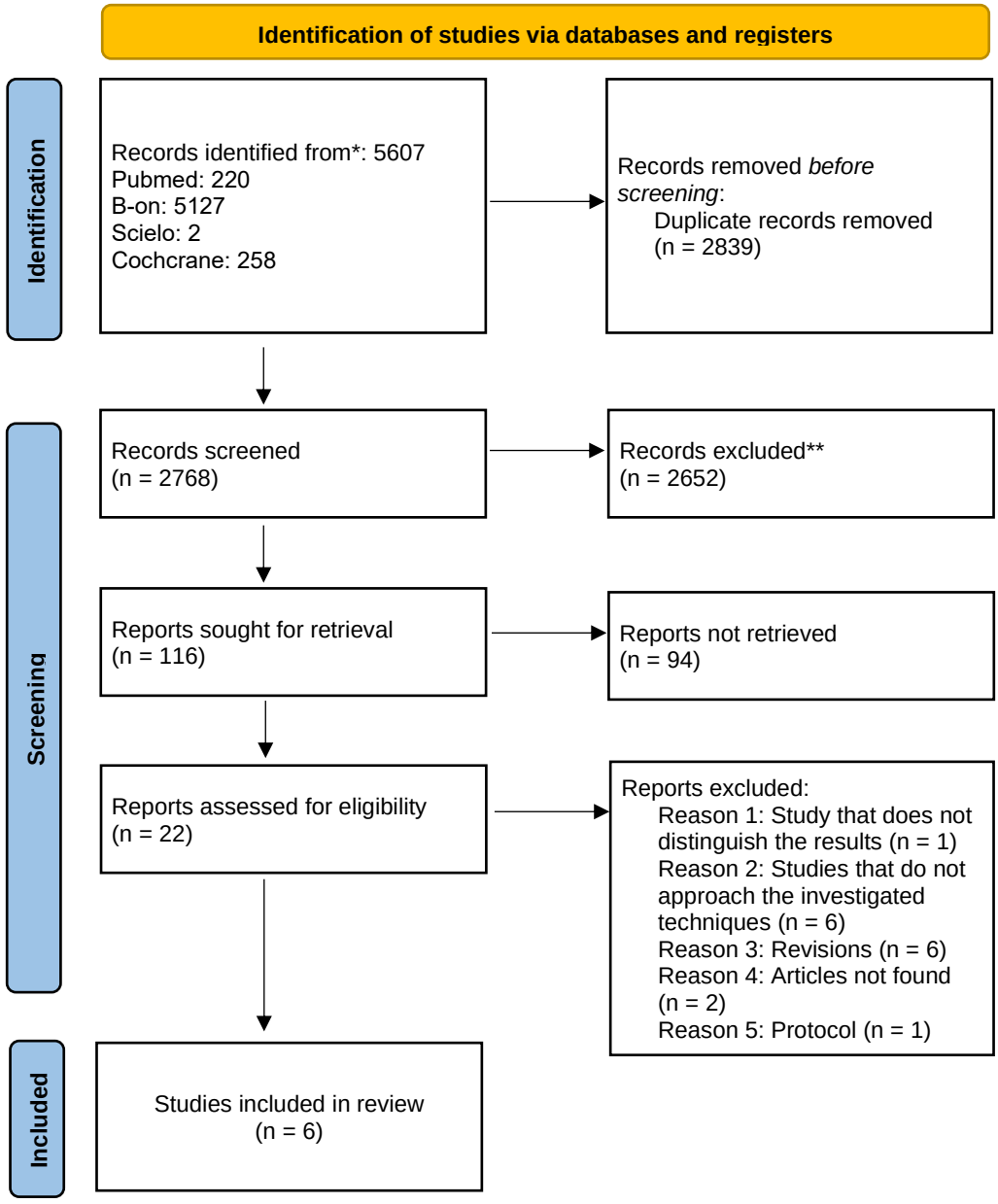
NOT APPLICABLE) Risk evaluation not applicable to this context.

III. DEVELOPMENT

3.1. Results

The instruction of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed throughout the whole process of selection of the articles. from a total of 5607 Studies 2839 have been removed before screening cause of duplicates, then 2652 were excluded by looking at the title, afterwards the reading of the abstract 94 other records have been eliminated from consideration. Therefore 22 Studies have been selected to be read and analyzed in all of their lengths, but just 6 of them included all the pre-imposed guidelines, of the 16 articles excluded 2 of them were eliminated from consideration because not found, the 2 reviewers (F.C) and (M.S.) tried in many ways to find them including using the UFP library and contact the authors.

Table 2. PRISMA flow diagram with information on the different stages of the article selection.



The methodological quality of the 6 studies assessed using a risk of bias tool of the Joanna Briggs Institute (JBI) is really high as it's clearly shown with the abundance of the color Green in the Table 3.

Table 3. Assessment of the methodological quality of the studies done using a risk of bias tool of the Joanna Briggs Institute (JBI)

	(Cortellini e Tonetti, 2011)	(Aslan, Buduneli e Cortellini, 2020)	(Mishra *et al.*, 2013)	(Aslan, Buduneli e Cortellini, 2017b)	(Cortellini e Tonetti, 2009)	(Aslan, Buduneli e Cortellini, 2021)
1. Were patient's demographic characteristics clearly described?						
2. Was the patient's history clearly described and presented as a timeline?						
3. Was the current clinical condition of the patient on presentation clearly described?						
4. Were diagnostic tests or assessment methods and the results clearly described?						
5. Was the intervention(s) or treatment procedure(s) clearly described?						
6. Was the post-intervention clinical condition clearly described?						
7. Were adverse events (harms) or unanticipated events identified and described?						
8. Does the case report provide takeaway lessons?						

Yes	No
Unclear	Not applicable

After the search phase on the modified minimally invasive surgical technique (M-MIST) and the entire papilla preservation (EPP), 6 articles demonstrating the efficacy of these two microsurgical approaches with improvement in periodontal clinical parameters were selected. The results presented below are described and summarized in tables 4, 5, 6, 7, 8, 9.

3.1.1. Cortellini & Tonetti (2011)

The aim of this parallel group, randomized, controlled clinical trial was to compare the clinical and radiographic efficacy of three treatment modalities in 45 intra-bony defects with a follow-up of 12 months. Each patient received treatment for a single defect. The modified minimally invasive surgical technique (M-MIST) (Cortellini e Tonetti, 2009) was used to reach every experimental site, and each one was meticulously debrided, On the instrumented and dried root surfaces was applied Ethylenediaminetetraacetic acid (EDTA). Then in one group (15 intrabony defects in 15 subjects with a mean age of 47.2 ± 8.5, range of 34–64 years, 8 females, 2 smokers) was used EMD (Emdogain, Institute Straumann AG, Basel, Switzerland) on the debrided root surface; in another group (15 intrabony defects in 15 subjects with a mean age of 53.5 ± 11.9, range of 28–71 years, 7 females, 2 smokers) was applied EMD+BMDX (BioOss, Geistlich, Switzerland). The third group (15 intrabony defects in 15 subjects with a mean age of 48.9 ± 7.9, range of 34–59 years, 6 females, 1 smoker) instead did not receive any application of regenerative material/device. The flaps were then sutured with modified internal mattress sutures. The patients underwent a rigorous post-operative supportive care program with weekly recalls for six weeks before being enrolled in a year-long, three-month periodontal supportive care program. At one year, clinical and radiological results were assessed. Primary closure was obtained in all treated sites at completion of surgery, but was maintained during the 6 weeks of early healing period in every treated site with the exception of one M-MIST EMD+BMDX site that had at week one a suture removal with a minor discontinuity of the inter-dental wound on the side of the defect-associated tooth. A small amount of BMDX granules were surfacing the soft tissues but were carefully removed. The subsequent week the gap presented itself closed. No hematoma, oedema, or inflammatory reactions were noted in any of the treated sites. No patient reported intra-operative or post-operative pain. Within group differences between baseline and 1 year were statistically significant in the three groups in terms of probing pocket depth reduction, clinical attachment level (CAL) gain and bone fill ($p<0.0001$). Comparisons

among the three groups showed no statistically significant difference in any of the measured clinical outcomes. In particular, CAL gains (p=0.639) of 4.1 ± 1.4 mm were observed in the M-MIST control group, 4.1 ± 1.2 mm in the EMD group and 3.7 ± 1.3 mm in the EMD+BMDX one. REC changes (p=1) of 2.1 ± 1.4 vs 2.4 ± 1.4 mm were observed in the M-MIST control group (not significant), 2.1 ± 1.4 vs 2.3 ± 1.4 mm in the EMD group (p=0.02) and 2.9 ± 1.8 vs 3.1 ± 2.1 mm in the EMD+BMDX one (not significant). PPD changes (p= 0.657) of 7.5 ± 1.6 vs 3.1 ± 0.6 mm were observed in the M-MIST control group (p<0.0001), 7.8 ± 0.9 vs 3.4 ± 0.6 mm in the EMD group (p<0.0001) and 7.3 ± 1.2 vs 3.3 ± 0.6 mm in the EMD+BMDX one (p<0.0001). FMBS changes of 10.3 ± 4.4 vs 7.0 ± 5. % were observed in the M-MIST control group, 10.4 ± 3.4 vs 5.7 ± 3.0% in the EMD group and 10.7 ± 4.1 vs 7.0 ± 3.6% in the EMD+BMDX one. The percentage radiographic bone fill of the intra-bony component was 77 ± 19% in the M-MIST control group, 71 ± 18% in the EMD group and 78 ± 27% in the EMD1BMDX group (Cortellini e Tonetti, 2011).

Table 4. Characteristics of the study included in the systematic review

Cortellini Tonetti, 2011

Type Study Follow Up	Sample Characterization	Clinical Features	Treatment	Adverse Effects	Results
Parallel group, randomized, controlled clinical trial 12 months	45 Patients Divided into three groups M-MIST (15 subjects mean age 48.9 ± 7.9, 34–59 years, 6 females, 1 smoker) M-MIST EMD (15 subjects mean age 47.2 ± 8.5, 34–64 years, 8 females, 2 smokers) M-MIST EMD + BDMX (15 subjects mean age 53.5 ± 11.9, 28–71 years, 7 females, 2 smokers)	Advanced periodontal disease, general good health, at least one isolated deep, predominantly interdental intra-bony defect were considered eligible for this study.	M-MIST (modified minimally invasive surgical technique) M-MIST EMD (modified minimally invasive surgical technique plus Emdogain) M-MIST EMD1BMDX (modified minimally invasive surgical technique plus Emdogain and BioOss)	Primary wound closure maintained in all treated sites, exception of one M-MIST EMD+BMDX site. No patient reported intra-operative or post-operative pain. Slight disconfort was controlled with medications (ibuprofen): 3 from the M-MIST (average of 600 mg pills 0.4 ±0.7, max 2), 4 from the EMD group (average 0.3 ±0.6, max 2), 4 from the EMD1BMDX group (average 0.5 ±1, max 3).	Baseline vs After Treatment M-MIST CAL 9.6 ±2.0 vs 5.5 ±1.6 REC 2.1 ±1.4 vs 2.4 ±1.4 PDD 7.5 ±1.6 vs 3.1 ±0.6 FMBS 10.3 ±4.4 vs 7.0 ±5.2 M-MIST EMD CAL 9.9 ±1.3 vs 5.7 ±1.7 REC 2.1 ±1.4 vs 2.3 ±1.4 PDD 7.8 ±0.9 vs 3.4 ±0.6 FMBS 10.4 ±3.4 vs 5.7 ±3.0 M-MIST EMD + BDMX CAL 10.1 ±2.4 vs 6.4 ±2.4 REC 2.9 ±1.8 vs 3.1 ±2.1 PDD 7.3 ±1.2 vs 3.3 ±0.6 FMBS 10.7 ±4.1 vs 7.0 ±3.6

3.1.2. Aslan, Buduneli e Cortellini (2020)

The aim of this single-centre, parallel group, randomised, controlled clinical trial was to compare the clinical and radiographic efficacy of the entire papilla preservation (EPP) technique with or without biomaterials (EPP EMD+BS). Three months following the conclusion of the initial periodontal therapy all the experimental sites were accessed with the "EPP" approach (Aslan, Buduneli e Cortellini, 2017b) and then carefully debrided. Subsequently on the instrumented root surfaces was applied Ethylenediaminetetraacetic acid (EDTA) gel (Pref-Gel, Institut Straumann, AG, Basel, Switzerland). In the test group (EPP EMD+BS) (15 intrabony defects in 15 subjects with a mean age of 44.93 ± 13.06, range of 22-

60 years, 5 females) was used a combination of EMD (Emdogain, Institut Straumann, AG, Basel, Switzerland) and deproteinized bovine-derived bone substitute (BS, Cerabone, Botiss Biomaterials GmbH, Berlin, Germany), while in the control group (EPP) (15 intrabony defects in 15 subjects with a mean age of 43.93 ± 12.85, range of 21-63 years, 7 females) was not used any regenerative biomaterial. Patients were signed up for a strict maintenance regimen that included recalls every week for the first month and then monthly checks for professional tooth cleaning for a period of one year. The clinical parameters were noted immediately before the regenerative surgery (baseline) and also 12 months after the regenerative periodontal surgery. Throughout the course of the 12-month trial, periodontal probing and any invasive clinical instruments were prohibited at the experimental site. Early healing phase was uneventful in all cases and 100% primary wound closure was maintained throughout the study period. Intragroup differences between baseline and 1-year were statistically significant in both groups in terms of clinical attachment level (CAL) gain and probing depth (PD) reduction ($p \leq 0.001$). No statistically significant differences were detected in gingival recession (REC) ($p=0.14$). No statistically significant differences were detected in terms of CAL gain (EPP 11.4 ± 2.17 $p=0.690$ after the follow-up of 12 months 5.56 ± 1.74 $p=0.6$) (EPP EMD+BS 11.66 ± 3.45 $p=0.690$ after 5.36 ± 1.85 $p=0.6$) (change of 6.3 ± 2.5 mm vs 5.83 ± 1.12 mm), PD reduction (EPP 9.26 ± 1.65 mm $p=0.409$ after 3.06 ± 0.79 mm $p=0.404$) (EPP EMD+BS 9.33 ± 2.87 mm $p=0.409$ after 2.83 ± 0.74 mm $p=0.404$) (change of 6.5 ± 2.65 mm vs 6.2 ± 1.33 mm $p<0.001$), or increase in gingival recession (EPP 2.13 ± 1.12 mm $p=0.697$ after 2.5 ± 1.4 mm $p=0.932$) (EPP EMD+BS 2.33 ± 1.23 mm $p=0.697$ after 2.53 ± 1.36 mm $p=0.932$) (-0.2 ± 0.25 mm $p=0.523$ vs -0.36 ± 0.54 mm $p=0.14$ $p=0.523$) between the groups treated with EPP EMD+BS or EPP alone. The content of this article is summarized in the Table 5. (Aslan, Buduneli e Cortellini, 2020).

Table 5. Characteristics of the study included in the systematic review

Aslan, Buduneli e Cortellini, 2020

Type Study Follow Up	Sample Characterization	Clinical Features	Treatment	Adverse Effects	Results
Single-centre, parallel group, randomised, controlled clinical trial 12 months	30 Patients Divided into two groups EPP alone (15 subjects mean age 43.93 ± 12.85 21-63 years, 7 females). EPP EMD+BS (15 subjects mean age 44.93 ± 13.06 22-60 years, 5 females).	1 isolated intrabony defect with (PD) ±7 mm,(CAL) ±8 mm an intrabony component ≥4 mm, involving predominantly the interproximal area of the affected tooth;(FMPS) and (FMBS) ± 20%	EPP (entire papilla preservation technique) EPP EMD+BS (entire papilla preservation technique plus Emdogain and deproteinized bovine-derived bone substitute)	No adverse effects were found Slight discomfort 1 patient (6.7%) EPP 0.73 ±0.88 mean additional painkiller tablets intake 2 patients (13.3%) EPP EMD+BS 0.87 ±0.74 mean additional painkiller tablets intake	Baseline EPP CAL 11.4 ± 2.17 vs 5.56 ± 1.74 REC 2.13 ± 1.12 vs 2.5 ± 1.4 PDD 9.26 ±1.65 vs 3.06 ±0.79 FMBS 10.2 ± 1.32 vs ? ± ? After Treatment EPP EMD+BS CAL 11.66 ± 3.45 vs 5.36 ± 1.85 REC 2.33 ± 1.23 vs 2.53 ± 1.36 PDD 9.33 ± 2.87 vs 2.83 ± 0.74 FMBS 9.4 ± 1.95 vs ? ± ?

3.1.3. Mishra *et al*. (2013)

The aim of this double-blinded, randomized, controlled, two-armed study was to evaluate the clinical and radiographic efficacy of the modified minimally invasive surgical technique (M-MIST) in the treatment of human intrabony defects with or without the use of local delivery of recombinant human platelet derived growth factor (rhPDGF-BB) gel. The 24 patients (12 male and 12 female) between 25 and 50 years for 6 months were divided in two group based on the technique used M-MIST + rhPDGF-BB or just the M-MIST. M-MIST (12 subjects and 16 intrabony defects, lost 1 patient with 2 defects) and M-MIST rhPDGF-BB (12 subjects and 15 intrabony defects, lost 1 patient with 1 defect). The mean probing depth (PD), clinical attachment level (CAL)($p<0.001$) and gingival recession, cementoenamel junction to base of the defect (CEJ-BD), defect depth (DD) and cementoenamel junction to alveolar crest (CEJ-AC), at baseline to 6 months post-operatively in both the groups were statistically significant. Inter-group comparison for gain in attachment level (CAL-G) ($p=0.294$), probing depth reduction (PD-R) ($p=0.269$) and change in gingival margin position linear bone growth

(LBG)(p=0.930), percentage bone fill, residual defect depth (residual DD) (p=0.803) and the change in alveolar crest position revealed no statistically significant differences. Gain in CAL and LBG was 3 ± 0.89 mm and 1.89 ± 0.6 in test group and 2.64 ± 0.67 mm and 1.85 ± 1.18 mm in control group, respectively, and did not show statistical significance p=0.294. Changes in REC and PPD was -0.82 ± 0.60 mm and 4.18 ± 0.60 in the test group and -0.55 ± 0.52 mm and 3.82 ± 0.87 mm in the control group, respectively, and did not show statistical significance p=0.270 p=0.269, meanwhile the differences in REC in the test group and control group were -0.55 ± 0.52 and -0.82 ± 0.60 p=0.270 respectively, the change in FMBS were statistically significant in the test group and not statistically significant in the control one. The content of this article is summarized in the Table 6. (Mishra *et al.*, 2013).

Table 6. Characteristics of the study included in the systematic review

Mishra *et al*., 2013

Type Study Follow Up	Sample Characterization	Clinical Features	Treatment	Adverse Effects	Results
Double-blinded, randomized, controlled, two armed study 6 months	24 patients (12 male and 12 female) between 25 and 50 years M-MIST + rhPDGF-BB M-MIST M-MIST 12 subjects 16 defects. (Lost 1 patient with 2 defects) M-MIST rhPDGF-BB 12 subjects 15 defects (Lost 1 patient with 1 defect)	Systemically healthy chronic periodontitis patients presenting (FMPS) and (FMBS) ≤20%, were included. Presence of one tooth with (PD) and (CAL) ≥ 5 mm associated with an interdental intrabony defect depth of ≥ 3 mm.	M-MIST (modified minimally invasive surgical technique) M-MIST rhPDGF-BB (modified minimally invasive surgical technique plus local delivery of recombinant human platelet derived growth factor rhPDGF-BB gel)	No adverse effects were found	Baseline vs After Treatment M-MIST CAL 6.91 ±0.70 vs ? ± ? r:2.64 ±.67 REC 0 ±0.0 vs ? ±? r:-0.55 ±0.52 PDD 7.64±0.67 vs ? ± ? r:3.82 ±0.87 FMBS 14.79 ±3.84 vs ? ± ? M-MIST rhPDGF-BB CAL 7.36 ±1.28 vs ? ± ? r:3.00 ±.89 REC 0.18 ±0.40 vs ? ± ? r:-0.82 ±0.60 PDD 7.73 ±1.19 vs ? ± ? r:4.18 ±0.60 FMBS 14.96 ±2.76 vs ? ± ?

3.1.4. Aslan, Buduneli e Cortellini (2017b)

This Case Report or Case Series evaluate 12 patients (12 intrabony defects, mean age of 42.6 ± 13.1, range of 22-60 years, 3 females) systemically healthy but with advanced periodontal disease, after the completion of a non-surgical periodontal therapy the patients received a regenerative periodontal treatment with "entire papilla preservation" technique subsequently on the air-dried root surfaces that were thoroughly debrided were applied Ethylenediaminetetraacetic acid (EDTA) gel (Pref-Gel, Institut Straumann AG, Basel, Switzerland) and enamel matrix derivative (Emdogain, Institut Straumann, AG, Basel, Switzerland). Then were placed into the defect porcine-derived bone substitutes (Gen-Os, OsteoBiol, Torino, Italy) and the flap was sutured with simple interrupted sutures. The patients underwent a rigorous post-operative supportive care program with weekly recalls for six weeks before being enrolled in a year-long, three-month periodontal supportive care program. The clinical periodontal parameters were noted at baseline (at least 3 months after the non-surgical periodontal therapy) and then after 12 months. The aim of this study is to evaluate the clinical performance of this novel tunnel-like surgical technique in the treatment of isolated deep intrabony defects. Early healing was uneventful in all cases, and 100% wound closure was maintained during the entire healing period. At 1-year, the average clinical attachment gain was 6.83±2.51 mm $p<0.001$, at baseline was 12.25 ± 3.64 then after 12 months 5.41 ± 2.02 mm. The average probing depth reduction was 7±2.8 mm $p<0.001$, at the start was 9.75 ± 3.07 and after 12 months 2.75 ± 0.75 mm, which was associated with minimal increase in gingival recession 0.16 ± 0.38 mm ($p=0.166$), at baseline was 2.5 ± 1.31 then after 12 months 2.66 ± 1.55 mm, in the end the full mouth bleeding score reduced from 9.08 ± 1.56 to 8.08 ± 1.67% ($p<0.01$). The content of this article is summarized in the Table 7. (Aslan, Buduneli e Cortellini, 2017b).

Table 7. Characteristics of the study included in the systematic review

Aslan, Buduneli e Cortellini, 2017b

Type Study Follow Up	Sample Characterization	Clinical Features	Treatment	Adverse Effects	Results
Case Report or Case Series 12 months	12 patients 12 defects mean age 42.6 ± 13.1, 22-60 years, 3 females	Advanced periodontal disease, general good health, at least one isolated 2- or 3-wall intrabony defect (PD) ≥ 7 mm, (CAL) ≥ 7 mm and at least 4 mm intrabony component involving predominantly the interproximal area of the affected tooth; (FMPS) and (FMBS) ≤ 20%.	EPP (entire papilla preservation technique)	No adverse effects were found, 1 patient reported very limited discomfort for the first 3 days after the surgery.	Baseline vs After Treatment EPP CAL 12.25±3.64 vs 5.41 ± 2.02 REC 2.5±1.31 vs 2.66 ± 1.55 PDD 9.75 ± 3.07 vs 2.75 ± 0.75 FMBS 9.08 ± 1.56 vs 8.08 ± 1.67

3.1.5. Cortellini & Tonetti (2009)

This clinical trial studied 20 patients (15 of the 20 selected sites mean age of 46.1 ± 10.3 with a range of 31–65 years, 9 females) with a follow-up of 12 months. This paper describes a modified surgical approach of the minimally invasive surgical technique (modified minimally invasive surgical technique, (M-MIST) and preliminarily evaluates its applicability and clinical performances in the treatment of isolated deep intrabony defects in combination with amelogenins. The patients were systemically healthy but with advanced periodontal disease, after the completion of a non-surgical periodontal therapy the patients received a regenerative periodontal treatment (M-MIST) then on the air-dried root surfaces that were thoroughly debrided were applied Ethylenediaminetetraacetic acid (EDTA) gel (Pref-Gel, Institut Straumann AG, Basel, Switzerland) and enamel matrix derivative (Emdogain, Institut Straumann, AG, Basel, Switzerland) and flaps were sutured with modified internal mattress sutures. The patients underwent a rigorous post-operative supportive care program with weekly recalls for six weeks before being enrolled in a year-long, three-month periodontal supportive care program. The clinical periodontal parameters were noted at baseline (at least 3 months after the non-surgical periodontal therapy) and then after 12 months. Early wound healing was uneventful: primary wound closure was attained and maintained in all sites. The 1-year clinical attachment level (CAL) gain was 4.5 ± 1.4 mm $p<0.0001$ in defects 6 ± 1.5 mm deep, at baseline was 9.7 ± 1.8 and after 12 months 5.13 ± 1 mm. Residual probing depth (PD) was 4.6 ± 1.5 mm

p<0.0001, at the start was 7.7 ± 1.5 then after 12 months 3.07 ± 0.6 mm. A minimal increase of 0.07 ± 0.3 mm p=0.167 in gingival recession between baseline 2 ± 1.3 and 1 year 2.07 ± 1.3 mm, was observed in the end the full mouth bleeding score reduced from 5.8 ± 3 to 3.7 ± 2% (p=0.055). The content of this article is summarized in the Table 8. (Cortellini e Tonetti, 2009).

Table 8. Characteristics of the study included in the systematic review

Cortellini & Tonetti, 2009

Type Study Follow Up	Sample Characterization	Clinical Features	Treatment	Adverse Effects	Results
Clinical trial 12 months	15 of the 20 selected sites mean age 46.1 ± 10.3, 31–65 years, 9 females	Advanced periodontal disease, general good health, at least one tooth with (PPD) and (CAL) ≥ 5 mm associated with an intrabony defect ≥ 3 mm involving predominantly the interdental space of the tooth. (FMPS) and (FMBS) ≤ 20%.	M-MIST (modified minimally invasive surgical technique)	No adverse effects were found	Baseline vs After Treatment M-MIST CAL 9.7 ±1.8 vs 5.13 ±1 REC 2 ±1.3 vs 2.07 ±1.3 PDD 7.7 ±1.5 vs 3.07 ±0.6 FMBS 5.8 ±3 vs 3.7 ±2

3.1.6. Aslan, Buduneli e Cortellini (2021)

This single-centered prospective study conducted from December 2016 (first patient in) to January 2019 (last patient out), observes 15 systemically healthy individuals with periodontitis stage III/IV (caucasian patients with a mean age of 47.73 ± 12.18, range of 21-63 years, 6 females) with a follow-up of 12 months. The aim of this study is to evaluate the clinical applicability of the entire papilla preservation technique (EPP) in the regenerative treatment of isolated deep intrabony defects using native collagen membrane and bone grafting materials. The EPP approach allowed surgical access to the defect and thoroughly debrided. Subsequently, the defect was filled with deproteinized bovine-derived bone substitute. Then a collagen barrier membrane was positioned after being trimmed with palatal positioning suture. The flap was secure with single interrupted sutures. The patients underwent a rigorous post-operative supportive care program, involving a meticulous professional plaque control, with weekly recalls for a month before being enrolled in a year-long monthly control visit for professional

tooth cleaning. The clinical periodontal parameters were noted at baseline (at least 3 months after the non-surgical periodontal therapy) and then after 12 months. At 1 week, healing of the 15 sites was uneventful. During the study, all sites showed 100% primary closure rate. At 1-year follow-up, an average CAL gain of 5.86 ± 1.28 mm ($p<0.0001$), at the start was 11.16 ± 1.81 and after 12 months 5.3 ± 1.19 mm, PD reduction of 6.1±1.47 mm ($p<0.0001$), at baseline was 9.03 ± 1.62 and then after 12 months 2.93 ± 0.59 mm, minimal increase in gingival recession of 0.23 ± 0.62 mm ($p=0.168$), at the start was 2.13 ± 1.3 and then after 12 months 2.36 ± 1.54 mm, in the end the full mouth bleeding score reduced from 9.8 ± 1.85 to 9.2 ± 1.52% ($p<0.05$) were observed. The content of this article is summarized in the Table 9. (Aslan, Buduneli e Cortellini, 2021).

Table 9. Characteristics of the study included in the systematic review

Aslan, Buduneli e Cortellini, 2021

Type Study Follow Up	Sample Characterization	Clinical Features	Treatment	Adverse Effects	Results
Single-centered prospective study 12 months	15 Caucasian patients mean age 47.73 ± 12.18, 21-63 years, 6 females	Advanced periodontal disease stage III/IV, general good health, single intrabony defect (PD) ≥ 6 mm, (CAL) ≥ 6 mm and at least 4 mm intrabony component in the interdental area; (FMPS) and (FMBS) ≤ 20%.	EPP GTR (entire papilla preservation technique plus inception of guided tissue regeneration)	No adverse effects were found	Baseline vs After Treatment EPP CAL 11.16 ± 1.81 vs 5.3 ± 1.19 REC 2.13 ± 1.3 vs 2.36 ± 1.54 PDD 9.03 ± 1.62 vs 2.93 ± 0.59 FMBS 9.8 ± 1.85 vs 9.2 ± 1.52

IV. DISCUSSION

4.1. M-MIST

The defect-associated interdental papilla could have been surgically approached with one of these two techniques, the simplified papilla preservation flap described by Cortellini, Prato and Tonetti in 1999 or the modified papilla preservation technique reported by Cortellini, Prato and Tonetti in 1995. When the width of the interdental space was 2 mm or narrower the choice was the simplified papilla preservation flap (SPPF) instead when the interdental sites were wider than 2 mm the modified papilla preservation technique (MPPT) was the better choice. The interdental incision (SPPF or MPPT) was extended to the buccal aspect of the two teeth proximal to the defect. To preserve the entire height and width of the gingiva these incisions were strictly intra-sulcular and their mesio-distal extension was kept at minimum (ideally, within the mid-buccal area of the involved teeth). This allowed for the reflection of a triangular buccal flap, which exposed the coronal edge of the buccal bone crest. Using a microblade (micro 6900, Advanced Surgical Technologies, Sacramento, CA, USA), the interdental papillary tissues were partially dissected in the bucco-lingual and corono-apical directions. The microblade sliced through the interdental tissues, separating the coronal part (essentially the supracrestal tissues) from the apical part (i.e., the "granulation" tissue filling the intrabony component of the defect) parts. The micro-blade was introduced with an inclination suitable to intercept the buccal side of the lingual bone crest, as close as possible to its coronal edge, to isolate the granulation tissue filling the intrabony component of the defect from the supra-crestal, papillary tissues. There were no lingual intrasulcular incisions made or interdental incisions made. Therefore, the supracrestal interdental tissues remained continuous with the palatal tissue, anchored to the root cement of the crest-associated tooth, and were not displaced. Using a micro-blade and a sharp mini curette (Gracey, Hu-Friedy), the granulation soft tissue was meticulously separated from the buccal and interdental bone walls and carefully removed from under the papilla. With the help of power-driven instruments (Soniflex Lux, Kavo, Germany) and mini curettes, the defect was removed, and the root was meticulously planed. All of the exposed root surface and remaining bone walls, which were partially covered by the non-elevated lingual and papillary soft tissues, were carefully reached. The buccal papillary flap was carefully protected with a periosteal elevator, slightly reflected, and periodically irrigated with saline to enable instrumentation. In order to access the root surface for

debridement, mini-curettes and sonic instruments were also carefully introduced through the interdental pocket of the tooth with the associated defect, between the preserved interdental papilla and the root surface. In order to preserve the stability of the papilla, care was made to avoid any disruption of the papillary fibrous attachment to the bone crest and to the crest-associated root. Ethylenediaminetetraacetic acid (EDTA) was administered to the root surface for 2 minutes at the conclusion of instrumentation, and the defect area was then thoroughly rinsed with saline. A single modified internal mattress suture (6-0 or 7-0 e-PTFE Goretex, WL Gore & Associates, Flagstaff, AZ, USA) was placed at the defect-associated interdental area before to the application of EMD. The suture was not tightened. On the rinsed and air-dried root surface, EMD was applied. In order to achieve primary closure of the papilla linked with the defect, the suture was finally tightened (Cortellini e Tonetti, 2001, 2005, 2007a, 2007b). A gauze wet with saline was gently placed into the defect for 5 min if or when persistent bleeding was observed at the end of defect/root instrumentation to halt bleeding before the application of Ethylenediaminetetraacetic acid (EDTA) and EMD (Cortellini e Tonetti, 2007b; Cortellini *et al.*, 2008). Using an operating microscope (Global Protege, St. Louis, MO) with a magnification of x 4 to x 16, all surgical procedures were carried out (Cortellini e Tonetti, 2001, 2005). When necessary, microsurgical instruments were used in addition to the standard periodontal set of instruments. The interdental papilla was elevated along with a lingual flap when the experimental defect extended far too much on the lingual side of the involved tooth, this was done to allow a proper debridement and EMD application at the lingual side. These surgeries were thus carried out in accordance with the MIST's guidelines (Cortellini e Tonetti, 2007a, 2007b). Ibuprofen was used to manage the discomfort following surgery. Patients were given a 600 mg dose at the conclusion of their surgery and told to take another tablet six hours later. Only if further doses were required to manage pain were they taken. Patients who had NSAID contraindications received 500 mg of acetaminophen at surgery and six hours later. It was prescribed protocol for the control of bacterial contamination consisting of systemic doxicycline (100 mg b.i.d. for 1 week), 0.12% chlorhexidine mouth rinsing three times per day and weekly prophylaxis (Tonetti *et al.*, 2002). For a period of two to three weeks, patients were instructed to refrain from chewing, flossing, and brushing in the treated area. Patients then resumed practicing good dental hygiene. After the "early healing phase," patients were put on a 3-month recall scheme for an entire year.

4.2. EPP

The first thing done in the procedure was to anesthetize the surgical site using articaine-epinephrine 1:100,000. To prevent both chemical (prolonged vasoconstriction) and physical (needle penetration) trauma to the gingival tissues trans-papillary infiltration was avoided. After the surgical site was anesthetized, it was performed bone sounding. The entire papilla preservation (EPP) technique is a tunnel-like approach of the defect-associated interdental papilla. To increase the visibility of the surgical site were used surgical loupes (3.3x magnification) with LED light illumination. In order to provide the necessary mechanical access to the intrabony defect, a buccal intra-crevicular incision was followed by a bevelled vertical releasing incision in the buccal gingiva of the adjacent interdental space and extended just beyond the mucogingival line. To elevate a buccal full thickness muco-periosteal flap was used a microsurgical periosteal elevator extending it from the vertical incision to the defect-associated papilla. To facilitate the interdental tunnel preparation under the papillary tissue was used a specifically designed angled tunnel elevator. The interdental papilla was carefully elevated in full thickness up to the intact lingual bone crest. The granulation tissue from the inner side of the interdental papilla associated with the defect was removed using a microsurgical scissor. The papilla was not excessively thinned in order to protect and not compromise the blood supply. A mini-curette was used to remove the granulation tissue. An ultrasonic scaler was used to gently remove any remaining calculus or subgingival plaque from the exposed root surface. After thoroughly rinsing the surgical region with sterile saline, the exposed surface was root-conditioned using 24% Ethylenediaminetetraacetic acid (EDTA) gel for two minutes to remove the smear layer. The exposed root surface was rinsed with sterile saline before being treated with EMD. The intrabony defect was then filled with a deproteinized porcine-derived bone substitute. During the application of the biomaterial, contamination with blood or saliva was avoided. There was no periosteal release incision made. The mucoperiosteal flap was readjusted with gentle pressure using saline-wetted gauze for 1 minute. For optimal wound closure of the surgical site was performed a microsurgical suturing technique with 7-0 monofilament polypropylene suture materials. Patients were given 600 mg of ibuprofen after surgery and told to take another dose in 8 hours. During the first post-operative week, systemic doxycycline (100 mg b.i.d.) was administered. For a period of four weeks, the patients were instructed not to use any mechanical oral hygiene products. The patients were instructed to use mouthwash containing 0.12% chlorhexidine digluconate twice day for one minute. Two weeks following the surgery, the sutures were removed.

CAL: Clinical attachment level is calculated from a fixed reference point (cementoenamel junction or CEJ), the distance from the CEJ to the base of the pocket. PD+REC

PPD: Probing pocket depth, measurement of the depth of a sulcus or periodontal pocket determined by measuring distance from a gingival margin to the base of the sulcus or pocket with a calibrated periodontal probe.

REC: Gingival recession, gingival recession is the exposure of the root surface resulting from migration of the gingival margin apical to the cementoenamel junction (CEJ)

FMBS: Full-mouth bleeding scores, the percentage of total surfaces that bleed at probing.

PRIMARY CLOSURE of the surgical sites was evaluated on a weekly basis for the first month after surgery.

This systematic review was designed to explore the clinical outcomes of the two microsurgical approaches modified minimally invasive surgical technique (M-MIST) and entire papilla preservation (EPP) both created to further reduce surgical invasiveness in the treatment of isolated vertical intrabony defects, to prevent wound failure and subsequent exposure of the biomaterials.

All the microsurgical approaches previous to the EPP, even the M-MIST, were based on the dissection of the defect-associated papilla risking so to traumatize the soft tissues both during the incision and during the suture, which was then followed by the implantation of biomaterials below the incision line.

Meanwhile, the entire papilla preservation uses a tunnel-like surgical approach that enables a direct visualization of the exposed root surface through an entry vertical releasing incision in a papilla contralateral to the defect-associated papilla that remains intact, as its vascular system. The entirely undamaged interdental papilla provides an intact gingival chamber to improve the wound healing process and stabilize the blood clot as it’s described in the two articles published by Aslan, Buduneli and Cortellini in 2017a and 2021.

The buccal flap can be elevated with the M-MIST to minimize flap elevation, this results in improved wound and blood clot stability during early wound healing and prevents the collapse of the papilla into the defect.

While in these 6 studies the entire papilla preservation had, in all cases, 100% wound closure observed during the entire healing period, primary wound healing of the incision, integrity of the interdental papilla, no biomaterial exposure; the modified minimally invasive surgical technique had one adverse event in a treated site with M-MIST EMD + BDMX (Emdogain + BioOss), reported in the article written by Cortellini and Tonetti published in 2011, which presented a suture removal at week 1 with a minor discontinuity of the interdental wound on the side of the defect-associated tooth. A small number of BMDX granules were surfacing in the soft tissues, therefore they were carefully removed. The gap looked to have closed by week 2.

When EPP is administered along with amelogenins and bone-like materials, published results show 100% primary closure in the early stages of wound healing. The application of barrier membranes in the last twenty years was decreased in favor of the use of amelogenins in order to minimize wound healing complications that were caused by the inadequate surgical skills challenged by the inter-dental space in which the membranes were supposed to be inserted and by the membrane that may cause a reduced blood perfusion to the single flap of the past techniques. The entire papilla preservation on the other hand doesn’t have this last problem so even with the application of a collagen barrier, appears to offer the best possible biomaterial protection and healing conditions as presented by Aslan, Buduneli and Cortellini in the articles published in 2017a, 2017b and 2021.

The most suitable indication for EPP for Aslan, Buduneli and Cortellini in 2021 is a two-wall non-containing intrabony defect with a missing buccal bone wall. On the contrary, this innovative surgical method is not advised for the treatment of many intrabony defects or intrabony defects without a one-wall component.

Cortellini and Tonetti in 2009 and 2011 published articles where it was explained how these kinds of defects need an access from the papilla or papilla reflection for defect debridement, in particular for the ones involving the lingual aspect of the tooth. The M-MIST has the same contraindications, elevation of the inter-dental soft tissues is required and a MIST is the preferable method when a defect wraps around the lingual face of a tooth.

With these innovative surgical approaches, it is no longer necessary to make large flap elevation and periosteal releasing incisions, which also improves patient-reported outcomes. In fact, Cortellini in 2012 affirmed that the flap design with unilateral papilla elevation, by leaving an

undamaged oral section of the defect-associated papilla, dramatically reduced both the incidence of individuals reporting pain or discomfort and the requirement for painkillers after surgery.

The surgical time for the M-MIST and EPP was specified in only 3 (Cortellini e Tonetti, 2009, 2011; Aslan, Buduneli e Cortellini, 2020) of the 6 Studies, the chair time was quite similar even though the M-MIST alone was shorter (52 ± 5,6; 56,5 ± 8,6 min) than the EPP alone (55,07 ± 7,86 min), also with the biomaterial the EPP resulted longer, EPP EMD+BS (65,4 ± 10,94 min) M-MIST EMD (54,2 ± 7,4 min) M-MIST EMD + BDMX (58,9 ± 6,2 min).

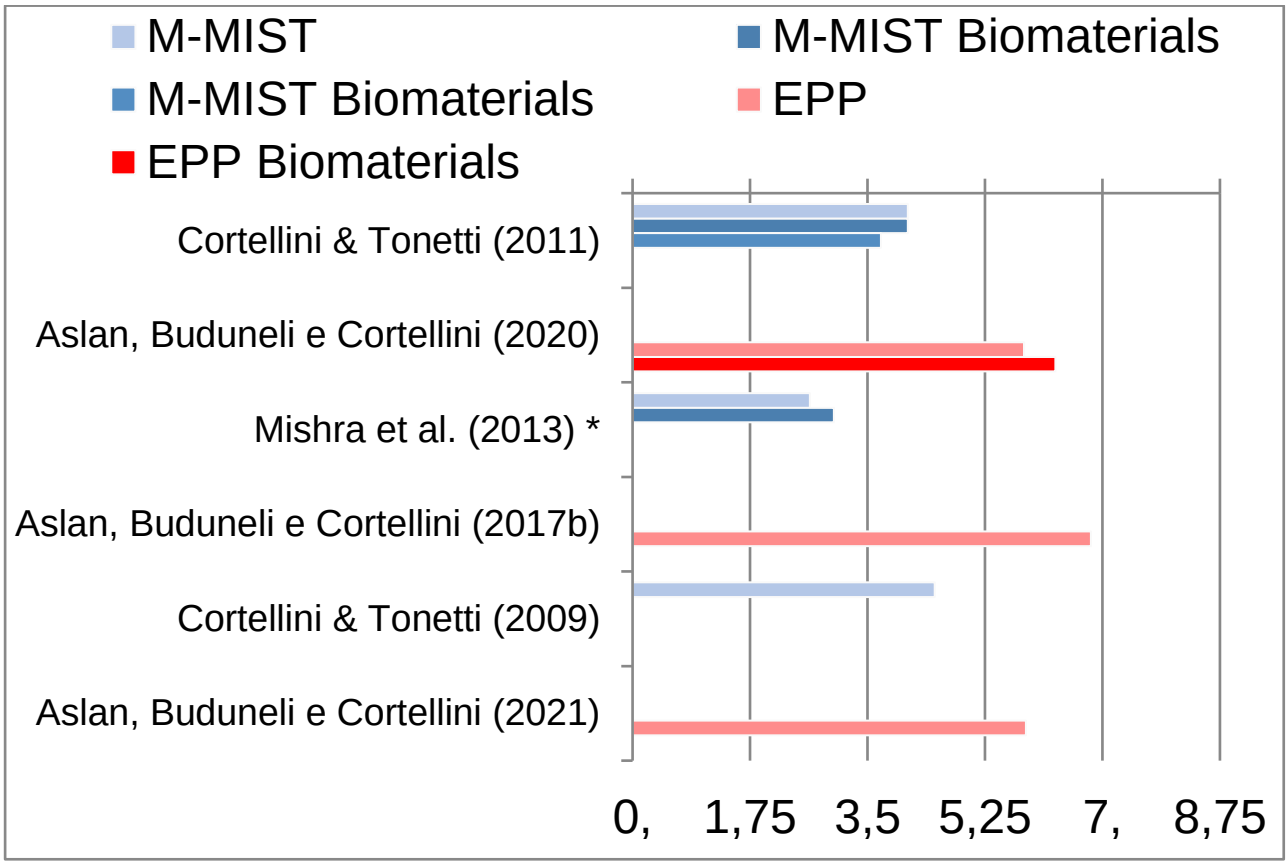
Both surgical approaches had excellent clinical outcomes, starting with the Clinical Attachment Level (CAL) gain, which, as its clearly shown on Table 10. and Graph 1., increased in every study and reached high clinical and statistical significance in differences between baseline and follow-up but never between the study groups, which typically produced a slight but never significant improvement. Although the two approaches had excellent CAL results it was noted a difference between EPP and M-MIST of at least 2mm, which can be justified both by the method but also by the substantially higher starting data of the intrabony defect.

Table 10. Clinical attachment level (CAL) data table comparison of the 6 articles.

CAL	CAL T0	CAL 6M	CAL 12M	CAL change
M-MIST	9.6 ± 2.0 p=0.758	/	5.5 ± 1.6 p=0.397	4.1 ± 1.4 p=0.639 p'<0.0001
M-MIST EMD	9.9 ± 1.3 p=0.758	/	5.7 ± 1.7 p=0.397	4.1 ± 1.2 p=0.639 p'<0.0001
M-MIST EMD + BDMX	10.1 ± 2.4 p=0.758	/	6.4 ± 2.4 p=0.397	3.7 ± 1.3 p=0.639 p'<0.0001
EPP	11.4 ± 2.17 p=0.690	/	5.56 ± 1.74 p=0.6	5.83 ± 1.12 p=0.983 p'<0.001
EPP EMD+BS	11.66 ± 3.45 p=0.690	/	5.36 ± 1.85 p=0.6	6.3 ± 2.5 p=0.983 p'<0.001
M-MIST	6.91 ± 0.70 p=0.32	? ± ?	/	2.64 ± 0.67 p=0.294 p'<0.001
M-MIST rhPDGF-BB	7.36 ± 1.28 p=0.32	? ± ?	/	3.00 ± 0.89 p=0.294 p'<0.001
EPP	12.25 ± 3.64 p=x	/	5.41 ± 2.02 p=x	6.83 ± 2.51 p=x p'<0.001
M-MIST	9.7 ± 1.8 p=x	/	5.13 ± 1.0 p=x	4.5 ± 1.4 p=x p'<0.0001
EPP	11.16 ± 1.81 p=x	/	5.3 ± 1.19 p=x	5.86 ± 1.28 p=x p'<0.0001

p intergoup; **p=x** only 1 group, intergoup impossibile; **NOT ss p>0.05** not statistically significant**; ?**=data not specified; **ss p<0.05** statistically significant

Graph 1. Clinical attachment level (CAL) change data table comparison of the 6 articles.



Mishra et al. (2013) * only had 6 months of follow-up instead of 12 months as the other 5 articles.

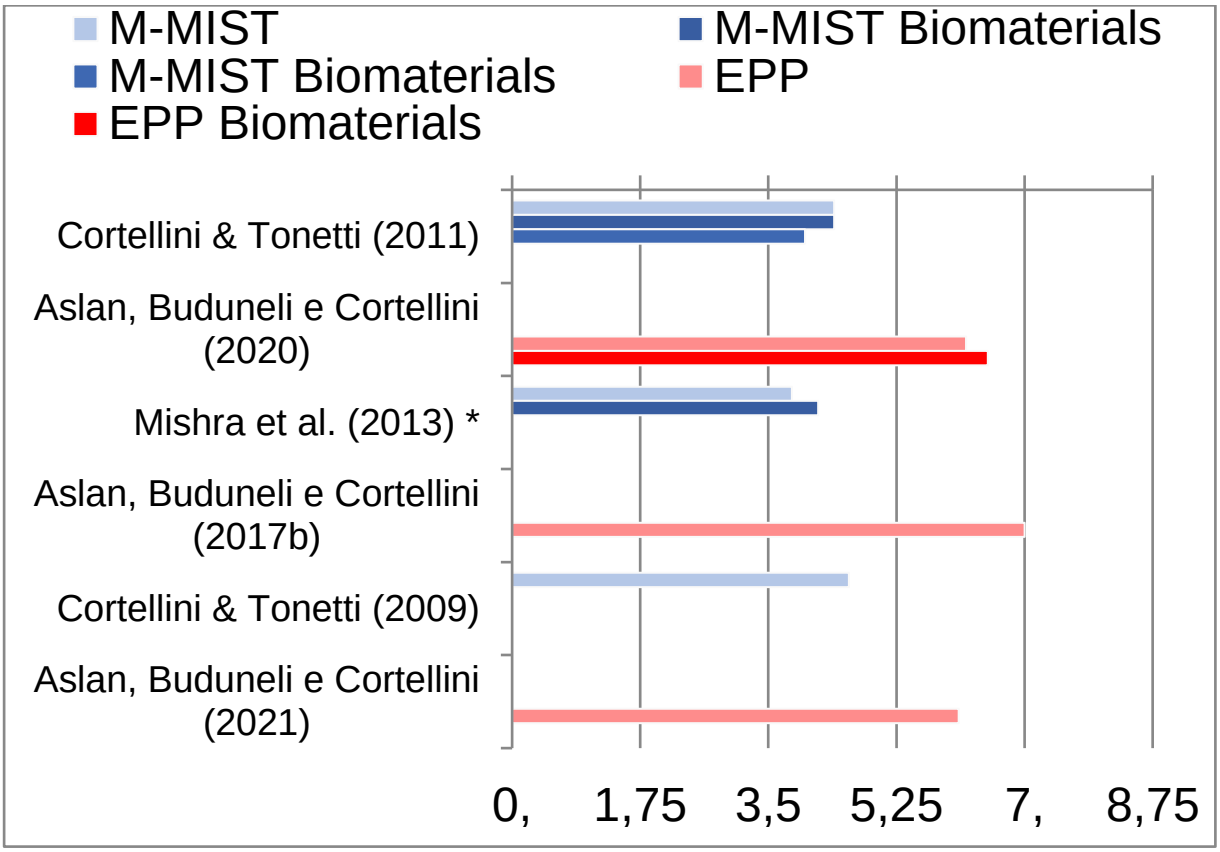
In Table 11. and Graph 2. it's displayed how every trial saw a decrease in probing pocket depth (PPD), and how the differences between baseline and follow-up reached high clinical and statistical significance. However, these was never the case of the difference between the technique and the technique plus biomaterials, which often resulted in a minor but never meaningful improvement. Even though both techniques produced outstanding CAL results, it was shown that EPP and M-MIST had a 2mm or greater discrepancy. Again, this disparity can be explained by both the method and the significantly higher intrabony defect starting data.

Table 11. Probing pocket depth (PPD) data table comparison of the 6 articles.

PPD	PPD T0	PPD 6M	PPD 12M	PPD change
M-MIST	7.5 ± 1.6 p=0.521	/	3.1 ± 0.6 p=0.327	4.4 ± 1.6 p=0.657 p'<0.0001
M-MIST EMD	7.8 ± 0.9 p=0.521	/	3.4 ± 0.6 p=0.327	4.4 ± 1.2 p=0.657 p'<0.0001
M-MIST EMD + BDMX	7.3 ± 1.2 p=0.521	/	3.3 ± 0.6 p=0.327	4.0 ± 1.3 p=0.657 p<0.0001
EPP	9.26 ± 1.65 p=0.409	/	3.06 ± 0.79 p=0.404	6.2 ± 1.33 p=0.866 p'<0.001
EPP EMD+BS	9.33 ± 2.87 p=0.409	/	2.83 ± 0.74 p=0.404	6.5 ± 2.65 p=0.866 p'<0.001
M-MIST	7.64 ± 0.67 p=0.83	? ± ?	/	3.82 ± 0.87 p=0.269 p'=?
M-MIST rhPDGF-BB	7.73 ± 1.19 p=0.83	? ± ?	/	4.18 ± 0.60 p=0.269 p'=?
EPP	9.75 ± 3.07 p=x	/	2.75 ± 0.75 p=x	7 ± 2.8 p=x p'<0.001
M-MIST	7.7 ± 1.5 p=x	/	3.07 ± 0.6 p=x	4.6 ± 1.5 p=x p'<0.0001
EPP	9.03 ± 1.62 p=x	/	2.93 ± 0.59 p=x	6.1 ± 1.47 p=x p'<0.0001

p intergoup; **p=x** only 1 group, intergoup impossibile; **NOT ss p>0.05** not statistically significant**; ?**=data not specified; **ss p<0.05** statistically significant

Graph 2. Probing pocket depth (PPD) change data table comparison of the 6 articles.



Mishra et al. (2013) * only had 6 months of follow-up instead of 12 months as the other 5 articles.

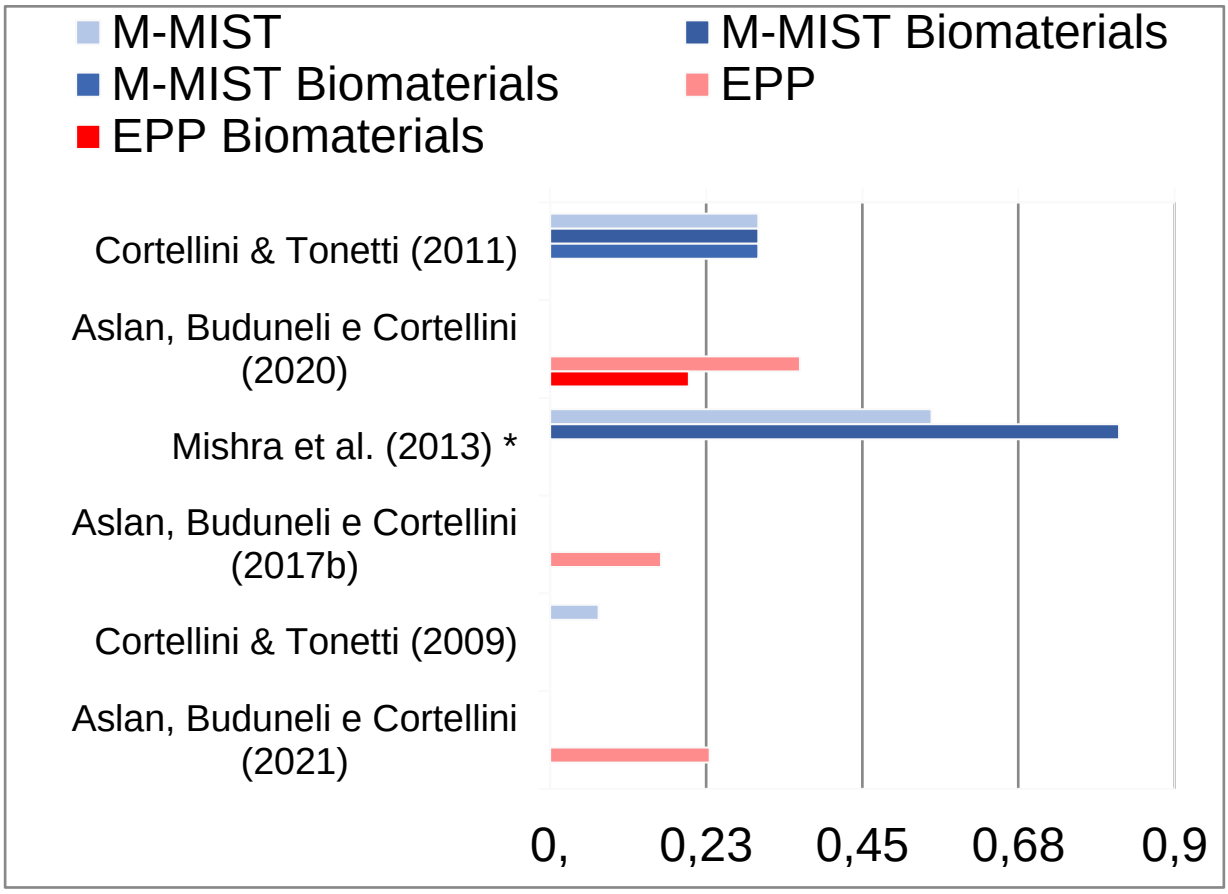
The gingival recession (REC) is an element that was set to avoid or at least limit, the EPP trials gave as a result always a minimal increase from baseline to follow-up that was also not clinically or statistically significant, as the difference between the technique and the technique plus biomaterials. On the other hand, the M-MIST studies also gave as a result a minimal increase from baseline to follow-up that was not clinically or statistically significant, all but one group, M-MIST EMD, study of Cortellini & Tonetti (2011), still the comparisons inter-groups had no statistically significant difference. All this data is summarized in the Table 12. and Graph 3. shown below.

Table 12. Recession of the gingival margin (REC) data table comparison of the 6 articles.

REC	REC T0	REC 6M	REC 12M	REC change
M-MIST	2.1 ± 1.4 p=0.307	/	2.4 ± 1.4 p=0.354	-0.3 ± 0.6 p=1 NOT ss
M-MIST EMD	2.1 ± 1.4 p=0.307	/	2.3 ± 1.4 p=0.354	-0.3 ± 0.5 p=1 p'=0.02
M-MIST EMD + BDMX	2.9 ± 1.8 p=0.307	/	3.1 ± 2.1 p=0.354	-0.3 ± 0.7 p=1 NOT ss
EPP	2.13 ± 1.12 p=0.697	/	2.5 ± 1.4 p=0.932	-0.36 ± 0.54 p=0.523 p'=0.14
EPP EMD+BS	2.33 ± 1.23 p=0.697	/	2.53 ± 1.36 p=0.932	-0.2 ± 0.25 p=0.523 p'=0.14
M-MIST	0 ± 0.0 p=0.17	? ± ?	/	-0.55 ± 0.52 p=0.270 p'=?
M-MIST rhPDGF-BB	0.18 ± 0.40 p=0.17	? ± ?	/	-0.82 ± 0.60 p=0.270 p'=?
EPP	2.5±1.31 p=x	/	2.66 ± 1.55 p=x	-0.16 ± 0.38 p=x p'=0.166
M-MIST	2 ± 1.3 p=x	/	2.07 ± 1.3 p=x	-0.07 ± 0.3 p=x p'=0.167
EPP	2.13 ± 1.3 p=x	/	2.36 ± 1.54 p=x	-0.23 ± 0.62 p=x p'=0.168

p intergoup; **p=x** only 1 group, intergoup impossibile; **NOT ss p>0.05** not statistically significant**; ?**=data not specified; **ss p<0.05** statistically significant

Graph 3. Recession of the gingival margin (REC) change data table comparison of the 6



articles.

Mishra et al. (2013) * only had 6 months of follow-up instead of 12 months as the other 5 articles.

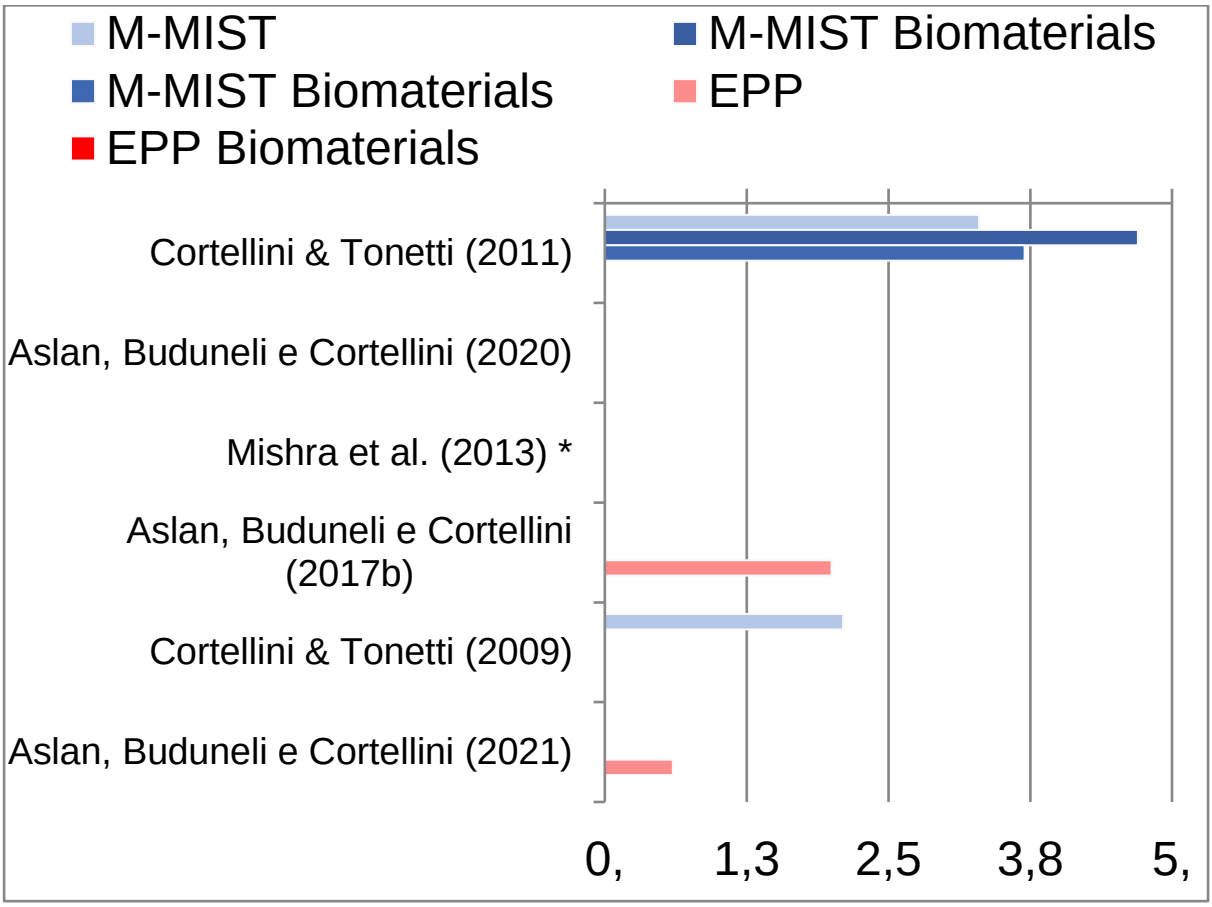
Finally, the full-mouth bleeding scores (FMBS) also decreased using both techniques, the differences between baseline and follow-up of the EPP, illustrated in the Table 13. and Graph 4., were found statistically significant in all the studies, instead in the M-MIST trials although the results seemed better than the EPP, the difference between baseline and follow-up wasn't considered significant when there weren't applied biomaterials.

Table 13. Full-mouth bleeding scores (FMBS) data table comparison of the 6 articles**.**

FMBS	FMBS T0	FMBS 6M	FMBS 12M	FMBS change
M-MIST	10.3 ± 4.4 p=0.964	/	7.0 ± 5.2 p=0.605	? ± ? p=? p'=?
M-MIST EMD	10.4 ± 3.4 p=0.964	/	5.7 ± 3.0 p=0.605	? ± ? p=? p'=?
M-MIST EMD + BDMX	10.7 ± 4.1 p=0.964	/	7.0 ± 3.6 p=0.605	? ± ? p=? p'=?
EPP	10.2 ± 1.32 p=0.2	/	? ± ? p=?	? ± ? p=? p'=?
EPP EMD+BS	9.4 ± 1.95 p=0.2	/	? ± ? p=?	? ± ? p=? p'=?
M-MIST	14.79 ± 3.84 p=0.89	? ± ?	/	? ± ? p=? Not ss
M-MIST rhPDGF-BB	14.96 ± 2.76 p=0.89	? ± ?	/	? ± ? p=? ss
EPP	9.08 ± 1.56 p=x	/	8.08 ± 1.67 p=x	? ± ? p=x p'<0.01
M-MIST	5.8 ± 3.0 p=x	/	3.7 ± 2.0 p=x	? ± ? p=x p'=0.055
EPP	9.8 ± 1.85 p=x	/	9.2 ± 1.52 p=x	? ± ? p=x p'<0.05

p intergoup; **p=x** only 1 group, intergoup impossibile; **NOT ss p>0.05** not statistically significant**; ?**=data not specified; **ss p<0.05** statistically significant

Graph 4. Full-mouth bleeding scores (FMBS) change data table comparison of the 6 articles**.**



Aslan, Buduneli e Cortellini (2020) and Mishra et al. (2013) didn't report enough data to display on the Graph.

All the data exhibited in the Tables and Graphs were taken from the 6 articles, there was no additional calculus done by the two reviewers except in Graph 4. Where the authors didn't include the FMBS change so the difference from T0 to TFinal where executed by the two reviewers

In the end we are witnessing the evolution of different flap designs applied to intrabony defects, first access flap alone resulted in in 1.57 ±0.26 mm of CAL gain, then the papilla preservation flaps alone improved the outcomes to 2.48 ±0.08 mm of CAL gain as described by Graziani *et al.* in 2012. After that there were the Modified flap designs with unilateral flap elevation, the M-MIST alone of Cortellini and Tonetti in 2009 registered 4.5 ± 1.4 mm, meanwhile the single-flap approach (SFA) alone of Trombelli *et al.* in 2009 recorded 4.5 ±1.1 mm of CAL gain, and ultimately the EPP alone of Aslan, Buduneli and Cortellini in 2017a displayed 6.83 ±2.51 of CAL gain. It seems like the more we move forward into a future of less invasive surgical

procedures with more complex flap designs the better the outcomes are, we must not forget that the study populations were different and not standardized, but still the integrity of the papilla that provides an intact gingival chamber to stabilize the blood clot that provides the possibility of early wound healing surely play its part.

IV. CONCLUSION

The modified minimally invasive surgical technique (M-MIST) and are the peak of microsurgical techniques, both techniques had excellent results in CAL gain, REC, PPD, FMBS, limited morbidity, and must be considered when treating an intrabony defect in an aesthetic area.

However, the EPP is recommended as one of the best approaches for achieving the most effective and safest results with the least morbidity, but the techniques still need to be further explored with protocols more standardized in terms of sample (population), operator experience, technique, follow-up and regeneration materials. Because these variables may have had a positive impact in the results of the EPP.

The future studies should be designed with a strict, precise and rigorous protocol, with larger sample, randomization of the study population, precise criteria of inclusion and exclusion avoiding confounding factors, longer follow up periods and the application of standardized surgical protocols.

BIBLIOGRAPHY

Aslan, S., Buduneli, N. e Cortellini, P. (2017a). Entire Papilla Preservation Technique: A Novel Surgical Approach for Regenerative Treatment of Deep and Wide Intrabony Defects. *International Journal of Periodontics & Restorative Dentistry*, 37(2), pp. 227–233.

Aslan, S., Buduneli, N. e Cortellini, P. (2017b). Entire papilla preservation technique in the regenerative treatment of deep intrabony defects: 1-Year results. *Journal of Clinical Periodontology*, 44(9), pp. 926–932.

Aslan, S., Buduneli, N. e Cortellini, P. (2020). Clinical outcomes of the entire papilla preservation technique with and without biomaterials in the treatment of isolated intrabony defects: A randomized controlled clinical trial. *Journal of Clinical Periodontology*, 47(4), pp. 470–478.

Aslan, S., Buduneli, N. e Cortellini, P. (2021). Reconstructive surgical treatment of isolated deep intrabony defects with guided tissue regeneration using entire papilla preservation technique: A prospective case series. *Journal of Periodontology*, 92(4), pp. 488–495.

Cortellini, P. (2012). Minimally invasive surgical techniques in periodontal regeneration. *Journal of Evidence Based Dental Practice*, 12(3), pp. 89–100.

Cortellini, P., Nieri, M., Pini Prato, G. e Tonetti, M. S. (2008). Single minimally invasive surgical technique with an enamel matrix derivative to treat multiple adjacent intra-bony defects: Clinical outcomes and patient morbidity. *Journal of Clinical Periodontology*, 35(7), pp. 605–613.

Cortellini, P., Prato, G. P. e Tonetti, M. S. (1995). The modified papilla preservation technique. A new surgical approach for interproximal regenerative procedures. *Journal of Periodontology*, 66(4), pp. 261–266.

Cortellini, P., Prato, G. P. e Tonetti, M. S. (1999). The simplified papilla preservation flap. A novel surgical approach for the management of soft tissues in regenerative procedures. *International Journal of Periodontics & Restorative Dentistry*, 19(6), pp. 589–99.

Cortellini, P. e Tonetti, M. S. (2001). Microsurgical approach to periodontal regeneration. Initial evaluation in a case cohort. *Journal of Periodontology*, 72(4), pp. 559–569.

Cortellini, P. e Tonetti, M. S. (2005). Clinical performance of a regenerative strategy for intrabony defects: scientific evidence and clinical experience. *Journal of Periodontology*, 76(3), pp. 341–350.

Cortellini, P. e Tonetti, M. S. (2007a). A minimally invasive surgical technique with an enamel matrix derivative in the regenerative treatment of intra-bony defects: A novel approach to limit morbidity. *Journal of Clinical Periodontology*, 34(1), pp. 87–93.

Cortellini, P. e Tonetti, M. S. (2007b). Minimally invasive surgical technique and enamel matrix derivative in intra-bony defects. I: Clinical outcomes and morbidity. *Journal of Clinical Periodontology*, 34(12), pp. 1082–1088.

Cortellini, P. e Tonetti, M. S. (2009). Improved wound stability with a modified minimally invasive surgical technique in the regenerative treatment of isolated interdental intrabony defects. *Journal of Clinical Periodontology*, 36(2), pp. 157–163.

Cortellini, P. e Tonetti, M. S. (2011). Clinical and radiographic outcomes of the modified minimally invasive surgical technique with and without regenerative materials: a randomized-controlled trial in intra-bony defects. *Journal of Clinical Periodontology*, 38(4), pp. 365–373.

Gagnier, J. J., Kienle, G., Altman, D. G., Moher, D., Sox, H. e Riley, D. (2013). The CARE guidelines: consensus-based clinical case report guideline development. *Journal of Dietary supplements*, 10(4), pp. 381–390.

Graziani, F., Gennai, S., Cei, S., Cairo, F., Baggiani, A., Miccoli, M., Gabriele, M. e Tonetti, M. (2012). Clinical performance of access flap surgery in the treatment of the intrabony defect. A systematic review and meta-analysis of randomized clinical trials. *Journal of Clinical Periodontology*, 39(2), pp. 145–156.

Harrel, S. K. e Rees, T. D. (1995). Granulation tissue removal in routine and minimally invasive procedures. *Compendium of Continuing Education in Dentistry*, 16(9), pp. 960–962.

Li, F., Yu, F., Xu, X., Li, C., Huang, D., Zhou, X., Ye, L. e Zheng, L. (2017). Evaluation of recombinant human FGF-2 and PDGF-BB in periodontal regeneration: a systematic review and meta-analysis. *Scientific Reports*, 7(1), p. 65.

Mishra, A., Avula, H., Pathakota, K. R. e Avula, J. (2013). Efficacy of modified minimally invasive surgical technique in the treatment of human intrabony defects with or without use of rhPDGF-BB gel–a randomized controlled trial. *Journal of Clinical Periodontology*, 40(2), pp. 172–179.

Nevins, M. L., Camelo, M., Rebaudi, A., Lynch, S. E. e Nevins, M. (2005). Three-dimensional micro-computed tomographic evaluation of periodontal regeneration: a human report of intrabony defects treated with Bio-Oss collagen. *International Journal of Periodontics & Restorative Dentistry*, 25(4), pp. 65–73.

Pei, X. (2021). New surgery approaches preserving entire papilla to treat isolated interdental intrabony defects: A narrative review. *Clinical and Experimental Dental Research*, 7(5), pp. 719–725.

Sali, D. D. e George, J. P. (2016). Demineralized Freeze Dried Bone Allograft With Amniotic Membrane in the Treatment of Periodontal Intrabony Defects-12 Month Randomized Controlled Clinical Trial. *Journal of Periodontology*, 11, pp. 1–18.

Takeda, K., Mizutani, K., Matsuura, T., Kido, D., Mikami, R., Noda, M., Buranasin, P., Sasaki, Y. e Izumi, Y. (2018). Periodontal regenerative effect of enamel matrix derivative in diabetes. *PLoS One*, 13(11), p. e0207201.

Tonetti, M. S., Lang, N. P., Cortellini, P., Suvan, J. E., Adriaens, P., Dubravec, D., Fonzar, A., Fourmousis, I., Mayfield, L. e Rossi, R. (2002). Enamel matrix proteins in the regenerative therapy of deep intrabony defects: A multicentre randomized controlled clinical trial. *Journal of Clinical Periodontology*, 29(4), pp. 317–325.

Trombelli, L., Farina, R., Franceschetti, G. e Calura, G. (2009). Single-flap approach with buccal access in periodontal reconstructive procedures. *Journal of Periodontology*, 80(2), pp. 353–360.

Zhang, C., Zhang, H., Yue, Z., Miao, L., Han, Y., Liu, K. e Hou, J. (2020). Modified minimally invasive surgical technique plus Bio-Oss Collagen for regenerative therapy of isolated interdental intrabony defects: study protocol for a randomised controlled trial. *BMJ Open*, 10(12), p. e040046.