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Adjunctive effect of a polylactide/polyglycolide copolymer in the treatment of deep periodontal intra-osseous defects: a randomized clinical trial

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Abstract

Aim: The aim of this study was to evaluate the clinical outcome of re-constructive surgery in human deep intra-osseous defects with the use of a polylactide/polyglycolide (PLA/PGA) copolymer graft in conjunction with an open flap debridement (OFD) procedure (test group) as compared with OFD procedure alone (control group).

Materials and Methods: Thirty-two patients, each contributing one defect, were selected and completed the 12-month follow-up period. Sixteen patients (eight males, mean age: 49.9 years) received the test treatment, 16 patients (nine males, mean age: 42.8 years) received the control treatment. Clinical recordings, assessed at baseline, 6 and 12 months post-surgery, included defect-specific plaque score, defect-specific bleeding score, probing depth (PD), clinical attachment level (CAL), and recession depth. Surgical procedure aimed to preserve supra-crestal soft tissues at defect site in order to ensure primary closure was used in all cases.

Results: Test and control treatment produced a significant CAL decrease and PD reduction at both 6 and 12 months with respect to baseline value ($p < 0.000$). At 6 months CAL was significantly greater in test compared with control group ($p = 0.019$). Twelve-month CAL gain was 3.6 ± 1.5 and 3.4 ± 1.4 mm for the test and control group, respectively. At 12 months no significant differences in any of the clinical parameters were observed between groups.

Conclusion: The results indicate that OFD with and without PLA/PGA graft provide clinically and statistically significant improvements in PD and CAL measurements. However, the additional use of PLA/PGA did not provide an additional benefit in terms of CAL gain and PD reduction compared with OFD procedure.

Key words: bone substitutes; periodontal disease/treatment; polylactic/polyglycolic acid

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Among treatment modalities, grafting of biomaterials/bone substitutes have been used with varying success to accomplish the re-construction of the lost periodontal attachment apparatus. A systematic review on the effect of grafting biomaterials and biological agents in the treatment of deep intra-osseous defects showed that a clinical benefit may be obtained from various bone substitutes used as an adjunct to open flap debridement (OFD) procedure. Overall, the results indicated that the implantation of bone substitutes produced a more favourable clinical attachment level (CAL) gain, probing depth (PD) reduction and increased defect fill when compared with OFD alone (Trombelli et al. 2002a).

Biodegradable polymers, especially those belonging to the family of polylactic acid (PLA) and polyglycolic acid (PGA), are playing an increasingly important role in bone re-constructive procedures.

Although extensively used in orthopaedics (Athanasiou et al. 1998), PLA/PGA biomaterials have been scarcely investigated in their cranio-maxillo-facial applications. Implantation of PLA-derived devices was studied to prevent alveolar osteitis or dry socket in extraction sites with contrasting results (Olson et al. 1982, Brekke et al. 1983, 1986a, b, Hooley & Golden 1995). Meadows et al. (1993) compared the treatment of periodontal intra-osseous defects with access flap alone, PLA implant and decalcified freeze-dried bone allograft. They found limited amount of osseous defect fill using both PLA and access flap alone.

Recently, a new copolymer (Fisiograft®, Ghimas s.r.l., Casalecchio di Reno, Italy) of 50% DL lactic acid and 50% glycolic acid (50 PLA:50 PGA) mixed with destrane 125 as excipient, has been marketed in different formulations, such as sponge, gel and powder. Fisiograft® has been successfully used for maxillary sinus lifting (Ghinzani 1998, Bucci Sabattini et al. 1999), as a space-making material in association with non-resorbable membranes (Leghissa et al. 1997, Leghissa & Leardi 1998), for ridge preservation (Serino et al. 2003) and ridge augmentation in conjunction with deproteinized bovine hydroxyapatite and non-resorbable membrane (Leghissa et al. 1998), and associated with split-crest technique (Leghissa 1999).

At present, no data is available regarding the possibility of re-constructing the periodontal tissues lost because of periodontal disease by means of access flap combined with PLA/PGA copolymer implant. Therefore, the aim of this study was to evaluate the clinical outcome of re-constructive surgery in human deep intra-osseous defects with the use of Fisiograft® in addition to an OFD procedure as compared with OFD procedure alone.

Materials and Methods

Experimental design

A prospective, randomized, parallel-arm clinical trial was designed to test the effectiveness of Fisiograft® in association with OFD with supra-crestal soft tissue preservation (Trombelli et al. 2002b) in deep intra-osseous defects (test group) as compared with OFD with supra-crestal soft tissue preservation alone (control group). Treatment outcome was evaluated clinically at 6 and 12 months following re-constructive surgery.

Study population

Patients were recruited among those seeking care for moderate-to-severe chronic and aggressive periodontitis at the Research Centre for the Study of Periodontal Diseases, University of Ferrara, Italy and at the Department of Periodontology, Complutense University, Madrid, Spain.

Patients were included if they presented at least one deep inter-proximal intra-osseous defect (intra-osseous component $\geqslant 4$ mm). Depth of the intra-osseous component of the defect (INTRA) was clinically and radiographically evaluated during the screening phase but had to be confirmed during surgery. If multiple defects were present, only the defect with greater clinical attachment loss was considered for analysis. Both smokers and non-smokers subjects were included, and smoking exposure (packs years) was recorded.

Subjects younger than 18 years and/or with a history of severe acute or chronic systemic disease, women pregnant or lactating, subjects taking medications known to affect the gingival status were excluded. Third molars, teeth affected by endodontic lesions and/or inadequate endodontic treatments, teeth showing restorations with overhanging margins, teeth with degree three mobility, and, in general, all teeth with a hopeless prognosis at the combined clinical and radiographic evaluation were not included. If the intra-osseous lesion extended into the furcation area, only the inter-proximal aspect of the defect was considered.

Pre-surgical phase

Prior to surgery, patients received a complete periodontal examination, oral hygiene instructions, and multiple sessions of periodontal debridement. Surgical treatment was performed at least 4–6 weeks after the completion of non-surgical phase.

Surgical procedure

Flap design was described in detail in a previous report (Trombelli et al. 2002b). Specifically, different incisions aimed to preserve supra-crestal soft tissues at defect site were used in order to ensure primary closure at suture. The choice of the surgical approach was based on anatomical considerations such as width of the inter-proximal space, extent and location of the defect, distance from contact point to bone crest, and apico-coronal dimension of keratinized gingiva. Vertical releasing incisions were performed when needed for better access and/or primary closure of the surgical wound.

Mucoperiosteal flaps were raised buccally and lingually in order to gain complete access to the defect. Defects were carefully debrided, and the root surfaces were scaled and planed with hand and ultrasonic instruments. At this time, intra-surgical measurements were recorded. In no cases was osteoplasty/ostectomy carried out. Defects were consecutively assigned to one of the two treatment procedures using a randomization list. A Fisiograft® sponge was fragmented into small pieces and placed into the bony lesions. Fragmentation provided a better adaptation of the material to defect morphology. Particular attention was paid to neither overfilling the defect, nor excessively compressing the material into the bony lesion. Sharp dissection of the tissues apical to the bone margin was performed to permit coronal displacement of the flap without any tension. Flaps were positioned at the pre-surgery level to achieve primary closure of the interdental area and were held in place by means of e-PTFE sutures (Gore-Tex™ CV-6 Suture Material, W.L. Gore and Associates, Flagstaff, AZ, USA) or 6-0 polypropylene (Prolene®, Ethicon, Somerville, NJ, USA). Selection of the suturing technique was based on flap design. No surgical dressing was used.

The control defects received an identical procedure except for the placement of Fisiograft®.

Post-surgical infection control

A 0.12% chlorexidine mouthwash, 10 ml t.i.d., was prescribed for 6 weeks post-surgery. No antibiotic therapy was administered post-surgery. In order to minimize traumatic injury to the marginal tissues, mechanical tooth cleaning was not allowed in the surgical area for the first 6 post-operative weeks. Sutures were removed after 14 days. At that time, presence of post-surgery complications were recorded.

The patients were recalled at 1, 2 and 4 weeks after surgery, then at 2, 3, 4, 5, 6, 9 and 12 months. Supportive care programme included professional supra-gingival polishing and scaling and oral hygiene reinforcement. No periodontal

probing and/or subgingival re-instrumentation of the surgically treated sites were performed prior to 6 months of healing.

Clinical recordings

All clinical recordings were performed immediately before surgery (baseline), at 6 and 12 months post-surgery. The following indices and clinical parameters were assessed:

(1) Defect-specific plaque score (DSPS). After the application of a disclosing erythrosin solution, defects exhibiting stain on visual inspection at the juxtagingival area were recorded as having plaque.
(2) Defect-specific bleeding score (DSBS). Defects bleeding within 10 s after probe insertion were recorded as positive.
(3) PD, measured from the gingival margin to the bottom of the pocket.
(4) CAL, measured from the cemento-enamel junction (CEJ) to the bottom of the pocket.
(5) Recession depth (REC), measured from the CEJ to the gingival margin.

DSPS, DSBS, PD, CAL and REC measurements were recorded at the deepest site of the selected inter-proximal defect. Probing measures were recorded by using a standard periodontal probe (UNC 15, HuFriedy, Chicago, IL, USA) with manual pressure of approximately 0.3 N.

A pre-trial calibration session was performed to obtain acceptable intra- and inter-examiner reproducibility in assessing clinical parameters. Patients and examiners were not blinded as to the treatment performed.

Intra-surgery recordings

The following intra-surgery measurements were recorded following defect debridement:

(1) distance from the CEJ to the bottom of the defect (CEJ-BD);
(2) distance from the most coronal extension of the inter-proximal bone crest to the bottom of the defect, i.e. the INTRA.

All intra-surgery recordings were performed at the deepest inter-proximal point of the defect by using a standard periodontal probe (UNC 15, HuFriedy).

Statistical analysis

The patient was regarded as the statistical unit. Data were expressed as mean standard deviation. Significance of mean differences between pre- and post-surgery scores was analysed using Student's *t*-test for paired observations. Differences between test and control groups were calculated using the chi-squared test for dichotomous variables or Student's *t*-test for unpaired observations. The level of significance was set at 5%.

Results

Thirty-two patients were included and completed the 12-month follow-up period. Twenty-two patients (11 test and 11 control) were treated at University of Ferrara, and 10 patients (five test and five control) at Complutense University. Mean age was 49.9 years (range: 28–64 years) for the test group, and 42.7 years (range: 35–56 years) for the control group. No statistically significant differences were found between groups for any of the patient characteristics at baseline except for age ($p = 0.018$) (Table 1).

A total of 32 defects (16 defects in each group) were considered for analysis. CEJ-BD was 11.1 ± 3.0 mm (range: 8–17 mm) for the test group, and 9.3 ± 2.7 mm (range: 5–15 mm) for the control group. INTRA was 6.2 ± 2.6 mm (range: 4–13 mm) in the test group, and 5.7 ± 1.2 mm (range: 4–8 mm) in the control group. No significant differences were observed for any of the intra-surgery defect characteristics between groups (Table 1).

Overall, nine defects were located in premolars/molars, five in canines and two in incisors in the test group, while nine defects were located in premolars/molars, two in canines an five in incisors in the control group. No differences were found between groups in arch and/or tooth location of the defects (Table 1).

In two patients in the test group, flap sloughing with a substantial loss of inter-dental soft tissue was observed at 2 weeks post-surgery. In the remaining patients post-operative healing was uneventful, and no adverse complications because of the use of the graft biomaterial were observed.

Clinical recordings

At baseline DSPS and DSBS were 31.3% and 87.5%, respectively, in test group, and 50.0% and 56.3%, respectively, in the control group. No statistically significant differences were detected between groups.

At 6 months DSPS shifted to 43.8% in the test group, and to 6.3% in the control group, the difference between groups being statistically significant ($p = 0.015$). At 12 months DSPS was 12.5% and 6.3% in test and control groups, respectively.

At 6 and 12 months DSBS were 43.8% and 18.8%, respectively, in the test group, and 25.0% and 12.5%, respectively, in the control group. Test treatment produced a significant decrease in DSBS at both 6 months ($p = 0.014$) and 12 months ($p < 0.000$). In the control group DSBS reduction was significant only at 12 months ($p = 0.004$). DSBS was not significantly different between groups at each observation interval.

Table 1. Patient and defect characteristics for test and control groups

Variable	Test ($n = 16$)	Control ($n = 16$)	*p*-value
Age (years)	49.9 ± 9.6	42.8 ± 6.5	0.018
Males/females	8/8	9/7	NS
Smokers (%)	8 (50.0)	6 (37.5)	NS
Smoking exposure (packs year)	13.3 ± 7.4	12.7 ± 4.6	NS
Baseline DSPS (%)	31.3	50.0	NS
Baseline DSBS (%)	87.5	56.3	NS
Maxillary/mandibular teeth	9/7	9/7	NS
Anterior/posterior teeth	7/9	7/9	NS
CEJ-BD (mm)	11.1 ± 3.0	9.3 ± 2.7	NS
INTRA (mm)	6.2 ± 2.6	5.7 ± 1.2	NS

DSPS, defect-specific plaque score; DSBS, defect-specific bleeding score; CEJ-BD, distance from the cemento-enamel junction to the bottom of the defect; INTRA, intra-osseous component of the defect; NS, not significant.

Table 2. Pocket probing depth and clinical attachment level in test and control group as measured (in mm) at baseline, 6 and 12 months following surgery (mm, mean ± standard deviation)

	PD			CAL			REC		
	baseline	6 months	12 months	baseline	6 months	12 months	baseline	6 months	12 months
Test ($N = 16$)	8.3 ± 2.1	$4.9 \pm 2.0^{*}$	$3.6 \pm 1.8^{*\#}$	10.1 ± 2.2	$7.7 \pm 3.0^{*}$	$6.5 \pm 2.4^{*\#}$	1.7 ± 1.6	$2.8 \pm 2.4^{\S}$	$2.9 \pm 2.3^{\P}$
Control ($N = 16$)	7.6 ± 1.2	$3.7 \pm 1.4^{*}$	$3.7 \pm 1.8^{*}$	8.6 ± 1.9	$5.3 \pm 2.5^{*}$	$5.3 \pm 2.3^{*}$	1.1 ± 1.1	1.6 ± 1.8	1.6 ± 1.8
$p^{\dagger}$	NS	NS	NS	NS	0.019	NS	NS	NS	NS

†Significance of differences between groups (Student's *t*-test for unpaired observations).
*Significantly different from baseline ($p < 0.000$).
§Significantly different from baseline ($p = 0.006$).
¶Significantly different from baseline ($p = 0.009$).
$^{\#}$Significantly different with respect to 6 months ($p < 0.000$).
CAL, clinical attachment level; PD, probing depth; REC, recession depth; NS, not significant.

Table 3. Clinical outcomes (mm, mean ± standard deviation) at 6 and 12 months following treatment in test and control groups

	Test ($N = 16$)	Control ($N = 16$)	*p*-value
CAL gain 6 months	2.3 ± 1.5	3.3 ± 1.6	NS
CAL gain 12 months	3.6 ± 1.5	3.4 ± 1.4	NS
PD reduction 6 months	3.4 ± 1.2	3.8 ± 1.3	NS
PD reduction 12 months	4.6 ± 2.0	3.9 ± 1.4	NS
REC increase 6 months	1.1 ± 1.3	0.5 ± 1.0	NS
REC increase 12 months	1.1 ± 1.5	0.6 ± 1.3	NS

CAL, clinical attachment level; PD, probing depth; REC, recession depth; NS, not significant.

Table 4. Distribution of patients in test and control groups according to clinical attachment level (CAL) gain as assessed at 12 months following surgery

	CAL gain (mm)		
	0–2	>2–4	>4
Test ($N = 16$)	4	8	4
Control ($N = 16$)	4	9	3

Table 2 shows pre- and post-surgery PD, CAL and REC recordings, as assessed in test and control groups. Baseline PD and CAL were 8.3 ± 2.1 and 10.1 ± 2.2 mm, respectively, for the test group, and 7.6 ± 1.2 and 8.6 ± 1.9 mm, respectively, for the control group. No significant differences were detected between groups at baseline.

Both test and control treatment produced a significant decrease in CAL at both 6 and 12 months with respect to baseline value ($p < 0.000$; Table 2). At 6 months, CAL gain was 2.3 ± 1.5 mm for the test group, and 3.3 ± 1.6 mm for the control group (Table 3). Six-month CAL was significantly greater in test compared with control group ($p = 0.019$; Table 2). At 12 months, CAL gain reached 3.6 ± 1.5 and 3.4 ± 1.4 mm for the test and control group, respectively, with comparable levels of CAL between groups (Tables 2 and 3). In the test group, 12-month CAL was significantly smaller than 6-month CAL ($p < 0.000$). At 12 months, four patients (25.0%) in the test group and three patients (18.7%) in the control group presented CAL gain >4 mm. No significant differences between groups were observed in frequency distribution of patients according to 12-month CAL gain (Table 4).

With respect to baseline value, both 6- and 12-month PD were significantly smaller in both test and control groups ($p < 0.000$; Table 2). PD reduction at 6 and 12 months was similar between groups (Table 3).

REC increased from baseline to both 6 and 12 months in both groups (Table 2). Six- and 12-month REC were significantly different from baseline in the test group ($p = 0.006$ and 0.009, respectively), but not in the control group. No significant differences in REC changes were observed between groups (Table 3).

Discussion

The aim of this trial was to evaluate the clinical outcome of re-constructive surgery in deep intra-osseous defects by means of OFD in conjunction with a PLA/PGA copolymer implant (Fisiograft®) as compared with OFD procedure alone. The results demonstrated that both treatment modalities provide clinically and statistically significant improvements in PD and CAL measurements. However, the use of PLA/PGA did not provide an additional benefit in terms of CAL gain and PD reduction compared with control procedure.

These findings are consistent with those reported in a previous study where a PLA graft was used for periodontal re-construction in deep intra-osseous defects (Meadows et al. 1993). No additional effect was observed when the polymer biomaterial was grafted as compared with OFD alone. Moreover, PLA implant resulted in a scarce improvement at 12 months after surgery in terms of both defect fill at re-entry (0.1 mm) and CAL gain (0.5 mm) (Meadows et al. 1993).

Overall, these results seem to indicate a limited adjunctive effect of biodegradable copolymers in periodontal re-constructive procedures. However, it should be noted that the magnitude of CAL gain observed in our material was sevenfold higher than that observed in the Meadows' study. Differences in treatment outcome between studies may be partly explained by different physico-chemical characteristics of the implanted biomaterials (PLA homopolymer granules *versus* PLA/PGA copolymer sponge), patient/defect selection, surgical technique adopted, and post-surgical infection control.

Historically, PLA/PGA polymers have been used to make biodegradable screw and fixation pins, rodes, plates, suture anchors and sutures (Agrawall et al. 1995). PLA, PGA and their copolymers have also been successfully used to fabricate bone graft substitutes and delivery systems for drugs or osteogenic proteins (Lee et al. 1994, Hetherington

et al. 1996, Sigurdsson et al. 1996). As the polymer degrades in vivo, it serves, not only as a vehicle for drug delivery, but also as a scaffold to support new bone formation.

Fisiograft® is a synthetic resorbable sponge formed by 50–50 lactide–glycolide polymer. This copolymer has shown the fastest degradation rate of the D-L lactide/glycolide biomaterials, with the polymer degrading in about 50–60 days (Eppley & Reilly 1997). In the previous study (Meadows et al. 1993) PLA granules were still evident at 6-month surgical re-entry. Histologic observation revealed that the defects were mostly filled with soft tissue surrounding the PLA particles, with limited bone formation and a chronic inflammatory infiltrate. Hollinger (1983) evaluated the healing capacity of experimentally induced osseous defects treated with 50 PLA:50 PGA implants. The hydrolytic degradation of the implant was associated with increasing formation of trabecular bone. Piattelli (2003) reported limited residual amount of PLA/PGA (1%) at 6–8 months after the implantation of Fisiograft®. Histomorphometric analysis revealed 43% of mineralized bone with complete absence of inflammatory response. Consistently, Fisiograft® sponge implanted in post-extraction sites resulted in the formation of matured, mineralized and well-structured bone after 6 months of healing. Particles of grafted material could not be identified in any of the biopsied site (Serino et al. 2003). Therefore, it may be hypothesized that PLA/PGA-derived polymers with varying degradation rates may differently influence the post-surgical healing process following periodontal re-constructive procedures.

In our material a specific surgical procedure was adopted to achieve primary closure in the inter-proximal area and consequently ensure wound stability during the healing process (Trombelli et al. 2002b). It has been shown that the creation of a secluded and protected environment may allow wound-healing process to occur undisturbed, eventually leading to periodontal regeneration (Wikesjö & Nilvéus 1990). Moreover, preservation of supra-crestal soft tissues may limit the collapse of the flap into the bone defect, thus optimizing available space for periodontal regeneration (Sigurdsson et al. 1994, Trombelli et al. 1999). Space-maintaining flap design and suturing technique may be of particular relevance to maximize the re-constructive outcome when treating a non-self-supporting defect without using any space-providing graft biomaterial or membrane device. The effectiveness of our surgical strategy was partly confirmed by the amount of mean CAL gain (3.4 mm) obtained in the control group, and may in part account for the lack of adjunctive effect of the PLA/PGA graft biomaterial.

In the present study a stringent infection control programme, based on oral hygiene reinforcement and professional polishing and scaling, was followed throughout the study. This programme resulted in a reduced supra-gingival plaque accumulation (DSPS) and sub-gingival inflammation (DSBS) during the healing process. Evidence suggest that a limited amount of bacterial deposits is of paramount importance to emphasize the regenerative potential of a periodontal surgical procedure (Kornman & Robertson 2000). In our study the adoption of such infection control programme seemed even more critical because of the large proportion of smokers (from one-third to one-half) included in the study population.

It is interesting to note that in the control group CAL significantly reduced from baseline to 6 months and remained stable thereafter. In contrast, in the test group CAL showed a significant decrease from baseline to 6 months, but levelled the extent of CAL gain observed in the control group only after 12 months of healing. As a consequence, 6-month CAL was significantly greater in test compared with control group. These observations seem to suggest that the PLA/PGA graft may have somewhat affected the early phase of the healing process, virtually by modifying the physico-chemical properties of the micro-environment during its degradation process and/or eliciting a foreign body reaction (Tatakis & Trombelli 1999). This hypothesis apparently contrasts with previous reports (Leghissa et al. 1997, Ghinzani 1998, Leghissa et al. 1998, Leghissa & Leardi 1998, Bucci Sabattini et al. 1999, Gatti et al. 1999, Leghissa 1999) where alveolar bone re-construction was achieved using Fisiograft® under different surgical conditions. The rate of osseous repair, as histomorphometrically analysed, was significantly accelerated in osseous sites treated with PLA–PGA as compared with untreated control sites (Serino et al. 2003). Further studies are needed to determine whether and to what extent Fisiograft® may exert an influence on the healing dynamics following periodontal re-constructive procedures.

In conclusion, within the limitations of the present study, the adjunctive use of a PLA/PGA copolymer in conjunction with OFD procedure in the treatment of deep periodontal intra-osseous defects did not result in any additional benefit when compared with OFD procedure alone.

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