

ARTICLE



Minimally invasive periodontal regeneration with the buccal approach: a systematic review and meta-analysis of clinical studies

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KEY POINTS

- Minimally invasive techniques are favorable in treating intrabony defects.
- Minimally invasive techniques are conservative approaches with good predictability.
- MIST, M-MIST, and papilla preservation techniques demonstrated their potential and efficacy to improve periodontal parameters with minimal morbidity.

OBJECTIVE: The aim of this study was to investigate clinical periodontal parameters after treatment using the Minimally Invasive Surgical Technique (MIST), Modified Minimally Invasive Surgical Technique (M-MIST), and/or any technique for papilla preservation, such as Entire Papilla Preservation (EPP), modified-papilla preservation technique (M-PPT), or simplified-papilla preservation technique (SPPT).

METHODS: The focus question was “For patients with periodontal intrabony defects (P), what is the best minimally invasive regenerative approach (I), comparing MIST, M-MIST, and papilla preservation techniques’ outcomes (C) to improve PD, CAL, GR, and periodontal stability (O)?” An online search was conducted on PubMed, Cochrane Library, and Embase. Only randomized clinical trials and case series with a minimum of 10 enrolled patients were included. The risk of bias was evaluated using the Critical Appraisal tools in JBI Systematic Reviews. The meta-analysis compared the data obtained for the periodontal parameters analyzed, and the heterogeneity was verified.

RESULTS: After the screening, nine articles were included. Seven studies applied MIST and its modifications; two used M-PPT, one SPPT, and one approached EPP. A general statistically significant PD reduction and CAL gain were noted between the groups, comparing baseline and follow-up for all articles, independently of the technique or materials used. Also, all studies showed a non-significant increase in the gingival recession. Four studies had a low risk of bias, four had a moderate risk, and only 1 had a high risk. Moderate heterogeneity was found in one analysis for CAL (65.73%); moderate and substantial heterogeneity was found in the PD results (71.91% and 89.19%); and no heterogeneity was found within all analyses for gingival recession (0%).

CONCLUSION: MIST, M-MIST, and papilla preservation techniques demonstrated their potential and efficacy to improve periodontal conditions of sites with intrabony defects with minimal morbidity.

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INTRODUCTION

Periodontal regenerative therapy aims to reconstruct intrabony defects, which is defined as a “periodontal defect within the bone surrounded by one, two, or three bony walls or a combination thereof”¹. Several factors can interfere with the biological response and outcomes obtained. They may be associated with local or systemic factors, surgical technique, or strategy chosen². Focusing on the surgical procedure, in 1995, a minimally invasive periodontal treatment was introduced³. It minimizes the wound size and flap reflection and permits the gentle handling of the soft and hard tissues. Then, the “minimally invasive surgery” and “micro-surgery”^{4–7} era was launched. In addition, it permits the use of operating microscopes/loupes and microsurgical instruments^{8–10}.

This era had new flap designs and the use of biomaterials, which can be considered the most relevant improvement. Moreover, this approach has limited morbidity and discomfort and increased the predictability and success rate^{4,5,11,12}.

In the ‘90s, two minimally invasive surgical techniques were developed: the modified papilla preservation technique (1995)¹³ and the simplified papilla preservation technique (1999)¹⁴. In 2007, the minimally invasive surgical technique (MIST)⁶ with minimal flap elevation emerged; in 2009, modified MIST (M-MIST), performing a minimal elevation only of the buccal area of the interdental papilla⁴; and in 2017, entire papilla preservation (EPP) technique¹⁵. These surgical procedures keep the flap as short as possible, with minimal exposure to the residual bone crest⁴,

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reaching a stable primary wound closure to seal the regenerated region^{13,14}, and permit an incident-free healing phase^{9,11,12,16}.

Those minimally invasive techniques have significantly increased the clinical success rate, using specific incisions on the interdental papilla where there is a bone defect, avoiding compromising the volume and integrity of the interdental tissues¹⁵. Also, it is possible to have early soft tissue healing and minimize papilla trauma, with a lower risk of apical migration of the gingival margin (gingival recession)^{17,18}, and to minimize surgical trauma and chair time, to increase flap stability, to allow stable primary closure of the wound, and to reduce discomfort and side effects.

Thus, researchers and clinicians have worked intensely to find the most conservative approach for treating periodontal defects. The objective of this systematic study was to investigate clinical periodontal parameters (pocket depth [PD], clinical attachment level [CAL], and gingival recession [GR]) after treatment with Minimally Invasive Surgical Technique (MIST), Modified-Minimally Invasive Surgical Technique (M-MIST), and/or any technique for papilla preservation, such as Entire Papilla Preservation (EPP), modified-papilla preservation technique (M-PPT), or simplified-papilla preservation technique (SPPT). The null hypothesis was that no techniques improved the clinical parameters compared to the control group.

MATERIALS AND METHODS

Protocol and focus questions

This systematic review followed the PRISMA (Preferred Reporting Items Systematic Review and Meta-Analyses) guidelines. Only articles with scientific evidence in treating intraosseous defects within minimally invasive periodontal surgery were investigated. For the development of this study, it was formulated the following

focused questions using the P.I.C.O. strategy (Population, Intervention, Comparison, and Outcome): "For patients with periodontal intrabony defects (P), what is the best minimally invasive regenerative approach (I), comparing MIST, M-MIST, and papilla preservation techniques' outcomes (C) to improve PD, CAL, GR, and periodontal stability?"

Search strategy

Electronic research was carried out in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, and Embase databases to identify studies applying MIST (Minimally Invasive Surgical Technique), M-MIST (Modified-Minimally Invasive Surgical Technique), and papilla preservation procedures. Moreover, a manual search was conducted on specific journals: *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Clinical Oral Investigations*, *The International Journal of Periodontics & Restorative Dentistry*, and *Journal of Periodontal Research*. The references of the included papers were crosschecked for possible additional studies, and the authors were contacted to clarify any doubt about the data.

Limitations were implemented, such as articles published within the last 10 years (February 2012–February 2022) and in English. The combination of MeSH terms and keywords associated with Boolean operators were: "minimally invasive" OR "periodontal regeneration" OR "intrabony defect" OR intraosseous OR intrabony OR angular OR vertical OR "papilla preservation" AND "buccal access flap" OR "guided tissue regeneration". The primary outcomes measured were (i) CAL gain, (ii) PD reduction, and (iii) GR reduction. All parameters must present baseline and follow-up data of the treated sites.

Eligibility criteria

The inclusion criteria were: (i) human studies, (ii) last 10 years (February 2012 – February 2022), (iii) publications in English

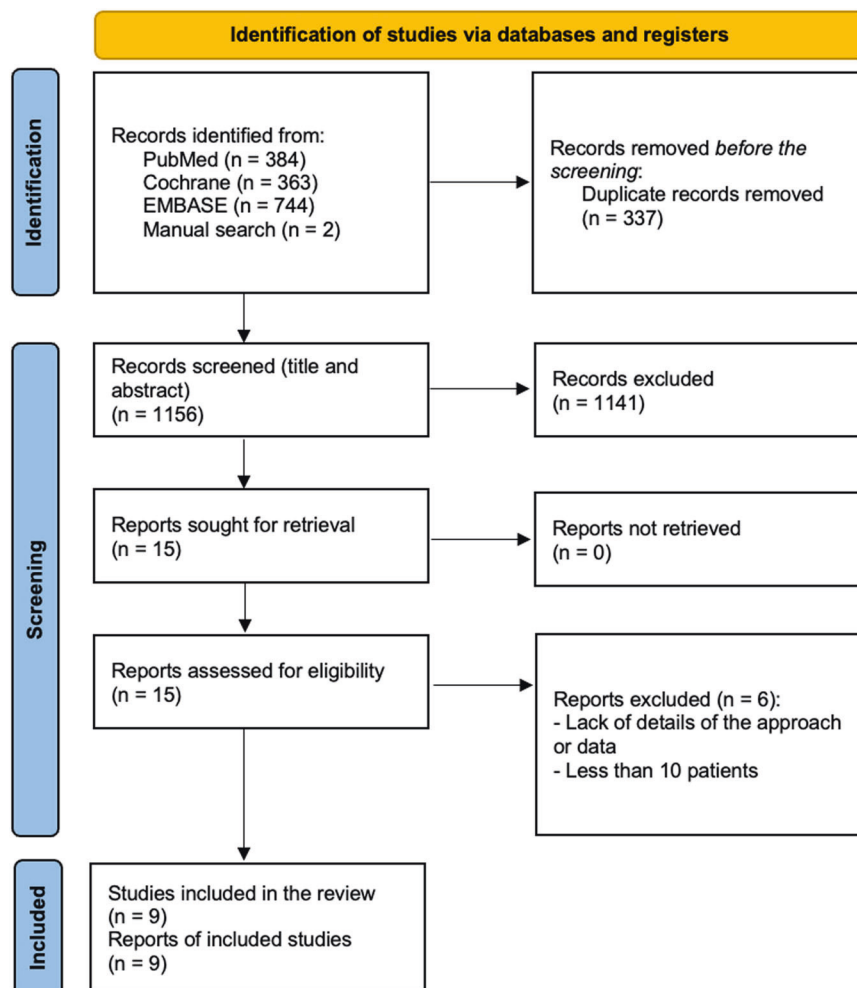


Fig. 1 PRISMA Flowchart for selection of the studies.

Table 1. Author, year of publication, type of study, title, goals, and conclusions obtained.

Author/year	Title	Objectives	Conclusion
Windisch et al., 2021 ²⁴	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	To evaluate the healing of intrabony defects treated with either minimally invasive surgical flaps or with modified or simplified papilla preservation techniques in conjunction with the application of an enamel matrix derivative (EMD).	The results have failed to show any differences in the measured parameters following treatment of intrabony defects with EMD, irrespective of the surgical technique employed. Clinical relevance: In intrabony defects, the application of EMD in conjunction with either MIST/M-MIST or M-PPT/SPPT resulted in substantial clinical improvements.
Liu et al., 2022 ²⁵	Efficacy of periodontal minimally invasive surgery with and without regenerative materials for treatment of intrabony defect: a randomized clinical trial	to determine the efficacy of MISTms (modified in suture) with and without regenerative materials for treating intrabony defects and to identify factors influencing 1-year clinical attachment level (CAL) gain.	MISTms is an effective treatment for intrabony defects. The regenerative materials do not show an additional effect on 1-year outcomes. Early wound healing and baseline CAL are factors influencing 1-year CAL gain. Clinical relevance: MISTms with and without regenerative materials are both effective treatments for intrabony defects.
Aslan et al., 2020 ¹⁸	Clinical outcomes of the entire papilla preservation technique with and without biomaterials in the treatment of isolated intrabony defects: A randomized controlled clinical trial	To compare the clinical efficacy of the entire papilla preservation technique (EPP) alone and combined with enamel matrix proteins plus bovine-derived bone substitutes (EPP EMD + BS) in treating isolated inter-dental intrabony defects.	Application of EPP with and without regenerative biomaterials resulted in significant amounts of CAL gain and PD reduction, with negligible increase in gingival recession. The addition of regenerative biomaterials does not improve the clinical outcomes of EPP alone.
Cortellini et al., 2017 ²⁵	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	Compare the long-term outcomes and costs of three treatment modalities in intra-bony defects.	Regeneration provided better long-term benefits than Flap: no tooth loss, less periodontitis progression, and less expense from re-intervention over 20 years. These benefits need to be interpreted in the context of higher immediate costs associated with regenerative treatment.
Grezzi et al., 2016 ²⁶	Minimally Invasive Surgical Technique in Periodontal Regeneration: A Randomized Controlled Clinical Trial Pilot Study	To compare two minimally invasive surgical techniques (MISTs) for the treatment of periodontal defects: (1) guided tissue regeneration (GTR) using resorbable mini membrane and particulate xenograft (DBBM); and (2) inductive periodontal regeneration (IPR) using enamel matrix derivatives and DBBM.	MIST with GTR or IPR demonstrated excellent outcomes 1year after surgery, with no differences between treatment groups.
Aimetti et al., 2017 ²²	A novel flapless approach versus minimally invasive surgery in periodontal regeneration with enamel matrix derivative proteins: a 24-month randomized controlled clinical trial	to compare the effectiveness of enamel matrix derivative (EMD) proteins in combination with flapless or flap procedures in periodontal regeneration of deep intrabony defects.	The flapless procedure may be successfully applied in the regenerative treatment of deep intrabony defects reaching clinical outcomes comparable with those of minimally invasive surgical approaches and may present important advantages in reducing operative chair time. Clinical relevance: EMD as an adjunct to non-surgical periodontal treatment may be considered a suitable option to treat defects, mainly in the anterior sextants.
Schincaglia et al., 2015 ²⁰	Single versus double flap approach in periodontal regenerative treatment	To compare the outcomes of a regenerative strategy based on recombinant human platelet-derived growth factor-BB (rhPDGF-BB, 0.3 mg/ml) and b-tricalcium phosphate (b-TCP) in the treatment of intraosseous defects accessed with the Single Flap Approach (SFA) versus Double Flap Approach based on papilla preservation techniques (DFA).	When combined with rhPDGF-BB and b-TCP, the SFA may result in similar clinical outcomes, better quality of early wound healing, and lower pain and consumption of analgesics during the first postoperative days compared to the DFA.
Farina et al., 2013 ²	Early postoperative healing following buccal single flap approach to access intraosseous periodontal defects	To evaluate the early postoperative healing of papillary incision wounds and its association with (1) patient/site-related factors and technical (surgical) aspects as well as with (2) 6-month clinical outcomes following buccal single flap approach (SFA) in the treatment of intraosseous periodontal defects.	At 2 weeks, buccal SFA may result in highly predictable complete flap closure.
Elsalam et al., 2020 ²¹	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	To evaluate the gain in clinical attachment and bone levels after treatment of the intra-bony defects by minimally invasive surgical technique when compared to open flap debridement.	Minimally invasive surgical techniques and open flap debridement were closely effective in improving the clinical parameters, including clinical attachment gain, probing depth reduction, and bone gain.

EPP entire papilla preservation technique, *EMD* enamel matrix derivative, *MIST* minimally invasive surgical technique, *M-MIST* modified-minimally invasive surgical technique, *GTR* guided-tissue regeneration, *DBBM* deproteinized bovine bone mineral, *CAL* clinical attachment level, *PD* pocket depth, *REC* recession, *NR* not reported.

Table 2. Clinical detail extracted from the included articles.

Author/year	Intervention	Patient (n)	Dropout (n)	Defect treated (n)	Smoker	Arch/teeth	Follow-up	CAL gain (mm)	PD reduction (mm)	REC increase (mm)
Windisch et al., 2021 ²⁴	MIST or M-MIST with EMD - test group M-PPT or SPPT (extending to the adjacent teeth) - control group	Test (N = 23; 9 M/14 F) Mean age: 48.9 ± 9.7 Control (N = 24; 10 M/14 F) Mean age: 47.8 ± 5.3	1 (test group) because he moved to another town (initial 24 in the test group)	23 24	2 (<10 cigarettes/day) 2	11 max. 12 mand. 16 max. 8 mand.	12 months	4.09 ± 1.68 (Baseline) 8.82 ± 1.92 (Re-evaluation) 4.78 ± 2.09 (P value 0.001) 3.79 ± 1.67 (Baseline) 8.71 ± 2.29 (Re-evaluation) 4.92 ± 1.59 (P value 0.001)	4.52 ± 1.34 (Baseline) 7.22 ± 1.17 (Re-evaluation) 2.78 ± 0.74 (P value 0.001) 4.04 ± 1.62 (Baseline) 7.25 ± 1.39 (Re-evaluation) 3.21 ± 0.83 (P value 0.001)	-0.35 ± 1.11 (Baseline) 1.65 ± 1.23 (Re-evaluation) 2.00 ± 1.88 (P value 0.15) -0.25 ± 1.03 (Baseline) 1.46 ± 1.25 (Re-evaluation) 1.71 ± 1.6 (P value 0.25)
Liu et al., 2022 ²⁵	MIST modified in suture alone or MIST combined with EMD	36 (ages between 24 and 63 years) MIST alone: 43.20 ± 9.50 (6 M/9 F) MIST combined: 36.63 ± 8.29 (8 M/8 F)	3 in the MIST alone group and 2 in the MIST combined (moved to another city or abroad)	36 MIST alone: 1 or 2 walls (5) / 3 walls (10) MIST combined: 1 or 2 walls (3) / 3 walls (13)	MIST alone: 1/14 MIST combined: 2/14 (<10 cigarettes/day)	MIST alone: 5 mand. 10 max. MIST combined: 6 mand. 10 max.	12 months	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 < 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 < 0.001)	Alone 0.03 ± 1.19 (Baseline) 1.20 ± 1.79 (Re-evaluation) 1.17 ± 1.48 (P = 0.915) With EMD -0.31 ± 0.93 (Baseline) 0.88 ± 1.36 (Re-evaluation) 1.19 ± 1.31 (P = 0.198)
Aslan et al., 2020 ¹⁸	EPP alone or EPP with EMD	30 EPP alone (n = 15), mean age 43.93 ± 12.85 years, range 21–63 years, 7 F/8 M EPP EMD + BS (n = 15), mean age 44.93 ± 13.06 years, range 22–60 years, 5 F/10 M	No	30 EPP alone (14 2-wall defects and 1 3-wall defect) EPP EMD + BS (13 2-wall defects and 2 3-wall defects)	Excluded	EPP alone (ant. = 7; post. = 8) EPP EMD + BS (ant. = 11; post. = 4)	12 months	Alone 5.83 ± 1.12 (Baseline) 11.4 ± 2.17 (Re-evaluation) 5.56 ± 1.74 (P < 0.001) With EMD 6.3 ± 2.5 (Baseline) 11.66 ± 3.45 (Re-evaluation) 5.36 ± 1.85 (P < 0.001)	Alone 6.2 ± 1.33 (Baseline) 9.26 ± 1.65 (Re-evaluation) 3.06 ± 0.79 (P < 0.001) With EMD 6.5 ± 2.65 (Baseline) 9.33 ± 2.87 (Re-evaluation) 2.83 ± 0.74 (P < 0.001)	Alone -0.36 ± 0.54 (Baseline) 2.13 ± 1.12 (Re-evaluation) 2.5 ± 1.4 (P = 0.14) With EMD -0.2 ± 0.25 (Baseline) 2.33 ± 1.23 (Re-evaluation) 2.53 ± 1.36 (P = 0.14)
Cortellini et al., 2017 ²³	M-PPT with titanium membrane (test) or Flap procedure according to the Modified Widman Flap approach (control)	15 (39.3 ± 6.4 years old), 10 F/5 M	1 (moved to another country)	15	2 smokers (self-reported, <20/day)	80% in the max. arch	1 and 20 years	Gain: 5.3 ± 2.2 (Baseline) 9.9 ± 3.2 (Re-evaluation (1 y)) 4.7 ± 1.8, (Re-evaluation (20 y)) 4.9 ± 2 (p < 0.0001 (baseline - 1 y)) p = 0.5830 (1 y - 20 y) (Baseline 9.5 ± 2.7), (Re-evaluation (1 y)) 7.1 ± 2.4, (Re-evaluation (20 y)) 8.9 ± 3.2 (p < 0.001 (baseline - 1 y)) p = 0.0006 (1 y - 20 y)	Reduction: 3.4 ± 2.4 (Baseline) 5.5 ± 2.9, (Re-evaluation (1 y)) 2.1 ± 0.5 (Re-evaluation (20 y)) 3 ± 0.9 (p = 0.001 (baseline - 1 y)) p = 0.0023 (1 y - 20 y) (Baseline 5.3 ± 1.8), (Re-evaluation (1 y)) 3.7 ± 1.3 (Re-evaluation (20 y)) 5.5 ± 2.7 (p = 0.001 (baseline - 1 y)) p = 0.0086 (1 y - 20 y)	NR

Table 2. continued

Author/year	Intervention	Patient (n)	Dropout (n)	Defect treated (n)	Smoker	Arch/teeth	Follow-up	CAL gain (mm)	PD reduction (mm)	REC increase (mm)
Grezi et al., 2016 ²⁵	MIST with EMD and DBBM (IPR) or MIST with resorbable membrane (GTR)	20 (range: 34 to 68 years) MIST + IPR (n = 10, 56 ± 8.15 years, 5 F/5 M) MIST + GTR (n = 10, 52.9 ± 10.25 years, 6 F/4 M)	-	20	Considered up to <10 cigarettes/day	NR	1 year	+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 = 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 = 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 = 0.62
Aimetti et al., 2017 ²²	MIST or M-MIST + EMD or Flapless group + EMD	15 (42.2 ± 6.1 years; 7 F/8 M) 15 (44.3 ± 8.1 years; 5 F/10 M)	-	15 15	Excluded	NR	1 and 2 years	3.5 ± 1.0 / 3.6 ± 0.9 mm -Baseline 9.0 ± 1.7 -Re-evaluation (1 Y) 5.5 ± 1.5 (p ≤ 0.001) -Re-evaluation (2 Y) 5.4 ± 1.6 (p ≤ 0.001) 3.1 ± 1.2 / 3.2 ± 1.1 mm -Baseline 9.4 ± 2.0 -Re-evaluation (1 Y) 6.3 ± 2.1 (p ≤ 0.001) -Re-evaluation (2 Y) 6.2 ± 2.3 (p ≤ 0.001)	3.6 ± 0.8 / 3.7 ± 0.6 mm -Baseline 7.3 ± 0.8 -Re-evaluation (1 Y) 3.7 ± 0.9 (p ≤ 0.001) -Re-evaluation (2 Y) 3.6 ± 0.9 (p ≤ 0.001) 3.4 ± 1.2 / 3.6 ± 1.0 mm -Baseline 7.5 ± 0.9 -Re-evaluation (1 Y) 4.1 ± 1.1 (p ≤ 0.001) -Re-evaluation (2 Y) 3.9 ± 0.9 (p ≤ 0.001)	-0.1 ± 0.3 / -0.1 ± 0.3 mm Baseline 1.7 ± 1.2 Re-evaluation (1 Y): 1.8 ± 1.1 (p > 0.05) Re-evaluation (2 Y): 1.8 ± 1.0 (p > 0.05) -0.3 ± 0.6 / -0.4 ± 0.7 mm Baseline 1.9 ± 1.8 Re-evaluation (1 Y): 2.2 ± 2.0 (p > 0.05) Re-evaluation (2 Y): 2.3 ± 2.6 (p > 0.05)
Schincaglia et al., 2015 ²⁰	Single flap approach (MIST) or Double flap approach (M-MIST)	15 13	1 (root fracture before the 6-month visit)	28 1-wall: 8 2-wall: 8 3-wall: 12	3 0	14 max. and 14 mand.	6 months	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 = 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 = 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 = 0.618
Farina et al., 2013 ²	Single flap approach (MIST) healing (I) Spontaneous (II) Hydroxyapatite-based graft + resorbable collagen membrane (III) Hydroxyapatite-based graft before surgery (IV) Enamel matrix derivative (EMD) (V) Hydroxyapatite-based graft + EMD	35 (24 M and 11 F) mean age, 51.4 ± 8.5 years age range, 34–65 years two poorly controlled type I diabetes (i.e., HbA1c ≥ 7.0% at the last exam) 25 defects (18 patients) 7 defects (7 patients) 6 defects (6 patients) 3 defects (3 patients) 2 defects (2 patients)	0	43	7 current smokers 4 former smokers	14 incisors 18 canines 7 PM 4 molars	6 months	3.4 ± 2.0 (Baseline 10.4 ± 2.6 Re-evaluation 7.0 ± 2.4) P < 0.001	4.7 ± 2.0 (Baseline 8.9 ± 2.0 Re-evaluation 4.2 ± 1.3) P < 0.001	-1.3 ± 1.4 (Baseline 1.5 ± 1.4 Re-evaluation 2.8 ± 2.1) P = 0.004

Table 2. continued

Author/year	Intervention	Patient (n)	Dropout (n)	Defect treated (n)	Smoker	Arch/teeth	Follow-up	CAL gain (mm)	PD reduction (mm)	REC increase (mm)
Elsalam et al., 2020 ²¹	MIST or Open flap debridement (OFD)	MIST (8 M; 3 F) - final 9; mean age 33.64 ± 3.26 y. OFD (5 M; 6 F); mean age 32.27 ± 2.05 y.	2	22 (11 defects per group)	Smokers were excluded	NR	6 months	2.54 ± 1.13 (Baseline) 6.54 ± 0.93 (Re-evaluation) 4.00 ± 1.18 P < 0.001 3.28 ± 0.95 (Baseline) 8.0 ± 2.14 (Re-evaluation) 4.72 ± 1.19 P < 0.001	2.1 ± 0.67 (Baseline) 6.27 ± 0.65 (Re-evaluation) 3.45 ± 0.69 P < 0.001 3.64 ± 1.1 (Baseline) 7.09 ± 1.51 (Re-evaluation) 3.45 ± 0.69 P < 0.001	NR

EPP entire papilla preservation technique, EMD enamel matrix derivative, MIST minimally invasive surgical technique, M-MIST modified-minimally invasive surgical technique, GTR guided-tissue regeneration, DBBM deproteinized bovine bone mineral, CAL clinical attachment level, PD pocket depth, REC recession, NR not reported, max. maxillary, mand. mandibular, PM premolar, ant. anterior, post. posterior, GRB guided-bone regeneration, M-PPT modified papilla preservation technique, SPPT simplified papilla preservation technique.

language, (iv) randomized controlled trials (RCTs) describing MIST, M-MIST, and/or papilla preservation surgical procedures in the field of periodontal surgery, (vi) a minimum of 10 patients must be reported with clinical, radiographic, and/or patient-related outcomes, and (vii) at least 6-month follow-up after the procedures. The exclusion factors were: (i) secondary studies (bibliographic review, narrative review, systematic review, and meta-analysis), (ii) in vitro studies, (iii) case reports, case series, retrospective study, (iv) studies without CAL, PD, and/or GR, and (v) inclusion of patients with systemic diseases.

Selection of articles and data extraction

Two independent reviewers (EP and FC) performed the appraisal, and a third reviewer (GVOF) was consulted in case of disagreement. The reviewers discussed the results based on the inclusion/exclusion criteria. Duplicate articles were removed. Firstly, it was analyzed the title and abstract. Subsequently, the studies that met the eligibility criteria and those with insufficient data in the abstract were selected for full-text evaluation. The following information was extracted from the articles: (i) author and year of publication, (ii) follow-up, (iii) sample size and the number of defects, and (iv) clinical characteristics and details (CAL gain, PD reduction, and GR reduction).

Quality assessment and risk of bias

The main domains used to assess the certainty of the evidence are risk of bias, inconsistency, indirectness of evidence, imprecision, and publication bias. Then, two independent investigators (FC and EP) performed the quality assessment, and in the case of divergences, a third researcher was consulted (GVOF). Critical Appraisal tool in JBI Systematic Reviews was used to determine the possibility of bias. Seven main quality criteria were examined, with 12 questions: (i) sequence generation, (ii) allocate concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessors, (v) incomplete data, (vi) selective outcome, and (vii) other sources of bias (such as funding or conflict of interest).

The risk of bias was sorted as below¹⁹: (a) low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met (all green [yes]) or at maximum 2 unclear; (b) moderate risk of bias ("plausible bias" data raises some doubt about the results) if one "no" (red) is found or up to 4 "unclear" criteria were met; (c) high risk of bias (plausible bias that seriously weakens confidence in the results) if honor more criteria were not met (at least 2 "no" (red) or ≥5 "unclear" is found); and (d) risk evaluation not applicable to this context.

Statistical analysis

The meta-analysis involved comparing the data obtained for the periodontal parameters analyzed. The observation period varied, and only studies with similar follow-ups were compared. All analyses were performed in Microsoft Excel (v. 16.73, Microsoft, Redmond, USA), where the fixed effect model was applied with a significance level of 5%. Heterogeneity between studies was quantified using the I² inconsistency test. Values between 0% and 30% were considered might not be important; between 31% and 50% may represent low heterogeneity; between 51% and 75% may represent moderate; and >75% were considered an indication of substantial heterogeneity.

RESULTS

Search screening

A total of 1491 articles were found through the electronic search (384 articles on PubMed, 363 at the Cochrane Library, and 744 articles on Embase), and 2 more articles were manually added. All duplicate articles (n = 337) were removed, resting 1156 articles. After analyzing the eligibility criteria, all non-relevant studies (n = 1141) were taken out (k = 0.92). Thereby, 15 studies followed for full-text reading (k = 0.98). Six were removed due to a lack of details or information, and less than 10 patients were treated, resulting in 9 articles included (Fig. 1).

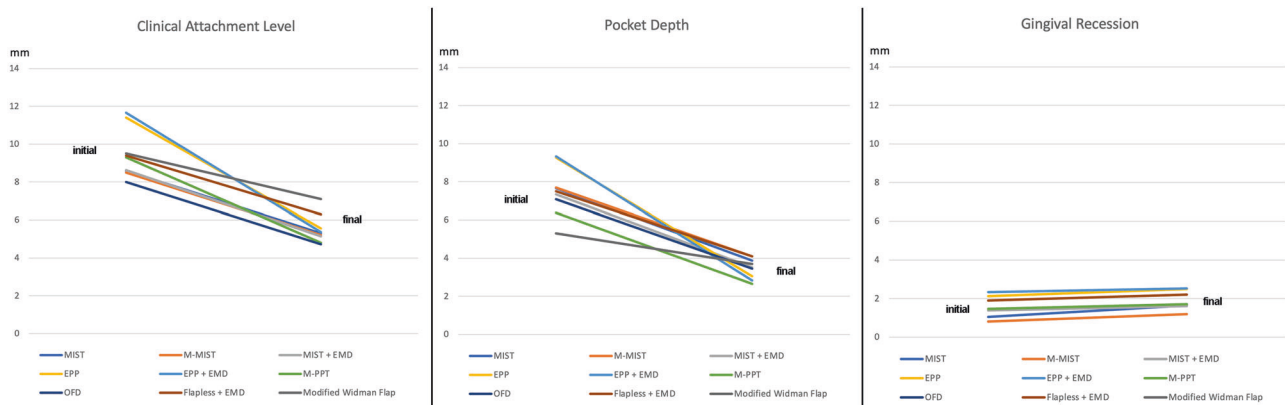


Fig. 2 *Clinical Attachment Loss (left) compared the baseline and outcome averages of the studies included per group; a general reduction can be observed, mainly when MIST and M-MIST are used. Pocket Depth (in the middle) had a similar trend to the previous graphic, again presenting a more robust PD reduction for MIST and M-MIST. Gingival recession (right) presents a slight, similar, and general increase from the baseline data to the re-evaluation.*

Demographic data and Follow-up

All RCTs included ($n = 9$) are detailed in Tables 1 and 2. 193 patients (59 females and 134 males) were enrolled, with a mean age of $44.16 (\pm 7.965)$ years, were enrolled; 222 intrabony defects were treated. Three articles presented 6-month follow-up^{2,20,21}; 6 had 1-year follow-up; only 2 studies showed periods larger than 1 year, Aimetti et al. (2017)²² had 1 and 2-year follow-up, and Cortellini et al. (2017)²³ had 1 and 20 years. Three articles excluded smokers to avoid bias; 19 current and 4 former smokers were found. No influence or adverse event was reported related to smokers. There were ten dropouts with the following justifications: (1) root fracture before the 6-month visits and (2) moved to another country or city.

Studies' details

Six studies used enamel matrix derivative (EMD) as adjunctive material^{2,18,22,24–26}. One used open flap debridement (OFD) as the control group²¹; Aimetti et al. (2017)²² used the flapless technique as the control group, whereas Cortellini et al. (2017)²³ used the modified Widman flap approach as the control; Farina et al. (2012)² also used different types of materials: (a) hydroxyapatite bone graft with a resorbable collagen membrane, (b) hydroxyapatite bone graft only, and (c) hydroxyapatite bone graft with EMD, or only collagen membrane for guided-tissue/bone regeneration (GTR/GBR)²⁶. One study used a bovine bone graft²⁶, and another used a titanium membrane²³.

Seven studies applied MIST and its modifications^{2,20–22,24–26}; two studies used Modified-papilla preservation technique (M-PPT)^{23,24}; one used simplified-papilla preservation technique (SPPT)²⁴; and one study approached EPP¹⁸.

Technically, the rationale for applying the MIST, M-MIST, or papilla preservation resides in preserving an intact interdental papilla, which may facilitate flap repositioning and suturing. Thus, it optimizes wound closure for primary intention healing and accelerates the re-establishment of the local vascular supply. MIST was described as an elevation of the interdental papillary tissues to uncover the interdental space, gaining complete access to the intrabony defect. In contrast, M-MIST proposed an approach/elevation with small buccal flap access to achieve the defect without elevation of the interdental papilla. The papilla preservation techniques were designed as tunnel-like approaches to the defect-associated inter-dental papilla.

Clinical findings

All findings are detailed in Table 2. All studies suggested the techniques evaluated, independently of the control or test group, had great regenerative potential and reached comparable clinical outcomes. A general statistically significant PD reduction and CAL gain were noted between the groups studied, comparing baseline and follow-up for all articles, independently of the technique or materials used (Fig. 2). Otherwise, no significant result was reported comparing groups when available. Also, there was a

non-statistically significant increase in the gingival recession in all studies, demonstrating that, even though clinical success was reached, this variable did not present improvement. Defects with non-supportive anatomy and a thin-scalloped gingival phenotype were identified as risk factors for increased buccal recession.

Regardless of whether used and adjunctive biomaterial, MIST and M-MIST demonstrated a greater improvement in periodontal tissue attachment and pocket depth reduction. Oppositely, all groups studied had a slight increase in GR. Studies that applied papilla preservation showed uneventful early healing and 100% wound closure 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 to regenerative biomaterials, possibly enhancing the stabilization of blood clots in deep intrabony defects, and leading to optimal clinical outcomes.

A controversy was found when applying EMD as an adjunct biomaterial. Grezzi et al. (2016)²⁶, Aslan et al. (2020)¹⁸, and Windisch et al. (2021)²⁴ had a non-significant improvement in the clinical results, which was controversial in Liu et al.'s (2022)²⁵ study, where the regenerative materials did not show an additional effect on the outcomes.

Risk of bias and meta-analysis

All included studies were qualitatively assessed (Fig. 3). A low risk of bias was found in four studies (Windisch et al., 2021 – 1²⁴; Aslan et al., 2020 – 3¹⁸; Aimetti et al., 2017 – 6²²; Schincaglia et al., 2015 – 7²⁰); other four studies had a moderate risk of bias (Liu et al., 2022 – 2²⁵; Cortellini et al., 2017 – 4²³; Grezzi et al., 2016 – 5²⁶; Elsalam et al., 2020 – 9²¹); whereas only one had a high risk (Farina et al., 2012 – 8²).

CAL assessment showed a general gain for all groups, slightly favoring the test groups. No significant differences in the overall outcome between 6 and 12 months, respectively 1.62 [1.20, 2.04] and 1.81 [1.53, 2.09]. The funnel plots present the existence of moderate heterogeneity only in the 12-month analysis for this parameter (65.73%) (Fig. 4). Contrasting CAL in the control group versus the test group, both six and 12-month evaluation presented results favoring the test group, even though there was no statistical significance, respectively 0.39 [–0.19, 0.96] and 0.13 [–0.11, 0.36]. A low heterogeneity was found within the groups' comparison at 12 months ($I^2 = 44.98\%$).

Similar results were observed in the variable PD, which improved during the appraisal period. The overall outcome between 6 and 12 months had no significant differences, respectively 2.87 [2.35, 3.39] and 2.66 [2.33, 3.00]. Low heterogeneity was found in the results at six months ($I^2 = 32.11\%$), whereas substantial heterogeneity was found in the PD results at 12 months (89.19%). Comparing the control and test for the PD outcome, after 6 and 12 months, no statistically significant result was found, respectively 0.15 [–0.42, 0.71] and 0.34 [0.0, 0.48]. However, at six months, no heterogeneity was reported ($I^2 = 0\%$); otherwise, at 12 months, a moderate level of heterogeneity was found (71.91%) (Fig. 5).

	1	2	3	4	5	6	7	8	9
1. Was true randomization used for assignment of participants to treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
2. Was allocation to treatment groups concealed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
3. Were treatment groups similar at the baseline?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were participants blind to treatment assignment?	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Yes
5. Were those delivering treatment blind to treatment assignment?	Yes	No	Unclear	Unclear	Unclear	Yes	Yes	No	No
6. Were outcomes assessors blind to treatment assignment?	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear
7. Were treatment groups treated identically other than the intervention of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was follow up complete? if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were participants analyzed in the groups to which they were randomized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

 Yes
  No
  Unclear
  Not applicable

Fig. 3 Risk of Bias of the included studies (Windisch et al., 2021 – 1; Liu et al., 2022 – 2; Aslan et al., 2020 – 3; Cortellini et al., 2017 – 4²⁵; Grezzi et al., 2016 – 5; Aimetti et al., 2017 – 6²⁶; Schincaglia et al., 2015 – 7²⁷; Farina et al., 2012 – 8²; Cosyn et al., 2012 – 9; Elsalam et al., 2020 – 10²⁹; Aslan et al., 2017 – 11; Aslan et al., 2020 – 12).

No heterogeneity was found within all analyses for gingival recession ($I^2 = 0\%$). A good balance was observed between groups and periods for the results on this parameter, as observed in Fig. 6.

DISCUSSION

Minimally invasive techniques are a reality. They have demonstrated a more conservative intervention for decades, providing

greater patient comfort and improved results. This systematic review investigated clinical periodontal parameters (PD, CAL, and GR), comparing the baseline data and outcomes for MIST, M-MIST, or any papilla preservation technique studied (EPP, M-PPT, or SPPT). Since minimally invasive techniques and flaps are based on reduced surgical access in the interdental area²⁷, using membrane alone or combined with bone grafts may be challenging^{28,29}.

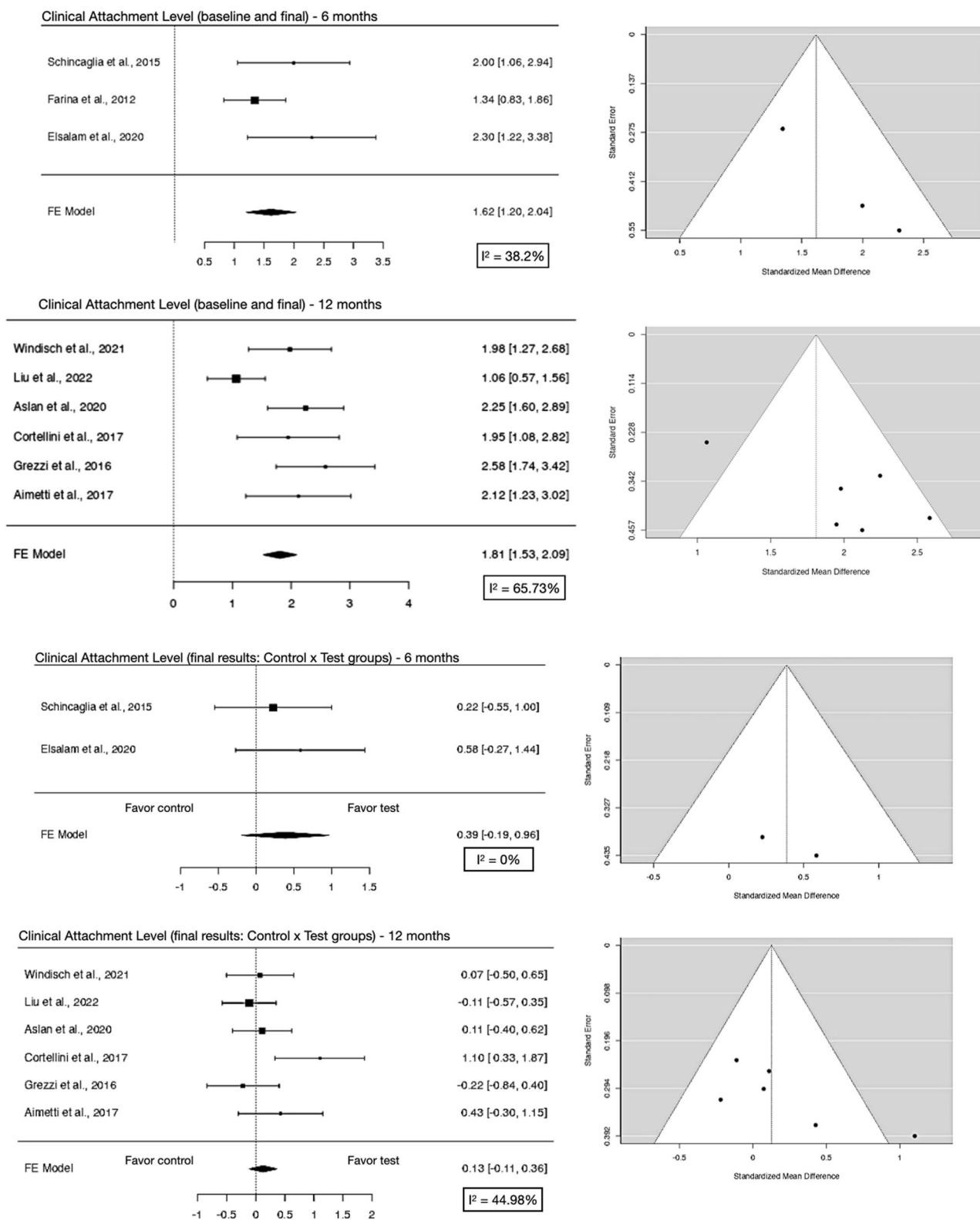


Fig. 4 Forest and funnel plots analyzing the CAL in 6 and 12 months (initial and final results and final results compared among studies).

It is essential to evaluate the PD associated with intrabony components. In our systematic study, the minimum baseline mean value found was 5.3 mm, but most studies had >6 mm for this parameter. In fact, deep intrabony defects (>6 mm) would require a more extended flap to provide adequate visibility for instrumentation³⁰, facilitating the use of a membrane. Three out of 9 studies included used some type of membrane. Grezzi et al. (2016)²⁶ compared MIST with EMD and DBBM against MIST with resorbable membrane (GTR), reporting no significant results when comparing outcomes of all clinical parameters evaluated ($p > 0.05$). Farina et al. (2012)² used a hydroxyapatite bone graft

with resorbable collagen membrane in 7 defects/patients; no membrane exposure or exfoliation of the biomaterial was observed after 2 weeks. All results had non-significant results for all defect studies ($p > 0.05$). Both aforementioned studies had non-valuable results to justify the use of a membrane, a fact that agrees with the literature. Otherwise, in a case series study, Aslan et al. (2020)⁵ applied EPP with GBR (collagen membrane) and found significant improvement for CAL and PD, contrasting previous studies. Similar findings using membrane were reported by Cortellini et al. (2017)²³, who treated patients with M-PPT and titanium membrane (non-resorbable); the authors presented

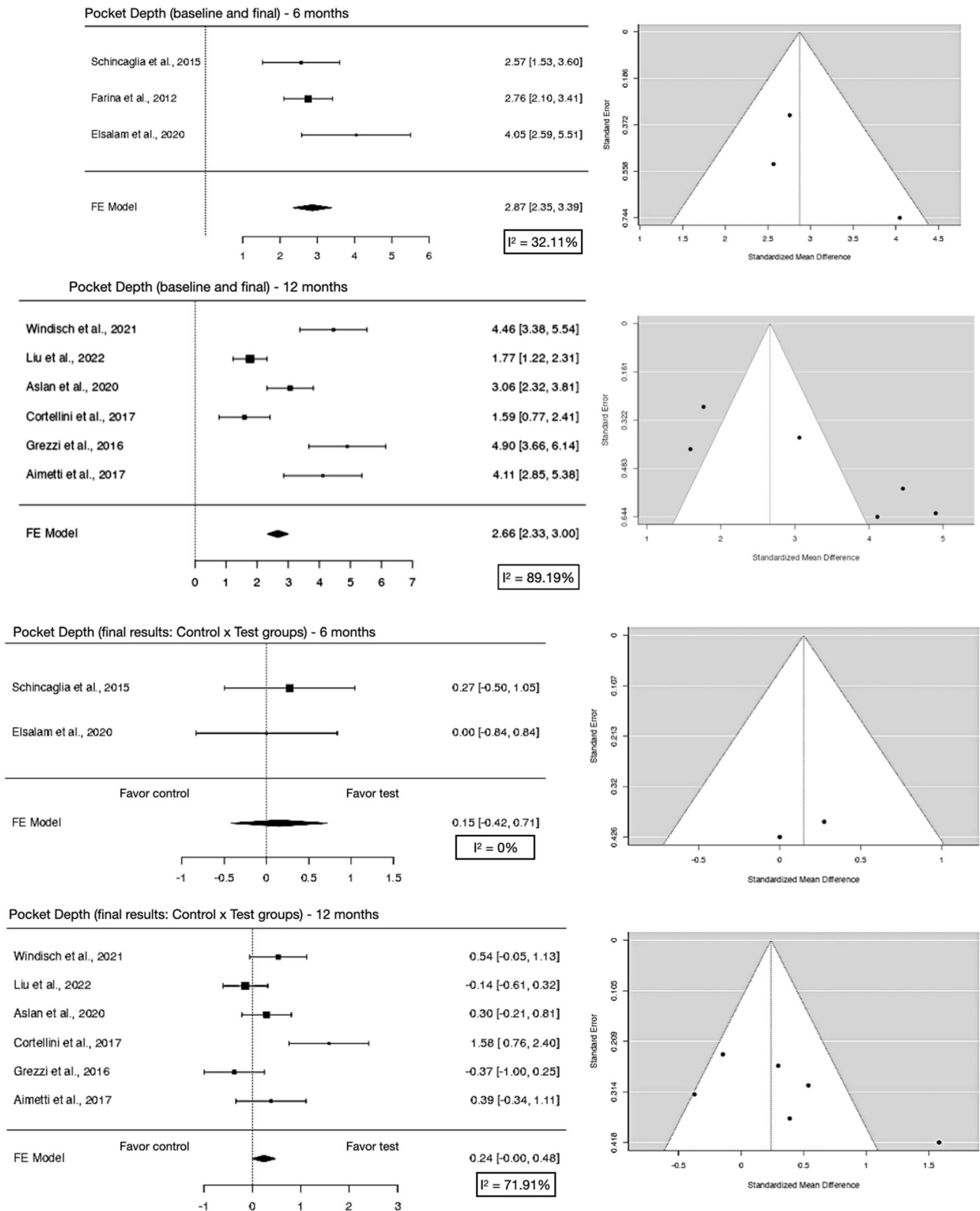


Fig. 5 Forest and funnel plots analyzing the PD in 6 and 12 months (initial and final results and final results compared among studies).

significant CAL gain (5.3 ± 2.2 mm, $p < 0.0001$) and PD reduction (3.4 ± 2.4 mm, $p = 0.001$). Then, it is possible to observe a contrast in the results found in the literature. The M-PPT and SPPT were originally proposed for membrane use, and for this reason, the residual margin of the crestal bone must be exposed for about 2-3 mm; the fact that mobilization is no longer necessary when applied EMD has led to the development of MIST and M-MIST.

Then, some studies considered the application of EMD as a co-adjuvant in intra-bony defect treatment. Even though EMD in combination with a minimally invasive surgical flap can be

applicable in any bone defect³⁰, when used in 3-wall intrabony defects associated with papilla preservation flaps, it yielded a 269% higher success chance than 1-wall defects to gain 3 mm CAL or more³¹. Another study (case series), Aslan et al. (2017)¹⁵, had significant data for the gain of CAL (gain of 6.83 ± 2.51 mm, $P < 0.001$) and reduction of PD (7.0 ± 2.8 mm, $P < 0.001$) when applied EPP with EDM. In our systematic review, observing other approaches (MIST or M-MIST with EMD^{22,24}, MIST with EMD and DBBM¹⁸, and EPP with EMD¹⁸), the outcomes were favorable for the parameters analyzed, although sometimes without

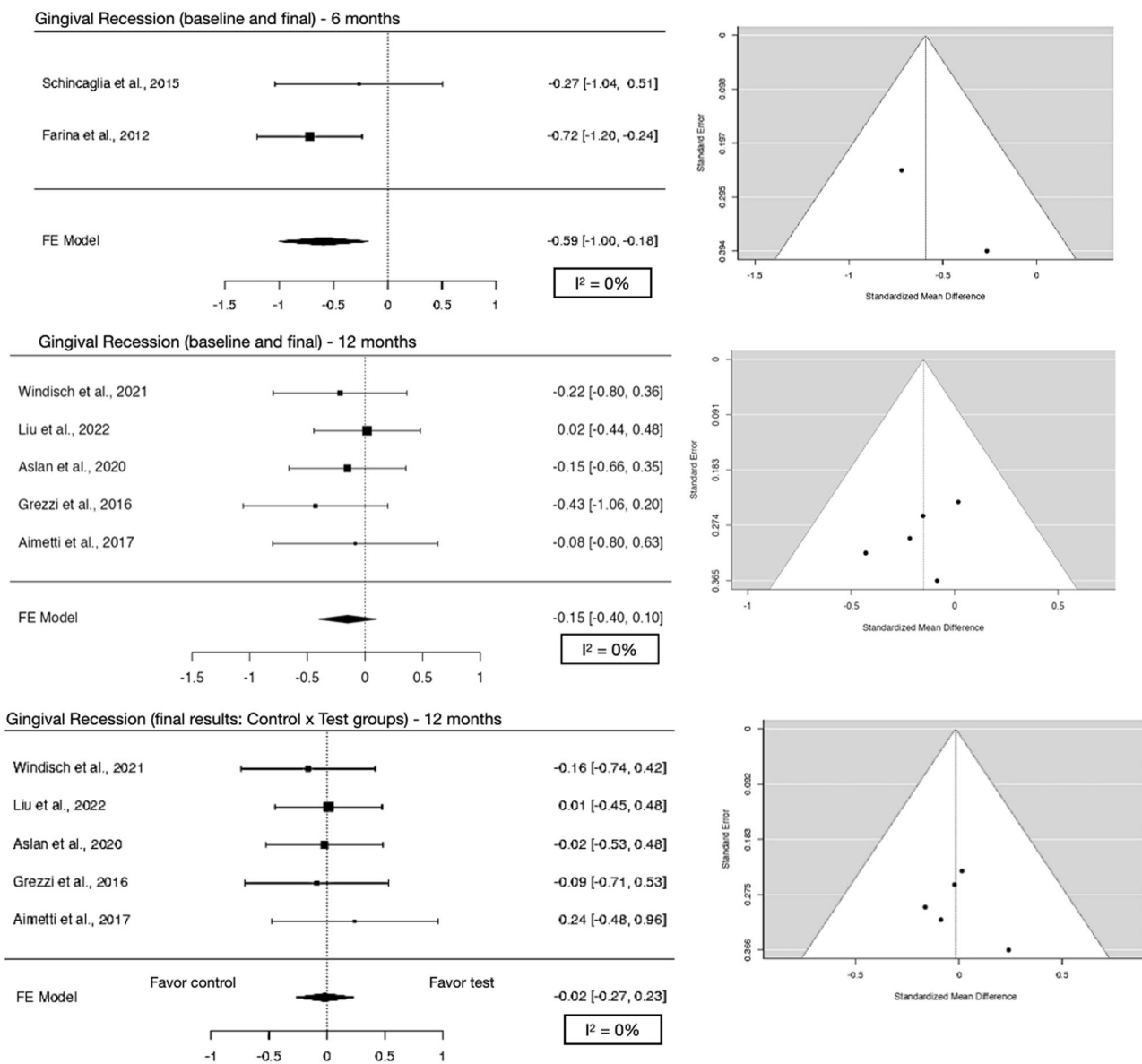


Fig. 6 Forest and funnel plots analyzing the GR in 6 and 12 months (initial and final results and final results compared among studies).

significance. On the other hand, comparing MIST with a modified suture against MIST with EMD²⁵, lower values were found for the group that used EMD. Moreover, in the most non-contained intrabony defects (79.3%) treated by means of EMD and papilla preservation flaps, a residual PD ≥ 6 mm was recorded after 12 months of follow-up³², at the same follow-up period, inferior data was presented by all other studies that used EMD, disagreeing of the Siciliano et al.'s results, with final mean PD ranging from 2.75 ± 0.75 mm to 4.31 ± 1.5 mm. For these reasons, non-contained intrabony defects were excluded from the present study.

The CAL gains observed in the included studies are compatible with the literature^{22,29,33}. Therefore, some studies had lower CAL gains, 2.54mm^{21} , while others had higher CAL gains, 6.83mm^{15} . This discrepancy may be due to the defect selection (morphology of the intrabony defects), materials used, and professional experience. In the present review, statistically significant CAL gain and PD reduction were measured in each group at 6 or 12 months, with no statistically significant differences recorded between the control and test groups, with a slight deviation favoring the test groups, as observed in the forest plots. The surgical approach may explain the small variance in the difference found between groups.

A common finding in all studies and groups was a minimal gingival recession increase, except for using MIST modified in

sutures²⁵, with a non-significant recession coverage mean of 0.03 (± 1.19). This fact may be explained by the passive coronal displacement of the vestibular extension of the flap during suturing²⁰. The GR had no heterogeneity, and the statistical result showed a similar standard of minimal increase. In addition, the choice of suturing material can exert any undesirable effect, i.e., it may be hypothesized that 5-0 monofilament sutures have a higher tendency to cause more compression on the wound, which might influence the healing. Wound closure is normally ensured with 6-0 or 7-0 sutures^{4,6} for MIST or M-MIST. Nevertheless, there is insufficient evidence demonstrating a negative influence of the size of the sutures on the clinical outcomes obtained in intrabony defects after regenerative surgery.

Two essential factors to be observed as inclusion criteria are if the patient had any systemic condition or was a smoker. In this study, no patients with systemic problems were included. Three articles excluded smokers; the other 6 included 19 current and 4 former smokers. Favorably, no adverse event was reported considering the smoking condition.

As a limitation of the present study, we observed a lack of standards in comparing techniques and types of co-adjuvant biomaterials implemented (EMD, resorbable or non-resorbable membranes, and different kinds of bone grafts). Also, we analyzed different minimally invasive techniques, which had different

approaches and eligibility criteria, such as smokers. We included clinical studies with the presence of RCTs and CS; this fact can be considered a limitation due to the limited number of RCTs published on this topic. Moreover, some studies (RCTs) had two groups for comparison; otherwise, other studies (CS) did not have a control group. Another limitation was the date limitation, including articles published between 2012 and 2022. A last limitation found was the short-term analysis done in a great part of the studies, six months and one year; we suggested more studies with longer-term evaluation.

CONCLUSION

Within the limitation of this review, MIST, M-MIST, and papilla preservation techniques are an actual reality in the field of periodontal regeneration, depending on the esthetic site and facility/ability of the flap repositioning, suturing, and initial clinical parameters. RCTs have demonstrated their potential and efficacy to improve periodontal conditions of sites with intrabony defects. The null hypothesis raised was accepted. The improvements are consistently associated with minimal patient morbidity. The chair time required to perform such surgery is shorter than that required for conventional surgical approaches. Therefore, all data must be carefully analyzed because of heterogeneity among studies.

DATA AVAILABILITY

All data is available within the manuscript.

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AUTHOR CONTRIBUTIONS

EP, FC, DC, AM, AH, MHS, JCHF, and GVOF were responsible for the conceptualization and design of the project. EP, FC, and GVOF were responsible for the data collection. EP, FC, DC, AM, AH, MHS, JCHF, and GVOF were responsible for the analysis and interpretation of data. EP, FC, DC, AM, AH, MHS, JCHF, and GVOF participated in the investigation, data curation, and drafting of the manuscript and contributed to revising the manuscript. All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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