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SYSTEMATIC REVIEW

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Clinical performance of minimally invasive periodontal surgery in the treatment of infrabony defects: Systematic review and meta-analysis

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Abstract

Aim: To assess the effectiveness, in terms of clinical performance and patient perception, of minimally invasive periodontal surgeries (MIPSs), and to compare MIPSs to traditional surgery in the treatment of periodontal infrabony defects.

Materials and Methods: An electronic search and a manual search were carried out to identify studies investigating clinical (CAL, PPD, REC), radiographic (bone fill) and patient's centred (VAS) outcomes at least 6 months after MIPSs. A linear mixed-effect model was used for meta-analysis. Subgroup analyses were performed according to the study quality (RCT or case series). A meta-analysis assessing differences in clinical parameters between MIPSs and traditional flaps was also performed.

Results: Meta-analysis from the 18 included studies revealed a PPD reduction of 4.24 mm (95% CI = 3.79–4.69 mm), a CAL gain of 3.89 mm (95% CI = 3.42–4.35 mm), a REC increase of 0.44 mm (95% CI = 0.11–0.77 mm), a radiographic bone fill gain of 58.25% (95% CI = 42.30%–74.21%) and a VAS value of 1.16 (95% CI = 0.78–1.54). Based on 2 RCTs, MIPSs are more effective than traditional surgery for PPD reduction (0.93 mm, 95% CI = 1.71–0.15) and CAL gain (1 mm, 95% CI = 1.75–.24).

Conclusion: Minimally invasive periodontal surgeries may be considered for the treatment of periodontal infrabony defects. However, the real effect cannot be systematically evaluated due to the paucity of studies comparing MIPSs to traditional flap for periodontal reconstructive surgery.

KEYWORDS

meta-analysis, minimally invasive, periodontal regeneration, periodontal surgery

1 | INTRODUCTION

In recent years, the concept of “minimally invasive” has been utilized in the medical–surgical field, indicating procedures and techniques with the objective of reducing the surgical area with benefits in terms of healing time, postoperative pain and risk of infection.

The term "minimally invasive surgical (MIS) procedure" in periodontal regeneration was introduced by Harrel and Rees (1995, Harrel, 1998). The authors described a minimally invasive approach for the treatment of intra-osseous defects, utilizing an intra-sulcular incision, maintaining the entire inter-dental papilla and elevating minimal flaps to have access to the bone defect. This technique yields significant reduction in probing pocket depth and improvement in attachment level with little increase in recession (Harrel, Nunn, & Belling, 1999).

It has been widely reported in the literature that periodontal regeneration of intra-bony defects leads to clinical attachment

level (CAL) gain, with probing pocket depth (PPD) reduction and minimal recession (REC) (Trombelli, Heitz-Mayfield, Needleman, Moles, & Scabbia, 2002). For this objective, surgical approaches supported by the widest literature are guided tissue regeneration (Nyman, Lindhe, Karring, & Rylander, 1982), demineralized freeze-dried bone allografts (Bowers et al., 1989) and enamel matrix proteins (Heijl, Heden, Svardstrom, & Ostgren, 1997), as well as the combination therapy of these (Schallhorn & McClain 1988; Zucchelli, Amore, Montebugnoli, & Sanctis, 2003).

The surgical techniques leading to periodontal regeneration in the last decades have become increasingly more efficient due to the utilization of modified incisions, aiming to obtain the preservation of the inter-dental tissue. These techniques, namely papilla preservation techniques, are designed to maintain the integrity of the body of the papilla, performing incision on the palatal side (Takei, Han, Carranza, Kennedy, & Lekovic, 1985) or on the buccal site (Cortellini, Pini Prato, & Tonetti, 1995, 1999). These incisions are reported to allow for better wound closure, protection of the coagulum and first intention healing.

In order to further reduce flap dimension, healing time and patient discomfort, new techniques were introduced: Cortellini and Tonetti (2007b) proposed a minimally invasive surgical technique (MIST) in the treatment of deep intra-bony defects with the application of enamel matrix derivative, to improve wound stability and limit patient discomfort. 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) and by Trombelli, Farina, Franceschetti, and Minenna (2007); Trombelli, Farina, Franceschetti, and Calura (2009) with a single-flap approach (SFA) in conjunction with a bioabsorbable membrane and a graft biomaterial. Nevertheless, it should be emphasized that these last two techniques are only applicable in defects with an extension prevalent on the buccal or oral side and the limited access requires the use of high magnifications with adequate illumination and microsurgical instruments (Cortellini & Tonetti, 2005, 2009; Trombelli et al., 2007; Trombelli et al., 2009).

Minimally invasive periodontal surgeries (MIPSs) seem to offer better results, due to reduced invasiveness, chair time, biologic cost and patient morbidity (Cortellini, 2012). However, the effectiveness of MIPSs remains to be clarified in terms of clinical performance and patient perception and the effect of these techniques when compared to more traditional flap approaches.

Therefore, the first objective of this systematic review was to investigate the effectiveness of MIPSs, in terms of clinical, radiographic and patient-related outcomes. The second objective was to compare MIPSs to more traditional flap approaches.

Clinical Relevance

Scientific rationale for the study: To evaluate the clinical performance and patient perception of minimally invasive periodontal surgeries in the treatment of intra-bony defects and to compare the efficacy of these surgical techniques with more traditional flaps.

Principal findings: Minimally invasive periodontal surgeries are associated with good clinical, radiographic and patient-related outcomes. There is a paucity of studies investigating differences between the two different approaches.

Practical implications: Clinicians should bear in mind that in the treatment of intra-bony defects, minimally invasive periodontal surgeries may be considered, although the real effect versus a traditional surgery cannot be systematically evaluated.

2 | MATERIALS AND METHODS

2.1 | Protocol development

A detailed protocol was designed according to the PRISMA (Preferred Reporting Items Systematic Review and Meta-Analyses) statement (Moher, Liberati, Tetzlaff, & Altman, 2009), in order to systematically review the literature regarding minimally invasive surgery in different field of dentistry.

In the present manuscript, written according to the PRISMA checklist, only the scientific evidence of minimally invasive surgery in periodontal surgery in the treatment of infrabony defects was investigated.

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

2.2 | Statement of question

What is the effectiveness, in terms of clinical (PPD reduction, CAL gain, REC change), radiographic (bone fill) and patient-related (VAS scores) outcomes, of minimally invasive periodontal procedures for the treatment of infrabony defects in periodontally compromised patients?

What is the effect, in terms of clinical (PPD reduction, CAL gain, REC change), radiographic (bone fill) and patient-related (VAS scores) outcomes, of minimally invasive periodontal procedures for the treatment of infrabony defects in periodontally compromised patients, compared with traditional reconstructive periodontal surgery?

2.3 | Search strategy

According to the described protocol, an electronic research and a manual research were carried out to identify studies testing a minimally invasive surgery, as reported by the authors in the description of the operative procedure. The research in the electronic databases was supplemented by cross-checking the bibliographies of the included articles, relevant reviews and by a manual search in the principal journals in the field of periodontics, implantology, endodontics and oral surgery (British Journal of Oral and Maxillofacial Surgery, Clinical Implant Dentistry and

Related Research, Clinical Oral Implants Research, Clinical Oral Investigations, European Journal of Oral Implantology, Implant Dentistry, International Endodontic Journal, International Journal of Oral & Maxillofacial Implants, International Journal of Oral & Maxillofacial Surgery, International Journal of Periodontics & Restorative Dentistry, Journal of Clinical Periodontology, Journal of Endodontics, Journal of Oral and Maxillofacial Surgery, Journal of Oral Implantology, Journal of Periodontal & Implant Science, Journal of Periodontology) up to November 2017.

The research on MEDLINE, EMBASE and Cochrane Oral Health Group specialist trials was conducted using the following combination of MeSH terms and text words: (minimally invasive) AND ((periodontal) OR dental) AND (((surgery) OR procedure) OR implant).

Intervention: (minimally [All Fields] AND invasive [All Fields] AND Fields: (periodontal [All Fields] OR ("dental health services" [MeSH Terms] OR ("dental" [All Fields] AND "health" [All Fields] AND "services" [All Fields]) OR "dental health services" [All Fields] OR "dental" [All Fields]))) AND Procedures: (((("surgery" [Subheading] OR "surgery" [All Fields] OR "surgical procedures, operative" [MeSH Terms] OR ("surgical" [All Fields] AND "procedures" [All Fields] AND "operative" [All Fields]) OR "operative surgical procedures" [All Fields] OR "surgery" [All Fields] OR "general surgery" [MeSH Terms] OR ("general" [All Fields] AND "surgery" [All Fields]) OR "general surgery" [All Fields]) OR ("methods" [MeSH Terms] OR "methods" [All Fields] OR "procedure" [All Fields])) OR implant [All Fields]).

Inclusion criteria:

- Human studies,
- Publications in English,
- Studies describing a "minimally invasive" surgical procedure in the field of periodontal surgery, bone augmentation, sinus lifting, implant placement and endodontic surgery. The definition used for minimally invasive surgery was as follows: every surgical intervention described as "minimally invasive," and
- 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.

Exclusion criteria:

- Publications reporting data of previous publications by the same authors and
- Case reports and narrative reviews.

In this manuscript, studies investigating clinical (CAL, PPD, REC), radiographic (bone fill) and patient-centred (VAS) outcomes at least 6 months after a minimally invasive periodontal surgery were included.

2.4 | Selection criteria

Initially, titles and abstracts of all reports will be screened independently by two reviewers (V.C. and V.D.R.). 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 (V.C. and V.D.R.). Any disagreement will be resolved by discussion with a third reviewer (M.C.). 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.

For the current systematic review and meta-analysis, only studies investigating a minimally invasive periodontal surgery in the treatment of infrabony defects have been evaluated.

2.5 | Data extraction and data synthesis

Two reviewers (V.C. and V.D.R.) independently extracted the data using specially designed data extraction forms. A table was created, for every field of application, with the following data for the included studies:

- Author, title, year
- Design and setting
- Number of participants (male/female, average age, age range, smokers/non-smokers)
- Details of treatment techniques
- Follow-up
- Outcomes [clinical (ΔPPD, ΔREC, ΔCAL), radiographic (bone fill) and patient's centred (VAS values)]

Authors of studies were contacted for clarification or missing information. Data were excluded until further clarification was available or if an agreement was not reached. When the results of a study were published more than once or results were detailed in a number of publications, the most complete data set was sought from all sources and included only once. The level of agreement between the two reviewers was calculated using Kappa statistics.

2.6 | Quality assessment

The quality assessment of the included studies was undertaken independently by two reviewers (V.C. and V.D.R.) based on the content of the articles (Needleman, Moles, & Worthington, 2000), using two quality assessment methods. The randomized controlled clinical trials were assessed by a commonly used three-item, five-point quality scale (Jadad et al., 1996). Trials were allocated a score between 0 (very poor) and 5 (rigorous). The cohort studies were assessed according to the Newcastle–Ottawa scale (Wells, O'Connell, Robertson, Peterson, & Welch, 2001), with a score from 0 to 9. The evidence level of the study was also assessed according to Oxford Centre for Evidence-Based Medicine recommendation (2009). A separate scoring for quality assessment was

obtained and independently assessed by two reviewers (V.C. and V.D.R.) to establish whether the study met the quality criteria in order to reduce the risk of bias. Any disagreement was resolved by discussion with a third reviewer (M.C.) in order to reach a consensus. The level of agreement between the two reviewers was calculated using Kappa statistics.

2.7 | Data analysis

Data from the selected studies were processed for analysis. Mean values and standard deviations will be extracted, with regard to clinical, radiographic and patient-centred outcomes. For dichotomous outcomes, the estimates will be expressed as relative risk ratio (RR) together with 95% CI. For continuous outcomes, standardized mean differences and 95% confidence intervals will be used to summarize the data for each study. Forest plots will be created to illustrate the effects of the different studies and the global estimation. SPSS Statistics TM software and custom procedures in R environment (ver. 3.5.2, www.r-project.org) will be used to perform all analyses. Statistical significance has been defined as a p value < 0.05.

Sensitivity analysis was performed excluding each of the studies step by step from the meta-analysis and evaluating the changes in the global estimation. The publication bias was evaluated using a funnel plot and Egger's linear regression method.

The Cochrane Q test was performed to assess the degree of heterogeneity between studies, and the I^2 statistic was used to describe the percentage of total variation across studies due to heterogeneity. Then, a linear mixed-effect model (Woolf's method) was fitted. In order to evaluate the possible variables causing heterogeneity, subgroup analysis was conducted.

3 | RESULTS

3.1 | Search results

The combined electronic and manual original research resulted in 1,338 papers. After title and abstract screening, 1,181 publications were excluded for incorrect topic or language. After full-text analysis, 50 articles were excluded on the basis of the inclusion criteria (Table S1). The remaining 106 papers fulfilling the inclusion criteria were processed for data extraction. Of these, only 25 papers reported data regarding studies investigating a minimally invasive periodontal surgery in the treatment of infrabony defects were selected for this manuscript. Corresponding author of the study, Schincaglia, Hebert, Farina, Simonelli, and Trombelli (2015), was contacted for clarification on reported VAS data. Eighteen studies were included in meta-analysis.

3.2 | Assessment of heterogeneity

The selected studies showed a considerable heterogeneity, and these characteristics are presented in Table 1.

3.2.1 | Study design and follow-up

Of the selected studies, 10 were randomized clinical trials (Aimetti, Ferrarotti, Mariani, & Romano, 2017, Cortellini, 2012, Ghezzi, Ferrantino, Bernardini, Lencioni, & Masiero, 2016, Mishra, Avula, Pathakota, & Avula, 2013, Ribeiro, Casarin, Palma, et al., 2011a, Ribeiro et al., 2013, Ribeiro, Casarin, Palma, et al., 2011b, Schincaglia et al., 2015, Trombelli, Simonelli, Pramstraller, Wikesjö, & Farina, 2010, Trombelli, Simonelli, Schincaglia, Cucchi, & Farina, 2012). All of them had a parallel design. Among these, five compared different techniques (Aimetti et al., 2017, Ribeiro, Casarin, Palma, et al., 2011b, Ribeiro et al., 2013, Schincaglia et al., 2015 and Trombelli et al., 2012), while the other five compared the role of different biomaterials with the same surgical technique. Remaining fifteen studies were case series (Cortellini, Nieri, Prato, & Tonetti, 2008; Cortellini, Pini Prato, Nieri, & Tonetti, 2009; Cortellini et al., 2009; Cortellini & Tonetti, 2007a, 2007b; Cortellini & Tonetti, 2007a, 2007b; Cosyn, Cleymaet, Hanselaer, & Bruyn, 2012; De Bruyckere et al., 2017; Harrel, 1998; Harrel, Abraham, Rivera-Hidalgo, Shulman, & Nunn, 2014, 2016; Harrel et al., 2017, 1999; Harrel, Wilson, & Nunn, 2005, 2010; Ribeiro, Nociti Júnior, Sallum, Sallum, & Casati, 2010; Trombelli et al., 2009). Of these, only two are retrospective (Harrel, 1998 and Harrel et al., 1999). Follow-up periods ranged between 6 months and 6 years.

3.2.2 | Population

The studies included a number of subjects ranging between 10 and 87. Only one study did not report the mean age of patients (Harrel, Wilson, & Nunn, 2005), while eleven did not report the age range of subjects (Aimetti et al., 2017, Ghezzi et al., 2016, Harrel et al., 1999, Harrel, Wilson, & Nunn, 2010, Harrel et al., 2005, Ribeiro, Casarin, Palma, et al., 2011a, Ribeiro et al., 2013, Ribeiro, Casarin, Palma, et al., 2011b, Ribeiro et al., 2010, Schincaglia et al., 2015, Trombelli et al., 2010). The overall age range of subjects analysed is 25–79 years. Only Harrel et al. (2005) did not report information about gender. Regarding smokers status, three studies included light (<10/die) and former smokers (Cortellini et al., 2008, Cortellini & Tonetti, 2007a, 2007b; Cortellini et al., 2009 and Ghezzi et al., 2016). Other four included smokers (Trombelli et al., 2009; Trombelli et al., 2010; Trombelli et al., 2012 and Schincaglia et al., 2015). Five studies did not report the smoking status of the participants (Harrel, 1998, 2005; Harrel, Abraham, Rivera-Hidalgo, Shulman, & Nunn, 2014; Harrel et al., 2017, 1999). In the remaining, fourteen smokers were excluded.

3.2.3 | Interventions and defect characteristics

The examined surgical techniques have many aspects in common. However, it is possible to detect some differences considering the indications and description given by each author.

A minimally invasive surgery (MIS) was used in four studies by the same authors (Harrel, 1998; Harrel et al., 1999, 2005, 2010).

TABLE 1 Characteristics of included studies

Authors	Title	Study design/ setting	Study group(s) (male/ female, average age, age range, smokers/ non-smoker)	Treatment(s)	Follow-up	Clinical/radiological outcomes	Patient's related outcomes
Aimetti et al., (2017)	"A Novel Flapless Approach versus Minimally Invasive Surgery in Periodontal Regeneration with Enamel Matrix Derivative Proteins: A 24-Month Randomized Controlled Clinical Trial."	RCT/ university	G1 (control): 15 (10/5, 44.3 ± 8.1 years, 0/15) G2 (test): 15 (8/7, 42.2 ± 6.1 years, 0/15)	G1: flapless debridement + EMD G2: MIST + EMD	24 m	Radiographic bone fill, PD reduction, CAL gain, REC, chair time	VAS discomfort/pain perceived at time of surgery and at 1 week
Cortellini et al., (2008)	"Single Minimally Invasive Surgical Technique with an Enamel Matrix Derivative to Treat Multiple Adjacent Intra-Bony Defects: Clinical Outcomes and Patient Morbidity."	Case series/ private practice	20 (6/14, 49.7 ± 8.3 years, 35–63, 0/20)	MIST + EMD	12 m	CAL, defect resolution, PD, REC	VAS
Cortellini & Tonetti, 2007a, 2007b; Cortellini et al., (2009)	"Minimally Invasive Surgical Technique and Enamel Matrix Derivative in Intra-Bony Defects. I: Clinical Outcomes and Morbidity." AND "Minimally Invasive Surgical Technique and Enamel Matrix Derivative in Intrabony Defects: 2. Factors Associated with Healing Outcomes."	Case series/ private practice	40 (14/26, 48.3 ± 9.8 years, 31–74, 5/35)	MIST + EMD	12 m	CAL gain, PD, REC, defect resolution	VAS
Cortellini & Tonetti, 2007a, 2007b	"A Minimally Invasive Surgical Technique with an Enamel Matrix Derivative in the Regenerative Treatment of Intra-Bony Defects: A Novel Approach to Limit Morbidity."	Case series/ private practice	13 (4/9, 43.1 ± 9.8 years, 34–63, 0/13)	MIST + EMD	12 m	PD, REC, CAL gain, defect resolution	NA
Cortellini et al., (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."	RCT/ private practice	45 (25/20, 49.86 years, 28–71, 0/45)	1) M-MIST 2) M-MIST + EMD 3) M-MIST + BMDX	12 m	REC, PD, CAL gain, bone fill, bone gain, surgical time	VAS discomfort
Cortellini et al., (2009)	"Improved Wound Stability with a Modified Minimally Invasive Surgical Technique in the Regenerative Treatment of Isolated Interdental Intrabony Defects."	Case series/ private practice	20 (8/12, 48.1 ± 10.4, 31–65, 0/15)	M-MIST	12 m	REC, PD, CAL, surgical time	NA
Cosyn et al., (2012)	"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."	Case series/ private practice and university	84 (39/45, 53 years, 28–79, 0/84)	MIST/M-MIST + BMDX	12 m	PD, CAL, bone fill, REC, PES	NA

(Continues)

TABLE 1 (Continued)

Authors	Title	Study design/ setting	Study group(s) (male/ female, average age, age range, smokers/ non-smoker)	Treatment(s)	Follow-up	Clinical/radiological outcomes	Patient's related outcomes
De Bruyckere et al., (2017)	"A 5-Year Prospective Study on Regenerative Periodontal Therapy of Infrabony Defects Using Minimally Invasive Surgery and a Collagen-Enriched Bovine-Derived Xenograft."	Case series/ private practice and university	84 (39/45, 53 years, 0/84)	MIST/M-MIST + collagen BMDX	5 y	PD, CAL, bone fill	NA
Ghezzi et al., (2016)	"Minimally Invasive Surgical Technique in Periodontal Regeneration: A Randomized Controlled Clinical Trial Pilot Study."	RCT/ private practice	20 (9/11, 54 ± 9 years, 34–68, na)	TEST: MIST + DBBM+resorbable membrane CONTROL: MIST + DBBM	12 m	CAL gain, PD, REC	NA
Harrel (1998)	"A Minimally Invasive Surgical Approach for Periodontal Bone Grafting."	Case series/ private practice	10 (5/5, 51, 8 years, 36–70, 0/10)	MIS	25 m	PD, CAL, mobility, teeth loss	NA
Harrel et al., (1999)	"Long-Term Results of a Minimally Invasive Surgical Approach for Bone Grafting."	Case series/ private practice	87 (43/44, 53.8 years, 0/87)	MIS	22 m	PD, CAL, prognosis	NA
Harrel et al., (2016)	"Videoscope-Assisted Minimally Invasive Periodontal Surgery: One-Year Outcome and Patient Morbidity."	Case series/ private practice	18 (6/12, 54.6 ± 11.6, 38–75, 0/18)	V-MIS	12 m	PD, CAL, REC	VAS
Harrel et al., (2014)	"Videoscope-Assisted Minimally Invasive Periodontal Surgery (V-MIS)."	Case series/ university	30 (7/23, 53.9 ± 9.8, 38–75)	V-MIS	6 m	PD, CAL, REC	NA
Harrel et al., (2017)	"Videoscope Assisted Minimally Invasive Surgery (VMIS): 36-Month Results."	Case series/ university	14 (5/9, 57 years, 38–75 years)	V-MIS	36 m	PD, CAL, REC	VAS
Harrel et al., (2010)	"Prospective Assessment of the Use of Enamel Matrix Derivative with Minimally Invasive Surgery: 6-Year Results."	Case series/ private practice	13 (8/5, 63.5 years, 0/13)	MIS	6 y	PD, CAL, REC	NA
Harrel et al., (2005)	"Prospective Assessment of the Use of Enamel Matrix Proteins with Minimally Invasive Surgery."	Case series/ private practice	16	MIS + EMD	11 m	PD, CAL, REC	NA
Mishra et al., (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"	RCT/ university	24 (12/12, 25–50, 0/24)	TEST: M-MIST + rhPDGF-BB CONTROL: M-MIST	6 m	CAL, lineal bone growth, PD, REC, defect depth, alveolar crest position, bone fill, FMPS, FMBS, MGI	NA
Ribeiro, Casarin, Palma, et al., (2011b)	"The Role of Enamel Matrix Derivative Protein in Minimally Invasive Surgery in Treating Intrabony Defects in Single-Rooted Teeth: A Randomized Clinical Trial."	RCT/ university	29 (11/19, 47.10 ± 6.89 years, 0/29)	TEST: MIST + EMD CONTROL:MIST	6 m	CAL, PD, GM, FMPS, FMBS, GCF markers, RX parameters	NA

(Continues)

TABLE 1 (Continued)

Authors	Title	Study design/ setting	Study group(s) (male/ female, average age, age range, smokers/ non-smoker)	Treatment(s)	Follow-up	Clinical/radiological outcomes	Patient's related outcomes
Ribeiro et al., (2013)	"Clinical and Microbiological Changes after Minimally Invasive Therapeutic Approaches in Intrabony Defects: A 12-Month Follow-Up."	RCT/ University	27 (10/17, 45, 37 years, 0/27)	TEST:MIST CONTROL: MINST	12 m	CAL, PD, GM, FMPS, FMBS, microbiological outcomes	NA
Ribeiro, Casarin, Palma, et al., 2011b	"Clinical and Patient-Centered Outcomes after Minimally Invasive Non-Surgical or Surgical Approaches for the Treatment of Intrabony Defects: A Randomized Clinical Trial."	RCT/ university	27 (10/17, 45.37 years, 0/27)	TEST:MIST CONTROL: MINST	6 m	CAL, PD, GM, FMPS, FMBS, chair time	VAS, patient satisfaction
Ribeiro et al., (2010)	"Use of Enamel Matrix Protein Derivative with Minimally Invasive Surgical Approach in Intra-Bony Periodontal Defects: Clinical and Patient-Centered Outcomes."	Case series/ university	12 (5/7, 47.4 ± 7 years, 0/12)	MIST + EMD	6 m	GM, PD, CAL, FMPS, FMBS	VAS
Schincaglia et al., (2015)	"Single versus double flap approach in periodontal regenerative treatment"	RCT/ university	T: 15 (9/6, 50.1 ± 14.8, 3/12) C: 13 (8/5, 46.7 ± 15.4, 0/13)	TEST: SFA + rhPDGF-BB + b-TCP CONTROL: DFA + rhPDGF-BB + b-TCP	6 m	PD, CAL, REC, linear defect fill, bleeding score	VAS
Trombelli et al., (2009)	"Single-Flap Approach with Buccal Access in Periodontal Reconstructive Procedures."	case series/ university	10 (8/2, 44.2 ± 8.7 years, 30–60, 2/8)	SFA + HA+collagen	10 ± 3 m	CAL, PD, REC, BOP	NA
Trombelli et al., (2010)	"Single Flap Approach with and without Guided Tissue Regeneration and a Hydroxyapatite Biomaterial in the Management of Intraosseous Periodontal Defects."	RCT/ university	24 (17/7, 50.95 years, 2/22)	TEST: SFA + HA+GTR CONTROL: SFA	6 m	CAL, PD, REC, BOP, EHI	NA
Trombelli et al., (2012)	"Single-Flap Approach for Surgical Debridement of Deep Intraosseous Defects: A Randomized Controlled Trial."	RCT/ university	28 (17/11, 49y, 36–62, 6/22)	TEST: SFA CONTROL: DFA	6 m	CAL, PD, REC, BOP	NA

Abbreviations: BOP, bleeding on probing; b-TCP, beta tricalcium phosphate; CAL, clinical attachment level; collagen BMDX, collagen-enriched bovine-derived xenograft; DBBM, derived bovine bone mineral; DFA, double-flap approach; EMD, enamel matrix derivative; FMPS/FMBS, full-mouth plaque/bleeding score; GTR, guided tissue regeneration; HA, hydroxyapatite; MINST, minimally invasive non-surgical technique; MIS, minimally invasive surgery; MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique; NA, not applicable; PD, probing depth; REC, recession; rhPDGF-BB, recombinant human platelet-derived growth factor; SFA, single-flap approach; V-MIS, videoscope-assisted minimally invasive surgery.

TABLE 2 Clinical, radiographic and patient's centred outcomes of included studies

Study	Study_ Design	Follow-up (months)	Study_ group (1/0)	*N* patients	Clinical_outcomes baseline			Clinical_outcomes			Bone fill %	VAS
					PD (mm)	Rec (mm)	CAL (mm)	Δ PD (mm)	Δ Rec (mm)	Δ CAL (mm)		
Aimetti et al. (2017)	RCT	24 m	0	15	7.5 ± 0.9	#	9.4 ± 2.0	3.6 ± 1.0	0.4 ± 0.7	3.2 ± 1.1	#	Procedure day 0.9 ± 1.1 1 week 1.1 ± 1.7
Aimetti et al. (2017)	RCT	24 m	1	15	7.3 ± 0.8	#	9.0 ± 1.7	3.7 ± 0.6	0.1 ± 0.5	3.6 ± 0.9	#	Procedure day 0.6 ± 0.9 1 week 0.8 ± 1.1
Cortellini et al., (2008)	CS	12 m	1	20 (44)	7.1 ± 1.4	1.6 ± 1.0	8.7 ± 1.7	−4.6 ± 1.3	0.2 ± 0.6	4.4 ± 1.4	#	Pain 19 ± 9 discomfort 21 ± 10 perception of hardship of surgical procedure 24 ± 12
Cortellini & Tonetti, 2007a, 2007b; Cortellini et al., (2009)	CS	12 m	1	40 (40)	8,2 ± 1.9	1.8 ± 1.6	10 ± 2.9	−5.2 ± 1.7	0.4 ± 0.7	4.9 ± 1.7	77.6 ± 21.9	Pain 19 ± 10 perception of hardship of surgical procedure 7 ± 12
Cortellini & Tonetti, 2007a, 2007b	CS	12 m	1	13 (13)	7.7 ± 1.8	1.0 ± 1.5	8.7 ± 2.7	−4.8 ± 1.8	−0.1 ± 0.9	4.8 ± 1.9	88.7 ± 20.7	#
Cortellini et al., (2011)	RCT	12 m	0	15	7.5 ± 1.6	2.1 ± 1.4	9.6 ± 2.0	−4.4 ± 1.6	0.3 ± 0.6	4.1 ± 1.4	77 ± 19	10.7 ± 2.1
Cortellini et al., (2011)	RCT	12 m	1	15	7.8 ± 0.9	2.1 ± 1.4	9.9 ± 1.3	−4.4 ± 1.2	0.3 ± 0.5	4.1 ± 1.2	71 ± 18	11.7 ± 0.7
Cortellini et al., (2011)	RCT	12m	2	15	7.3 ± 1.2	2.9 ± 1.8	10.1 ± 2.4	−4.0 ± 1.3	0.3 ± 0.7	3.7 ± 1.3	78 ± 27	12.3 ± 3.1
Cortellini et al., (2009)	CS	12 m	1	15	7.7 ± 1.5	2.0 ± 1.3	9.7 ± 1.8	−4.6 ± 1.5 c	0.1 ± 0.3	4.5 ± 1.4	#	#
Cosyn et al., (2012)	CS	12 m	1	84	7.8 ± 1.5	2.2 ± 1.5	10 ± 2.3	−3.5 ± 1.6	mf 0.5 ± 0.7 id 0.3 ± 0.7	3.1 ± 1.6	53 ± 35	#
De Bruyckere et al., (2017)	CS	60 m	1	84	7.8 ± 1.5	2.2 ± 1.5	10 ± 2.3	−3.3 ± 2.2	0.15 ± 0.9	3.0 ± 2.1	#	#
Ghezzi et al., (2016)	RCT	12 m	1	10	8.2 ± 1.3	1.0 ± 1.1	9.2 ± 1.9	−4.9 ± 1.2	0.5 ± 0.85	4.4 ± 1.17	#	#
Ghezzi et al., (2016)	RCT	12 m	2	10	7.8 ± 2.4	0.7 ± 0.67	8.5 ± 2.2	−4.7 ± 2.36	0.7 ± 0.95	4.0 ± 1.82	#	#
Harrel (1998)	CS	25 m	1	10	7.2	#	10	−4.1	#	4.2	#	#
Harrel (1999)	CS	21 m	1	87 (194)	#	#	#	−4.58	#	4.87	#	#
Harrel et al., (2016)	CS	12 m	1	18	6.41 ± 0.70	0.78 ± 0.94	7.19 ± 1.17	−4.11 ± 0.98	−0.48 ± 0.65	4.58 ± 1.19	#	0.8 (2w)
Harrel et al., (2014)	CS	6 m	1	30	4.3 ± 0.5	0.7 ± 0.72	5.0 ± 0.7	−3.88 ± 1.02	−0.13 ± 0.61	4.04 ± 1.38	#	#
Harrel et al., (2017)	CS	36 m	1	14	6.42 ± 0.73	0.70 ± 0.96	7.13 ± 1.04	−3.80 ± 1.18	−0.36 ± 0.64	4.16 ± 1.18	#	#
Harrel et al., (2010)	CS	72	1	13 (142)	6.6 ± 1.3	1.0 ± 1.2	7.5 ± 1.7	−3.78 ± 2.12	−0.08 ± 1.28	3.70 ± 1.15	#	#

(Continues)

TABLE 2 (Continued)

Study	Study_ Design	Follow-up (months)	Study_ group (1/0)	*N* patients	Clinical_outcomes baseline			Clinical_outcomes			Bone fill %	VAS
					PD (mm)	Rec (mm)	CAL (mm)	Δ PD (mm)	Δ Rec (mm)	Δ CAL (mm)		
Harrel et al., (2005)	CS	11m	1	16 (160)	6.61 ± 1.73	#	7.73 ± 1.95	−3.56 ± 1.31	−0.01	3.57 ± 1.75	#	#
Mishra et al., (2013)	RCT	6m	1	12 (15)	7.73 ± 1.19	0.18 ± 0.40	7.36 ± 1.3	−4.18 ± 0.60	0.82 ± 0.60	3.00 ± 0.89	36.20 ± 17.74	#
Mishra et al., (2013)	RCT	6m	0	12 (16)	7.64 ± 0.67	0 ± 0	6.91 ± 0.7	−3.82 ± 0.87	0.55 ± 0.52	2.64 ± 0.67	35.02 ± 10.99	#
Ribeiro, Casarin, Palma, et al., (2011a)	RCT	6 m	1	14	7.1 ± 1.7	5.3 ± 1.9	12.2 ± 2.0	−3.56 ± 2.07	0.46 ± 0.87	3.02 ± 1.94	#	#
Ribeiro, Casarin, Palma, et al., (2011a)	RCT	6 m	0	15	7.1 ± 1.1	3.9 ± 1.46	11.0 ± 1.9	−3.5 ± 0.88	0.54 ± 0.58	2.82 ± 1.19	#	#
Ribeiro et al., (2013)	RCT	12m	1	14	7.1 ± 1.1	3.7 ± 1.1	10.7 ± 1.5	−3.50 ± 0.87	0.59 ± 0.6	2.8 ± 1.14	#	#
Ribeiro et al., 2013	RCT	12 m	0	13	6.3 ± 0.9	4.96 ± 1.66	11.2 ± 2.1	−3.19 ± 0.71	0.58 ± 0.83	2.58 ± 1.13	#	#
Ribeiro, Casarin, Palma, et al., (2011b)	RCT	6 m	1	14	7.1 ± 1.1	3.7 ± 1.1	10.7 ± 1.5	−3.51 ± 0.90	0.48 ± 0.51	2.85 ± 1.19	#	Pain TO: 0.54 ± 0.81 pain T1: 0.48 ± 0.89 very satisfied: 92.85% satisfied: 7.15%
Ribeiro, Casarin, Palma, et al., (2011b)	RCT	6m	0	13	6.3 ± 0.9	4.96 ± 1.66	11.2 ± 2.1	−3.13 ± 0.67	0.45 ± 0.46	2.56 ± 1.12	#	Pain TO: 0.48 ± 0.66 pain T1: 0.38 ± 0.63 very satisfied: 92.30% satisfied: 7.7%
Ribeiro et al., (2010)	CS	6 m	1	12	7.2 ± 1.67	5.0 ± 1.89	12.1 ± 2.2	−3.63 ± 2.23	0.94 ± 1.59	3.10 ± 2.02	#	Satisfaction: very satisfied 100% pain T0 5.68 ± 7.33
Schincaglia et al., (2015)	RCT	6 m	0	13	8.7 ± 2.0	1.1 ± 1.3	9.7 ± 2.5	−4.1 ± 1.7	0.1 ± 0.7	4.0 ± 1.9	2.0 ± 2.3	Pain day 7:13.2 ± 27.7
Schincaglia et al., (2015)	RCT	6 m	1	15	7.7 ± 1.5	0.8 ± 1.3	8.5 ± 1.6	−3.6 ± 1.1	0.4 ± 1.3	3.2 ± 1.4	2.0 ± 1.3	Pain day 7:1.0 ± 2.1
Trombelli et al., (2009)	CS	10 m	1	10	9.0 ± 2.8	2.2 ± 1.9	11.2 ± 2.6	−5.2 ± 2.6	0.4 ± 1.5	4.8 ± 2.7	#	#
Trombelli et al., (2010)	RCT	6 m	1	12	9.1 ± 2.6	2.1 ± 1.7	11.4 ± 2.4	−5.3 ± 2.4	0.4 ± 1.4	4.7 ± 2.5	#	#
Trombelli et al., (2010)	RCT	6 m	0	12	8.5 ± 1.8	0.7 ± 0.9	9.2 ± 2.4	−5.3 ± 1.5	0.8 ± 0.8	4.4 ± 1.5	#	#
Trombelli et al., (2012)	RCT	6 m	1	14	8.7 ± 1.7	0.7 ± 0.8	9.4 ± 2.1	−5.2 ± 1.6	0.7 ± 0.8	4.5 ± 1.1	#	#
Trombelli et al., (2012)	RCT	6m	0	14	7.4 ± 1.2	0.9 ± 1.0	8.4 ± 1.7	−3.9 ± 1.1	0.5 ± 1.1	3.4 ± 1.4	#	#

Abbreviations: CS, case series; 0, 1, 2, etc. (4° column): test/control groups; RCT, randomized clinical trial.

It is characterized by very small split-thickness incisions and sharp dissection of the tissue that do not extend beyond the immediate area of bone loss and help retain the graft material placed in the defect; flap is then replaced at or coronal to the pre-surgical position and closed with a vertical mattress suture. MIS was best suited for a moderately broad, isolated inter-proximal defect with little or no extension of bone loss to the buccal or lingual aspects.

The same authors used in three studies (Harrel et al., 2014, 2017; Harrel, Abraham, Rivera-Hidalgo, Shulman, & Nunn, 2016) a videoscope-assisted minimally invasive surgery (V-MIS), a MIS performed only at one single side (buccal or lingual) with the aid of a videoscope placed in the surgical site.

The minimally invasive surgical technique (MIST) was used in eleven studies by different authors (Aimetti et al., 2017; Cortelini et al., 2008; Cortellini et al., 2009; Cortellini & Tonetti, 2007a, 2007b; Cortellini & Tonetti, 2007a, 2007b; Cosyn et al., 2012; De Bruyckere et al., 2017; Ghezzi et al., 2016; Ribeiro, Casarin, Palma, et al., 2011a; Ribeiro, Casarin, Palma, et al., 2011b; Ribeiro et al., 2013, 2010), with the aid of an operating microscope. It consists of an envelope full-thickness flap extended to the buccal and lingual aspects of the two teeth adjacent to the defect to expose 1–2 mm of the residual bone crest; flaps are then repositioned without any coronal displacement, and the suturing approach consists of a single modified internal mattress suture. This approach embraced pure three-wall inter-proximal defects, with two- and/or one-wall subcomponents.

The subsequent modified minimally invasive surgical technique (M-MIST), used in five studies by different authors (Cortellini et al., 2009; Cortellini & Tonetti, 2011; Cosyn et al., 2012; De Bruyckere et al., 2017; Mishra et al., 2013), differs in the absence of inter-dental and/or lingual incisions, leaving and no displacing the supracrestal inter-dental tissues; the mesiodistal flap extension involved only the defect-associated papilla and part of the buccal aspects of the two teeth neighbouring the defect.

A single-flap approach (SFA) was used in four studies by the same authors (Schincaglia et al., 2015, Trombelli et al., 2009; Trombelli et al., 2010; Trombelli et al., 2012) with the aid of magnifying loupes. It consists of an envelope full-thickness flap only on the defect side, whose mesiodistal extension must guarantee proper access to defect and graft/membrane positioning; split thickness is allowed for the flap replacement without tension, and horizontal internal mattress suture is used. SFA was indicated for intra-osseous defects characterized by an extension prevalent on the buccal side.

A minimally invasive non-surgical technique or a flapless approach, used as control group in three studies by different authors investigating a MIPS (Aimetti et al., 2017; Ribeiro, Casarin, Palma, et al., 2011b; Ribeiro et al., 2013), was characterized by a flapless scaling and root planing with mini-curettes and ultrasonic devices with specific thin and delicate tips.

Regarding the use of grafts, these were tested in fourteen studies (Aimetti et al., 2017, Cortellini et al., 2008, Cortellini & Tonetti, 2007a, 2007b; Cortellini et al., 2009, Cortellini & Tonetti, 2011, Cosyn et al., 2012, De Bruyckere et al., 2017, Ghezzi et al., 2016, Harrel et al., 2005, Ribeiro, Casarin, Palma, et al., 2011a, Ribeiro et al., 2010, Schincaglia et al., 2015, Trombelli et al., 2009, Trombelli et al., 2010) (for details, see Table 1).

More details on baseline characteristics of the sample defects are shown in Table 2.

Between RCTs, two studies (Trombelli et al., 2012, Schincaglia et al. 2015) compared a single-flap approach (SFA) with a double-flap approach (DFA), three studies (Aimetti et al., 2017; Ribeiro, Casarin, Palma, et al., 2011b; Ribeiro et al., 2013) compared a minimally invasive surgical technique with a minimally invasive non-surgical technique or flapless approach and the other five compared the use of different grafts or biologic agents with the same flap design (Cortellini & Tonetti, 2011; Ghezzi et al., 2016; Mishra et al., 2013; Ribeiro, Casarin, Palma, et al., 2011a; Trombelli et al., 2010).

3.2.4 | Outcomes

Data regarding clinical measurements (PPD reduction, CAL gain, REC change), radiographic bone fill and patient's reported outcomes were extracted from selected studies. All studies assessed PPD reduction and CAL gain. Only two studies did not asses REC change (Harrel, 1998 and Harrel et al., 1999). In three studies, data about radiographic bone fill were recorded (Cortellini & Tonetti, 2011; Cosyn et al., 2012; Mishra et al., 2013).

In nine studies (Aimetti et al., 2017; Cortellini et al., 2008; Cortellini et al., 2009; Cortellini & Tonetti, 2007a, 2007b; Cortellini & Tonetti, 2011; Harrel et al., 2016; Harrel et al., 2017; Ribeiro, Casarin, Palma, et al., 2011b; Ribeiro et al., 2010 and Schincaglia et al. 2015), patients received a 100-mm horizontal visual analog scale (VAS) to note their experience of pain/discomfort.

3.3 | Assessment of quality

Assessment of quality is presented in Table S2. For RCTs, the JADAD score was recorded. Four studies out of ten RCTs (Mishra et al., 2013, Schincaglia et al. 2015, Trombelli et al., 2010, Trombelli et al., 2012) scored 5, four studies (Aimetti et al., 2017; Ghezzi et al., 2016; Ribeiro, Casarin, Palma, et al., 2011a; Ribeiro, Casarin, Palma, et al., 2011b) scored 3 and only two studies (Cortellini & Tonetti, 2011 and Ribeiro et al., 2013) scored 2. For case series, Newcastle–Ottawa score was recorded. Only Ribeiro et al., 2010 scored 3, three scored 4 (Harrel, 1998, Harrel et al., 2014 and Harrel et al., 2005) and two scored 5 (Harrel et al., 1999 and Trombelli et al., 2009). All other studies scored 6 (Cortellini et al., 2008, 2009; Cortellini & Tonetti, 2007a, 2007b; Cosyn et al., 2012; De Bruyckere et al., 2017; Harrel et al., 2016, 2017, 2010). For all studies, CEBM levels of evidence were assigned.

3.4 | Study outcomes

The study outcomes are presented in Table 2. Baseline defect characteristics showed a substantial homogeneity between studies, except Harrel et al., 2014, Ribeiro, Casarin, Palma, et al., 2011a, Ribeiro, Casarin, Palma, et al., 2011b and Ribeiro et al., 2010: PPD values

ranged between 4.3 and 9.1 mm, CAL values ranged between 5 and 12.2 mm, and REC values ranged between 0.7 and 5.3 mm. Five meta-analyses (PPD reduction, CAL gain, REC change, bone fill, VAS) were performed with all included articles, and subgroup analysis was performed according to the study quality (RCT or case series). Meta-analysis assessing differences in clinical parameters between MIPSs and traditional extended flaps was also performed. All the model results were calculated using random effect estimate.

3.5 | MIPSs: all included articles

In 25 treatment groups, the mean PPD reduction was 4.24 mm (95% CI = 3.79 to 4.69 mm) and the Z value was 18.3439 (p < .001) (Figure 1a). In the same twenty-five groups, the CAL change resulted in a mean gain of 3.89 mm (95% CI = 3.42 to 4.35 mm) and the Z value is 16.3096 (p < .001) (Figure 2a). In twenty-two groups, the mean REC increase was 0.44 mm (95% CI = 0.11–0.77 mm) with a Z value of 2.6100 (p = .0091) (Figure 3a). Regarding radiographic bone fill, only six treatment groups were included in the meta-analysis. The mean percentage gain was 58.25% (95% CI = 42.30%–74.21%) with a Z value of 7.1557 (p < .001). For this outcome, an elevated risk of bias is shown in funnel plot figure (Figure S2a). Considering the VAS values, eight groups were included in the statistical analysis. The mean recorded value was 1.16 (95% CI = 0.78–1.54) with a Z value of 6.0251 (p < .001) (Figure 4a).

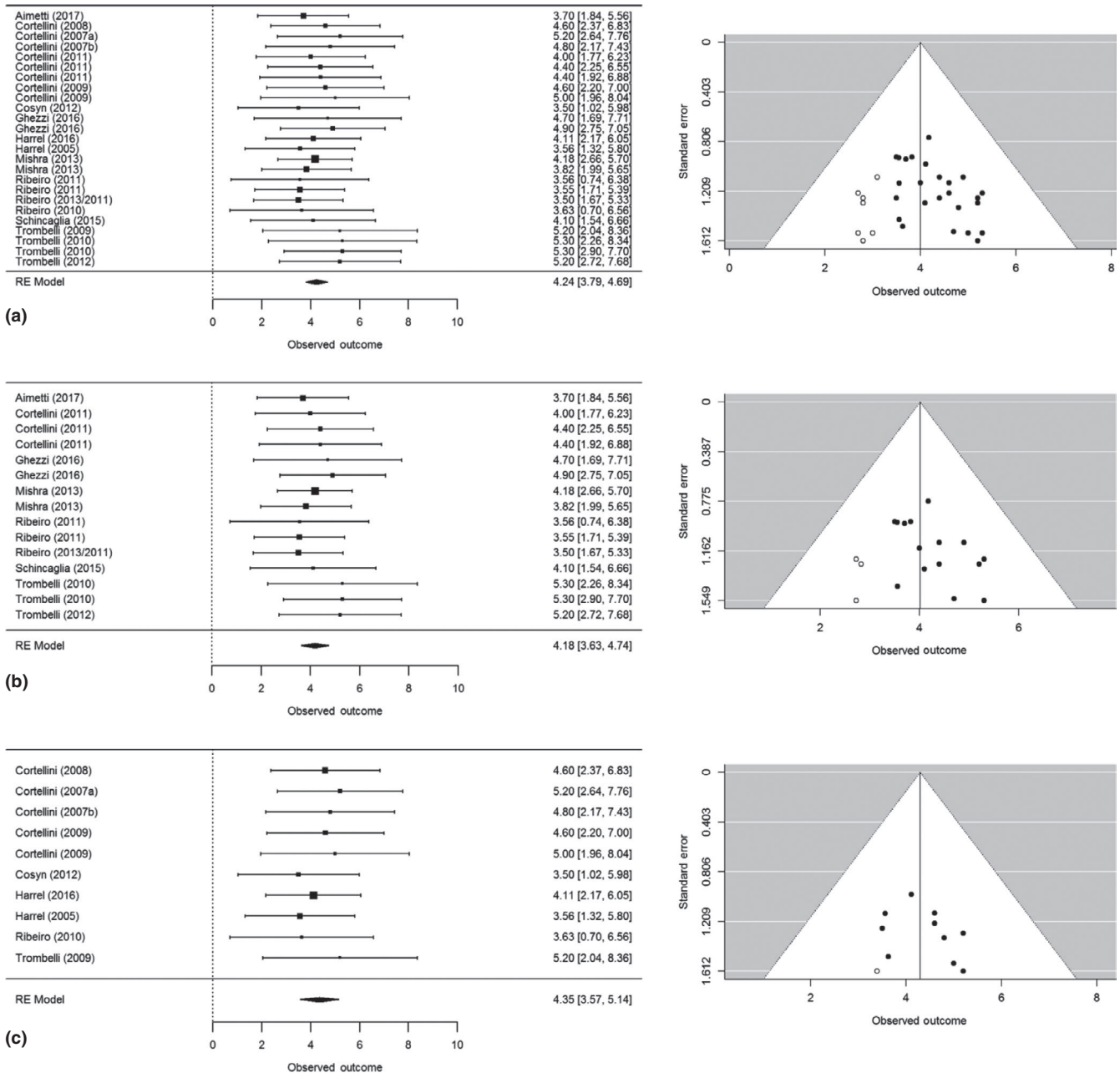

FIGURE 1 Forest and funnel plot of PPD reduction in MIPSs procedures. (a) all included articles, (b) RCTs, (c) case series

3.6 | MIPSs: RCTs

In fifteen treatment groups, the mean PPD reduction was 4.18 mm (95% CI = 3.63–4.74 mm) and the Z value was 14.7827 ($p < .001$) (Figure 1b). In the same fifteen groups, the CAL change resulted in a mean gain of 3.71 mm (95% CI = 3.14–4.28 mm) and the Z value is 12.7020 ($p < .001$) (Figure 2b). In fifteen groups, the mean REC increase was 0.56 mm (95% CI = 0.13–0.98 mm) with a *Z* value of 2.5443 ($p = .011$) (Figure 3b). In five treatment groups, the mean percentage of radiographic bone fill was 59.29% (95% CI = 40.04% to 78.55%) with a *Z* value of 6.0343 ($p < .001$). For this outcome, an elevated risk of bias is shown in funnel plot figure (Figure S2b). In six treatment groups, the mean VAS recorded value was 1.10 (95% CI = 0.71–1.49) with a Z value of 5.4707 ($p < .001$) (Figure 4b).

3.7 | MIPSs: case series

In ten treatment groups, the mean PPD reduction was 4.35 mm (95% CI = 3.57–5.14 mm) and the Z value was 10.8686 ($p < .001$) (Figure 1c). In the same ten groups, the CAL change resulted in a mean gain of 4.25 mm (95% CI = 3.44–5.06 mm) and the Z value

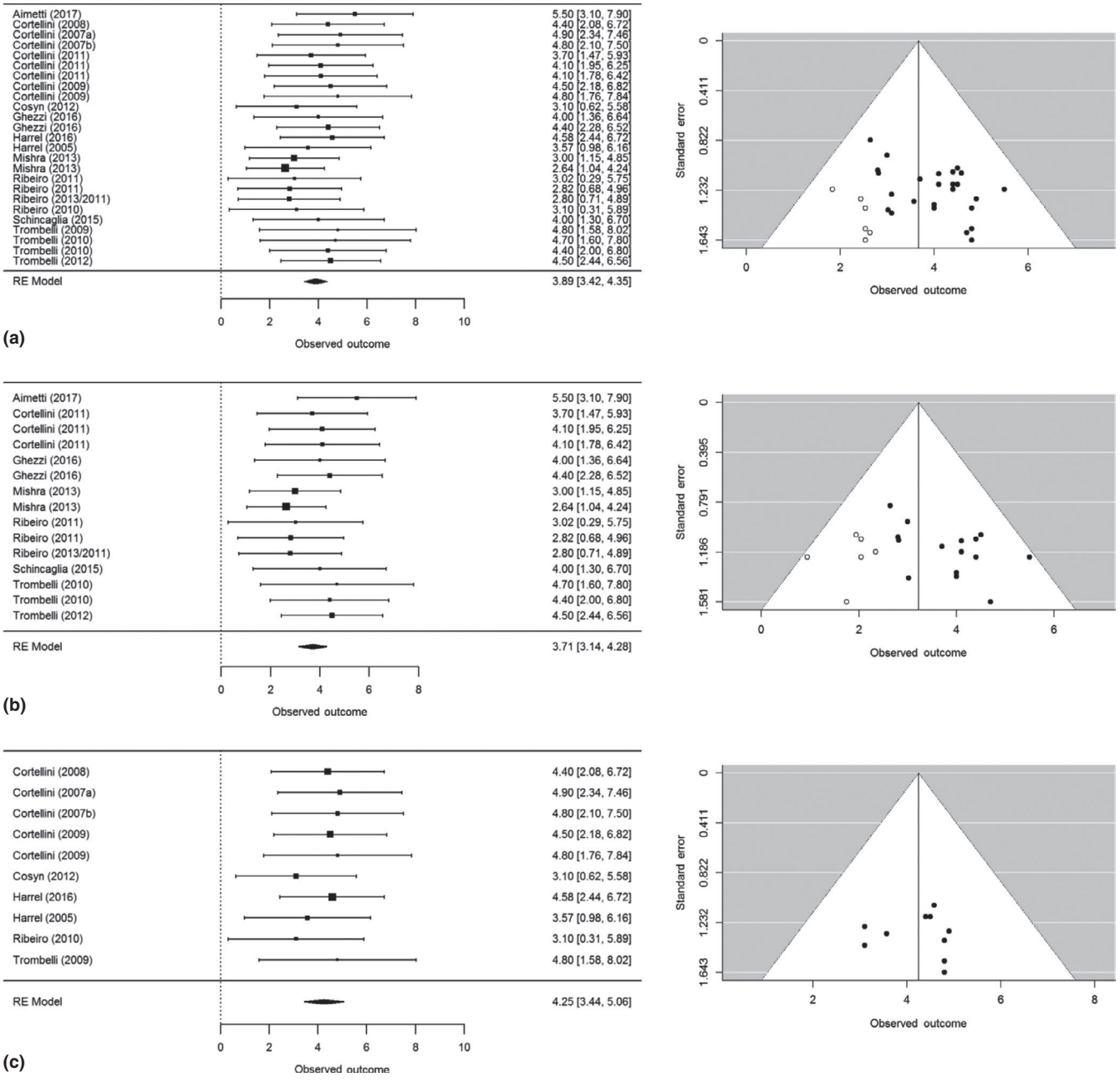

FIGURE 2 Forest and funnel plot of CAL gain in MIPSs procedures. (a) all included articles, (b) RCTs, (c) case series

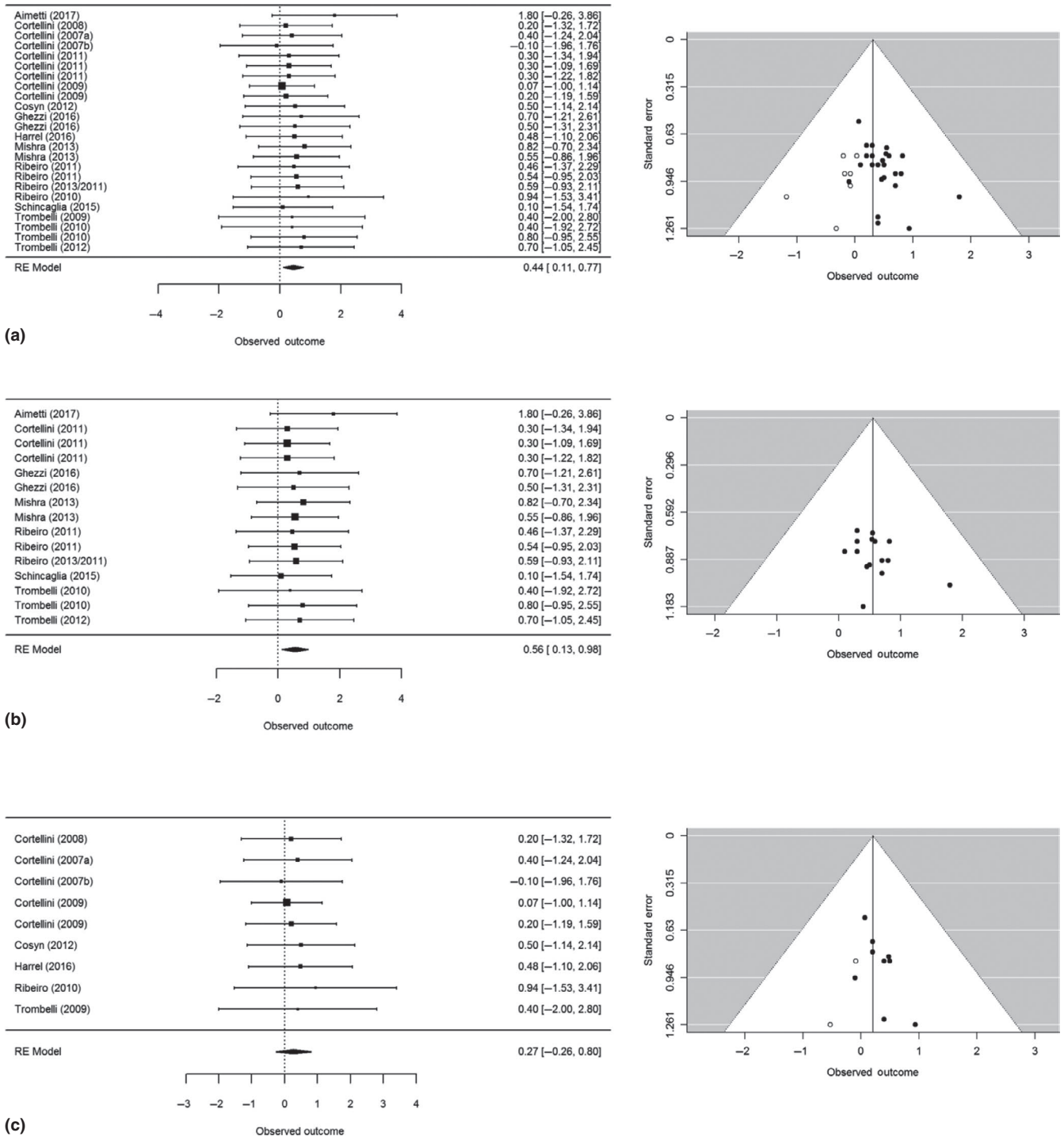

FIGURE 3 Forest and funnel plot of REC change in MIPSs procedures. (a) all included articles, (b) RCTs, (c) case series

is 10.2862 (p < .001) (Figure 2c). In the same ten groups, the mean REC increase was 0.27 mm (95% CI = −0.26 to 0.80 mm) with a Z value of 1.0060 (p = .3144) (Figure 3c). In one treatment group, the mean percentage of radiographic bone fill was 53% (95% CI = 41.40% to 64.60%) with a Z value of 8.9586 (p < .001) (Figure S2c). In two treatment groups, the mean VAS recorded value was 1.90 (95% CI = 0.55–3.25) with a Z value of 2.7606 (p < .001) (Figure 4c).

3.8 | MIPSs versus traditional flaps

Two studies (Trombelli, 2012 and Schincaglia 2015) were included in the meta-analyses (Figure 5) comparing the efficacy of a MIPSs (single-flap approach, SFA) and a traditional surgery (double-flap approach, DFA). The MIPS was more effective in terms of PPD reduction, with a mean difference of 0.93 mm (95% CI = 1.71–0.15; Z value = 2.3281; p = .0199), and CAL gain, with a mean difference of

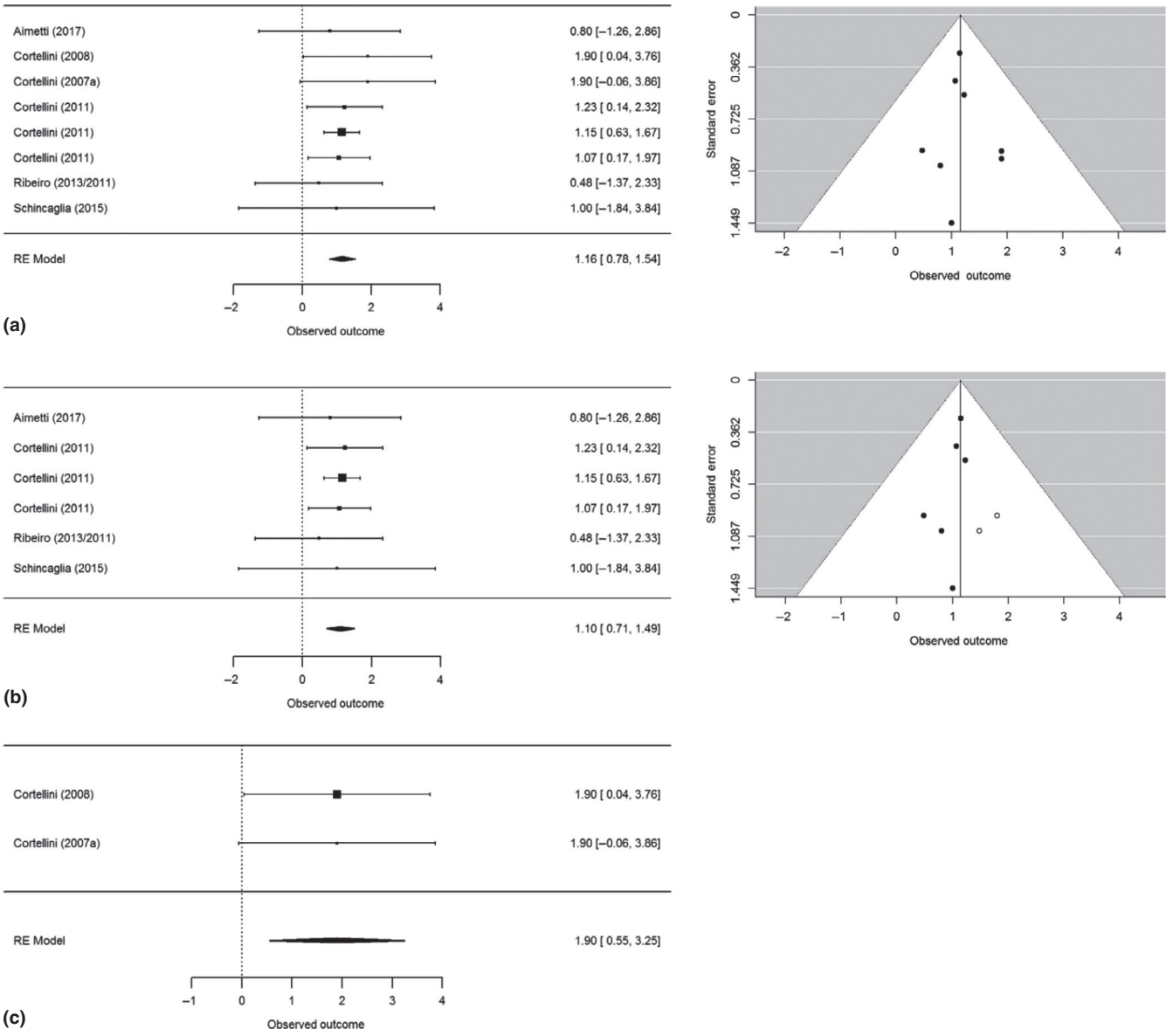

FIGURE 4 Forest and funnel plot of VAS in MIPSs procedures. (a) all included articles, (b) RCTs, (c) case series

1 mm (95% CI = 1.75–0.24; *Z* value = 2.5885; *p* = .0096). A non-significant difference was observed for REC change (mean difference of 0.02 mm; 95% CI = −0.51 to 0.55; Z value = 0.0749; *p* = .9403).

4 | DISCUSSION

The primary objective of this study was to investigate the clinical effectiveness of MIPS in terms of clinical, radiographic and patient-centred outcomes. Results of meta-analyses including all types of studies (RCTs and case series) are encouraging: besides high values of mean PPD reduction (4.24 mm) and CAL gain (3.89 mm), a minimal mean REC increase (0.44 mm) was recorded. Furthermore, a mean gain of 58.25% in radiographic bone fill and a quite low VAS record (1.16) was observed.

Subgroup analysis was performed according to the study quality (RCT or case series). Although a statistical analysis was not performed, the three different meta-analysis (one for all included studies, one for RCTs and one for case series) revealed small differences for observed PPD reduction (4.24 mm. for all studies, 4.18 mm. for RCTs and 4.35 mm. for case series), REC increase (0.44 mm for all studies, 0.56 mm. for RCTs and 0.27 mm. for case series) and CAL gain (3.89 mm. for all studies, 3.71 mm for RCTs and 4.25 mm for case series). Small differences were also observed for bone fill (58.25% for all studies, 59.29% for RCTs and 53% for case series) and the reported VAS record (1.16 for all studies, 1.10 for RCTs and 1.90 for case series).

A certain amount of heterogeneity can be found when the surgical procedures are analysed in detail. The term "minimally invasive" indicates very different procedures and has been used to describe

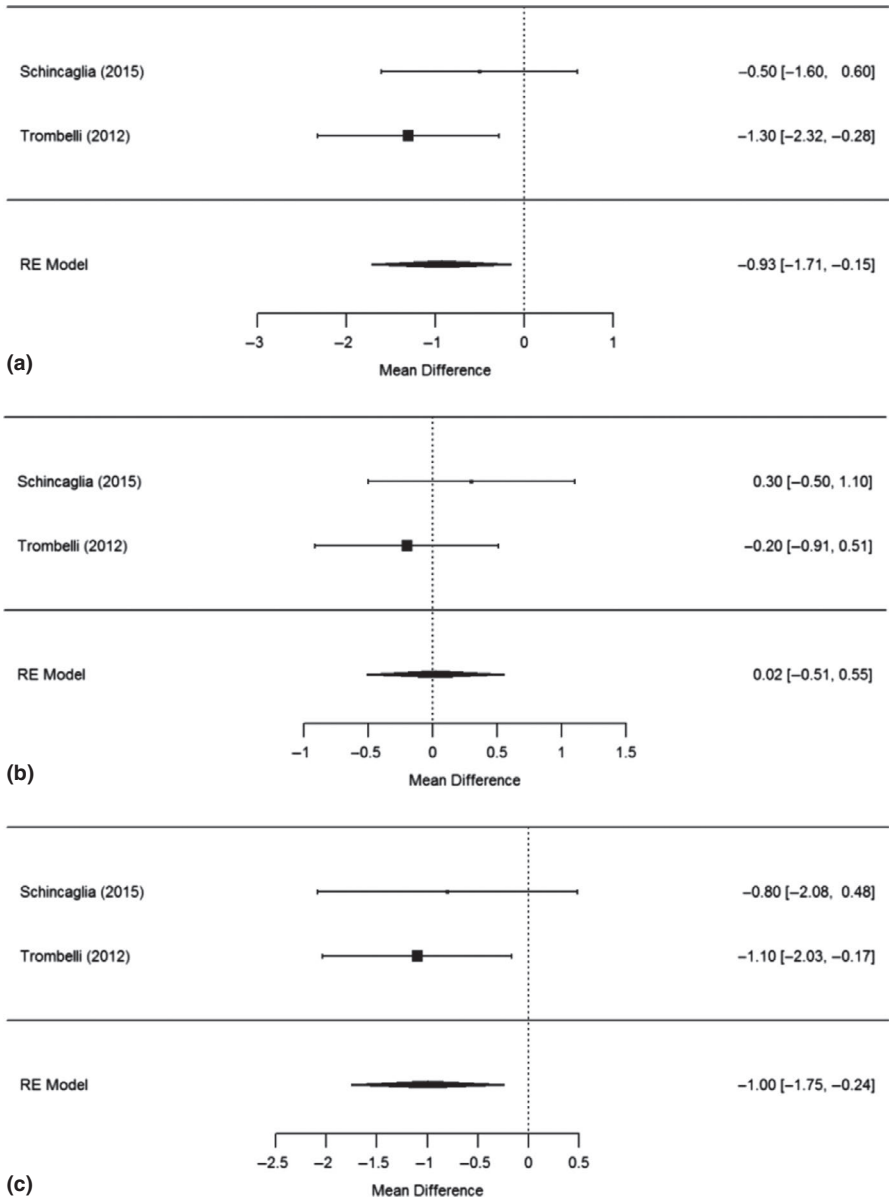

FIGURE 5 Forest plot of mean differences in PPD, CAL, REC between MIPS and traditional surgery

both a single flap and a double flap. A slight difference among techniques used is also detectable when considering the mesiodistal extension of sulcular incisions performed.

Only two included studies (Trombelli et al., 2012, Schincaglia et al. 2015) compared a SFA to a DFA, allowing for a meta-analysis exploring mean differences between a MIPS (SFA) and a traditional surgery (DFA). The result of the meta-analysis is that SFA is more effective in terms of CAL gain and PPD reduction. Aside from these two studies, no included study compared a minimally invasive approach to a traditional one in the treatment of periodontal infrabony defects.

However, based on a substantial homogeneity of the characteristics of the defects at baseline, results from this systematic review on the effectiveness of MIPSs could be correlated with others from similar systematic reviews analysing the clinical performance of a traditional periodontal surgery in the treatment of infrabony defects, both with or without the use of regenerative materials.

Considering the great differences in data treatment and statistical analysis, mean values of clinical outcomes obtained by minimally invasive approaches with the use of different types of membranes, biomaterials and/or biologic agents (EMD and rhPDGF-BB) seem to be comparable or even better than outcomes obtained by conventional ones (Esposito, Grusovin, Papanikolaou, Coulthard, & Worthington, 2009; Kao, Nares, & Reynolds, 2015; Needleman, Tucker, Giedrys-Leeper, & Worthington, 2005; Trombelli et al., 2002). However, it should be noticed that in a more in-depth analysis of individual papers, these differences are not so clear. Comparing data extracted for our review with data from traditional GTR approaches, it is not easy to find a greater advantage when using MIPSs: some treatment groups seem to achieve even better results with traditional approaches in PPD reduction and CAL gain at the same time of follow-up (Cortellini & Tonetti, 2005; Siciliano et al., 2011; Stavropoulos & Karring, 2004; Stavropoulos, Mardas, et al. 2005, Stavropoulos & Karring, 2004). This seems to be true when

analysing REC changes: in almost all articles comparing the clinical effects of different traditional procedures, a certain amount of gingival recession increase is recorded, as reported in the present systematic review (0.44 mm) considering only minimally invasive approaches. As we know, aesthetic considerations can no longer be ignored when a surgical procedure is planned. Generally, most of the standard periodontal surgeries for treating infrabony defects are closely associated with a recession of gingival margin. Limiting the mesiodistal extension of the incision to allow a minimal flap reflection and the maintenance of pre-existing papilla shape and height could be another advantage of MIPS in terms of REC reduction and aesthetic results (Cortellini & Tonetti, 2007b). Nevertheless, it is important to consider that the presence of either a non-supportive defect anatomy or thin-scalloped gingival biotype was identified as a risk factor for REC increase on the midfacial aspect, even when a minimally invasive approach is performed (Cosyn et al., 2012). The possibility to avoid statistically and clinically significant changes in the position of the soft tissues when treating vertical bony defects can be also accomplished by coronally advancing an envelope buccal flap with more extended dimension during the surgery (Zucchelli & De Sanctis, 2008).

In thirteen studies of this systematic review, no biomaterials or biologic agents were used in at least one analysed group. The use of biomaterials or membranes does not seem to contribute to the improvement of clinical periodontal parameters after a minimally invasive periodontal surgery (Cortellini & Tonetti, 2011; Liu, Hu, Zhang, Li, & Song, 2016). This is not true for the traditional periodontal surgery, since the absence of a regenerative material has a significant impact on the effectiveness of these surgical procedures (Needlemann et al., 2005). A systematic review with meta-analysis on the clinical performance of periodontal surgery without regenerative materials for the treatment of intra-bony defects demonstrated a CAL gain of 1.65 mm., a PD reduction of 2.80 mm. and a REC increase of 1.26 mm., and a subgroup analysis based on the type of flap showed a CAL gain of 1.44–3.52 for papilla preservation flaps and 1.25–1.89 mm for access flaps (Graziani et al., 2012). Differences in the clinical outcomes between MIPS and traditional surgery may be explained by the very high percentage of primary closure of the wound obtained with MIPS (Cortellini & Tonetti, 2007b; Harrel et al., 2005), creating a safer environment for periodontal regeneration. In fact, space maintenance and clot stability are key factors in determining the success of regenerative therapy (Cortellini, 2012). The precise management of the surgical site, obtained by the use of magnification instruments, could facilitate clot stability and maturation, good flap perfusion and space maintenance (Cortellini et al., 2009; Trombelli et al., 2010). These intrinsic aspects of MIPS may also explain why a substantial amount of PPD reduction and CAL gain can be achieved even when the use of biomaterials or membranes is not associated with minimally invasive approaches (Liu et al., 2016).

Another advantage of MIPSs could be the individual patient's response. A very low mean VAS values, for pain/discomfort, were recorded in studies included in this review. However, neither follow-up time nor the same perception was analysed. Moreover, a very limited number of studies reported this outcome and it should be emphasized that only a single study (Schincaglia et al. 2015) evaluated differences in patients' pain perception by means of a VAS at different time points after a single-flap or a double-flap approach, observing lower pain during the first postoperative days for SFA compared with the DFA.

Considering the results of this review and the limitations of the statistical analysis conducted, due mostly to heterogeneity of included studies and the difficulty in comparing minimally invasive approaches to traditional ones, there is a need for further studies in order to explore the real effect of a minimally invasive approach when treating periodontal infrabony defects and the real benefit for the patient in terms of reduced morbidity and higher satisfaction. The effective role of regenerative strategies (biomaterials, membranes and biological agents) should be also carefully investigated while using this approach, in order to understand the real balance between costs and benefits (very intense training programmes and the use of magnification tools for practitioners vs. a lower biological cost for patients).

5 | CONCLUSION

MIPS may be considered for the treatment of periodontal infrabony defects, due to good clinical outcomes in terms of PPD reduction and CAL gain and minimal REC increase. However, the real effect cannot be systematically evaluated due to the paucity of studies comparing MIPSs to traditional flap for periodontal reconstructive surgery.

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CONFLICT OF INTEREST

The authors report no conflict of interests related to the study.

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