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REVIEW ARTICLE

Minimal invasiveness in the surgical treatment of intraosseous defects: A systematic review

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1 | INTRODUCTION

The persistence of deep pockets associated with intraosseous defects following active, nonsurgical therapy (steps I-II of periodontal therapy) represents an indication to surgical treatment.[1] When intraosseous defects are treated with open flap debridement, a significant reduction in probing depth and gain in clinical attachment[2,3] may be obtained through a reparative process characterized by the formation of a long junctional epithelium, as described in classical studies.[4,5] As reported by histological and clinical studies, the adjunctive use of regenerative devices (e.g., membranes; enamel matrix derivative; autogenous bone grafts, demineralized freeze-dried bone allograft, natural bone mineral) to open flap debridement may result in a significant qualitative (i.e., amount of regenerated attachment apparatus)[6–10] and quantitative (i.e., probing parameters)[3,7–9,11–13] improvement of the outcomes. In this context, in the recent European Federation of Periodontology Clinical Practice Guidelines, the use of regenerative technologies—used either alone or in combination—may be recommended in an attempt to maximize the clinical results, especially when treating defects with unfavorable morphology (ie, one-wall/two-walls components and/or wide defect angle).[1]

As in other surgical fields, the concept of invasiveness in periodontal regenerative surgery is broad and encompasses several aspects, mainly related to patient perception or objectively assessed by the operator. These include postoperative morbidity (ie, interference of the surgical procedure with daily activities) and discomfort, aesthetic impact, chair time, and costs (for surgery, follow-up visits, and management of complications). While all the aspects listed above may be considered as descriptors of invasiveness, technical elements such as flap design, the extension of the surgical field, the complexity of the procedure (including the use of regenerative devices and the learning curve), as well as perioperative and postoperative pharmacological and antimicrobial protocols, represent its common determinants.

In the last few decades, technical and technological innovations have been proposed in an attempt to minimize the invasiveness of periodontal regenerative procedures while maintaining or enhancing their regenerative performance. Based on preclinical evidence indicating that flap design has an impact on the quality of wound maturation,[14–16] surgical techniques characterized by a limited flap extension without vertical releasing incisions were proposed to minimize the surgical impact on vascular supply, promote a faster revascularization, and optimize the primary intention healing and wound stability. These techniques, whose distinctive element is the elevation of a single flap to access the defect (ie, the Single Flap Approach[17,18] and Modified Minimally Invasive Surgical Technique[19]), were demonstrated to enhance the clinical outcomes of the procedure when compared with traditional techniques based on the elevation of double flaps.[20,21]

Also, technological advancements have made new regenerative devices available, the application of which are technically less demanding (as in the case of gels compared with membranes). This contributed to simplification of the surgical procedure (eg, eliminating the need for an additional surgical procedure, as for resorbable membranes and bone substitutes compared with nonresorbable membranes and autogenous bone grafts, respectively) and a reduction of chair time.[22,23] Lastly, other perioperative and postoperative pharmacological protocols have been investigated in an effort to favorably modulate the healing phase and reduce the incidence and severity of postoperative complications. In this respect, technologies (eg, low-level laser therapy) have been proposed to improve the

biocompatibility of the exposed root surface and enhance wound healing.[24–26] Also, the use of systemic antibiotic therapies in the postoperative phase has been considered to improve clinical outcomes and prevent postoperative infections.[27]

Several systematic reviews have evaluated the impact of flap design[2,28–30] and regenerative technology,[3,31,32] as well as perioperative and postoperative protocols,[27] on the clinical outcomes of a periodontal regenerative procedure. Differently, the relevance of the same factors on invasiveness (as derived from a systematic review comprehensively considering the pertinent literature) currently remains unknown. The following observations, however, seem to encourage a systematic review specifically addressing this issue: (a) within the context of a periodontal regenerative procedure, the surgical technique used to access the intraosseous defect was shown to reflect on postsurgery pain intensity and dose of analgesics,[21] and promising data on pain, discomfort, and incidence/severity of complications have been reported for new flap designs proposed as minimally invasive in recent prospective studies[19,33]; (b) in some controlled trials, the use of resorbable membranes and bone substitutes was associated with similar clinical outcomes compared with nonresorbable membranes and autogenous bone grafts, respectively, thus indicating the possibility of eliminating the need for additional surgeries for membrane removal and autogenous bone harvesting without affecting the reconstructive performance of the procedure[34,35]; (c) when compared within a randomized controlled study design, gels containing bioactive agents have shown comparable clinical outcomes compared with more technically demanding devices such as membranes[36,37]; (d) therapies based on the combination of two or more regenerative devices do not necessarily perform better than monotherapies.[38–40] Also, in some randomized controlled trials, substantial improvements in clinical parameters were obtained following open flap debridement with and without a regenerative technology, thus suggesting that in specific cases the invasiveness of the intervention can be reduced by simplifying or renouncing the application of regenerative devices[41,42]; and (e) specific adjunctive perioperative and postoperative protocols have been shown to reduce postoperative pain and limit the increase in gingival recession.[26]

The present systematic review was performed to summarize the evidence from controlled studies evaluating whether and to what extent specific aspects of the periodontal regenerative procedure (including surgical technique and regenerative technology, as well as perioperative and postoperative adjunctive protocols) may reduce the invasiveness of the latter.

2 | REVIEW

2.1 | Focused questions

The aim of the present systematic review was to answer the following focused questions: (a) What is the effect of flap design on the invasiveness of regenerative treatment of periodontal intraosseous defects? (b) What is the effect of the regenerative technology on the invasiveness of the surgical treatment of periodontal intraosseous defects? (c) Might specific perioperative or postoperative clinical and/or pharmacological protocols reduce the invasiveness of the regenerative treatment of periodontal intraosseous defects?

2.2 | Literature search strategy

An electronic literature search was performed for studies suitable for the present review published up to 30 June 2021.

A primary search was conducted on MEDLINE using the following combination of search terms and Boolean operators: "(intraosseous OR intrabony OR angular OR vertical) AND periodont*". Filters "randomized clinical trial" and "controlled clinical trial" were activated. An additional search was performed on SCOPUS and the bibliography of the most recent and influential systematic reviews on the topic. Only studies written in English were considered.

2.3 | Article selection

For focused questions 1 and 2, both addressing surgery-related technical aspects, article selection was structured according to the following PICOS system:

- participants (P): adult patients with at least one intraosseous periodontal defect (as detected either clinically and/or radiographically) associated with a periodontal pocket (probing depth > 4 mm) following treatment phase I and II[1];
- intervention (I): access flap (irrespective of flap design and extension) for defect debridement either alone (open flap debridement) or followed by the application of a regenerative device (ie, a membrane device for guided tissue regeneration; enamel matrix derivative; growth factors; preparate from autologous blood; bone grafts/substitutes, or combinations thereof);
- comparison (C): any flap surgery differing from the Intervention for flap design (focused question 1) or number and/or type of regenerative devices (focused question 2);
- outcome measures (O): studies reporting data on at least one of the following descriptors of invasiveness (which were considered as the primary outcome measures of the review) were included: patient-reported outcome measures, intrasurgery and postsurgery complications (as self-reported by the patient or objectively assessed by the operator), oral health-related quality of life, aesthetic impact (as either reported by the patient using questionnaires/scales or objectively assessed in terms of postoperative gingival recession), costs, and chair time. No restrictions in terms of observation period were applied for primary outcomes. Data on secondary outcomes (ie, tooth survival, clinical attachment gain, probing depth reduction) were extracted (if available) only from included studies reporting data on one or more of the primary outcomes. For secondary outcomes, the minimum observation period was 6 months;

- studies (S): prospective, parallel-arm,or split-mouth controlled trials (either randomized or not). No restriction was applied in terms of treatment group size.

For focused question 3, article selection was referred to the following PICOS system:

- participants (P): adult patients undergoing regenerative treatment of at least one intraosseous periodontal defect (as detected either clinically and/or radiographically) associated with a periodontal pocket (probing depth > 4 mm) following treatment phase I and II[1];
- intervention (I): specific perioperative and/or postoperative protocol (including drugs, antimicrobials, biostimulation) aimed at reducing the invasiveness of the surgical procedure;
- comparison (C): perioperative and/or postoperative protocol different from the intervention, placebo, or no treatment;
- outcome measures (O): studies reporting data on at least one of the following descriptors of invasiveness (which were considered as the primary outcome measures of the review) were included: patient-reported outcome measures, intrasurgery and postsurgery complications (as self-reported by the patient or objectively assessed by the operator), oral health-related quality of life, aesthetic impact (as either reported by the patient using questionnaires/scales or objectively assessed in terms of postoperative gingival recession), costs, and chair time. No restrictions in terms of observation period were applied for primary outcomes. Data on secondary outcomes (ie, tooth survival, clinical attachment gain, probing depth reduction) were extracted (if available) only from included studies reporting data on one or more of the primary outcomes. For secondary outcomes, the minimum observation period was 6 months;
- studies (S): prospective, parallel-arm,or split-mouth controlled trials (either randomized or not). No restriction was applied in terms of treatment group size.

2.4 | Search results and descriptions of the included studies

The flowchart of article screening and selection is shown in Figure 1.

Thirteen articles (13 studies) were included (Table 1) and contributed to the review as follows:

- one parallel-arm randomized controlled trial included a comparative evaluation of postoperative pain and analgesic consumption following periodontal regenerative surgery performed according to different flap designs[21];
- five parallel-arm randomized controlled trials performed a comparative evaluation of periodontal regenerative treatment vs access flap alone in terms of intraoperative and postoperative pain and morbidity, chair time, and/or costs[42–46];

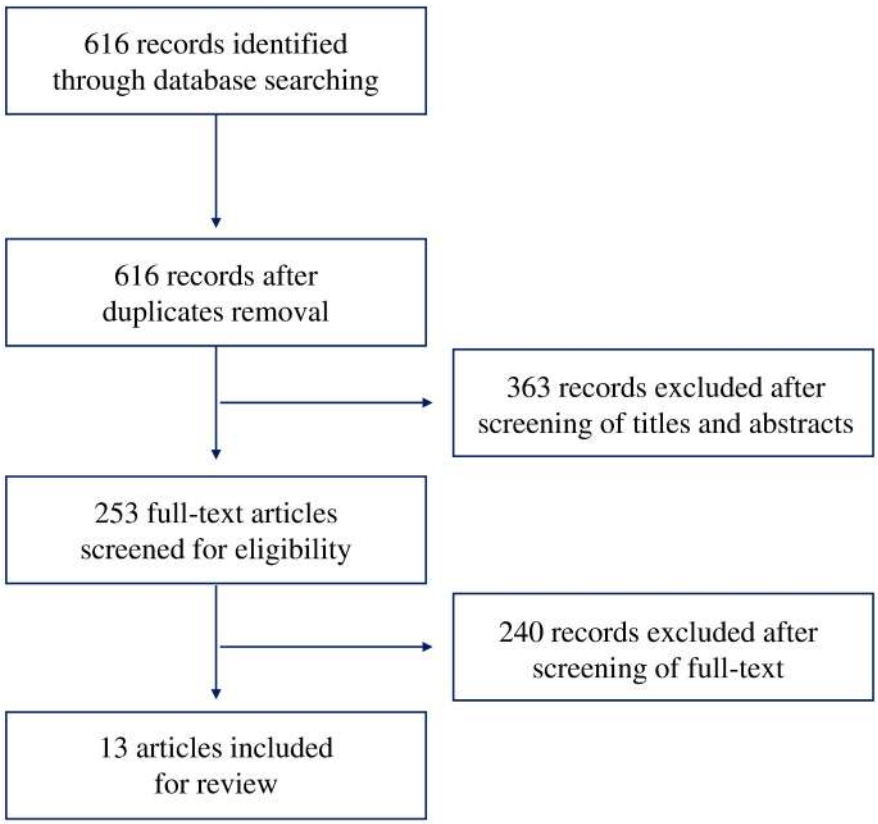

FIGURE 1 Flowchart of article screening and selection

TABLE 1 Characteristics of the studies included in the review

First author (year)	Study design/ Setting	Intervention 1			Intervention 2			Intervention 3			Parameters related to the invasiveness of the procedure
		n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	
Cortellini (2001)	Parallel-arm RCT/private practice and university	56	SPPT	Resorbable membrane	57	SPPT	none	-	-	-	• Chair time (min) • Level of intraoperative pain (VAS) • Hardship of the procedure (VAS) • Level of postoperative pain (VAS) • Duration of postoperative pain (h) • Postoperative morbidity • Postoperative complications (edema, hematoma, suppuration) • Membrane exposure
Tonetti (2004)	Parallel-arm RCT/private practice and university	83	MPPT/SPPT	EMD	83	MPPT/SPPT	none	-	-	-	• Chair time (min) • Level of intraoperative pain (VAS) • Hardship of the procedure (VAS) • Level of postoperative pain (VAS) • Duration of postoperative pain (h) • Number of analgesic tablets • Postoperative morbidity • Postoperative complications (edema, hematoma, suppuration, presence of granulation tissue, wound dehiscence) • Root sensitivity • Patient perception of outcomes 1 y after treatment (benefits/ disadvantages)

(Continues)

TABLE 1 (Continued)

First author (year)	Study design/ Setting	Intervention 1			Intervention 2			Intervention 3			Parameters related to the invasiveness of the procedure
		n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	
Sipos (2005)	Split-mouth RCT/ university	11	MPPT/SPPT	EMD + nonresorbable (e-PTFE) membrane	11	MPPT/SPPT	EMD	-	-	-	• Chair time (min) • Membrane exposure • Duration of postoperative pain (d) • Postoperative complications (lost suture, hemorrhage, headaches, limited mouth opening) • Number of analgesic tablets
Jepsen (2008)	Parallel-arm RCT/private practice and university	38	MPPT/SPPT	EMD+SBC	35	MPPT/SPPT	EMD	-	-	-	• Postoperative pain within first 7 d (no/ mild/moderate/ severe) • Postoperative complications (bleeding, swelling, wound dehiscence)
Ozcelik (2008)	Split-mouth RCT/ university	11	Full-thickness buccal and lingual flaps	EMD+LLLT	11	Full-thickness buccal and lingual flaps	EMD	-	-	-	• Level of postoperative pain (VAS) • Duration of postoperative pain (d) • Postoperative complications (gingival swelling, gingival color)
Cortellini (2011)	Parallel-arm RCT/ private practice	15	M-MIST	EMD+DBBM	15	M-MIST	EMD	15	M-MIST	none	• Chair time (min) • Intraoperative pain • Hardship of the procedure • Level of postoperative pain (VAS) • Postoperative complications (edema, hematoma, wound dehiscence) • Number of analgesic tablets

TABLE 1 (Continued)

First author (year)	Study design/ Setting	Intervention 1			Intervention 2			Intervention 3			Parameters related to the invasiveness of the procedure
		n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	
Jayakumar (2011)	Parallel-arm RCT/university and hospital	27	Full-thickness buccal and palatal/lingual flaps	rhPDGF-BB + β-TCP	27	Full-thickness buccal and palatal/ lingual flaps	β-TCP	-	-	-	• Postoperative pain (yes/no) • Postoperative complications (gingival swelling, fever, tooth mobility)
Schincaglia (2015)	Parallel-arm RCT/ university	15	SFA	rhPDGF-BB + β-TCP	14	MPPT/SPPT	rhPDGF-BB + β-TCP	-	-	-	• Level of postoperative pain (VAS) • Number of analgesic tablets • Quality of wound healing
Cortellini[a] (2017)	Parallel-arm RCT/private practice and university	15	MPPT	Titanium reinforced e-PTFE membrane	15	Buccal and lingual full thickness mucoperiosteal flaps	e-PTFE membrane	15	MWF	none	• Costs (related to either surgery or maintenance over 20 y) • Disease recurrence and tooth loss at 20 y
Aoki[b] (2020)	Parallel-arm RCT/ hospital and private practice	22	MPPT/SPPT	rhFGF-2 + DBBM	22	MPPT/SPPT	rhFGF-2	-	-	-	• Perception of oral health (OHRQL-J) at 6, 12, and 24 mo after treatment • Tooth mobility
Aslan (2020)	Parallel-arm RCT/ private practice and university	15	EPP	EMD + DBBM	15	EPP	none	-	-	-	• Chair time (min) • Postoperative complications (edema, hematoma) • Intraoperative pain • Hardship of the procedure (VAS) • Level of postoperative pain (VAS) • Number of analgesic tablets

TABLE 1 (Continued)

First author (year)	Study design/ Setting	Intervention 1			Intervention 2			Intervention 3			Parameters related to the invasiveness of the procedure
		n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	n° patients (ITT population)	Flap design	Regenerative/ reconstructive technology	
Lee (2020)	Parallel-arm RCT/hospital university	23	Full-thickness mucoperiosteal flap with intrasulcular incisions	EMD + DBBM	23	Full-thickness mucoperiosteal flap with intrasulcular incisions	EMD	-	-	-	• Chair time • Duration of postoperative pain (d) • Level of postoperative pain (VAS) • Postoperative complications (swelling severity and duration, spontaneous bleeding, ulceration, dehiscence and/or fenestration)
Sánchez (2020)	Parallel-arm Quasi RCT/ university	10	CAF or papilla preservation techniques	XBS + PDL-MSCs	10	CAF or papilla preservation techniques	XBS	-	-	-	• Patient quality of life (OHIP-14) at 15 d and 12 mo after surgery • Number of analgesic tablets • Satisfaction with the aesthetic appearance at 12 mo after treatment (VAS) • Level of postoperative pain • Postoperative complications (swelling, dentine hypersensitivity) • Quality of wound healing

Abbreviations: β-TCP, beta-tricalcium phosphate; CAF, coronally advanced flap (Zucchelli and De Sanctis, 2008); DBBM, deproteinized bovine bone mineral; EMD, enamel matrix derivative; e-PTFE, expanded polytetrafluoroethylene; EPP, entire papilla preservation[33]; ITT, intention to treat; LLLT, low-level laser therapy; M-MIST, modified minimally invasive surgical technique[42]; MPPT, modified papilla preservation technique[54]; MWF, modified Widman flap (Ramfjord and Nissle, 1974); OHIP-14, Oral Health Impact Profile; OHRQL-J, Oral Health-Related Quality of Life - Japan; PDL-MSCs, periodontal ligament-derived mesenchymal stem cells; RCT, randomized controlled trial; rhFGF-2, recombinant human fibroblast growth factor-2; rhPDGF-BB, recombinant human platelet-derived growth factor–BB; SBC, synthetic bone graft substitute (mixture of 60% hydroxyapatite and of 40% of beta tricalcium phosphate); SPPT, simplified papilla preservation technique[55]; SFA, single flap approach[17,18]; VAS, visual analog scale; XBS, xenogeneic bone substitute.

[a]20-y follow-up of a RCT.[54]

[b]This study is the 2-year follow-up of the RCT by Saito et al. (*J Clin Periodontol*. 2019:46, 332–341). Since all the results reported in the study by Saito et al. (2019) have been reported and implemented in the study of Aoki et al. (J Clin Periodontol. 2021;48:91-99), only the study of AokY et al. 2021 was considered for the present review.

- seven articles (five parallel-arm randomized controlled trials, one split-mouth randomized controlled trial, one parallel-arm, quasi-randomized controlled trial) performed a comparative evaluation of regenerative periodontal treatment based on combination therapies vs monotherapies in terms of intraoperative and postoperative pain and morbidity, chair time, and/or costs[39,42,47–51];
- one article reported the results of a split-mouth randomized controlled trial evaluating the efficacy of intrasurgical and postsurgical low-level laser bio stimulation on postoperative pain and swelling after a periodontal regenerative procedure.[26]

2.5 | Methodology used for data synthesis

Because of differences in experimental design, outcome measure systems, and observation intervals that were found among the included studies, no meta-analysis could be performed. Therefore, data were summarized according to a narrative style.

2.6 | Assessment of risk of bias in the included studies

For randomized controlled trials, the methodological quality assessment was performed using version 2 of the Cochrane tool for assessing the risk of bias in randomized trials.[52] Five main domains for risk of bias were assessed: randomization process, deviations from the intended interventions, missing outcomes data, measurement of the outcomes, and selection of the reported results. When assigning the risk of bias related to the domain "measurement of the outcomes", the assessment was referred to the primary outcomes of the review. A risk of bias judgment (among "low risk of bias", "some concerns", or "high risk of bias") was assigned to each domain (depending on the descriptions given for each field) and to the entire study.

For the included quasi-randomized controlled trial study, a methodological quality assessment was performed according to the Risk of Bias in Nonrandomized Studies of Interventions.[53] Seven main domains for risk of bias were assessed: bias because of confounding, bias in selection of participants into the study, bias in classification of interventions, bias resulting from deviations from intended interventions, bias because of missing data, bias in the measurement of outcomes, and bias in selection of the reported result. Bias in measurement of the outcomes was judged in relation to the primary outcomes of the review. A risk of bias judgment (among "low risk of bias," "moderate risk of bias," "serious risk of bias," "critical risk of bias," or "no information") was assigned to each domain (depending on the descriptions given for each field) and to the entire study.

2.7 | Synthesis of the main findings

2.7.1 | What is the effect of flap design on the invasiveness of the surgical regenerative treatment of intraosseous defects?

One study[21] contributed this section. The main study characteristics and findings are reported in Table 2. Twenty-nine intraosseous

TABLE 2 Main findings of the only controlled study (parallel-arm randomized controlled trial) evaluating the effect of flap design on the invasiveness of a periodontal regenerative procedure in the treatment of intraosseous defects

	Intervention 1	Intervention 2		
First author (year)	Flap design/ regenerative technology	Flap design/ regenerative technology	Postoperative pain and number of analgesic tablets	Postoperative morbidity and complications
Schincaglia et al (2015)	SFA/rhPDGF-BB+ β-TCP	DFA/rhPDGF-BB+ β-TCP	*Postoperative pain* At day 1, 2, and 6 postsurgery, a significantly greater level of postoperative pain was self-reported after Intervention 2 compared with Intervention 1 *Number of analgesics* Total dose of analgesics assumed during the first 2 postoperative wk after Intervention 1 and 2: Intervention 1: 2.73 ± 5.04 Intervention 2: 8.69 ± 11.6 At day 1 postsurgery, a significantly greater number of analgesics was used after Intervention 2 compared with Intervention 1 (3.2 ± 2.9 vs 1.1 ± 2.2, respectively)	Intervention 1: 12 and 8 sites showed complete flap closure (EHI = 1, 2, 3) and optimal wound healing (EHI = 1), respectively Intervention 2: 6 and 3 sites showed complete flap closure (EHI = 1, 2, 3) and optimal wound healing (EHI = 1), respectively

Abbreviations: β-TCP, beta-tricalcium phosphate; DFA, Double Flap Approach performed according Modified Papilla Preservation Technique[54] or Simplified Papilla Preservation Technique[55]; EHI, Early Healing Index[56]; rhPDGF-BB, recombinant human platelet-derived growth factor–BB; SFA, Single Flap Approach.[17,18]

defects with a varying number of residual bony walls (ranging from mainly one to mainly three) were randomly assigned to surgical access according to the Single Flap Approach[17,18] (Figure 2) or the Double Flap Approach[54,55] (Figure 3). While the single flap approach consisted of a single mucoperiosteal flap elevated on the vestibular or lingual/palatal side (depending on defect extension), leaving the supracrestal interproximal soft tissues undetached, the Double Flap Approach was characterized by the elevation of full thickness flaps on both buccal and lingual/palatal aspects according to papilla preservation techniques.[54,55] Both treatments with Single Flap Approach and Double Flap Approach showed similar mesio-distal extension of the flap, with no differences in the number of teeth/papillae included in the surgical area. Moreover, no vertical releasing incisions were performed in either the Single Flap Approach or Double Flap Approach groups. Irrespective of treatment allocation, all defects received recombinant human platelet-derived growth factor–BB plus beta-tricalcium phosphate at the completion of defect degranulation and root debridement.

Lower postoperative pain (as evaluated on a 100-mm visual analog scale) was experienced throughout the whole postsurgical period (from day 1 to day 14 after surgery) after the Single Flap Approach compared with the Double Flap Approach, with the intergroup difference reaching statistical significance at the early observation intervals (day 1 at 08:00 a.m., 01:00 p.m., and 08:00 p.m.; day 2 at 01:00 p.m. and 08:00 p.m.) and on the sixth day after surgery. A significantly higher dose of self-administered rescue analgesic (ie, 600-mg ibuprofen tablets) was registered on day 1 after treatment in the Single Flap Approach group compared with the Double Flap Approach group (1.1 ± 2.2 and 3.2 ± 2.9, respectively; $P = .019$). The mean dose of analgesic taken within the first 2 postoperative weeks was 2.73 ± 5.04 and 8.69 ± 11.6 in the Single and Double Flap Approach groups, respectively, with the difference not reaching statistical significance. These results were ascribed, at least in part, to the better quality of early wound healing at the incision margin, as observed in the Single Flap Approach group at 2 weeks following surgery. In particular, 53% of sites accessed according to the Single Flap Approach showed optimal wound closure (ie, Early Healing Index[56] = 1), while only 23% of sites in the Double Flap Approach group showed the same quality of healing.

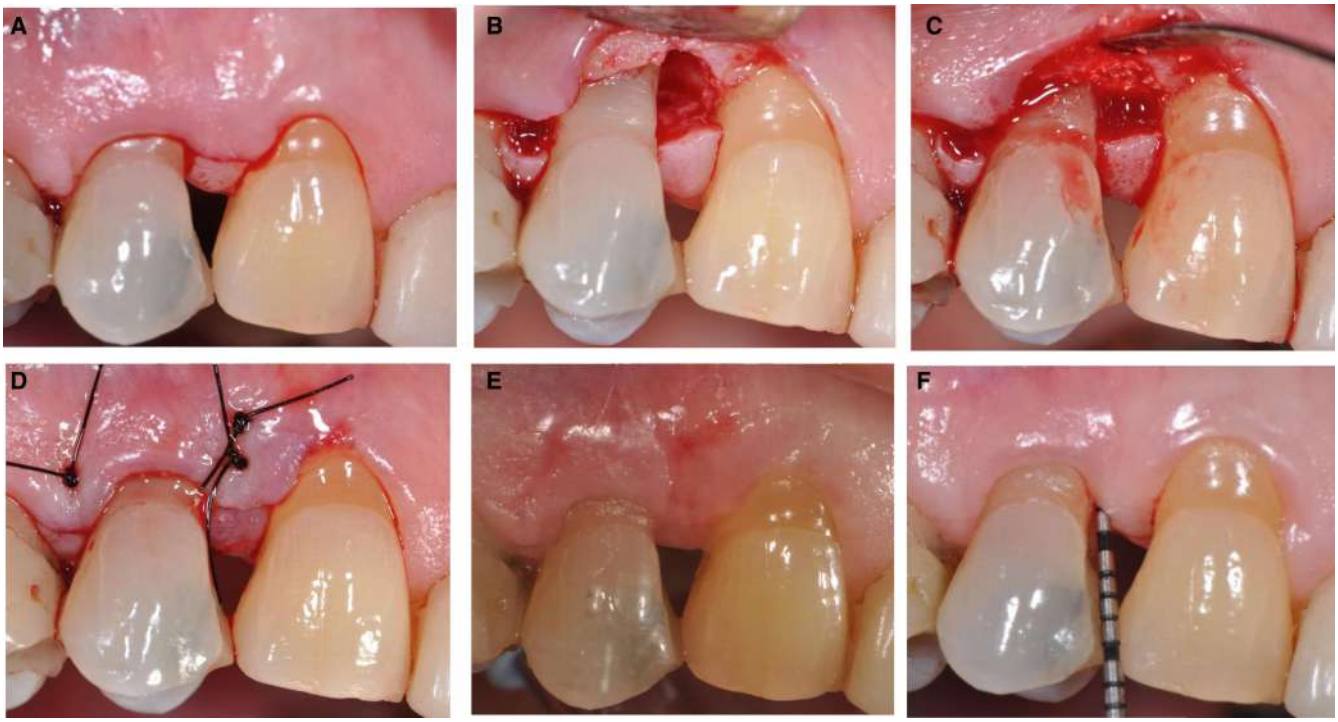

FIGURE 2 Treatment of a periodontal intraosseous defect with a buccal Single Flap Approach (Trombelli et al[17,18]) and rh-PDGF-BB plus β-TCP. A, A buccal envelope flap without vertical releasing incisions is elevated. Sulcular incisions are made following the gingival margin of the teeth included in the surgical area. The mesio-distal extension of the flap is kept limited while ensuring access for defect debridement. An oblique or horizontal, butt-joint incision is made at the buccal aspect of the interdental papilla overlying the intraosseous defect. An adequate amount of supracrestal soft tissue remains connected to the undetached papilla to ensure subsequent flap adaptation and suturing. B, A microsurgical periosteal elevator is used to raise a flap only on one side (buccal or oral), leaving the other portion of the interdental supracrestal soft tissues undetached. C, The intraosseous component of the defect is filled with β-TCP mixed with rh-PDGF-BB. D, For wound closure, a horizontal internal mattress suture is placed between the flap and the base of the attached papilla to ensure repositioning of flap. A second internal mattress suture (vertical or horizontal) is placed between the most coronal portion of the flap and the most coronal portion of the papilla as needed. E, Clinical aspect at suture removal (2 wk postsurgery). F, At 6 mo postsurgery, pocket probing depth amounts to 4 mm (reprinted from Schincaglia et al[21]). β-TCP, beta-tricalcium phosphate; rh-PDGF-BB, recombinant human platelet-derived growth factor–BB

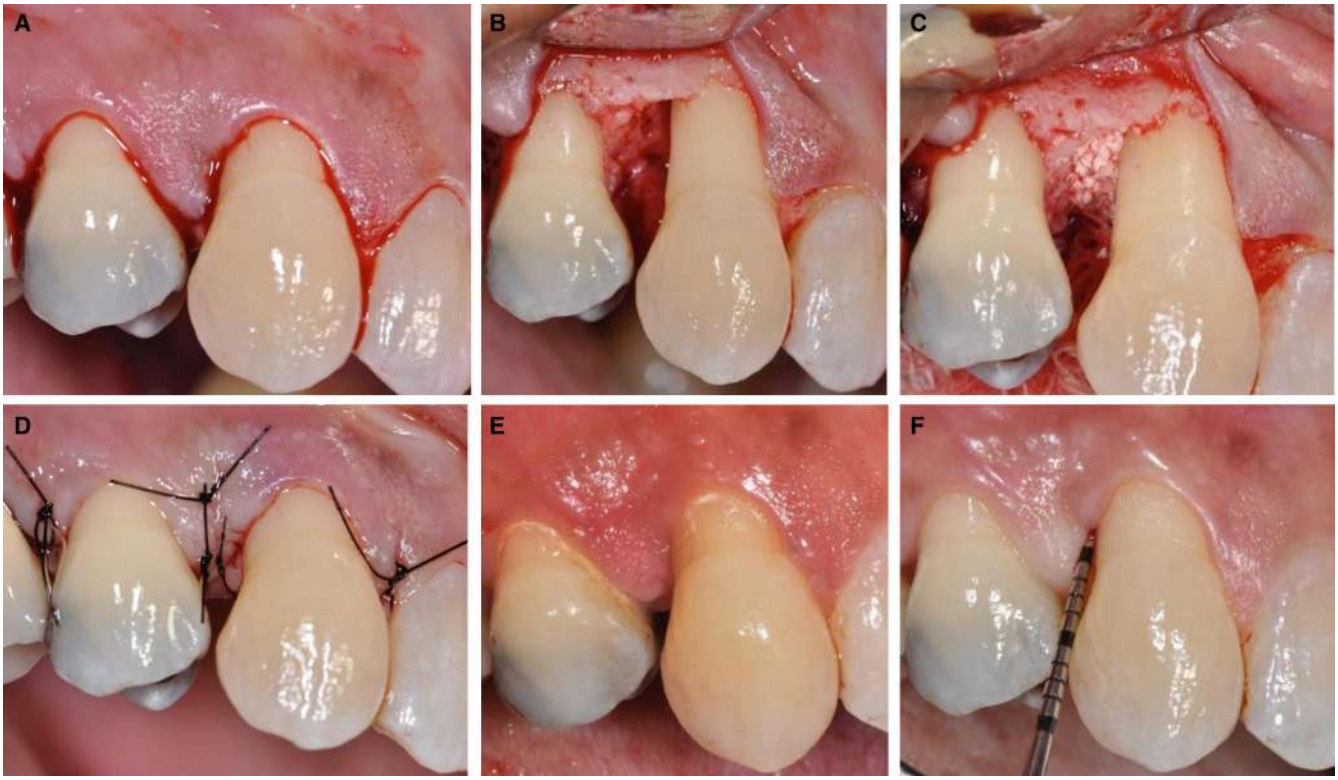

FIGURE 3 Treatment of a periodontal intraosseous defect with a Double Flap Approach (SPPF; Cortellini et al[55]) and rh-PDGF-BB plus β-TCP. A, An envelope flap without vertical releasing incisions is elevated on either the buccal or palatal aspect. Sulcular incisions are made following the gingival margin of the teeth included in the surgical area. The mesio-distal extension of the flap is kept limited while ensuring access for defect debridement. An incision is made at the buccal aspect of the interdental papilla overlying the intraosseous defect according to the SPPF.[55] B, A microsurgical periosteal elevator is used to raise a flap on both buccal and palatal sides. C, The intraosseous component of the defect is filled with β-TCP mixed with rh-PDGF-BB. D, Primary closure is achieved according to the suturing technique of the SPPF.[55] First, a horizontal, "offset" internal mattress suture is placed in the defect-associated interdental space. The interdental tissue above the defect is then closed with two interrupted sutures. E, Clinical aspect at suture removal (2 wk postsurgery). F, At 6 mo postsurgery, pocket probing depth amounts to 3 mm (reprinted from Schincaglia et al[21]). β-TCP, beta-tricalcium phosphate; rh-PDG-BB, recombinant human platelet-derived growth factor–BB; SPPF, simplified papilla preservation flap

Secondary outcomes

Both the Single Flap Approach and the Double Flap Approach resulted in a minimal increase in interproximal gingival recession (0.1 ± 0.7 and 0.4 ± 1.3, respectively), without a significant intergroup difference. Moreover, when combined with recombinant human platelet-derived growth factor–BB plus beta-tricalcium phosphate, the single flap approach resulted in greater, although not significantly, clinical attachment gain and probing depth reduction than the double flap approach. Mean 6-month clinical attachment gain and probing depth reductions were 4.0 and 4.1 mm, respectively, in the single flap approach group, and 3.2 and 3.6 mm, respectively, in the double flap approach group.

2.7.2 | What is the effect of the regenerative technology on the invasiveness of the regenerative treatment of intraosseous defects?

2.7.2.1 | *Periodontal regenerative treatment vs open flap debridement*

The list of studies contributing this section as well as their main characteristics and findings are reported in Table 3.

All studies incorporated an evaluation of the effect of a regenerative technology on the invasiveness of open flap debridement in the treatment of an intraosseous defect. The following regenerative/reconstructive technologies were considered: guided tissue regeneration with resorbable[43] or nonresorbable[45] membranes, enamel matrix derivative alone[42,44] or in combination with deproteinized bovine bone mineral.[42,46] Invasiveness was evaluated in terms of postoperative pain, morbidity, postoperative complications, surgery-related chair time, and costs, as well as patient perception of the outcomes at 1 year following treatment administration. All studies included an evaluation of the clinical outcomes of the investigated procedures, while only one study reported radiographic outcomes.[42]

Questionnaires and the visual analog scale were used to evaluate the self-reported levels of pain perceived during either the surgical procedure[42–44] or the early healing phase.[42–44,46]

Intraoperative pain

For intraoperative pain levels, no significant effect of the adjunctive use of a resorbable membrane was reported in the study by Cortellini et al[43]—where pain was assessed on a 100-mm visual

TABLE 3 Main findings of the included studies comparing periodontal regenerative treatment and open flap debridement for parameters related to invasiveness

	Intervention 1	Intervention 2					
First author (year)	Flap design and regenerative technology	Flap design used to perform OFD	Intraoperative pain and hardship of the procedure	Postoperative pain and dose of analgesics	Postoperative morbidity and complications	Surgery-related chair time	Costs	Other parameters
Cortellini (2001)	SPPT + resorbable membrane	SPPT	*Intraoperative pain* 30.4% and 28.6% of patients reported moderate pain following Intervention 1 and 2, respectively, with no significant difference in pain intensity (Intervention 1: 14 ± 14 VAS units; Intervention 2: 21 ± 15 VAS units) *Hardship of the procedure* No significant difference in the hardship of the procedure between Intervention 1 (VAS units 24 ± 25) and Intervention 2 (VAS units 22 ± 23) was reported	*Postoperative pain* No significant difference in the prevalence of subjects experiencing postoperative pain after Intervention 1 and 2 was reported Postoperative pain level after Intervention 1 and 2 was 28.1 ± 20 and 26.4 ± 17.6 VAS units, respectively No significant difference in pain duration between Intervention 1 and 2 (14.1 ± 15.6 vs 24.7 ± 39.1 h, respectively) was reported	*Postoperative morbidity* 35.7% and 32.1% of patients reported interference with daily activities after Intervention 1 and 2, respectively, with no significant difference in the duration of the interference (Intervention 1: 2.7 ± 2.3 d; Intervention 2: 2.4 ± 1.3 d) *Postoperative complications* During the 1st week after surgery, postoperative edema was significantly more prevalent after Intervention 1 During the 1st week after surgery, the prevalence of postoperative hematoma was 7.3% and 5.4% after Intervention 1 and 2, respectively Suppuration was never observed after either Intervention 1 or 2 Incidence of membrane exposure at 3 wk following Intervention 1: 53.3%	Intervention 1 was significantly longer than Intervention 2 (98.7 ± 45.7 min vs 74.9 ± 33.6, respectively)		

TABLE 3 (Continued)

	Intervention 1	Intervention 2					
First author (year)	Flap design and regenerative technology	Flap design used to perform OFD	Intraoperative pain and hardship of the procedure	Postoperative pain and dose of analgesics	Postoperative morbidity and complications	Surgery-related chair time	Costs	Other parameters
Tonetti (2004)	MPPT/SPPT + EMD	MPPT/SPPT	*Intraoperative pain* 35% and 27% of patients reported moderate intraoperative pain after Intervention 1 and 2, respectively, with no significant difference in pain intensity (Intervention 1: 20.5 ± 15.7 VAS units; Intervention 2: 18.4 ± 15.6 VAS units) *Hardship of the procedure* No significant differences in the hardship of the procedure was reported for Intervention 1 (28 ± 25 VAS units) and Intervention 2 (23 ± 24 VAS units)	*Postoperative pain* No significant difference in the prevalence of patients reporting postoperative pain after Intervention 1 or 2 (50% vs 58%, respectively) was observed No significant difference in pain level was reported after Intervention 1 and 2 (VAS units: 28 ± 20 vs 31 ± 23, respectively) No significant difference in pain duration was reported after Intervention 1 and 2 (31 ± 58 vs 27 ± 31 h, respectively) *Number of analgesics* No significant difference in the number of analgesics was reported after Intervention 1 (4.3 ± 4.5) and Intervention 2 (5.3 ± 5.2)	*Postoperative morbidity* 29.5% and 23.8% of patients reported interferences with daily activities after Intervention 1 and 2, respectively Interference with daily activity: Intervention 1: 3.6 ± 2.5 d, Intervention 2: 3.2 ± 2.1 d *Postoperative complications* No significant differences were observed after Intervention 1 and 2 in terms of: • postoperative edema • postoperative hematoma • wound dehiscence (complicated healing was observed in 21.7% and 19.2% of subjects treated with Intervention 1 and 2, respectively) • root sensitivity • suppuration (never observed)	Although not significantly, Intervention 1 was longer than Intervention 2 (80 ± 34 vs 76 ± 36 min, respectively)		*Patient perception of the outcomes 1 y after treatment* No significant differences in terms of patient perception of the outcomes at 1 y after Intervention 1 and 2 were reported
Cortellini (2011)	M-MIST + EMD	M-MIST	*Intraoperative pain* No intraoperative pain was reported by patients undergoing either Intervention 1 or Intervention 2 *Hardship of the procedure* None of the treated patients reported personal feeling of hardship of the procedure	*Postoperative pain* Discomfort was reported by 2 patients treated with Intervention 1 (VAS units 11.5 ± 0.7) and by 3 patients treated with Intervention 2 (VAS units 10.7 ± 2.1) *Number of analgesics* After Intervention 1, 4 patients needed rescue analgesics (average number of tablets: 0.3 ± 0.6). After Intervention 2, 3 patients needed analgesics (average number of tablets: 0.4 ± 0.7)	*Postoperative complications* No edema and hematoma were noted after both Intervention1 and 2 During the first 6 wk after surgery, primary intention closure was maintained in all treated sites	Intervention 1: 54.2 ± 7.4 min; Intervention 2: 52.9 ± 5.6 min		

TABLE 3 (Continued)

First author (year)	Intervention 1: Flap design and regenerative technology	Intervention 2: Flap design used to perform OFD	Intraoperative pain and hardship of the procedure	Postoperative pain and dose of analgesics	Postoperative morbidity and complications	Surgery-related chair time	Costs	Other parameters
Cortellini (2011)	M-MIST + EMD + DBBM	M-MIST	*Intraoperative pain* No intraoperative pain was reported by patients treated with either Intervention 1 or Intervention 2 *Hardship of the procedure* None of the treated patients reported personal feeling of hardship of the procedure	*Postoperative pain* Discomfort was reported by 4 patients treated with Intervention 1 (12.3 ± 3.1 VAS units) and by 3 patients treated with Intervention 2 (10.7 ± 0.7 VAS units) *Number of analgesics* After Intervention 1 and Intervention 2, 4 and 3 patients, respectively, needed rescue analgesics The average number of tablets used was 0.5 ± 1 after Intervention 1 and 0.4 ± 0.7 after Intervention 2	*Postoperative complications* No edema or hematoma were observed after both Intervention1 and 2 During the first 6 wk after surgery, primary intention closure was maintained at all sites except one treated with Intervention 1	Intervention 1: 58.9 ± 6.2 min; Intervention 2: 52.9 ± 5.6 min		
Cortellini (2017)	MPPT/buccal and lingual mucoperiosteal flaps + nonresorbable (e-PTFE) membrane	MWF			-		Average estimated costs of interventions were higher for Intervention 1 (1183€) compared with Intervention 2 (549€) Mean cumulative costs for Intervention 2:501.27 ± 210.54€ (Initially higher costs partly offset by lower need and cost for retreatment) Mean cumulative costs for Intervention 1: 159.00 ± 88.95 € (buccal and lingual mucoperiosteal flaps plus nonresorbable membrane) or 99.79 ± 54.14 € (MPPT plus nonresorbable membrane)	*Lost teeth* Over 20 y, two teeth were lost after Intervention 2. No teeth were lost after Intervention 1 *Disease recurrence* Over 20 y, patients undergoing Intervention 2 and 1 experienced 15 and 11 recurrences, respectively

TABLE 3 (Continued)

First author (year)	Intervention 1	Intervention 2						
	Flap design and regenerative technology	Flap design used to perform OFD	Intraoperative pain and hardship of the procedure	Postoperative pain and dose of analgesics	Postoperative morbidity and complications	Surgery-related chair time	Costs	Other parameters
Aslan et al. (2020)	EPP+EMD+DBBM	EPP	*Intraoperative pain* No intraoperative pain was reported by patients undergoing either Intervention 1 or Intervention 2 *Hardship of the procedure* None of the treated patients reported personal feeling of hardship of the surgical procedure at the end of the intervention	*Postoperative pain* No significant difference was observed between Intervention 1 and Intervention 2 in terms of postoperative discomfort. Slight discomfort was reported by 2 patients treated with Intervention 1 (9.33 ± 9.03 VAS units) and by 1 patient treated with Intervention 2 (8.33 ± 9.03 VAS units) *Number of analgesics* No significant difference in the number of analgesics was reported after Intervention 1 (0.87 ± 0.74) and Intervention 2 (0.73 ± 0.88)	*Postoperative complications* No edema or hematoma were observed after both Intervention1 and Intervention 2	Intervention 1 was significantly longer than Intervention 2 (65.4 ± 10.94 vs 55.07 ± 7.86 min, respectively)		

Abbreviations: DBBM, deproteinized bovine bone mineral; EMD, enamel matrix derivative (Emdogain); e-PTFE, expanded polytetrafluoroethylene; EPP, entire papilla preservation[33]; M-MIST, modified minimally invasive surgical technique[42]; MPPT, modified papilla preservation technique[54]; MWF, modified Widman flap (Ramfjord and Nissle, 1974); OFD, open flap debridement; SPPT, simplified papilla preservation technique[55]; VAS, visual analog scale.

analog scale (guided tissue regeneration: 14 ± 14; open flap debridement: 21 ± 15; P = .305)—despite a significantly higher number of periosteal incisions being needed in the guided tissue regeneration group to achieve primary intention closure. Similarly, no effect on intraoperative pain was observed for the additional use of a biologic agent with or without a scaffold biomaterial in the other studies.[42,46] Absence of pain was reported by all patients treated with enamel matrix derivative, enamel matrix derivative plus deproteinized bovine bone mineral, and open flap debridement in the study by Cortellini and Tonetti,[42] or with enamel matrix derivative plus deproteinized bovine bone mineral, and open flap debridement in the study by Aslan et al.[46] In the study by Tonetti et al,[44] moderate intraoperative pain was recorded in 35% of patients treated with enamel matrix derivative and 27% of patients treated with open flap debridement, with no significant intergroup differences.Postoperative pain and morbidity

Irrespective of the regenerative strategy (ie, guided tissue regeneration with resorbable membrane, enamel matrix derivative alone or with deproteinized bovine bone mineral), no significant difference in visual analog scale scores related to postoperative pain were reported by patients treated with a regenerative procedure or open flap debridement. In the study by Cortellini et al,[43] more than 50% of patients treated with either resorbable membrane or open flap debridement reported no postoperative pain during the first postoperative week, while pain intensity (expressed by a visual analog scale score of 100) in the remaining patients was 28.1 ± 20 for guided tissue regeneration and 26.4 ± 17.6 for open flap debridement. No intergroup differences were observed in pain duration, which lasted on average 14.1 ± 15.6 hours in the guided tissue regeneration group and 24.7 ± 39.1 hours in the open flap debridement group. In the study by Tonetti et al,[44] 50% and 58.8% of patients treated with enamel matrix derivative and open flap debridement, respectively, experienced postoperative pain during the first postoperative week, the mean intensity of which amounted to 28 ± 20 visual analog scale units for enamel matrix derivative and 31 ± 23 visual analog scale units for open flap debridement, without significant intergroup differences. No differences between the treatment groups were observed also for pain duration (enamel matrix derivative: 31 ± 58 hours; open flap debridement: 27 ± 31 hours). Consistently, similarly low visual analog scale scores for postoperative discomfort were reported following treatment with enamel matrix derivative (11.5 ± 0.7) and open flap debridement (10.7 ± 2.1) in the study by Cortellini and Tonetti.[42] Based on results from two studies, postoperative pain levels appear not to be influenced by the combination of enamel matrix derivative and deproteinized bovine bone mineral. In this respect, patients treated with enamel matrix derivative plus deproteinized bovine bone mineral or open flap debridement reported a similar, slight discomfort (enamel matrix derivative + deproteinized bovine bone mineral: 12.3 ± 3.1; open flap debridement: 10.7 ± 2.1, as assessed with a visual analog scale score 1 week after surgery) in the study by Cortellini and Tonetti,[42] and showed no difference in either the prevalence of postoperative slight discomfort (enamel

matrix derivative + deproteinized bovine bone mineral: 13.3%; open flap debridement: 6.7%) or postoperative pain intensity, as assessed on a visual analog scale during the first post operative week (enamel matrix derivative + deproteinized bovine bone mineral: 9.33 ± 9.03; open flap debridement: 8.33 ± 9.38) in the study by Aslan et al.[46]

No significant differences in the dose of analgesics were reported after regenerative treatment with enamel matrix derivative alone or in combination with deproteinized bovine bone mineral compared with open flap debridement. The mean number of analgesics used during the first week following treatment with enamel matrix derivative and open flap debridement was 4.3 ± 4.5 and 5.3 ± 5.2, respectively, in the study by Tonetti et al,[44] and 0.3 ± 0.6 and 0.4 ± 0.7, respectively, in the study by Cortellini and Tonetti.[42] For studies including a comparative evaluation of enamel matrix derivative plus deproteinized bovine bone mineral and open flap debridement, the dose was 0.5 ± 1 and 0.4 ± 0.7, respectively, in the study by Cortellini and Tonetti,[42] and 0.87 ± 0.74 and 0.73 ± 0.88, respectively, in the study by Aslan et al.[46]

Studies consistently indicated that the adjunctive use of a regenerative technology does not interfere significantly on the impact of the intervention on daily activities. In the study by Cortellini et al,[43] 35.7% of patients treated with resorbable membranes and 32.1% of patients treated with open flap debridement reported that the surgical procedure interfered with daily activity for an average of 2.7 ± 2.3 and 2.4 ± 1.3 days, respectively, without significant intergroup differences. In the study by Tonetti et al,[44] interference with daily activities was reported after surgery by 29.5% and 23.8% of patients treated with enamel matrix derivative and open flap debridement, respectively. The duration of the effect (mean number of days) was similar between groups (enamel matrix derivative: 3.6 ± 2.5; open flap debridement: 3.2 ± 2.1).

Postoperative complications and surgery-related chair time

The impact of regenerative devices on postoperative complications (including edema, hematoma, suppuration, wound dehiscence, and root sensitivity) was assessed through questionnaires.

In the study by Cortellini et al,[43] the use of a resorbable membrane was associated with a significantly greater prevalence of postoperative edema compared with open flap debridement at 1-week postsurgery, while a small hematoma was observed in a minority of patients in both groups (guided tissue regeneration: 5.4%; open flap debridement: 7.3%). Suppuration never occurred.[43] Differently, the additional use of enamel matrix derivative with or without deproteinized bovine bone mineral did not have a significant impact on postoperative complications. In the study by Tonetti et al,[44] a similar frequency of postsurgical edema, hematoma, and wound dehiscence was observed after open flap debridement with/without enamel matrix derivative application. In all treated cases, the prevalence of postsurgical complications was higher during the first week after surgery and rapidly decreased thereafter. Moreover, root sensitivity occurred in 45% and 35% of patients treated with enamel matrix derivative and open flap debridement, respectively, and no significant intergroup differences were observed. In both groups, a greater prevalence of root sensitivity occurred 3 weeks after treatment and decreased over the following weeks.[44] Similar results were reported by other Authors, who reported no edema or hematoma and a low prevalence of wound dehiscence after treatment with enamel matrix derivative plus deproteinized bovine bone mineral, enamel matrix derivative alone, and open flap debridement,[42] or enamel matrix derivative plus deproteinized bovine bone mineral and open flap debridement.[46]

The magnitude of the increase in surgery-related chair time because of the adjunctive use of regenerative devices was dependent on the type and number of devices. The adjunctive use of enamel matrix derivative was associated with a slight, nonsignificant increase in chair time: the duration of the surgical procedure for the enamel matrix derivative and open flap debridement treatments was 80 ± 34 vs 76 ± 36 minutes, respectively, in the study by Tonetti et al[44] and 54.2 ± 7.4 vs 52.9 ± 5.6 minutes, respectively, in the study by Cortellini and Tonetti.[42] A significantly longer chair time compared with open flap debridement was recorded when enamel matrix derivative and deproteinized bovine bone mineral were combined (52.9 ± 5.6 vs 58.9 ± 6.2 minutes, respectively), as reported in the study by Cortellini and Tonetti.[42] Consistently, Aslan et al.[46] reported a chair time of 55.07 ± 7.86 and 65.4 ± 10.94 minutes for open flap debridement and enamel matrix derivative plus deproteinized bovine bone mineral, respectively, the intergroup difference being statistically significant. A statistically significant and clinically relevant impact of the regenerative technology on chair time was also demonstrated for guided tissue regeneration: additional 24 minutes were needed on average to place a resorbable membrane during open flap debridement.[43]

Surgery-related costs and aesthetic impairment

Surgery-related costs were evaluated in a study population randomly assigned to receive guided tissue regeneration or open flap debridement and monitored over an observation period of 20 years.[45] The higher costs paid for regenerative treatment were compensated over time by higher tooth retention and less need for surgical re-intervention/tooth replacement in the guided tissue regeneration group. Although clearly recognizing the benefits of surgical treatment in terms of "improvement of gingival health" and "tooth preservation", however, patients may consider the additional costs of the regenerative technology a disadvantage.[44]

Secondary outcomes

In the studies included in the present review, open flap debridement determined improvements in clinical outcomes (consisting in significant clinical attachment gain and probing depth reduction) compared with baseline when performed either alone or in combination with regenerative devices. The significance of the adjunctive effect of regenerative devices differed among studies. When compared with open flap debridement, the additional use of a resorbable membrane resulted in significantly higher clinical attachment gain (3.5 ± 2.1 vs 2.6 ± 1.8 mm) and a lower prevalence of residual sites

with a probing depth of 6 mm or higher (5.5% vs 18.5%) in the study by Cortellini et al.[43] The additional use of enamel matrix derivative resulted in significantly higher clinical attachment gain (3.1 ± 1.5 vs 2.5 ± 1.5 mm) and probing depth reduction (3.9 ± 1.7 vs 3.3 ± 1.7 mm) in the study by Tonetti et al,[57] but not in the study by Cortellini and Tonetti.[42] Two studies consistently reported similar clinical attachment gain and probing depth reduction for the association between enamel matrix derivative plus deproteinized bovine bone mineral and open flap debridement.[42,46]

2.7.2.2 | *Periodontal regenerative treatment based on monotherapies vs combined therapies*

Table 4 summarizes the evidence on the invasiveness of periodontal regenerative treatment performed using monotherapies or combined therapies. Comparisons included enamel matrix derivative with/without nonresorbable membrane,[39] enamel matrix derivative with/without graft material,[42,47] recombinant human fibroblast growth factor-2 with/without deproteinized bovine bone mineral,[51] deproteinized bovine bone mineral with/without enamel matrix derivative,[49] collagenated deproteinized bovine bone mineral with/without autologous periodontal ligament-derived mesenchymal stem cells,[50] and beta-tricalcium phosphate with/without recombinant human platelet-derived growth factor–BB.[48]

Postoperative pain and analgesic consumption

High heterogeneity in postoperative pain and discomfort was observed among studies comparing monotherapies and combined therapies. In four studies, regenerative treatment with either mono or combined technologies resulted in a similar perception of postoperative pain, as reported by patients 1 week after surgery.[42,47,48,50] In this respect, two studies[42,47] reported a similar prevalence and intensity of postoperative pain when enamel matrix derivative alone or in association with a scaffold biomaterial was used as a regenerative technology. In the study by Jepsen et al,[47] a similar prevalence of patients treated with enamel matrix derivative or enamel matrix derivative plus synthetic bone substitute reported an absence of pain (41.7% and 43.6%, respectively), as well as mild, moderate, and severe pain. Likewise, patients treated with enamel matrix derivative or enamel matrix derivative plus deproteinized bovine bone mineral reported a similar, slight discomfort (enamel matrix derivative: 11.5 ± 0.7, enamel matrix derivative + deproteinized bovine bone mineral: 12.3 ± 3.1, as assessed with a visual analog scale score 1 week after surgery) in the study by Cortellini and Tonetti.[42] A similar prevalence of pain, without significant intergroup differences, was also reported when beta-tricalcium phosphate was used alone or in combination with recombinant human platelet-derived growth factor–BB[48] and a similar level of mild/moderate pain was reported when collagenated deproteinized bovine bone mineral was used with/without periodontal ligament-derived mesenchymal stem cells.[50] By contrast, other studies reported a different postoperative course in terms of pain intensity among patients treated with mono vs combined therapies. While in the study by Sipos et al[39] the additional use of a membrane resulted in higher postoperative pain in patients treated with enamel matrix derivative, thus favoring enamel matrix derivative-based monotherapy, in the study by Lee et al,[49] the combination of enamel matrix derivative with deproteinized bovine bone mineral was associated with lower postoperative pain values compared with deproteinized bovine bone mineral alone, thus suggesting that the additional use of enamel matrix derivative may favorably modulate the tolerability of deproteinized bovine bone mineral monotherapy.

No significant differences in the dose of analgesics were reported after regenerative treatment performed with mono or combined technologies. In the study by Sánchez et al,[50] the dose of analgesics was not dependent on the adjunctive use of periodontal ligament-derived mesenchymal stem cells in patients treated with collagenated deproteinized bovine bone mineral. Similarly, no difference in the use of analgesics was observed by Cortellini and Tonetti[42] between patients receiving enamel matrix derivative alone or combined with deproteinized bovine bone mineral. Two patients treated with enamel matrix derivative and four patients treated with enamel matrix derivative plus deproteinized bovine bone mineral used analgesics, and the mean dose was similar between the groups (enamel matrix derivative group: 0.3 ± 0.6 pills; enamel matrix derivative + deproteinized bovine bone mineral group: 0.5 ± 1 pills).

Postoperative complications and surgery-related chair time

A high consistency was observed among studies comparing mono and combined therapies in terms of postoperative complications. The regenerative treatments compared in terms of postoperative complications were enamel matrix derivative with or without graft material (synthetic bone substitute),[47] graft material (deproteinized bovine bone mineral) with or without enamel matrix derivative,[49] and collagenated deproteinized bovine bone mineral with/without periodontal ligament-derived mesenchymal stem cells.[50] Among studies, similar findings were reported for the quality of postoperative wound healing (ie, wound closure at the defect-associated interdental papilla) as evaluated through the Early Healing Index[56] or dichotomous assessment (ie, the presence/absence of dehiscence and fenestrations).[47,49,50] In the study by Jepsen et al,[47] no differences in Early Healing Index were detected after treatment with enamel matrix derivative or enamel matrix derivative plus deproteinized bovine bone mineral at 1 and 2 weeks after surgery. Sánchez et al[50] reported similar values of Early Healing Index at 1, 2, 4, and 12 weeks after treatment with collagenated deproteinized bovine bone mineral with or without periodontal ligament-derived mesenchymal stem cells, with no significant intergroup differences at any of the observation intervals. Moreover, an absence of dehiscence or fenestrations was observed with a similar prevalence in patients receiving deproteinized bovine bone mineral alone (81.8%) or deproteinized bovine bone mineral plus enamel matrix derivative (95%) 2 weeks after surgery in the study by Lee et al.[49] Consistent with observations on the Early Healing Index, the type of therapy (mono or combined) did not show an influence on postoperative edema, swelling, hematoma, dentine hypersensitivity, and spontaneous bleeding.[39,42,47–50]

TABLE 4 Main findings of the included studies comparing monotherapies and combination therapies for periodontal regenerative procedures in terms of parameters related to invasiveness

	Intervention 1 (monotherapy)	Intervention 2 (combination therapy)					
First author (year)	Flap design and regenerative technology	Flap design and regenerative technology	Intraoperative pain and hardship of the procedure	Postoperative pain and number of analgesic tablets	Postoperative complications	Chair time	Additional parameters
Sipos (2005)	MPPT/SPPT + EMD	MPPT/SPPT + EMD + nonresorbable (e-PTFE) membrane		*Postoperative pain* Postoperative pain duration was significantly lower after Intervention 1 compared with Intervention 2 (1.4 ± 1.4 vs 3.5 ± 2.2 d, respectively)	*Postoperative complications* 6 wk after Intervention 2, 8 sites showed minor membrane exposure (1-2 mm) and 2 sites showed advanced exposure (>3 mm) Additional number of days with postoperative discomfort (mean 0.2 d, range 0-1.0 d) were recorded after membrane removal in Intervention 2	Intervention 2 was longer than Intervention 1 (73.3 ± 29.0 vs 64.8 ± 26.6 min, respectively)	
Jepsen (2008)	MPPT/SPPT + EMD	MPPT/SPPT + EMD + SBC		*Postoperative pain* Absence of postoperative pain was reported by the 41.7% of patients treated with Intervention 1 and 43.6% of patients treated with Intervention 2	*Postoperative complications* Intervention 1 and 2 resulted in: • similar prevalence of patients reporting a complete absence of postsurgical bleeding (80.6% after Intervention 1 and 79.5% after Intervention 2); • similar prevalence of patients reporting no swelling (33.3% and 30.8% after Intervention 1 and 2, respectively); • similar prevalence of sites showing optimal wound healing (EHI = 1) at 7 and 14 d after surgery		

TABLE 4 (Continued)

First author (year)	Intervention 1 (monotherapy) Flap design and regenerative technology	Intervention 2 (combination therapy) Flap design and regenerative technology	Intraoperative pain and hardship of the procedure	Postoperative pain and number of analgesic tablets	Postoperative complications	Chair time	Additional parameters
Cortellini (2011)	M-MIST + EMD	M-MIST + EMD + DBBM	*Intraoperative pain* No intraoperative pain was reported by patients receiving either Intervention 1 or Intervention 2 *Hardship of the procedure* None of the treated patients reported personal feeling of hardship of the procedure	*Postoperative pain* Discomfort was reported by 2 patients treated with Intervention 1 (11.5 ± 0.7 VAS units) and by 4 patients treated with Intervention 2 (12.3 ± 3.1 VAS units) *Number of analgesics* After Intervention 1 and Intervention 2, 4 patients in each group needed rescue analgesics The average dose (number of tablets) was 0.3 ± 0.6 after Intervention 1 and 0.5 ± 0.1 after Intervention 2	*Postoperative complications* No edema or hematoma were observed after each Intervention During the first 6 wk after surgery, primary intention closure was maintained at all sites (except from 1 site in Intervention 2 group who showed discontinuity of the interdental wound)	Intervention 1: 54.2 ± 7.4 min; Intervention 2: 58.9 ± 6.2 min	
Jayakumar (2011)	Full-thickness buccal and palatal/lingual flaps + β-TCP	Full-thickness buccal and palatal/lingual flaps + rhPDGF-BB + β-TCP		*Postoperative pain* No significant difference in postoperative pain was found between Interventions	*Postoperative complications* No significant differences in swelling, tooth mobility and fever were reported by patients receiving either Intervention 1 or 2		
Aoki (2020)	MPPT/SPPT + rhFGF-2	MPPT/SPPT + rhFGF-2 + DBBM			*Postoperative complications* No significant difference in tooth mobility was observed after Intervention 1 and 2 at 6, 12, and 24 mo after treatment		*Evaluation of the oral health related quality of life* No significant changes in the mean total OHRQL-J scores were recorded at 6, 12, and 24 mo after Intervention 1 and Intervention 2

TABLE 4 (Continued)

First author (year)	Intervention 1 (monotherapy) Flap design and regenerative technology	Intervention 2 (combination therapy) Flap design and regenerative technology	Intraoperative pain and hardship of the procedure	Postoperative pain and number of analgesic tablets	Postoperative complications	Chair time	Additional parameters
Lee (2020)	Full-thickness flap + DBBM	Full-thickness flap + EMD + DBBM		*Postoperative pain* Significantly greater postoperative pain level was recorded after Intervention 1 compared with Intervention 2 Pain duration was significantly longer after Intervention 1 compared with Intervention 2	*Postoperative complications* No significant differences in swelling severity and duration were observed between Interventions No significant differences in the prevalence of postoperatory spontaneous bleeding, ulcerations, and wound dehiscence were observed between Interventions	Intervention 2 was longer than Intervention 1 (41.3 ± 9.9 vs 38.5 ± 11.1 min, respectively) although differences did not reach statistical significance	
Sánchez (2020)	CAF or papilla preservation techniques + XBS	CAF or papilla preservation techniques + XBS + PDL-MSCs		*Number of analgesics* A higher number of analgesics was used after Intervention 2 (4.6 ± 4.2) compared with Intervention 1 (2.4 ± 3.2), although differences did not reach statistical significance *Postoperative pain* Mild/moderate postoperative pain was similarly reported after Intervention 1 or 2	*Postoperative complications* Intervention 1 and 2 resulted in similar postoperative swelling, dentine hypersensitivity and postoperative healing (as evaluated at 1, 2, 4, and 12 wk after surgery)		*Satisfaction with aesthetic appearance* Lower satisfaction was reported after Intervention 2 (7.38 ± 2.9 VAS units) compared with Intervention 1 (8.80 ± 2.82 VAS units), although the difference did not reach statistical significance *Evaluation of the patient well-being and oral health related quality of life* No significant differences in patient well-being and quality of life were reported after Intervention 1 (OHIP-14: 4.2±2.9 and 2.7±3.4, as evaluated 15 days and 12-months post-surgery, respectively) and Intervention 2 (OHIP-14:5.7±3.1 and 7.0±10.73, as evaluated 15 days and 12-months post-surgery, respectively) and Intervention 2 (OHIP-14:5.7 ± 3.1 and 7.0 ± 10.73, as evaluated 15 d and 12-mo postsurgery, respectively)

Abbreviations: β-TCP, beta-tricalcium phosphate; CAF, coronally advanced flap technique (Zucchelli and De Sanctis, 2008); DBBM, deproteinized bovine bone mineral; EHI, Early Healing Index[56]; EMD, enamel matrix derivative (Emdogain); e-PTFE, expanded polytetrafluoroethylene; M-MIST, modified minimally invasive surgical technique[42]; MPPT, modified papilla preservation technique[54]; OHIP-14: Oral Health Impact Profile; OHRQL-J, Oral Health-Related Quality of Life - Japan; PDL-MSCs, periodontal ligament-derived mesenchymal stem cells; rhFGF-2, recombinant human fibroblast growth factor-2; rhPDGF-BB, recombinant human platelet-derived growth factor–BB; SBC, synthetic bone graft substitute (mixture of 60% hydroxyapatite and of 40% of beta tricalcium phosphate); SPPT, simplified papilla preservation technique[55]; VAS, visual analog scale; XBS, xenogeneic bone substitute.

TABLE 5 Main findings of the only controlled study (split-mouth randomized controlled trial) evaluating the effect of a specific perioperative and postoperative protocol on the invasiveness of a periodontal regenerative procedure in the treatment of intraosseous defects

First author (year)	Intervention 1	Intervention 2	Postoperative pain and dose of analgesics	Postoperative morbidity and complications
	Flap design and regenerative technology	Flap design and regenerative technology		
Ozcelik et al (2008)	Full mucoperiostal buccal and lingual access flaps + EMD	Full mucoperiostal buccal and lingual access flaps + EMD + LLLT	*Postoperative pain* Significantly lower pain was reported in the first and second postoperative days by patients undergoing Intervention 2 compared with patients undergoing Intervention 1	*Postoperative complications* Significantly lower number of patients showing a pronounced gingival swelling was observed during the first postoperative week after Intervention 2 compared with Intervention 1

Abbreviations: EMD, enamel matrix derivative (Emdogain); LLLT, low-level laser therapy.

Data consistently showed a longer surgery-related chair time for combined therapies compared with monotherapies. To what extent chair time was prolonged because of application of the combined therapy seemed to vary depending on the regenerative technology. In particular, the mean additional time to combine enamel matrix derivative to a scaffold biomaterial varied from 3[49] to 5 minutes,[42] while it amounted to an 8 extra minutes to place a membrane at a site treated with enamel matrix derivative.[39] In all studies, however, the differences in surgery-related chair time between monotherapies and combined therapies did not reach statistical significance.

Quality of life and satisfaction with aesthetic appearance

Two recent studies evaluated the quality of life, as assessed according to the Oral Health Impact Profile Questionnaire - 14[50] and the Oral Health-Related Quality of Life tool,[51] in patients undergoing regenerative surgery with mono vs combined therapy. While one study did not find a significant impact of the regenerative strategy (recombinant human fibroblast growth factor-2 vs recombinant human fibroblast growth factor-2 plus deproteinized bovine bone mineral) on the quality of life, as evaluated at 6, 12, and 24 months after surgery,[51] in the other study, patients' well-being and quality of life at 15 days and 1 year after treatment were found to be superior following monotherapy (deproteinized bovine bone mineral) compared with combined therapy (periodontal ligament-derived mesenchymal stem cells plus deproteinized bovine bone mineral).[50]

In the study by Sánchez et al,[50] patients receiving collagenated deproteinized bovine bone mineral with or without periodontal ligament-derived mesenchymal stem cells were asked to rate on a 10-mm visual analog scale their satisfaction with the aesthetic appearance of the surgical site at 12 months after surgery. No significant difference in patient satisfaction was recorded between mono and combined therapy. From an objective standpoint, a mean gingival recession increase of 1 mm was observed in both groups, without statistically significant intergroup differences.

Secondary outcomes

From a clinical standpoint, both mono and combined therapies resulted in significant improvements in the clinical parameters, with the majority of studies failing to find differences between the two types of therapies at a follow-up ranging from 6 to 24 months. Similar clinical efficacy in terms of clinical attachment gain and probing depth reduction were reported for the following comparisons: enamel matrix derivative vs enamel matrix derivative plus deproteinized bovine bone mineral[42,47]; enamel matrix derivative vs enamel matrix derivative plus resorbable membrane[39]; deproteinized bovine bone mineral vs deproteinized bovine bone mineral plus enamel matrix derivative[49]; deproteinized bovine bone mineral vs deproteinized bovine bone mineral plus periodontal ligament-derived mesenchymal stem cells[50]; and recombinant human fibroblast growth factor-2 vs recombinant human fibroblast growth factor-2 plus deproteinized bovine bone mineral.[51] Differently, one study reported significantly higher clinical attachment gain and probing depth reduction after treatment with combined therapy (beta-tricalcium phosphate plus recombinant

FIGURE 4 Risk of bias summary of studies evaluating the invasiveness of: A, Different access flap designs; B, Periodontal regenerative treatments vs open flap debridement; C, Monotherapies vs combined regenerative therapies; and D, Different perioperative and postoperative protocols. RCTs, randomized controlled trials

human platelet-derived growth factor–BB) compared with monotherapy (beta-tricalcium phosphate) at 3 and 6 months after treatment.[48]

2.7.3 | May specific perioperative or postoperative protocols reduce the invasiveness of the intervention?

One randomized controlled trial evaluating the adjunctive effect of a low-level laser biostimulation at intraosseous defects treated with enamel matrix derivative contributed this section.[26] The main study characteristics and findings are reported in Table 5. Biostimulation was performed with a diode laser with a wavelength of 588 nm and with an overall energy density per irradiation in 5 minutes of 4 J/cm^2. Overall, laser biostimulation was administered in sessions of 10 minutes each (5 minutes on the buccal aspect and 5 minutes on the lingual/palatal aspect) during surgery (after defect debridement), at the completion of the surgical treatment, and each postoperative day up to 5 days postsurgery.

The adjunctive use of low-level laser bio stimulation resulted in lower pain values (as reported on a 100-mm visual analog scale) during the entire postoperative period (from the first to the seventh day after surgery), with the difference between treatment groups reaching statistical significance at day 1 and day 2 following surgery.

This finding was paralleled by a significantly lower swelling in the first postoperatory week in patients who underwent biostimulation compared with controls.

Satisfaction with aesthetic appearance was not evaluated through questionnaires, but data on gingival recession increase were available from the study.

Secondary outcomes

The adjunctive use of biostimulation on enamel matrix derivative-based treatment resulted in a significantly lower increase in interproximal gingival recession at 6 and 12 months after surgery. Also, significant probing depth reduction and clinical attachment gain

were observed at the 6- and 12-month follow-up in both groups, without significant intergroup differences.

2.8 | Risk of bias

The risk of bias in the included studies is illustrated in Figure 4.

The only randomized controlled trial evaluating the effect of flap design on the invasiveness of a periodontal regenerative procedure[21] was classified as "some concerns" (Figure 4A).

All randomized controlled trials comparing the invasiveness of periodontal regenerative treatments and open flap debridement[42–46] were classified as "some concerns" (Figure 4B).

The risk of bias, as evaluated in studies comparing mono and combined therapies in terms of invasiveness, is illustrated in Figure 4C. Six out of seven studies[39,42,47–49,51] were classified as "some concerns", while one quasi-randomized study[50] was at low risk of bias.

Figure 4D shows the risk of bias of the single study evaluating the effect of a specific perioperative and postoperative protocol based on low-level laser therapy on invasiveness.[26] The study was judged to be at a high risk of bias.

3 | CONCLUDING REMARKS

The present systematic review focused on aspects (related to either the surgical procedure per se or to perioperative and postoperative adjunctive treatments) that may reduce the invasiveness of the intervention. A systematic literature search was performed for controlled clinical trials, and 13 articles were included. Although pertinent scientific evidence could be retrieved for each focused question of the review, it must be considered that two out of the three focused questions (1 and 3) were supported by evidence from a single study, and the risk of bias was classified as "some concerns" for the majority of included studies.

Based on the results of one randomized controlled trial[21] showing "some concerns" when evaluated for risk of bias, the selection of flap design was demonstrated to impact significantly on the invasiveness of the regenerative procedure. In particular, by preferring the Single Flap Approach[17,18] to the Double Flap Approach based on papilla preservation techniques,[54,55] better quality of early wound healing and a more tolerable postoperative course (in terms of postoperative pain and need for analgesics) can be obtained when performing a regenerative surgery with a bioactive agent and a graft material. Also, the Single Flap Approach allows for maintaining (if not improving, as suggested by a nonsignificant tendency to greater clinical attachment gain and probing depth reduction compared with the Double Flap Approach) a high reconstructive performance of the procedure.[21] This observation is confirmed by recent systematic reviews, where the Single Flap Approach was associated with 1 and 0.93 mm greater clinical attachment gain and probing depth reduction, respectively, compared with the Double Flap Approach,[28] or was characterized by the best clinical performance among flap designs used within an enamel matrix derivative-based regenerative procedure.[30]

Overall, data from the present review seem to indicate that, whenever appropriate, the Single Flap Approach or its variants[17–19,58] should be considered as the flap of choice to perform a minimally invasive periodontal regenerative procedure. The use of the Double Flap Approach should be restricted to cases where defect anatomy prevents the possibility of performing adequate root and defect instrumentation through access created on only one aspect (buccal or lingual/palatal).[59] Among patients undergoing the Single Flap Approach in the study by Schincaglia et al,[21] none was excluded due to insufficient surgical access or a defect extension preventing adequate root and defect instrumentation, thus indicating that Single Flap Approach is applicable in the vast majority of cases. This consideration is further confirmed by epidemiological studies on the morphology of intraosseous defects that suggest that a single surgical access may represent a suitable option in a substantial proportion of vertical osseous defects.[60,61]

Recent systematic reviews showed that combination therapies (ie, guided tissue regeneration + graft or enamel matrix derivative + graft) are generally superior (in terms of clinical attachment gain and residual probing depth) to either monotherapies or open flap debridement.[3,12] Combination therapies are currently considered the strategy of choice when treating (a) defects with unfavorable morphology (ie, characterized by a dominant one-wall component and wide defect angle), where the space-making effect of membranes and graft may limit flap collapse and enhance the stability of the blood clot[3,40]; and (b) defects located in aesthetically sensitive areas, where they have been shown to mitigate the interproximal gingival recession increase compared with monotherapies or open flap debridement.[62–64] Within the present systematic review, it was evaluated if and in which clinical scenarios the simplification of the regenerative strategy (through the selection of a monotherapy or open flap debridement) may favorably impact on invasiveness while maintaining a high clinical performance of the intervention. Based on findings from the included studies (all classified as "some concerns" when evaluated for risk of bias), the impact varies according to the regenerative technology that is considered, favoring monotherapies in some cases but combination therapies under other conditions. In particular: (a) when treating a three-wall intraosseous defect with enamel matrix derivative, the additional use of a nonresorbable expanded polytetrafluoroethylene membrane significantly increases the invasiveness of the intervention in terms of pain, complications, and surgery-related chair time. Moreover, its use is not justified by an enhancement of clinical outcomes[39]; (b) the application of enamel matrix derivative at one-wall intraosseous defects receiving deproteinized bovine bone mineral may limit postoperative pain intensity and duration,[49] probably because of the anti-inflammatory effect of enamel matrix derivative[23]; (c) the additional use of a nonautogenous (synthetic or xenogeneic) graft material at defects with varying morphology receiving either a bioactive agent (enamel matrix derivative, recombinant human platelet-derived growth factor–BB, recombinant

human fibroblast growth factor-2) or periodontal ligament-derived mesenchymal stem cells does not affect the invasiveness of the intervention while resulting in an improvement of the clinical performance[42,47,48,50,51]; and (d) when performed through the elevation of a single flap, open flap debridement may represent a valid option to reduce surgery-related chair time and costs compared with regenerative treatment based on enamel matrix derivative with or without deproteinized bovine bone mineral, while maintaining similar clinical outcomes.[42,46]

Data from a single randomized controlled trial at high risk of bias suggest that the invasiveness of a periodontal regenerative procedure can be favorably modulated through the perioperative and postoperative application of low-level laser biostimulation.[26] It must be considered, however, that the application of low-level laser therapy is associated with additional costs and a longer chair time for its administration during surgery and additional recall visits. Moreover, the adjunctive clinical benefit of low-level laser biostimulation in periodontal therapy is still a matter of debate.[25,26,65,66] Overall, these results should be interpreted with caution, and call for further studies evaluating the potential of such technology in periodontal regenerative surgery.

4 | RECOMMENDATIONS FOR PRACTICE

According to the results of the present systematic review, the following recommendations can be given to the clinician who is willing to perform a regenerative treatment of periodontal intraosseous defects according to a minimally invasive approach:

1. The selection of a flap design based on the elevation of a single (buccal or lingual) flap positively influences the intensity of postoperative pain and improves the quality of early wound healing compared with double flaps based on papilla preservation techniques.
2. The impact of the regenerative technology on invasiveness depends on the type of device: while the adjunctive use of a membrane is associated with significantly longer surgery-related chair time and higher postoperative pain, the adjunctive use of enamel matrix derivative or a graft material improved or did not influence, respectively, the invasiveness of the intervention.
3. Compared with regenerative treatment, open flap debridement performed through the elevation of a single access flap may represent a valid option to reduce surgery-related chair time and costs. However, a histological evaluation of the nature of the reconstructed tissues at defect sites undergoing open flap debridement with single flap access is still lacking, and the presurgery conditions (eg, probing depth, defect severity, defect morphology), which may benefit from this type of approach in terms of invasiveness, have not yet been defined;
4. Intraoperative and postoperative low-level laser biostimulation of the defect site may favorably modulate the postoperative course.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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