

Elisa Pasqualini

**MINIMAL INVASIVE PERIODONTAL REGENERATION WITH BUCCAL
APPROACH: SYSTEMATIC REVIEW**

Universidade Fernando Pessoa
Faculdade de Ciências da Saúde

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A handwritten signature in black ink, appearing to read 'E. Pasqualini', with a stylized flourish at the end.

*Trabalho apresentado a Universidade Fernando Pessoa
como parte dos requisitos para obtenção do
grau de Mestre em Medicina Dentaria*

Porto, 2023

SUMARIO

Este trabalho é uma revisão sistemática na qual exploro a eficácia de diferentes técnicas cirúrgicas minimamente invasivas (MIST), técnicas cirúrgicas minimamente invasivas modificadas (M-MIST) e preservação da papila inteira (EPP) para o tratamento de defeitos intra-ósseos em termos de ganho de nível de inserção clínica (CAL) e redução da profundidade de bolsa periodontal (PPD) e pesquisa de recessão gengival (REC) procurando de ter melhores resultados e menos trauma para os pacientes. Fiz um protocolo de revisão detalhado que foi elaborado de acordo com a diretriz PRISMA. A pesquisa online foi realizada no PubMed, Cochrane Library e Embase. Apenas ensaios clínicos randomizados (RCTs), séries de casos (CSs) e estudos controlados (CTs) com um mínimo de 10 pacientes relatando resultados clínicos, radiográficos e/ou relacionados ao paciente, testando procedimento MIST ou M-MIST ou EPP, com ou sem aplicação de ferramenta regenerativa para tratamento de defeito intra-ósseo e apenas com incisão vestibular foram incluídos.

SUMMARY

This work is a systematic review in which I explore the efficacy of different minimal invasive surgical technique (MIST), modified minimal invasive surgical technique (M-MIST) and entire papilla preservation (EPP) approaches for the treatment of intra-bony defect in terms of clinical attachment level (CAL) gain and periodontal pocket depth (PPD) reduction and gingival recession (REC) searching with one shows to have better results and less trauma for the patients. I made a detailed review protocol was designed according to PRISMA guideline. Online search was conducted on PubMed, Cochrane library and Embase. Only randomized clinical trials (RCTs), case series (CSs) and controlled studies (CTs) with a minimum of 10 patients reporting clinical, radiographic and/or patient related outcomes at least, testing MIST or M-MIST or EPP procedure, with or without the application of a regenerative tool for the treatment of intra-bony defect and only with buccal incision were included.

AGRADECIMENTOS

Graças aos meus pais, os meus modelos de vida que me ensinaram empenho e perseverança, dedicação e tenacidade. Ensinaram-me a nunca me instalar e a exigir sempre o melhor, mas também a ser grato e feliz por tudo o que tenho e sou.

Graças a Alessio que me apoiou, me acompanhou e que acredita em mim por vezes até mais do que eu.

Graças ao meu orientador que foi capaz de me valorizar e que me tem dado e continua a dar-me estímulos para o meu crescimento profissional e um modelo a que aspirar.

Neste caminho, percebi que o limite é apenas onde escolhemos colocá-lo.

INDEX

I.introduction	1
II. Materials and Methods	2
2.1 Protocol development	2
2.3 statement of questions	2
2.3 Search strategy	3
2.4 Risk of bias in individual studies	4
III. Results	5
3.1. Search results	5
3.2 Technical implication	9
3.3 Clinical studies and outcomes	9
IV.Discussion	11
V.Conclusion	13
Bibliography	14

TABLES AND GRAPHICS INDEX

Critical Appraisal tools table	8
Approaching outcomes table	9
Graphic n.1	12
Graphic n.2	12
Graphic n.3	12

ABSTRACT

Objective: The aim of this systematic review was to explore the efficacy of different minimal invasive surgical technique (MIST), modified minimal invasive surgical technique (M-MIST) and entire papilla preservation (EPP) approaches for the treatment of intra-bony defect in terms of clinical attachment level (CAL) gain and periodontal pocket depth (PPD) reduction and gingival recession (REC) searching with one shows to have better results and less trauma for the patients.

Methods: A detailed review protocol was designed according to PRISMA guideline. Online search was conducted on PubMed, Cochrane Library and Embase. Only randomized clinical trials (RCTs), case series (CSs) and controlled studies (CTs) with a minimum of 10 patients reporting clinical, radiographic and/or patient related outcomes at least, testing MIST or M-MIST or EPP procedure, with or without the application of a regenerative tool for the treatment of intra-bony defect and only with buccal incision were included.

Results: According to the inclusion and exclusion criteria applied to the research, 12 articles came out and they are the results of this work. These 12 articles were evaluated according to the risk of bias (low, not clear, high or not applicable) and finally showed positive values according to the various techniques studied.

Keywords:(((minimally invasive) OR (periodontal regeneration)) OR (intra-bony defect)) AND (buccal access flap) OR (guided tissue regeneration)

I. INTRODUCTION

The regeneration of periodontal support is one of the goals of periodontal therapy to improve the long-term clinical outcomes of teeth periodontally compromised by intraosseous and interradicular defects.(Lindhe, 2018)

The authors reported that the results of regenerative therapy are influenced by several factors associated with the patient, site and surgery, such as plaque control, probing bleeding rate (BoP), smoking habits, morphology defects and selected surgical strategy. (Lindhe, 2018)(Farina *et al.*, 2013)

In the last 30 years, surgical reconstruction of lost periodontium has been evolved into a minimally invasive treatment to limit morbidity and increase the success rate.(Cortellini, 2009)(Aslan, 2020)

In this evolutionary path, researchers have been focused not only on the effect of biomaterials, but also on the innovation of flap design, in this sense each step plays an important role in the results, such as the incision design, the flap model, debridement methods, material location, flap repositioning and suturing.

The most relevant developments, however, have been observed in the continuous evolution of flap design and soft tissue management. To promote early soft tissue healing, minimize papilla trauma and reduce postoperative gingival recession, techniques such as papilla conservation have been proposed (Takei, Han, Carranza, Kenney, & Lekovic, 1985). Papilla conservation (PPT) (Cortellini, Prato, & Tonetti, 1995) and the simplified papilla conservation technique (Cortellini, Prato, & Tonetti, 1999), that have greatly increased the clinical success rate in periodontal surgery, however, involve an incision of the interdental papilla associated with the defect that can compromise the volume and integrity of the interdental tissues.(Aslan, 2017)

The use of biomaterials to "fill in" a defect rather than barriers to "cover" a defect facilitated the development of new flap models that ushered the era of "minimally invasive surgery" and "microsurgery". (Cortellini, 2007) (Rasperini, 1999) (Cortellini, 2009) (Aslan, 2020)

Describing the minimally invasive surgical technique, the authors emphasize the need to keep the flap as short as possible with minimal exposure of the residual bone crest. (Cortellini, 2009)

The implementation of microsurgical techniques has further increased the rate of primary wound closure and an early, incident-free healing phase (Tibbets & Shanelec 1998, Cortellini & Tonetti, 2001). The adoption of microsurgery has paved the way for minimally invasive

surgical approaches with nipple elevation (MIST) proposed by Cortellini and Tonetti in 2007. This approach was subsequently modified (M-MIST) by the same authors with a very limited elevation of the buccal side alone of the inter-dental papilla (2009). Recently, in reconstructive periodontal surgery for deep intraosseous defects, a new surgical technique has been introduced, the whole papilla preservation (PPE) technique for the regenerative treatment of isolated deep intraosseous defects. (Aslan, 2020, 2017, 2020)

The main objective of this systematic review was to investigate the results in terms of PD, CAL and REC provided by each of these techniques, comparing clinical success and satisfaction in terms of pain and discomfort perceived by the patient.

II. MATERIALS AND METHODS

2.1 Protocol development

In this review paper, the authors report according to PRISMA (Preferred Reporting Items Systematic Review and Meta-Analyses) checklist, only articles with scientific evidence in the treatment of intraosseous defects in the context of minimally invasive periodontal surgery were investigated.

Further manuscripts are planned to report on outcomes of minimally invasive surgery in other fields of dentistry.

2.2 Statement of questions

What do we need to know?

What could we achieve?

What is the effectiveness in term of clinical outcomes?

Which technique will be better for the patients in term of clinical aspect?

For the development of this work, it was formulated a clinical question, through the P.I.C.O. strategy:

- Population: periodontal patients with intrabony defects.
- Intervention: minimally invasive regenerative approach to intrabony defects in periodontal patients.

- Comparison: computation of MIST, M-MIST and EPP techniques in minimally invasive regenerative approach to intrabony defects in periodontal patients.
- Outcome: between the analyzed articles how are the results of each technique in terms of PD, CAL and GR and stability during time?
- Investigation: which minimally invasive surgical technique will show the best long-terms clinical outcomes?

2.3 Search strategy

According to the described protocol, an electronic research on PubMed, Cochcrane Central Register of Controlled Trials (CENTRAL) and Embase and a manual research were carried out to identify studies testing:

- MIST (Minimally Invasive Surgical Technique)
- M-MIST (Modified Minimally Invasive Surgical Technique)
- EPP (Entire Papilla Preservation)

Additionally, hand search covering the last 10 years was performed on Journal of Clinical Periodontology, Journal of Periodontology, Clinical Oral Investigations, The International Journal of Periodontics and Restorative Dentistry and Journal of Periodontal Research. The references of included and relevant papers were checked for possible additional studies, and authors were contacted to clarify any doubt about data.

The research in the electronic databases was supplemented by crosschecking the bibliographies of the included articles, relevant reviews and by a manual search in the principal journals in the field of periodontology up to February 2022.

The research on PubMed, Embase and Cochrane Library was conducted using the following combination of MeSH terms and text words:

(((((minimally invasive) OR (periodontal regeneration)) OR (intrabony defect)) AND (buccal access flap)) OR (guided tissue regeneration).

Inclusion criteria:

- Human studies,
- Last 10 years
- Publications in English,
- Studies describing MIST, M-MIST and EPP surgical procedure in the field of periodontal surgery,

- Case series (CSs), controlled studies (CTs) and randomized controlled trials (RCTs) with a minimum of 10 patients reporting clinical, radiographic and/or patient-related outcomes at least
- 6 months after the procedure
- Extract individual data of the author

Exclusion criteria:

- Secondary studies (bibliographic review, systematic review and meta-analysis)
- In-vitro studies
- Non-human realized clinical studies

Outcome measures:

- Clinical attachment level (CAL) gain
- Periodontal pocket depth (PPD) reduction
- Gingival recession (REC) had to be expressed as the average difference baseline/follow-up of the treated sites in millimeters.

The reviewer did not make any additional calculations on CAL gain, PPD reduction and REC

2.4 Risk of bias in individual studies

Two review authors (Filipe Castro and Elisa Pasqualini) performed the quality assessment of the included studies using Critical Appraisal tools in JBI Systematic Reviews to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. Initially, titles and abstracts of all reports will be screened independently by two reviewers: FC and EP. Subsequently, the studies appearing to meet the inclusion criteria, or those with insufficient data in the title and abstract to make a clear decision, will be selected for the evaluation of the full manuscript.

The evaluation of the full manuscript will be carried out independently by the same two reviewers (F.C. and E.P.). All studies meeting the inclusion criteria will undergo a validity assessment.

The reasons for rejecting studies at this or at subsequent stages will be recorded. Special attention will be paid not to duplicate publications in order to avoid a likely bigger impact of the same data in the overall result.

Seven main quality criteria were examined outcome reporting: sequence generation, allocast concealment, blinding of participants and personnel blinding of outcome assessors, incomplete data and selective outcome.

Risk of bias in the included studies was categorized as below:

- A. Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
- B. Unclear risk of bias " plausible bias" data raises some doubt about the results) if one or more criteria were partly met.
- C. High risk of bias (plausible bias that seriously weakens confidence in the results) if honor more criteria were not met.
- D. Risk evaluation not applicable to this context.

III. RESULTS

3.1. Search results

Online search was conducted on PubMed, Cochrane Library and Embase, only articles from the last 10 years (2012-2022) were evaluated.

Initial research led to:

- On PubMed: 384 results across Clinical Trial, Comparative Study, Controlled Clinical Trial, randomized Controlled Trial;

- In Embase : 744 articles in the subject area of Medicine and Dentistry, putting as “article type”: Research articles (712), Case reports (26), Practice guidelines (6), Software publications; as “publication title”: Journal of Oral and Maxillofacial Surgery (187), Journal of Surgical Research (139), International Journal of Oral and Maxillofacial Surgery (123), Journal of Cranio-Maxillofacial Surgery (122), The American Journal of Pathology (94), Free Radical Biology and Medicine (79) 2 articles of relevance were added to the search by removing the filters

- At the Cochrane Library: 363 Trials

All non-relevant articles (ex: based on other arguments, done on implants, on animals, focused on materials or endodontic injury) were excluded. The most relevant works with the theme of this article were then chosen, namely:

- From Pubmed 9 articles

- From Embase 1 articles

- From Cochrane 12 articles

6 articles were repeated between Pubmed and Cochrane; 2 were reviews, 1 had no publicly available datasets and other 1 was not found, 2 were clinical trial proposal. 2 more articles had been added by manual.

The final search led to 12 articles that can be included in this work:

1. The role of surgical flap design (minimally invasive flap vs. extended flap with papilla preservation) on the healing of intrabony defects treated with an enamel matrix derivative: a 12-month two-center randomized controlled clinical trial. Peter Windisch, Vincenzo Iorio-Siciliano, Daniel Palkovics, Luca Ramaglia, Andrea Blasi, Anton Sculean. Published online: 7 September 2021. *Clinical Oral Investigations* (2022) 26:1811–1821 <https://doi.org/10.1007/s00784-021-04155-5> (Windisch *et al.*, 2022)
2. Efficacy of periodontal minimally invasive surgery with and without regenerative materials for treatment of intrabony defect: a randomized clinical trial. Bei Liu, Xiangying Ouyang, Jun Kang, Shuangying Zhou, Chao Suo, Lingqiao Xu, Jianru Liu, Wenyi Liu. Published online: 20 August 2021. *Clinical Oral Investigations* (2022) 26:1613–1623. <https://doi.org/10.1007/s00784-021-04134-w>. (Liu *et al.*, 2022)
3. Clinical outcomes of the entire papilla preservation technique with and without biomaterials in the treatment of isolated intrabony defects: A randomized controlled clinical trial. Serhat Aslan, Nurcan Buduneli, Pierpaolo Cortellini. Accepted: 4 January 2020. *Journal of Clinical Periodontology*, DOI: 10.1111/jcpe.13255 (Aslan, 2020)
4. Periodontal regeneration compared with access flap surgery in human intra-bony defects 20-year follow-up of a randomized clinical trial: tooth retention, periodontitis recurrence and costs . Pierpaolo Cortellini, Jacopo Buti, Giovanpaolo Pini Prato, Maurizio S. Tonetti. Published: 13 October 2016. *Journal of Clinical Periodontology* <https://doi.org/10.1111/jcpe.12638> (Cortellini *et al.*, 2017)
5. Minimally Invasive Surgical Technique in Periodontal Regeneration: A Randomized Controlled Clinical Trial Pilot Study. Carlo Ghezzi, Luca Ferrantino, Luigi Bernardini, Margherita Lencioni, Silvia Masiero. Published: *Int J. Periodontics Restorative Dent.* 2016 Jul-Aug;36(4):475-82. doi: 10.11607/prd.2550. PMID: 27333004.(Ghezzi *et al.*, 2016)
6. A novel flapless approach versus minimally invasive surgery in periodontal regeneration with enamel matrix derivative proteins: a 24- month randomized controlled clinical trial. Aimetti, M., Ferrarotti, F., Mariani, G.M. et al.. Published 05 April 2016. *Clin Oral Invest* (2017) 21, 327–337. <https://doi.org/10.1007/s00784-016-1795-2>. (Aimetti *et al.*, 2017)

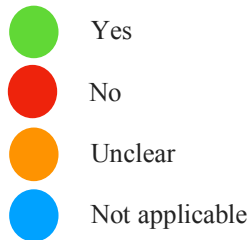
7. Single versus double flap approach in periodontal regenerative treatment. Gian Pietro Schincaglia, Eric Hebert, Roberto Farina, Anna Simonelli, Leonardo Trombelli Published: 28 April 2015. Journal of Clinical Periodontology. <https://doi.org/10.1111/jcpe.12409>. (Schincaglia *et al.*, 2015)
8. Early postoperative healing following buccal single flap approach to access intraosseous periodontal defects . Roberto Farina & Anna Simonelli & Alessandro Rizzi & Mattia Pramstraller, Alessandro Cucchi, Leonardo Trombelli. Published: 9 September 2012. Clin Oral Invest (2013) 17:1573–1583. Doi: 10.1007/s00784-012-0838-6. (Farina *et al.*, 2013)
9. Regenerative periodontal therapy of infrabony defects using minimally invasive surgery and a collagen-enriched bovine- derived xenograft: a 1-year prospective study on clinical and aesthetic outcome. Cosyn J, Cleymaet R, Hanselaer L, De Bruyn H. J Clin Periodontol 2012; 39: 979–986. Doi: 10.1111/j.1600-051X.2012.01924.x. (Cosyn J. et al, 2012)
10. Evaluation of Gain in Clinical Attachment and Bone Levels after Treatment of Patients with Intra-bony Defects by Minimally Invasive Surgical Technique versus Open Flap Debridement: A Randomized Controlled Clinical Trial. Mohamed Gamal Abd Elsalam, Ahmed Abd Elsamad, Ahmed Mohamed Elbarbary, Omniya Mostafa Abuldahab. Published in March 2020 . Ain Shams Dental Journal Vol. XXIII. (Gamal Abd Elsalam, 2020)
11. Entire papilla preservation technique in the regenerative treatment of deep intrabony defects: 1-Year results. Serhat Aslan, Nurcan Buduneli , Pierpaolo Cortellini. Accepted: 16 July 2017. Journal of Clinical Periodontology. Doi: 10.1111/jcpe.12780. (Aslan, 2017)
12. Reconstructive surgical treatment of isolated deep intrabony defects with guided tissue regeneration using entire papilla preservation technique: A prospective case series. Serhat Aslan, Nurcan Buduneli , Pierpaolo Cortellini. Accepted 30 July 2020. Journal of Clinical Periodontology. Doi: 10.1002/JPER.20-0288. (Aslan, 2020)

There were be used Critical Appraisal tools for use in JBI Systematic Reviews to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. (JBI, 2020)

Articles were analyzed by both authors (E.P and F.C).

Minimal invasive periodontal regeneration with buccal approach: a systematic review

	1	2	3	4	5	6	7	8	9	10	11	12
1. Was true randomization used for assignment of participants to treatment groups?	●	●	●	●	●	●	●	●	●	●	●	●
2. Was allocation to treatment groups concealed?	●	●	●	●	●	●	●	●	●	●	●	●
3. Were treatment groups similar at the baseline?	●	●	●	●	●	●	●	●	●	●	●	●
4. Were participants blind to treatment assignment?	●	●	●	●	●	●	●	●	●	●	●	●
5. Were those delivering treatment blind to treatment assignment?	●	●	●	●	●	●	●	●	●	●	●	●
6. Were outcomes assessors blind to treatment assignment?	●	●	●	●	●	●	●	●	●	●	●	●
7. Were treatment groups treated identically other than the intervention of interest?	●	●	●	●	●	●	●	●	●	●	●	●
8. Was follow up complete? if not, were differences between groups in terms of their follow up adequately described and analyzed?	●	●	●	●	●	●	●	●	●	●	●	●
9. Were participants analyzed in the groups to which they were randomized?	●	●	●	●	●	●	●	●	●	●	●	●
10. Were outcomes measured in the same way for treatment groups?	●	●	●	●	●	●	●	●	●	●	●	●
11. Were outcomes measured in a reliable way?	●	●	●	●	●	●	●	●	●	●	●	●
12. Was appropriate statistical analysis used?	●	●	●	●	●	●	●	●	●	●	●	●



3.2 Technical implications

The previously cited studies propose two different minimally invasive approaches to intrabony defects. The MIST (Aimetti *et al.*, 2017; Cosyn J. *et al.*, 2012; Farina *et al.*, 2013; Gamal Abd Elsalam, 2020; Ghezzi *et al.*, 2016; Liu *et al.*, 2022; Schincaglia *et al.*, 2015; Windisch *et al.*, 2022) includes the elevation of the interdental papillary tissues to uncover the interdental space, gaining complete access to the intrabony defect, the M-MIST (Cortellini *et al.*, 2017; Schincaglia *et al.*, 2015; Windisch *et al.*, 2022) proposes an approach in which the access to the defect is gained through the elevation of a small buccal flap, without elevation of the interdental papilla; finally the “Entire papilla preservation” (Aslan, 2020, 2017, 2020) technique designed as a tunnel-like approach of the defect-associated inter-dental papilla.

3.3 Clinical studies and outcomes

Case series (CSs), controlled studies (CTs) and randomized controlled trials (RCTs) reporting outcomes on the application of MIST, M-MIST and EPP approaches are shown in the following table:

	Study type	Intervention	No pax	N. defect	Cal gain	Pd reduction	GR increase
1) Peter Windisch <i>et al</i> 2021	RCTs	MIST or M-MIST with EMD	23	23	4.09 ± 1.68 (Baseline 8.82±1.92 Re-evaluation 4.78±2.09) P value 0.001	4.52 ± 1.34 (Baseline 7.22±1.17 Re-evaluation 2.78±0.74) P value 0.001	0.35 ± 1.11 (Baseline 1.65±1.23 Re-evaluation 2.00±1.88) P value 0.15
2) Bei Liu <i>Et al</i> 2021	RCTs	MIST modified in suture alone Or With EMD	36	36	Alone 2.53 ± 1.80 (Baseline 7.83 ± 1.84 Re-evaluation 5.30±1.41) With EMD 2.00 ± 1.38 (Baseline 7.50±1.61 Re-evaluation 5.50±2.08) P value <0.001	Alone 2.50±1.22 (Baseline 6.63±0.83 Re-evaluation 4.13±0.88) With EMD 2.31±1.47 (Baseline 6.63±1.06 Re-evaluation 4.31±1.50) P value <0.001	Alone 0.03 ± 1.19 (Baseline 1.20±1.79 Re-evaluation 1.17±1.48) P value 0.915 With EMD -0.31±0.93 (Baseline 0.88±1.36 Re-evaluation 1.19±1.31) P value 0.198

Minimal invasive periodontal regeneration with buccal approach: a systematic review

	Study type	Intervention	No pax	N. defect	Cal gain	Pd reduction	GR increase
3) Aslan S. Buduneli N. Cortellini P 2020	RCTs	EPP alone EPP with EMD	30	30	Alone 5.83 ± 1.12 (Baseline 11.4±2.17 Re-evaluation 5.56±1.74 P value <0.001 With EMD 6.3 ± 2.5 (Baseline 11.66±3.45 Re-evaluation 5.36±1.85) P value <0.001	Alone 6.2±1.33 (Baseline 9.26±1.65 Re-evaluation 3.06±0.79) P value <0.001 With EMD 6.5 ± 2.65 (Baseline 9.33±2.87 Re-evaluation 2.83±0.74 P value <0.001	Alone -0.36±0.54 (Baseline 2.13±1.12 Re-evaluation 2.5±1.4) P value 0.14 With EMD -0.2 ± 0.25 (Baseline 2.33±1.23 Re-evaluation 2.53±1.36 P value 0.14
4) Pierpaolo Cortellini et al 2016	RCTs	M-MIST with titanium membrane	15	15	5.3 ± 2.2 (Baseline 9.9±3.2 Re-evaluation 4.7 ± 1.8 P value 0.001	3.4 ± 2.4 (Baseline 5.5 ± 2.9 Re-evaluation 2.1±0.5 P value 0.001	
5) Carlo grezzi et al 2016	RCTs	MIST with EMD and DBBM (IPR) MIST with reabsorbable minimembrane (GTR)	20	20	+IPR 4.4 ± 1.17 (Baseline 9.2 ± 1.9 Re-evaluation 4.8±1.4 +GTR 4.0 ± 1.82 (Baseline 8.5±2.2 Re-evaluation 4.5±1.27) P value 0.56	+IPR 4.9 ± 1.20 (Baseline 8.2 ± 1.3 Re-evaluation 3.3±0.48 +GTR 4.04-5.76 (Baseline 7.8 ±2.4 Re-evaluation 3.1±0.57 P value 0.81	+IPR 0.5 ± 0.85 (Baseline 1.0 ± 1.10 Re-evaluation 1.5±1.18 +GTR 0.7 ±0.95 (baseline 0.7±0.67 Re-evaluation 1.4±1.07) P value =.62
6) Mario Aimetti et al 2017	RCTs	MIST	15	15	3.6 ± 0.9 (Baseline 9.0 ± 1.7 Re-evaluation 5.4± 1.6) P value <0.001	3.6 ± 1.0 (Baseline 7.3 ± 0.8 Re-evaluation 3.6 ± 0.9) P value <0.001	-0.1 ± 0.5 (Baseline 1.7 ± 1.2 Re-evaluation 1.8 ± 1) P value <0.001
7) Gian Pietro Schincaglia et al 2015	RCTs	Single flap approach (MIST) Double flap approach M-MIST)	12	18	Single flap 4.0 ± 1.9 (Baseline 9.7 ± 2.5 Re-evaluation 5.7 ± 2.6) Double flap 3.2 ± 1.4 (Baseline 8.5 ± 1.6 Re-evaluation 5.2 ± 1.6) P value 0.316	Single flap 4.1 ± 1.7 (Baseline 8.7 ± 2.0 Re-evaluation 4.5 ± 1.6) Double flap 3.6 ± 1.1 (Baseline 7.7 ± 1.5 Re-evaluation 4.1 ± 1.2) P value 0.413	Single flap -0.1 ± 0.7 (Baseline 1.1 ± 1.3 Re-evaluation 1.2 ± 1.5) Double flap -0.4 ± 1.3 (Baseline 0.8 ± 1.3 Re-evaluation 1.2 ± 1.6) P value 0.618
8) Roberto Frina et al 2012	RCTs	MIST	35	43	3.4 ± 2.0 (Baseline 10.4±2.6 Re-evaluation 7.0±2.4) P value <0.001	4.7 ± 2.0 (Baseline 8.9±2.0 Re-evaluation 4.2±1.3) P value <0.001	1.3 ± 1.4 (Baseline 1.5±1.4 Re-evaluation 2.8±2.1) P value 0.004
9) Cosyn J, et al 2012	CS	MIST	84	84	3,1 (Baseline 10.00 Re-evaluation 6.9 P value <0.001	3,5 (baseline 7.8 Re-evaluation 4.3) P value <0.001	0,3 (Baseline 2.2 Re-evaluation 2.5 P value 0.002
10) Mohamad Gamal Abd Elsalam et al. 2020	RCTs	MIST	7	22	2.54 ± 1.13 (Baseline 6.54±0.93 Re-evaluation 4.00±1.18) P value <0.001	2,1 (baseline 6.27±0.65 Re-evaluation 3.45±0.69) P value <0.001	
11) Aslan S. Buduneli N. Cortellini P. 2017	CS	EPP+ EDM	12	12	6,83± 2.51 (Baseline 12.25 ± 3.64 Re-evaluation 5.41±2.02) P value <0.001	7 ± 2.8 (Baseline 9.75 ± 3.07 Re-evaluation 2.75±0.75) P value <0.001	0.16 ± 0.38 (Baseline 2.5 ± 1.31 Re-evaluation 2.66±1.55) P value 0.166
12) Aslan S. Buduneli N. Cortellini P. 2020	CS	EPP + bone grafting materials and collagen membrane	15	15	5.86 ± 1.28 (Baseline 11.16 ± 1.81 Re-evaluation 5.3 ± 1.19) P value <0.001	6.1 ± 1.47 (Baseline 9.03 ± 1.62 Re-evaluation 2.93 ± 0.59) P value <0.001	0.23 ± 0.62 (Baseline 2.13 ± 1.3 Re-evaluation 2.36 ± 1.54) P value 0.168

IV. DISCUSSION

A statistically significant PD reduction was noted in each group between baseline and the revaluation / follow-up period.

Neither in the first study nor in the second, any statistically significant differences were found in any of the evaluated parameters.

A controversy is shown about the application of EMD in conjunction with either MIST/M-MIST : in the article of Windisch et al. (Windisch *et al.*, 2022) seems to result in substantial clinical improvements but in the articles of Aslan and Liu (Aslan, 2020; Liu *et al.*, 2022) the regenerative materials do not show an additional effect on outcomes.

Also the study of Ghezzi (Ghezzi *et al.*, 2016) shows no statistically significant differences in clinical variables were found between the group with EMD and DBBM.

And the other group MIST with reabsorbable minimembrane (GTR) at baseline. Defect configuration (one, two, or three walls) and tooth position were also well balanced between the two groups.

Early wound healing and baseline CAL are factors influencing 1-year CAL gain.

Studies with EPP show early healing uneventful and 100% wound closure was maintained during the entire healing period.

Tunnel-like “EPP” technique may limit the risk of wound failure particularly in the early healing phase, thereby preventing exposure of regenerative biomaterials, possibly enhancing stabilization of blood clot in deep intrabony defects and leading to optimal clinical outcomes.

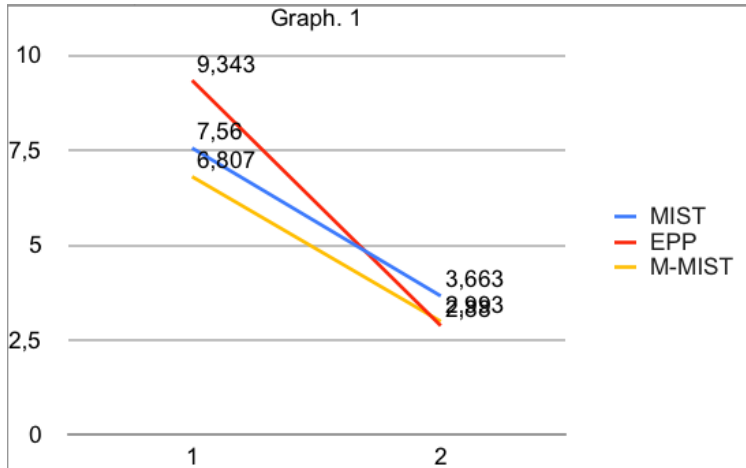
Where regeneration were compared with open flap (for example study of Cortellini in 2016), it provided better long-term benefits than Flap: no tooth loss, less periodontitis progression and less expense from re-intervention.

All those studies can suggest that is MIST (as well as M-MIST and EPP) that has great intrinsic regenerative potential and reach comparable clinical outcomes with those minimally invasive surgical approaches.

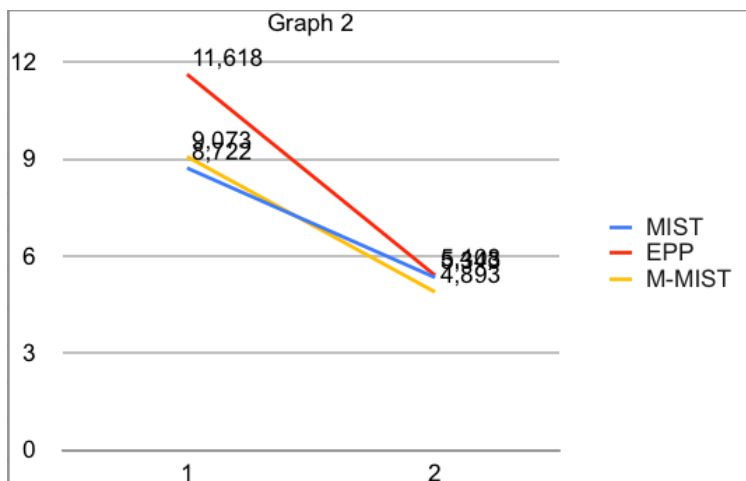
They showed substantial similar outcomes when used alone or in association with different reconstructive technologies and appeared to be at least similarly effective. The rationale for the application of the MIST, M-MIST or EPP resides in the preservation of an intact interdental papilla, which may facilitate flap repositioning and suturing, thus optimizing wound closure for primary intention healing, as well as accelerate the re-establishment of the local vascular supply.

Defects with a non-supportive anatomy and a thin-scalloped gingival biotype were identified as risk factors for advanced vestibular REC increase.

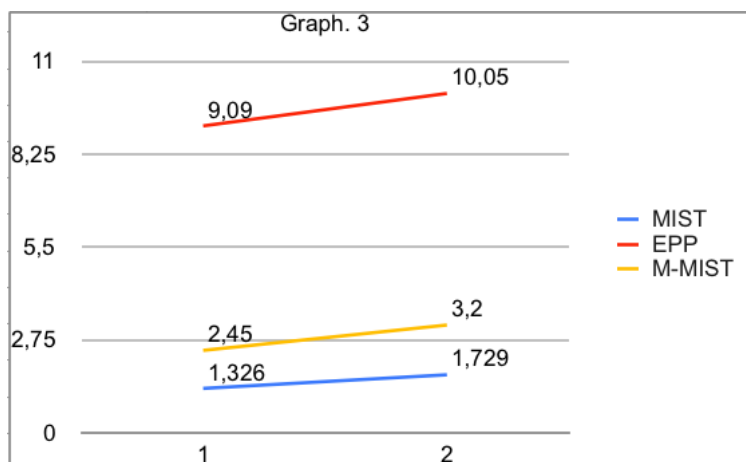
Every study shows an improvement in CAL gain and PD reduction, associated with minimal increase in gingival recession.



The first graph shows the pocket depth (PD) trend from baseline to reevaluation using the averages of the values emerging from the studies divided according to the technique used (MIST, M-MIST or EPP).



The second graph shows the improvement in the clinical level of attachment (CAL) from the baseline to the reevaluation according to the average of the parameters emerging from the studies and divided due to the technique used (MIST, M-MIST or EPP).



The third graph shows the minimum increase in gingival recession (GR) from the baseline to the reevaluation identifiable with any of the three techniques analyzed (MIST, M-MIST or EPP).

V. CONCLUSION

MIST, M-MIST and EPP might be considered a true reality in the field of periodontal regeneration depending on aesthetic site, possibility and facility of flap repositioning, suturing and pocket initial deep. Case series, controlled studies and randomized controlled trials have demonstrated its potential to greatly improve the periodontal conditions of sites associated with intrabony defects, proving its efficacy. These clinical improvements are consistently associated with very limited morbidity to the patient during the surgical procedure, as well as in the postoperative period. Chair time required to perform such a surgery is by far shorter than the chair time required for more conventional surgical approaches. For the future it is desirable a stepwise decisional algorithm should support clinicians in choosing the proper approach which will bring the best long terms clinical outcomes.

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