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Complete List of Authors:	Schincaglia, Gian Pietro; Division of Periodontology, School of Dental Medicine, University of Connecticut Health Center Hebert, Eric; Division of Periodontology, School of Dental Medicine, University of Connecticut Health Center Farina, Roberto; Research Centre for the Study of Periodontal Diseases, Dipartimento Discipline Medico Chirurgiche Comunicazione e Comportamento; Simonelli, Anna; University of Ferrara, Department of Periodontology Trombelli, Leonardo; University of Ferrara, Department of Periodontology
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Single versus Double Flap Approach in Periodontal Regenerative Treatment

Gian Pietro Schincaglia [1,2]
Eric Hebert [1]
Roberto Farina [2]
Anna Simonelli [2]
Leonardo Trombelli [2,*]

[1] Division of Periodontology, School of Dental Medicine, University of Connecticut Health Center, Farmington, CT
[2] Research Center for the Study of Periodontal and Peri-Implant Diseases, University of Ferrara, Italy
[*] corresponding Author

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ABSTRACT

Aim: to compare the outcomes of a regenerative strategy based on recombinant human platelet-derived growth factor–BB (rhPDGF-BB, 0.3 mg/ml) and β-tricalcium phosphate (β-TCP) in the treatment of intraosseous defects accessed with the Single Flap Approach (SFA) versus Double Flap Approach based on papilla preservation techniques (DFA).

Materials and Methods: Fifteen and 13 defects, randomly assigned to SFA or DFA, respectively, were grafted with rhPDGF-BB + β-TCP. Probing parameters were assessed before and 6 months after surgery. Pain (VAS_{pain}) was self-reported using a visual analog scale.

Results: Twelve SFA sites and DFA 6 sites showed complete flap closure at 2 weeks post-surgery. No significant differences in 6-month changes in probing parameters and radiographic defect fill were found between groups. Significantly lower VAS_{pain} was observed in SFA group compared to DFA group at day +1, +2 and +6. A significantly greater number of analgesics were consumed in the DFA group compared to the SFA group at day +1.

Conclusions: When combined with rhPDGF-BB and β-TCP, the SFA may result in similar clinical outcomes, better quality of early wound healing, and lower pain and consumption of analgesics during the first postoperative days compared to the DFA.

CLINICAL RELEVANCE

Scientific background: The Single Flap Approach (SFA) *per se* seems to be at least as clinically effective as the double flap approach (DFA) performed according to the papilla preservation techniques (Cortellini et al. 1995, 1999) to treat intraosseous defects.

Principal findings: When combined with recombinant human platelet-derived growth factor (rhPDGF-BB) and β-tricalcium phosphate (β-TCP), SFA resulted in better quality of early wound healing, lower pain and dose of analgesics during the first postoperative days compared to DFA.

Practical implications: When applicable due to defect morphology, the SFA seems to represent a less invasive option to access intraosseous defects for treatment with rhPDGF-BB + β-TCP compared to DFA.

INTRODUCTION

The Single Flap Approach (SFA) is a simplified, minimally-invasive surgical approach to access intraosseous periodontal defects (Trombelli et al. 2007, 2009, 2010). The basic underlying principle of the SFA consists of the elevation of a limited mucoperiosteal flap to allow access to the defect from either the buccal or oral aspect only, depending on the main buccal/oral extension of the lesion, allowing the interproximal supracrestal gingival tissues to remain intact. The SFA represents a valuable reconstructive procedure *per se* (Trombelli et al. 2010, 2012), and a pilot study (Trombelli et al. 2012) indicated that the SFA is at least as clinically effective as the elevation of a flap at both buccal and oral aspects according to the papilla preservation techniques (Cortellini et al. 1995, 1999). In addition, the SFA was effective when used in association with various reconstructive technologies, including graft materials, membranes and bioactive agents (Trombelli et al. 2009, 2010, Farina et al. 2013, 2014). Cortellini & Tonetti (2009) published a similar surgical approach, namely the modified MIST, which is based on the elevation of a single buccal flap and that was successfully used alone or in combination to different regenerative technologies to treat deep intraosseous defects (Cortellini & Tonetti 2011).

It is well established that currently available regenerative technologies may enhance the clinical performance of access flap protocols (Trombelli et al. 2002; Needleman et al. 2006; Esposito et al. 2009). In particular, the association of recombinant human platelet derived growth factor (rhPDGF-BB) with graft materials in the treatment of periodontal defects has been evaluated *in vivo* (Camelo et al. 2003, Nevins et al. 2003, 2005, McGuire et al. 2006, Rosen et al. 2011, Thakare & Deo 2012, Nevins et al. 2013; see Trombelli & Farina 2008, Kaigler et al. 2011, Darby & Morris 2013 for review). When the combination of two different doses of rhPDGF-BB (0.3 and 1.0 mg/ml) with β-tricalcium phosphate (β-TCP) were compared with β-TCP alone in the treatment of deep intra-

osseous defects, the rate of gain in clinical attachment was shown to be more rapid in the low-dose rhPDGF-BB + β-TCP group when compared to the control group at 3 months post-surgery. Although no significant difference in clinical attachment gain was observed between sites treated with or without rhPDGF-BB at 6 months following surgery, both rhPDGF-BB formulations were significantly more effective than the control group in the improvement of linear bone growth and percentage of bone defect fill at 6 months (Nevins et al. 2005).

The objective of the present investigation was to compare the clinical, radiographic, and patient-centered outcomes of a regenerative strategy based on the use of rhPDGF-BB + β-TCP in deep intraosseous periodontal defects accessed with SFA versus DFA.

MATERIALS & METHODS

Ethical aspects

The study protocol was approved from the Internal Review Board of the University of Connecticut, Farmington, Connecticut (US) (protocol number: #12-098-2; date of approval: 18/1/2012). All the clinical procedures were performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines (GCPs). Each patient signed an informed consent form before participation.

Study design

The study was designed as a single center, parallel-arm, double-blind, randomized controlled trial. Except for the soft tissue management (SFA or DFA), the clinical procedures for both groups were identical.

The Research Centre for the Study of Periodontal and Peri-implant Diseases, University of Ferrara, Italy, was the Coordinating Center and was responsible for protocol preparation, treatment allocation and radiographic measurements. The Division of Periodontology, School of Dental Medicine, University of Connecticut Health Center, Farmington, Connecticut (US), was the Clinical Center and was responsible for patient recruitment, treatment and collection of pertinent documentation.

Visit schema and procedures for each visit are reported in Appendix 1.

Screening procedures

Patients were recruited among those diagnosed with chronic or aggressive periodontitis in the post-graduate periodontology clinic at University of Connecticut Health Center. An initial evaluation, including medical and dental history, clinical examination, and radiographic examination, was conducted to determine patient eligibility for the study.

Inclusion and exclusion criteria are reported in Appendix 2. Briefly, patients with at least one intraosseous periodontal defect associated with probing depth ≥ 6mm were included in the study.

Pre-surgical procedures

Each patient had full-mouth sessions of scaling and root planing using mechanical and hand instrumentation and received personalized oral hygiene instructions. The surgical phase was delayed until the patient achieved a minimal residual inflammation and optimal soft tissue conditions at the defect site. Patients did not enter the surgical phase of the trial until full-mouth plaque score (O'Leary et al. 1972) and full-mouth bleeding score were lower than 20%.

Allocation and allocation concealment

Each eligible patient was given a subject randomization number. An independent investigator, not involved in clinical procedures, generated the randomization list for treatment allocation using a freeware (http://www.graphpad.com/quickcalcs/randomize1.cfm). This information was concealed in sealed envelopes, which were opened before the surgical treatment. The surgeon was not aware of the group assignment (SFA or DFA) until the day of surgery. The examiners responsible for clinical (E.H., A.S.) and radiographic (A.S.) measurements, as well as the patient, remained blinded with respect to treatment allocation.

Surgical procedures

The same experienced operator (G.P.S.) performed all surgeries using 4.0 magnifying loops. The site of surgery was anesthetized using lidocaine-epinephrine 1:100,000. Transcrevicular probing (bone sounding) was performed pre-surgery to determine the characteristics of the bony defect, such as defect morphology and extension, probing bone level, and horizontal component of bone loss.

In the SFA group, the surgical access was obtained through the elevation of a buccal or oral mucoperiosteal flap for defects with a prevalent extension (as assessed by pre-operative bone sounding) on the buccal or oral side, respectively, as previously detailed (Trombelli et al. 2007, 2009) (Figure 1). SFA consisted of an envelope flap. The mesio-distal extension of the flap was kept as limited as possible while ensuring proper access for defect debridement and graft positioning and stabilization. Sulcular incisions were performed on the buccal or oral side (for defects with a prevalent extension on the buccal or oral side, respectively) following the gingival

margin of the teeth included in the surgical area. In the interproximal area (i.e., at the level of the interdental papilla) overlying the intraosseous defect, an oblique or horizontal incision was made following the profile of the underlying bone crest. The distance between the tip of the papilla and the apico-coronal level of the interdental incision was based on the apico-coronal dimension of the supracrestal soft tissues. The greater the distance from the tip of the papilla to the underlying bone crest (as assessed by pre-operative probing), the more apical (i.e., close to the base of the papilla) the incision in the interdental area. This was done to provide an adequate amount of untouched supracrestal soft tissue connected to the undetached papilla on the opposite side to ensure flap adaptation and suturing and to warrant proper access to the intraosseous defect for debridement and graft positioning. All defects were approached by elevating a flap only on the buccal or oral side and leaving the opposite portion of the interdental supracrestal soft tissues undetached. The full-thickness elevation of the marginal portion of the flap was performed with a microsurgical periosteal elevator. Partial-thickness dissection was limited to the apical portion of the flap to ensure flap replacement and suturing without tension.

In the DFA group, the defect-associated interdental tissue was approached with surgical techniques for the preservation of the interdental papilla, namely the simplified papilla preservation flap (SPPF) (Cortellini et al. 1999) or the modified papilla preservation technique (MPPT) (Cortellini et al. 1995) based on the anatomical characteristics of the surgical site (Cortellini & Tonetti 2005) (Figure 2). Mesio-distal extension of the buccal and oral incisions was influenced by defect morphology and severity. In other words, the flap could involve the teeth adjacent to the tooth presenting the defect to ensure proper root and defect debridement. Releasing incisions were never performed. Full-thickness flap reflection was performed on both buccal and oral aspects to provide adequate visibility of the bone crest on both buccal and oral aspects.

Root and defect debridement were performed using hand and ultrasonic instruments. After surgical debridement, defects were grafted with rhPDGF-BB + β-TCP (GEM 21S®; Osteohealth Company, Shirley, NY, US). β-TCP was combined with rhPDGF-BB (0.3 mg/ml) and allowed to sit for ≥ 10 minutes to permit binding of the rhPDGF-BB protein to the β-TCP before being placed into the defect.

Wound closure was obtained according to the original suturing technique of either SFA (Trombelli et al. 2007, 2009) (Figure 1) or MPPT (Cortellini et al. 1995) and SPPF (Cortellini et al. 1999) (Figure 2) with a non-resorbable monofilament suture (Monosof™ 6.0; Covidien, Mansfield, MA, US).

Post-surgery procedures

At the end of each session, patients were prescribed a rescue analgesic (Ibuprofen 600 mg) to be used as needed. Sutures were removed at 2 weeks post-surgery. The patients were asked to abstain from mechanical oral hygiene procedures in the surgical area for 4 weeks. A 0.12% chlorhexidine mouth rinse (10 mL BID/2 wks) was used to support local plaque control. Each patient was inserted into a monthly recall program for 3 months and was reviewed according to personal needs thereafter. Each session included reinforcement of oral hygiene procedures and supragingival plaque removal. Subgingival scaling was performed following completion of the study at 6 months post-surgery.

Examiners' calibration

Before the study initiation, a calibration session was performed to evaluate (i) the intra-examiner agreement in the assessment of clinical recordings (Cohen's coefficient k= 0.86) and (ii) the intra-examiner agreement in the assessment of radiographic measurements (Kendall τ coefficient for intra-examiner agreement: 0.89).

Clinical parameters

Immediately before surgery and at 6 months post-surgery, studied parameters were recorded at 6 sites (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) of the tooth exhibiting the intraosseous defect using a periodontal probe (UNC 15, Hu-Friedy, Chicago, IL, USA) with 1-mm increments and applying approximately 0.3-N force. Measurements were rounded to the nearest mm. The following clinical measurements were performed by the same examiner (E.H): pocket probing depth (PPD), clinical attachment level (CAL), and gingival recession (REC). In addition, local bleeding score (BS) was recorded as positive when bleeding on probing was present at the surgical site.

At the completion of the intra-surgical debridement, the distance between the CEJ and the base of the defect as well as the depth of the intrabony component (measured as the distance between the deepest point of the defect and the most coronal point of the alveolar crest at the adjacent tooth) were assessed with a UNC 15 periodontal probe. The configuration of the defect with respect to the number of bony walls was also recorded.

Using digital photographs taken at 2 weeks post-surgery, wound healing was evaluated using the Early Healing Index (EHI) (Wachtel et al. 2003) by an examiner (A.S.) involved in previous trials that included the assessment of EHI (Farina et al. 2013). Kendall τ coefficient for intra-examiner

agreement for EHI was 0.97.

Radiographic parameters

Periapical radiographs were obtained immediately before surgery and 6 months after surgery. The films were digitized, and the following linear radiographic measurements were performed by the same examiner (A.S) using dedicated software (NIS Elements™; Nikon Instruments S.P.A. Campi Bisenzio, Firenze, Italy):

- CEJ-base of the defect (CEJ-BD): distance (in mm) between the CEJ and the most apical extension of the defect (i.e., where the periodontal ligament space was considered having a normal width);
- CEJ-bone crest (CEJ-BC): distance (in mm) between the CEJ and the bone crest of the adjacent tooth;
- ANGLE (Steffensen & Webert 1989): defect angle (in degrees) defined by the line connecting the most apical point of the defect and the CEJ of the tooth presenting the intraosseous defect and the line connecting the most apical point of the defect and the point where the bone crest touched the neighboring tooth.

For each patient, linear defect fill (lDF) was calculated as the difference between pre-surgery CEJ-BD and 6-month CEJ-BD.

Patient-centered outcomes

A visual analog scale (VAS, 100 mm) was used to assess the patient's self-perceived pain (VAS_{pain}). Self-recordings of VAS_{pain} were performed immediately after surgery, at 8 a.m., 1 p.m. and 8 p.m. on each postoperative day up to the 3rd day, and at 8 p.m. on the 4th, 5th and 6th, 7th and

14th postoperative day.

Patients were also asked to record the postoperative consumption (timing, dosage) of the rescue analgesic.

Statistical analysis

Statistical software (Statistica v8.0; Tulsa, OK, US) was used for data analysis. A *per protocol* analysis was conducted with the patient being regarded as the statistical unit. The aspect of the tooth topographically related to the intraosseous defect presenting the largest CAL value at pre-surgery was used for comparisons and statistical analysis of outcome variables. Data was expressed as mean ± standard deviation (SD).

Intra-group and inter-group comparisons were performed with the Wilcoxon signed-rank test and the Mann Whitney rank-sum test, respectively. For nominal and ordinal data the Chi-square test and Mann-Whitney rank-sum test were used, respectively. Two-way Friedman's ANOVA was used to evaluate the effect of time and treatment on VAS_{pain}. The level of significance was set at 5% for all statistical tests.

Sample size was set *a priori* at 15 subjects/treatment arm based on logistic considerations, the results of a previous RCT (Trombelli et al. 2012) and the pilot nature of this trial. A post-hoc calculation of the statistical power of the study, performed assuming a standard deviation of CAL change of 1 mm and using the *per protocol* size of each treatment group, revealed that the study

had a power of 82.7% to detect a inter-group difference in CAL change of 1.1 mm (as previously reported by Trombelli et al. 2012) using a parametric test with a 0.05 two-sided significance level.

RESULTS

Study population

Twenty-nine patients (15 in SFA group, 14 in DFA group), each contributing 1 defect, were included. The experimental period was comprised between July 2012 (date of first surgery) and August 2014 (last follow-up visit). In the SFA group, 13 defects were accessed with a buccal SFA, while 2 defects were accessed with an oral SFA. Data on the mesio-distal extension of the flap in SFA and DFA groups is reported in Table 1 as the frequency distribution of patients in each group according to the number of teeth and papillae involved in surgery. In particular, a mean of 2.7 ± 0.7 papillae were involved in each SFA procedure, while 2.5 ± 0.5 buccal papillae and 2.2 ± 0.4 oral papillae were involved in each DFA procedure (Table 1). None of the patients in the SFA group was excluded from the study because of insufficient surgical access or an extension of the defect morphology preventing adequate root and defect instrumentation. One patient in the DFA group exited the study due to root fracture before the 6-month visit. All 28 patients who completed the study fully complied with the study procedures.

Patient and defect characteristics in SFA and DFA groups are reported in Table 2. No significant differences were observed between groups in terms of age, gender and smoking status as well as defect location and severity. Patient distribution according to defect morphology significantly differed between groups ($p < 0.05$), with 1-wall defects more prevalent in DFA group while 2- and 3-wall defects more prevalent in the SFA group (Table 2).

Clinical parameters

EHI is reported in Table 3. A significant difference in patient distribution according to EHI was observed between groups (p= 0.025). In particular, 12 sites in the SFA group and 6 sites in the DFA group showed complete flap closure (i.e., EHI= 1, 2 or 3). The frequency of sites showing optimal wound healing (i.e., EHI= 1) was 8 and 3 in the SFA and DFA group, respectively.

Pre-surgery and 6-month post-surgery values of the clinical measurements as well as their 6-month changes are reported in Table 4. Pre-surgery, no significant inter-group differences in CAL, PPD, REC and prevalence of BS+ sites were observed. Both treatments resulted in significant 6-month CAL gain and PPD reduction, with no significant increase in REC. At 6 months, no significant differences in CAL, PPD and REC were found between groups (Table 4). At 6 months, the prevalence of BS+ sites remained unvaried compared to pre-surgery in both groups.

Radiographic parameters

In two patients in the DFA group, 6-month radiographs were not suitable for radiographic measurements. These patients were excluded from radiographic analysis. The pre-surgery and 6-month radiographic measurements in SFA and DFA groups are reported in Table 4.

Pre-surgery, no significant differences in CEJ-BD, CEJ-BC, and ANGLE were observed between groups.

At 6 months, both treatment groups showed a significant reduction in CEJ-BD. IDF was 2.0 ± 2.3 mm and 2.0 ± 1.3 mm in the SFA and DFA group, respectively. No significant changes in CEJ-BC

were observed in both groups at 6 months compared to pre-surgery. When groups were compared in terms of 6-month CEJ-BD, CEJ-BC (Table 4) and IDF, no significant differences were found.

Patient-Centered Outcomes

VAS_{pain} in SFA and DFA groups throughout the first 14 postoperative days is illustrated in Figure 3. Time and treatment showed a significant effect on VAS pain ($p < 0.001$). Significantly lower values of VAS_{pain} were observed in SFA group compared to DFA group at day 1 (8 a.m., 1 p.m., 8 p.m.), day 2 (1 p.m., 8 p.m.) and day 6 (Figure 3).

The mean total dose number of analgesics during the first 2 postoperative weeks was 2.73 ± 5.04 in the SFA group, and 8.69 ± 11.6 in the DFA group. A significantly greater number of analgesics was used in the DFA group compared to the SFA group (3.2 ± 2.9 vs 1.1 ± 2.2, respectively) at day +1 ($p = 0.019$) (Table 5).

DISCUSSION

The regenerative potential of the combination of rh-PDGF-BB with graft materials in general (Trombelli & Farina 2008, Kaigler et al. 2011), and β-TCP, in particular (Thakare & Deo 2012), in the treatment of human periodontal defects accessed with conventional double flap designs is well established. The present study was designed to evaluate whether and to what extent the clinical outcomes of a procedure based on a rh-PDGF-BB / β-TCP combination are similar when combined to either DFA or SFA. This study paralleled a previous RCT where SFA was compared to DFA when used to access 2-3 walled intraosseous defects in absence of any regenerative technology (Trombelli et al. 2012). The purpose of these 2 companion studies was, therefore, to assess whether and to what extent the SFA (with or without a regenerative technology) may be

regarded as a suitable option for the surgical debridement of an intraosseous lesion. Clinical and patient reported outcomes were considered to test the null hypothesis. The fact that the investigated technology is not commercially available in several countries (although limiting the generalizability of the procedure) seems not to influence the scientific validity of the study design and the robustness of the results.

In the SFA group, the mean 6-month CAL gain was 4.0 mm, exceeding the mean improvements in CAL (3.2 mm) observed in the DFA group (although the difference did not reach statistical significance) and those reported in previous studies applying the same technology in conjunction with conventional, double flap designs (Nevins et al. 2005, 2013; Thakare & Deo 2012). Similarly, when deep intraosseous defects received surgical debridement without additional use of reconstructive devices (i.e., graft materials or membranes) or bioactive agents, SFA favored 1-mm greater CAL gain and PPD reductions compared to access with DFA (Trombelli et al. 2012), largely exceeding CAL gain values reported for conventional access flaps (Graziani et al. 2012). In the light of these findings and the minimal postoperative increase in REC (0.1 mm) observed in the SFA group, the surgical access obtained according to the SFA principles seems to optimize the regenerative outcomes as well as minimize the esthetic impairment of the patient following regenerative treatment of intraosseous defects with a combination of rh-PDGF-BB and β-TCP.

In the SFA group, the tendency to show better reconstructive outcomes compared to DFA may in part be due to the better quality of early wound healing at the incision margin (as assessed at 2 weeks with the EHI). Consistently, SFA either alone or in combination with a reconstructive technology led to a consistently higher incidence of complete flap closure at 2 weeks post-surgery (Farina et al. 2013). Overall, these data indicate that the SFA may promote proper conditions for

wound stability compared to conventional DFA, impacting positively on the clinical effectiveness of the procedure.

Patients in SFA group reported lower postoperative pain and dose of rescue analgesics compared to the DFA group. Differences between groups may be due to the different invasiveness of the investigated procedures (Table 1). This consideration is corroborated further by the results of a previous study on the clinical outcomes of another technique (i.e., minimally invasive surgical technique, MIST) based on the elevation of a double flap and characterized by a more limited mesio-distal extension (in terms of interdental spaces/papillae involved) compared to the DFA as adopted in this study. On average, the VAS pain scores reported by Cortellini & Tonetti (2007) for MIST within the first 2-3 postoperative days (19 ± 10) were intermediate between those recorded for DFA and SFA in this study (Figure 3). Moreover, it can be speculated that the operative time, which was previously demonstrated to influence the severity of postoperative pain following periodontal surgical procedures (Griffin et al. 2006, Tan et al. 2014), may have been longer for DFA than SFA. The prescription of analgesics was not standardized with the intention to consider the self-administration of ibuprofen as an indirect outcome of the level of postoperative pain. Although this may have introduced a potential bias for VAS validity, when VAS and dosage of analgesics spontaneously taken by the patient were jointly considered, data indicate that SFA may result in a more tolerable postoperative course when compared to DFA.

The different distribution of patients observed in SFA and DFA groups according to defect morphology may represent a potential source of bias since it has been reported that defect morphology is associated with varying regenerative potential (Selvig et al. 1993, Tonetti et al. 1996, Tonetti et al. 2002, Silvestri et al. 2003, Cortellini et al. 2009). However, when considering the

relationship between defect configuration and the clinical outcome of intraosseous defects treated with a combination of biological agents and graft biomaterial, the evidence is limited and not conclusive (Kao et al 2014). In particular, previous studies based on the use of rhPDGF-BB and β-TCP seem to indicate that defect morphology has a limited impact on the outcomes of periodontal regenerative procedures. One- to 2-wall intraosseous defects showed similar bone fill compared to 3-wall/circumferential defects at either 6 (Nevins et al. 2005) or 36 months (Nevins et al. 2013) post-surgery.

In conclusion, the current results indicate that: (i) deep intraosseous periodontal defects, accessed with the SFA or conventional papilla preservation techniques, may be effectively treated with careful debridement and root planing in combination with a composite graft of rhPDGF-BB (0.3 mg/ml) and β-TCP; and (ii) when used in combination with rhPDGF-BB/β-TCP technology, surgical access performed in accordance with SFA principles may result in better quality of early wound healing, lower pain and consumption of analgesics during the first postoperative days compared to the use of traditional papilla preservation techniques.

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CONFLICT OF INTERESTS

Prof. L. Trombelli has received a consulting fee from the Osteohealth Company for designing and coordinating the study.

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TABLE LEGEND

Table 1. Frequency distribution of patients in SFA and DFA groups according to the number of teeth and papillae involved in surgery.

Table 2. Patient and defect characteristics in SFA and DFA groups.

Table 3. Distribution of patients in SFA and DFA groups according to the Early Healing Index (as assessed at defect sites 2 weeks following surgery).

Table 4. Clinical recordings and radiographic measurements in SFA and DFA groups. * Negative value for REC indicates an increase.

Table 5. Self-reported dose (expressed as mean ± SD) of rescue analgesics assumed during the first two postoperative weeks in SFA and DFA groups.

FIGURE LEGEND

Figure 1. Treatment of a periodontal intraosseous defect with a buccal Single Flap Approach and rh-PDGF-BB plus β-TCP. a. An envelope flap without vertical releasing incisions is performed. 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 weeks post-surgery). **f.** At 6 months post-surgery, pocket probing depth amounts to 4 mm.

Figure 2. Treatment of a periodontal intraosseous defect with a Double Flap Approach (simplified papilla preservation flap, SPPF; Cortellini et al. 1999) and rh-PDGF-BB plus β-TCP. a. An envelope flap without vertical releasing incisions is performed. 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 (Cortellini et al. 1999). **b.** A microsurgical periosteal elevator is used to raise a flap on both buccal and oral 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 (Cortellini et al. 1999). 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 weeks post-surgery). **f.** At 6 months post-surgery, pocket probing depth amounts to 3 mm.

Figure 3. Mean VAS_{pain} in SFA and DFA groups. **: $p < 0.01$; *: $p < 0.05$.

APPENDIX LEGEND

Appendix 1. Visit schema.

Appendix 2. Inclusion and exclusion criteria.

Table 1. Frequency distribution of patients in SFA and DFA groups according to the number of teeth and papillae involved in surgery.

	SFA (n= 15)	DFA (n= 13)	
n° of teeth involved in surgery	n° patients	n° patients	
2	1	1	
3	8	8	
4	5	4	
5	1	0	
n° of papillae involved in surgery	n° patients	n° patients (buccal aspect)	n° patients (oral aspect)
2	6	7	10
3	7	6	3
4	2	0	0

Table 1. Patient and defect characteristics in SFA and DFA groups.

	SFA (n = 15)	DFA (n = 13)	p
Patient characteristics			
gender (males/females)	9/6	8/5	1
age (years) (mean ± SD)	50.1 ± 14.8	46.7 ± 15.4	0.821
smokers (yes/no)	3/12	0/13	0.226
Defect characteristics			
dental arch (maxillary/mandibular)	7/8	7/6	0.708
tooth type (incisors/canines/premolars/molars)	3/2/5/5	3/2/4/4	1
CEJ - base of the defect (mm, as assessed during surgery) (mean ± SD)	10.3 ± 2.4	8.8 ± 1.5	0.142
intrabony component (mm, as assessed during surgery) (mean ± SD)	7.7 ± 2.6	5.8 ± 1.5	0.058
defect configuration (bony walls) as assessed during surgery (n° of defects) mainly 1-wall mainly 2-wall mainly 3-wall	 1 6 8	 7 2 4	0.032

Table 2. Distribution of patients in SFA and DFA groups according to the Early Healing Index (as assessed at defect sites 2 weeks following surgery).

	SFA (n = 15)	DFA (n = 13)	p
Early Healing Index			
score 1 (complete flap closure – no fibrin line in the inter-proximal area)	8	3	0.025
score 2 (complete flap closure – fine fibrin line in the inter-proximal area)	3	3	
score 3 (complete flap closure – fibrin clot in the inter-proximal area)	1	0	
score 4 (incomplete flap closure – partial necrosis of the inter-proximal tissue)	3	5	
score 5 (incomplete flap closure – complete necrosis of the interproximal tissue)	0	2	

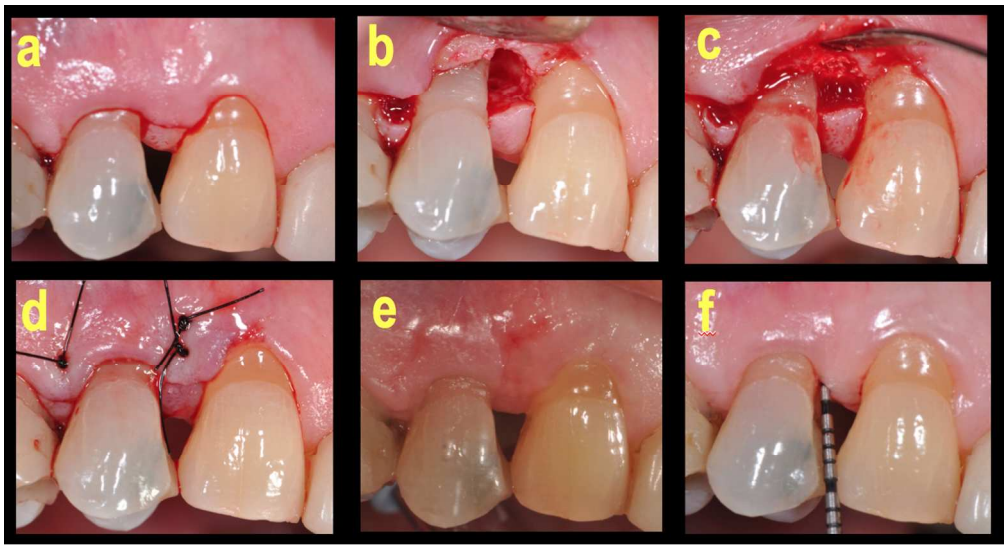
Table 3. Clinical recordings and radiographic measurements in SFA and DFA groups.

	pre-surgery	6 months	p	6-month change*
Clinical recordings				
CAL (mm) SFA DFA *p*	9.7 ± 2.5 8.5 ± 1.6 *0.339*	5.7 ± 2.6 5.2 ± 1.6 *1*	*<0.001* *0.001*	4.0 ± 1.9 3.2 ± 1.4 *0.316*
PPD (mm) SFA DFA *p*	8.7 ± 2.0 7.7 ± 1.5 *0.254*	4.5 ± 1.6 4.1 ± 1.2 *0.496*	*<0.001* *0.001*	4.1 ± 1.7 3.6 ± 1.1 *0.413*
REC (mm) SFA DFA *p*	1.1 ± 1.3 0.8 ± 1.3 *0.363*	1.2 ± 1.5 1.2 ± 1.6 *0.363*	*0.529* *0.343*	-0.1 ± 0.7 -0.4 ± 1.3 *0.618*
BS (positive/negative) SFA DFA *p*	8/7 7/6 *1*	8/7 2/11 *0.055*	*1* *0.097*	-
Radiographic measurements				
ANGLE (degrees) SFA DFA *p*	31.9 ± 11.6 33.6 ± 9.9 *0.495*			
CEJ-BD (mm) SFA DFA *p*	8.1 ± 3.4 8.0 ± 2.2 *0.683*	6.1 ± 2.3 5.9 ± 2.2 *0.838*	*0.003* *0.005*	-
CEJ-BC (mm) SFA DFA *p*	3.2 ± 1.7 3.2 ± 1.7 *0.891*	2.9 ± 1.6 2.7 ± 1.3 *0.646*	*0.268* *0.333*	-

* Negative value for REC indicates an increase.

Table 4. Self-reported dose (expressed as mean ± SD) of rescue analgesics assumed during the first two postoperative weeks in SFA and DFA groups.

	postoperative day													
	+1	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**	**+8**	**+9**	**+10**	**+11**	**+12**	**+13**	**+14**
SFA	1.1 (± 2.2)	0.9 (± 1.7)	0.3 (± 0.7)	0.2 (± 0.4)	0.1 (± 0.4)	0	0.1 (± 0.3)	0	0	0	0	0	0	0.1 (± 0.3)
DFA	3.2 (± 2.9)	1.8 (± 2.7)	1.5 (± 2.7)	0.5 (± 1.1)	0.5 (± 1.1)	0.5 (± 1.1)	0.3 (± 0.9)	0	0	0	0	0	0	0.2 (± 0.8)
p	*0.019*	*0.277*	*0.217*	*0.751*	*0.586*	*0.316*	*0.683*	1	1	1	1	1	1	*0.964*



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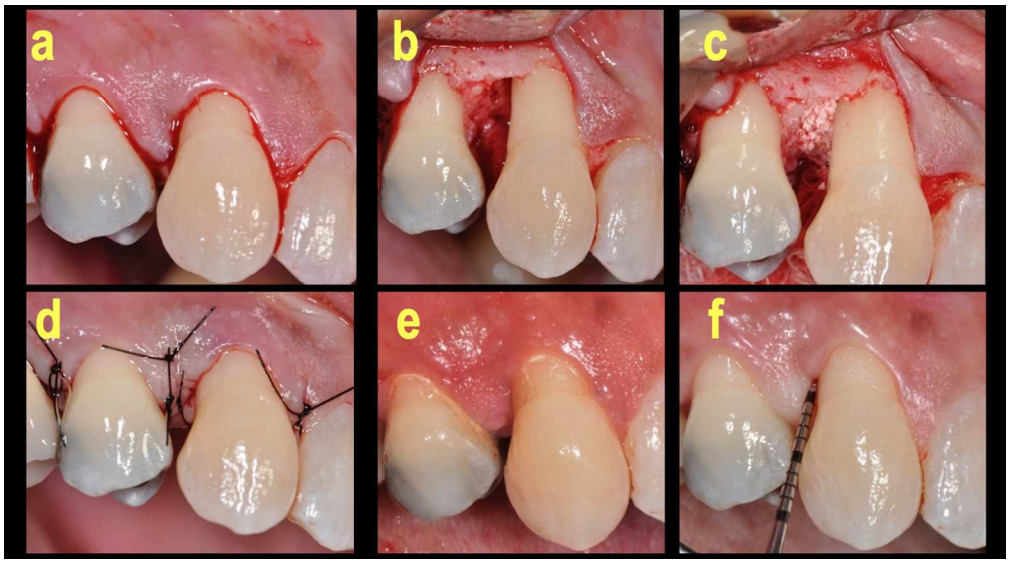

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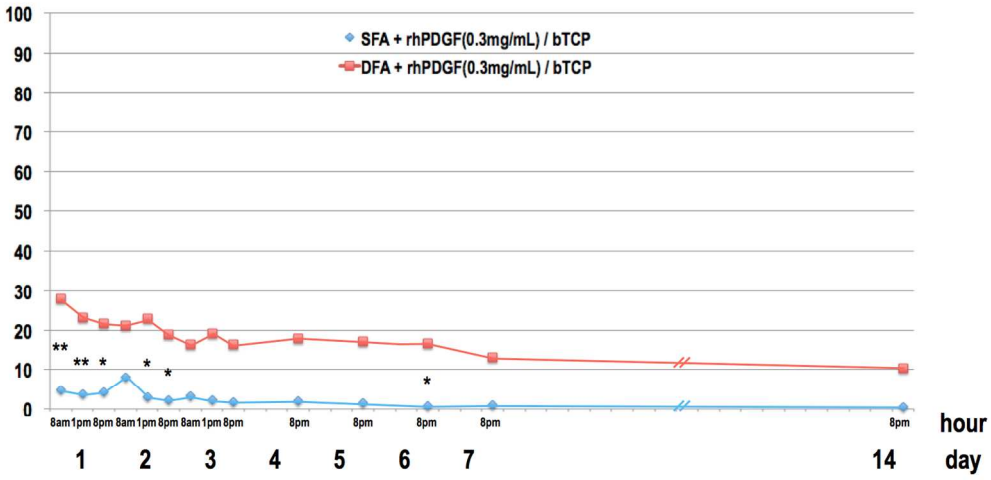

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Appendix 1. Visit schema.

	screening	initial therapy	surgery	suture removal	follow-up	follow-up
		day -28	day 0	day +14	day +36/ +56 / +84	day +180
informed consent	X					
subject demographics	X					
medical and dental history	X					
inclusion / exclusion criteria	X					
randomization			X			
periapical radiographs			X			X
clinical recordings (CAL, PPD, REC, BS)			X			X
VAS questionnaire			X			
suture removal				X		
scaling and root planing		X				X
professional prophylaxis / OHI		X			X	X
clinical photography			X	X	X	X

Appendix 2. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• ≥ 18 years of age • provision of informed consent • diagnosis of chronic or aggressive periodontitis • presence of at least one intraosseous defect (as detected on periapical radiographs) associated with pocket probing depth ≥ 6mm • Full Mouth Plaque Score (O'Leary *et al.*, 1972) and Full Mouth Bleeding Score < 20% at the time of the surgical procedure	*Conditions that prevented study participation*: • time constrain that prevented returning to follow up visit • inability to follow investigator's instruction • no compliance with the study requirements • simultaneous participation in other studies *Systemic conditions*: • conditions requiring chronic routine use of antibiotics or requiring prolonged use of steroids • long-term use of bisphosphonate (≥ 3 years) • history of leukocyte dysfunction or deficiencies, bleeding disorders, neoplastic disease requiring radiation or chemotherapy, metabolic bone disorder, uncontrolled endocrine disorders, HIV infection • use of investigational drugs or devices within 30 days of study period • alcoholism or drug abuse • smoking >10 cigarettes per day *Local conditions (experimental tooth)*: • İnadequate restoration • endodontic lesions • inadequate endodontic treatment • untreated carious lesion • third molars were excluded

Revision of the manuscript entitled

"Single versus Double Flap Approach in Periodontal Regenerative Treatment"

(manuscript ID: CPE-11-14-5409.R1)

Editor in Chief

I had the opportunity to see an oral presentation of this paper by the first author at the Italian Perio Society meeting and I think there is a need for some clarifications. Authors have reported single vs double flap approaches as a homogeneous (almost standardized) procedure but in the oral presentation illustrating the cases it became apparent that this may not tell the full story. Images presented showed that buccal access to the defects was achieved with a variation of approaches: some as described by Trombelli et al in 2007, others as described by Cortellini and Tonetti as MIST in 2007 and other as modified MIST. 2009 These procedures are different in a variety of ways and in particular they involve a different degree of elevation of the buccal flap (and palatal flap for MIST).

WE AGREE WITH THE EDITOR IN CHIEF THAT WE HAVE TO BRING MORE CLARITY ON THE SURGICAL TECHNIQUES ADOPTED IN BOTH SFA AND DFA GROUPS.

WE BELIEVE THAT A SUBSTANTIAL OVERLAPPING EXISTS BETWEEN SFA AND M-MIST, INCLUDING ASPECTS RELATED TO THE INTERDENTAL INCISIONS AND FLAP MANAGEMENT. ACCORDING TO THE ORIGINAL DESCRIPTION, SFA IS CHARACTERIZED BY A FLAP ELEVATION ON EITHER BUCCAL OR ORAL ASPECT, LIMITED MESIO-DISTAL EXTENSION OF THE (BUCCAL/ORAL) FLAP AND MAINTENANCE OF THE INTEGRITY OF THE PAPILLA OVERLYING THE INTRABONY DEFECT (TROMBELLI ET AL. 2007). IN PARTICULAR, THE MESIO-DISTAL EXTENSION OF THE FLAP IS KEPT AS LIMITED AS POSSIBLE WHILE ENSURING PROPER ACCESS FOR DEFECT DEBRIDEMENT (TROMBELLI ET AL. 2009). WHICH MEANS, THAT THE PRIORITY IN TERMS OF FLAP EXTENSION WAS GIVEN TO PROVIDE ADEQUATE SURGICAL ACCESS, SOMETIMES EXTENDING THE BUCCAL INCISION TO INVOLVE THE PAPILLA OF ADJACENT TEETH IN ORDER TO AVOID VERTICAL RELEASING INCISIONS. THESE CHARACTERISTICS ARE WELL ILLUSTRATED IN FIGURE 1, WHICH WAS THE SAME SFA CASE PRESENTED BY ONE OF THE AUTHORS (G.P.S.) AT THE SIDP MEETING. THE MATERIALS & METHODS ARE NOW IMPLEMENTED WITH A DESCRIPTION OF THE TECHNICAL ASPECTS OF THE SFA. IN CONTRAST, WHEN ORIGINALLY DESCRIBED (CORTELLINI & TONETTI 2009), THE AUTHORS STATED THAT IN THE M-MIST "*the interdental incision … was extended to the buccal aspect of the two teeth adjacent to the defect. … and their mesio-distal extension was kept at minimum (ideally, within the mid-buccal area of the involved teeth) to allow the reflection of a triangular buccal flap.*".

WITH RESPECT TO THE DFA GROUP, THE DEFECT-ASSOCIATED INTERDENTAL TISSUE WAS APPROACHED WITH SURGICAL TECHNIQUES FOR THE PRESERVATION OF THE INTERDENTAL PAPILLA, NAMELY THE SIMPLIFIED PAPILLA PRESERVATION FLAP (SPPF) (CORTELLINI ET AL. 1999) OR THE MODIFIED PAPILLA PRESERVATION TECHNIQUE (MPPT) (CORTELLINI ET AL. 1995) BASED ON THE ANATOMICAL CHARACTERISTICS OF THE SURGICAL SITE (CORTELLINI & TONETTI 2005). MESIO-DISTAL EXTENSION OF THE BUCCAL AND ORAL INCISION WAS INFLUENCED BY DEFECT MORPHOLOGY AND SEVERITY. IN OTHER WORDS, THE FLAP COULD INVOLVE THE TEETH ADJACENT TO THE TOOTH PRESENTING THE DEFECT TO ENSURE PROPER ROOT AND DEFECT DEBRIDEMENT. RELEASING INCISIONS WERE NEVER PERFORMED. FULL-THICKNESS FLAP REFLECTION WAS PERFORMED ON BOTH BUCCAL AND LINGUAL ASPECTS TO PROVIDE ADEQUATE VISIBILITY OF THE BONE CREST ON BOTH BUCCAL AND ORAL ASPECTS. IN THIS RESPECT, IT SEEMS THAT CASES TREATED IN DFA GROUP, AS NOW DESCRIBED IN DETAILS, MAY ONLY PARTLY BE RECONNECTED TO MIST, AS REPORTED IN THEIR VARIANTS BY CORTELLINI & TONETTI 2007. TO DESCRIBE THE DFA PROCEDURE, WE HAVE IMPLEMENTED THE MANUSCRIPT TEXT (SEE M/M SECTION) WITH ADDITIONAL DETAILS AND INCLUDED FIGURE 2 WHICH ILLUSTRATES THE CASE PRESENTED AT THE SIDP MEETING.

It seemed - in the oral presentation - that the degree of mesio-distal and apical extension of the buccal flap elevation was associated with the defect anatomy (different needs to elevate to gain access to the defect resulting in elevation of 1 to 3 papillae) at least for the single flap approach. Was the same true also for the double flap approach according to the principles of MIST?. It happens that the randomization did not result in homogeneous prevalent anatomy between the two groups. As a consequence the need to elevate the flaps based on single and double approaches may have been different. Following on the hypothesis that flap extension may be a major determinant of post-op pain and discomfort this has the potential to bias the results in such a small population.

WE TOTALLY AGREE WITH THE EDITOR. SINCE THE VARIABILITY IN TERMS OF MESIO-DISTAL EXTENSION BETWEEN SFA AND DFA GROUPS MAY HAVE AFFECTED THE TREATMENT OUTCOMES (POSTOPERATIVE PAIN, NUMBER OF ANALGESIC TABLETS), WE HAVE REPORTED SUCH SURGICAL VARIABLE IN A SPECIFIC TABLE (NOW TABLE 1).
IN ADDITION, WE HAVE IMPLEMENTED THE DISCUSSION SECTION AS FOLLOWS: "*Patients in SFA group reported lower postoperative pain and dose of rescue analgesics compared to the DFA group. Differences between groups may be due to the different invasiveness of the investigated procedures (Table 1). This consideration is corroborated further by the results of a previous study on the clinical outcomes of another technique (i.e., minimally invasive surgical technique, MIST), based on the elevation of a double flap and characterized by a more limited mesio-distal extension (in terms of interdental spaces/papillae involved) compared to the DFA as adopted in this study. On average, the VAS pain scores reported by Cortellini & Tonetti (2007) for MIST within the first 2-3 postoperative days (19 ± 10) were intermediate between those recorded for DFA and SFA in this study (Figure 3). Moreover, it can be speculated that the operative time, which was previously demonstrated to influence the severity of postoperative pain following periodontal surgical procedures (Griffin et al. 2006, Tan et al. 2014), may have been longer for DFA than SFA.*"

I think that this is an important study that addresses an important principle. Please consider addressing the questions above to make the conclusions more transparent and adherent to the facts.

WE HAVE ADDRESSED ALL THE ISSUES RAISED BY THE EDITOR IN CHIEF, THE ASSOCIATE EDITOR, AND REFEREE #1. WE HOPE THAT THE MANUSCRIPT IS NOW MORE TRANSPARENT AND ADHERENT TO THE FACTS.

It would also seem important that you provide in an appendix an illustration of the variety of way buccal access was achieved in order for readers to understand better the spectrum of procedures that you employed (from the single flap approach, to the MIST and M-MIST).

ACCORDING TO THE EDITOR SUGGESTION, WE HAVE NOW BETTER DEFINED THE SURGICAL PROCEDURES (SFA, DFA), ADDED A TABLE ADDRESSING THE ISSUE OF THE FLAP EXTENSION (TABLE 1), AND A FIGURE TO DESCRIBE THE DFA (FIGURE 2).

Associate Editor
The authors have only partially addressed the issue related to the credit to the Cortellini and Tonetti group: the wording does not significantly change the message.

WE HAVE TRIED TO GIVE ALL THE CREDIT TO PERTINENT LITERATURE, INCLUDING THOSE BY CORTELLINI AND TONETTI, THROUGHOUT DIFFERENT SECTIONS OF THE MANUSCRIPT.

Referee: 1

Abstract: conclusions of the abstract do not match conclusions of the paper and do not fully support the statements of the Clinical Relevance paragraph. In particular, Authors should underline that SFA is not applicable in all cases and better underline why, when applicable, it should be preferred to DFA. Following small changes in these two parts, the paper deserves publication.

WITH REGARD TO THE CONCLUSIONS OF THE ABSTRACT SECTION, WE HAVE REPHRASED THE PARAGRAPH IN ORDER TO BE CONSISTENT WITH THE CONCLUSIONS OF THE MAIN TEXT: "*When combined with rhPDGF-BB and β-TCP, the SFA may result in similar clinical outcomes, better quality of early wound healing, and lower pain and consumption of analgesics during the first postoperative days compared to the DFA.*".

WE TOTALLY AGREE WITH THE REVIEWER THAT THE POSSIBILITY TO APPLY THE CONCEPT OF THE SINGLE FLAP APPRACH VS A CONVENTIONAL DOUBLE FLAP PROCEDURE IS DEPENDENT ON THE DEFECT MORPHOLOGY. ON THE BASIS OF THESE CONSIDERATIONS, WE HAVE REPHRASED THE PRACTICAL IMPLICATIONS OF THE CLINICAL RELEVANCE SECTION AS FOLLOWS: "*When applicable due to defect morphology, the SFA seems to represent a less invasive option to access intraosseous defects for treatment with rhPDGF-BB + β-TCP compared to DFA.*"