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Single Flap Approach versus Double Flap Approach in the treatment of periodontal intraosseous defects with recombinant human platelet-derived growth factor and β-tricalcium phosphate. A pilot study

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. *Presenting Author

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SUMMARY

Aim: to compare 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 access with SFA or DFA, respectively, were grafted with rhPDGF-BB + β-TCP. The Early Wound Healing Index (EHI) was evaluated at 2 weeks post-surgery. Probing parameters were assessed before surgery and at 6 months post-surgery. Post-surgical pain (VASpain) was self-reported using a visual analog scale.

Results: Twelve sites in the SFA group and 6 sites in the DFA group showed complete flap closure (i.e., EHI= 1-3). No significant differences in 6-month changes in probing parameters and radiographic linear defect fill were found between groups. Significantly lower VASpain 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, SFA results in better quality of early wound healing, lower pain and use of analgesics during the first postoperative days 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, being at least as clinically effective as the elevation of a flap at both buccal and oral aspects according to the papilla preservation techniques (double flap approach, DFA) (Trombelli et al. 2012). In addition, the SFA or similar flap designs were effective when used in association with various reconstructive technologies, including graft materials, membranes and bioactive agents (Cortellini & Tonetti 2009, Trombelli et al. 2010, Farina et al. 2014).

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 (rhPDGFBB) 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 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. Importantly, both rhPDGF-BB formulations were significantly more effective than the control group (β-TCP + buffer) 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 AND 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.

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 Table 1. Briefly, patients with at least on intraosseous periodontal defect associated with probing depth ≥ 6mm were included in the study.

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)*: • inadequate restoration • endodontic lesions • inadequate endodontic treatment • untreated carious lesion • third molars were excluded

Table 1. *Inclusion and exclusion criteria.*

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 procedure - 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).

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).

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) or MPPT (Cortellini et al. 1995) and SPPF (Cortellini et al. 1999) with a nonresorbable monofilament suture (Monosof™ 6.0; Covidien, Mansfield, MA, US) (Figure 1).

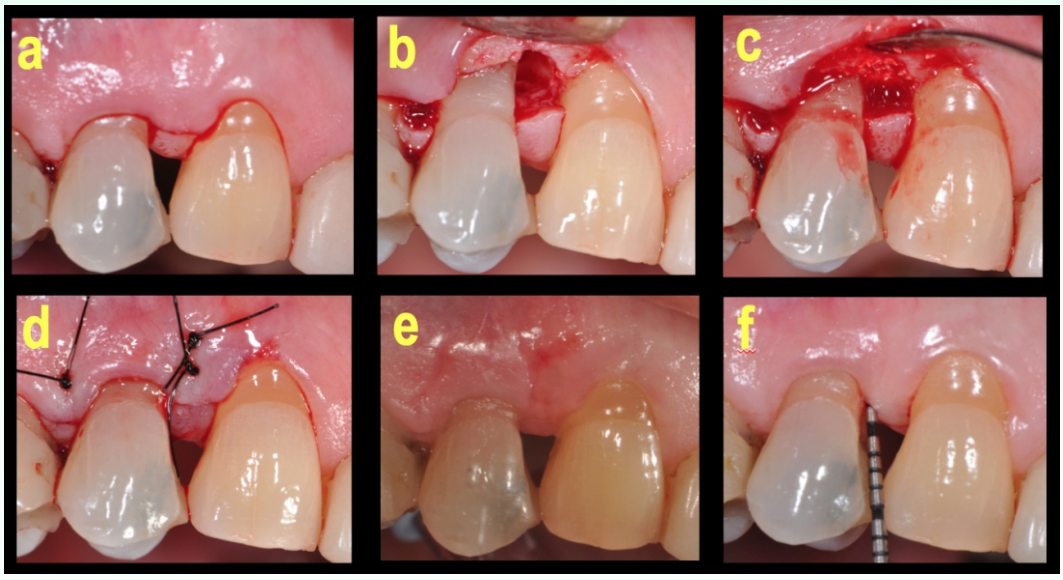

Fig. 1

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 intraexaminer 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 manual pressure sensitive 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 (IDF) 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 (VASpain). Self-recordings of VASpain 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 presurgery 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 VASpain. The level of significance was set at 5% for all statistical tests.

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. 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).

	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. *Patient and defect characteristics in SFA and DFA groups.*

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.

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

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.

	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. *Clinical recordings and radiographic measurements in SFA and DFA groups.*

Patient-Centered Outcomes - VASpain in SFA and DFA groups throughout the first 14 postoperative days is illustrated in Figure 1. Time and treatment showed a significant effect on VAS pain (p< 0.001). Significantly lower values of VASpain 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 2).

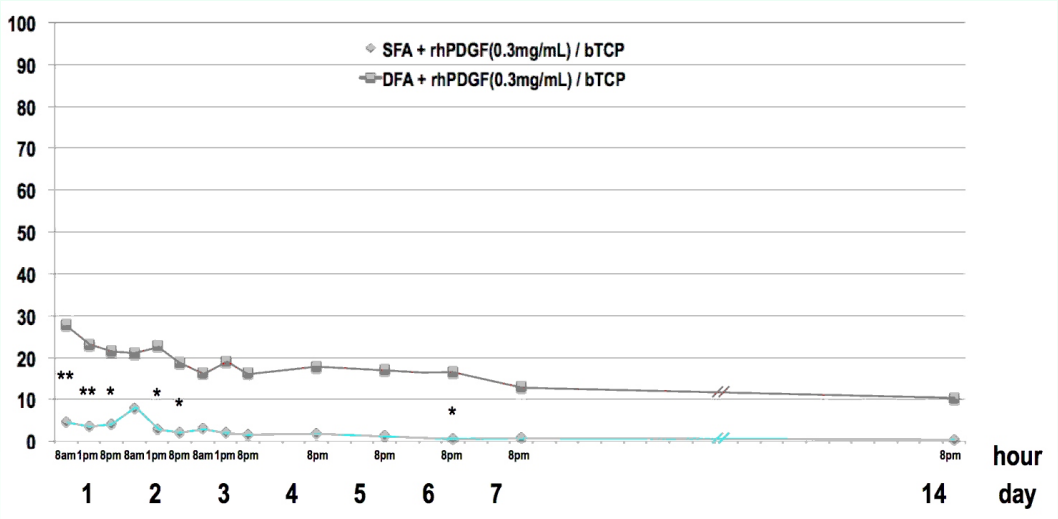

Fig. 2

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).

	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*

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

CONCLUSIONS

The results of the present study 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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