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Periodontal healing following reconstructive surgery: effect of guided tissue regeneration using a bioresorbable barrier device when combined with autogenous bone grafting. A randomized controlled clinical trial

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Abstract

Objective: The objective of this randomized-controlled clinical trial was to evaluate the adjunctive effect of guided tissue regeneration (GTR) using a bioresorbable polylactic acid (PLA) barrier device when combined with autogenous bone grafting in the treatment of deep intra-bony periodontal defects.

Material and Methods: Forty systemically healthy patients (20 females; mean age 53 years; non-smokers) participated in the study. Using a parallel-group study design, one intra-bony defect in each of 20 subjects received GTR using the bioresorbable PLA barrier device (Atrisorb®), combined with autogenous bone grafting. One intra-bony defect in each of the remaining 20 subjects received bone grafting solo (control). Treatments were evaluated at 9 months post-surgery.

Results: One patient (GTR) was withdrawn from the study due to circumstances unrelated to the study. Eighty-nine per cent of the PLA barriers became exposed within 3 weeks following surgery. Pre-surgery probing depths for GTR and control intra-bony defects averaged (± SE) 7.1 ± 0.3 mm. Significant probing depth reduction (2.7 ± 0.3 *versus* 2.4 ± 0.4 mm), attachment-level gain (1.7 ± 0.3 *versus* 1.7 ± 0.5 mm), and bone fill (1.2 ± 0.4 *versus* 1.2 ± 0.5 mm) were observed for the GTR and control sites, respectively ($p \leqslant 0.02$). However, there were no statistically significant differences between treatment protocols.

Conclusions: The results suggest that GTR using the bioresorbable PLA barrier device does not provide additional value to reconstructive surgery including autogenous bone grafting in intra-bony periodontal defects.

Key words: barrier membrane; bone graft; guided tissue regeneration; periodontal regeneration; polylactic acid; wound healing

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Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.
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Table 1. Patient characteristics

	GTR ($N = 20$)	Control ($N = 20$)	p-value
Age (means ± SD)	52.6 ± 5.4	53.7 ± 5.0	0.52
Males/females	9/11	11/9	0.53
Maxillary anterior/pre-molars	9/5	8/8	0.43
Mandibular anterior/pre-molars	4/2	3/1	0.78

GTR, guided tissue regeneration.

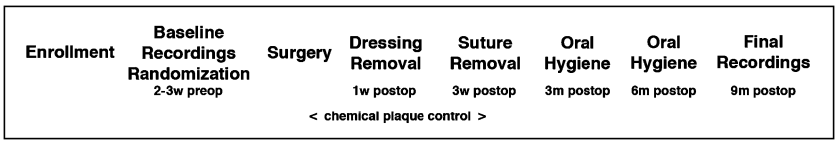

Fig. 1. Flow chart of the study.

Human case studies and studies using discriminating animal models have pointed to a considerable native biologic potential for regeneration of the periodontal attachment, i.e., formation of new cementum, alveolar bone, and a functionally oriented periodontal ligament (Nyman et al. 1982, Gottlow et al. 1986, Sigurdsson et al. 1994, Wikesjö et al. 2003a, b, c). Critical clinical components for successful outcomes are: (1) wound stability during the early healing sequence (Wikesjö & Nilvéus 1990, Haney et al. 1993); (2) space provision to allow the migration and proliferation of cells from the periodontal ligament and alveolar bone along the periodontally exposed root (Haney et al. 1993, Sigurdsson et al. 1994, Trombelli et al. 1999, Wikesjö et al. 2003a, b, c); and (3) conditions favouring primary intention healing, i.e., the wound space remains protected from bacterial contamination and infection (Haney et al. 1993, Sigurdsson et al. 1994, Wikesjö et al. 2003b).

A large body of clinical studies has applied the principles of guided tissue regeneration (GTR) to resolve periodontal intra-bony and furcation defects (for a review, see Cortellini & Tonetti 2000, Sanz & Giovannoli 2000). Outcomes from such studies have been rather variable, suggesting that the understanding of the fundamental biology for periodontal regeneration is incomplete or its clinical application is difficult to master or complicated by events compromising periodontal wound healing (for a review, see Needleman et al. 2006, Polimeni et al. 2006).

Clinicians often opt to use bone biomaterials (for a review, see Nasr et al. 1999) with the intent to support regeneration of periodontal tissues (for a review, see Rosen et al. 2000). Bone derivatives or bone substitutes have been used discretely and in combination(s) with GTR with considerably variable outcomes (for a review, see Trombelli et al. 2002, Needleman et al. 2006). Histologic case studies may be interpreted to suggest that autogenous bone grafts have a potential to stimulate periodontal regeneration (Froum et al. 1983, Stahl et al. 1983). Clinical studies using autogenous bone grafts may also suggest that bone grafting supports regeneration of periodontal structures (Schallhorn et al. 1970, Froum et al. 1976, Renvert et al. 1985). Few, if any, reports have concerned the effect of autogenous bone grafts combined with GTR in the surgical management of periodontal defects. The objective of this randomized-controlled clinical trial was to evaluate the adjunctive effect of GTR using a bioresorbable polylactic acid (PLA) barrier device when combined with autogenous bone grafting in the treatment of deep intra-bony periodontal defects.

Material and Methods

Patient and site selection

Forty systemically healthy patients (20 females; mean age 53 years; range 42–67 years; non-smokers), recruited from the patient pool of the principal investigator (P. N.-Ø.), exhibiting chronic periodontitis with localized or generalized advanced loss of attachment including one or more periodontal defects with a probing depth >6 mm, were enrolled in the study (Table 1). A further inclusion criterion comprised the presence of an associated inter-proximal intra-bony defect with a depth (alveolar crest − fundus of defect) >4 mm as measured with a probe during surgery. Sites associated with root concavities/furrows or furcation defects were excluded. The patients had completed basic periodontal therapy including scaling, root planing, and oral hygiene training at the time of enrollment approximately 3 weeks before the surgeries. They all exhibited high oral hygiene standards. This study was conducted in a private practice setting. The study protocol followed the Declaration of Helsinki. Subjects who agreed to participate signed an informed consent form.

Using a parallel-group design, patients/intra-bony defects were assigned to receive GTR combined with autogenous bone grafting (GTR; 20 subjects) or autogenous bone grafting solo (control; 20 subjects) using a computer-generated random code provided by the study sponsor. Subject numbers were assigned at the baseline examination in consecutive order by the principal investigator. The sample size used has been usual in previous studies for this type of clinical evaluation. A flow chart of the study is shown in Fig. 1.

Treatment procedures

All surgical procedures were performed by one experienced periodontist (P. N.-Ø.). Mucoperiosteal flaps were elevated for defect access including granulation tissue removal and root surface debridement following routine anaesthesia and sulcular incisions. Considerable care was taken to preserve the inter-dental tissues (Nygaard-Østby et al. 1996). This surgical protocol was used to preserve gingival tissues for optimal defect coverage at wound closure. Autogenous bone was harvested from the chin area using a 5 mm diameter trephine burr. Harvested bone was crushed into smaller pieces and implanted to fill the intra-bony defect following granulation tissue

Table 2. Intra-surgery defect characteristics (means ± SE in mm)

	GTR ($N = 19$)	Control ($N = 20$)	p-value
Total defect depth	5.58 ± 0.36	5.40 ± 0.26	0.69
3-wall component	3.89 ± 0.17	4.10 ± 0.21	0.45
Defect width	7.21 ± 0.38	7.80 ± 0.30	0.23
Defect sector (°)	97.63 ± 4.03	104.50 ± 6.22	0.36

GTR, guided tissue regeneration.

removal and root debridement. For the GTR defect sites, a chair-side-prepared bioresorbable PLA barrier device (Atrisorb®, Atrix Laboratories Inc., Fort Collins, CO, USA) extending 3 mm over the defect margins was placed to cover the autogenous bone graft. The control sites received the autogenous bone graft solo. The muco-periosteal flaps were repositioned to cover implanted materials and sutured (Gore Tex® Suture CV-5, W. L. Gore & Associates Inc., Flagstaff, AZ, USA).

The post-surgery protocol included administration of amoxicillin (500 mg; 2 × daily) and ibuprofen (400 mg; 4 × daily) for 10 days. A periodontal dressing was used the first week post-surgery. Mechanical plaque control was not performed in the surgical and adjacent areas for 3 weeks. Thus, plaque control was maintained by rinsing with a chlorhexidine solution (Peridex® 0.12%, Procter & Gamble, Cincinnati, OH, USA; 3 × daily) until suture removal at 3 weeks post-surgery. The subjects were then exposed to repeat oral hygiene instructions as warranted and had their teeth scaled and polished at 3, 6, and 9 months post-surgery.

Recordings

Three trained, masked examiners (V. B., O. N., H. K. N.) with long-term experience of periodontal registrations performed defect specific recordings, each examiner scoring the same subjects throughout the study. Duplicate recordings, approximately 10 days apart, were performed in a subset of patients to document examiner reliability. The recordings included: oral hygiene standards (Silness & Løe 1964); gingival health (Løe & Silness 1963), both recorded for the defect associated and the adjacent tooth; probing depths; bleeding-on-probing; attachment levels; probing bone levels (recorded following local anaesthesia; the probe was forced through the soft tissue towards the bone until definite tissue resistance was encountered); gingival recession; and tooth mobility (Miller 1938). Recordings were made to the nearest mm at the mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual, and mesio-lingual aspects of the defect-associated teeth using a periodontal probe (CP 15 UNC, Hu Friedy, Chicago, IL, USA). Attachment levels, probing bone levels, and gingival recession were recorded from the cemento-enamel junction.

Intra-surgery recordings, made after defect debridement, included total defect depth, depth of the three-wall intra-bony component defect width, and defect sector (Nygaard-Østby et al. 1996). Briefly, the total defect depth was determined by measuring the distance from the alveolar crest to the fundus of the defect from its buccal and lingual inter-proximal aspects, and averaging the values. The depth of the three-wall component was determined as the distance from the most apical inter-proximal bone crest to the fundus of the defect. Defect width was determined as the buccal–lingual extension of the defect at the alveolar crest. Defect sector was the crestal circumference of the defect estimated relative to the circumference of the defect-associated tooth and expressed in degrees thereof (Table 2).

Clinical photography was used to document the defects and progression of healing. Radiographic examinations were performed as part of the patient's general treatment protocol pre- and at 6 and 9 months post-surgery. Pathological tissue alterations, device exposure, or other pertinent clinical observations related to the surgery were recorded.

Statistical analysis

A sample size of 17 subjects in each experimental group was estimated to be necessary to detect a difference of 1.0 ± 1.0 mm between treatments with a significance level of 5% and a power of 80%. An estimated 15–20% dropout was allowed in the final sample size calculation. Comparison of patient demographics between groups was performed using a t-test and a χ^2 test; the means and standard deviations are reported accordingly. Linear models taking into account the longitudinal nature of the data were used to perform the statistical analysis of the clinical variables. The distribution of the data was assessed, and no substantial departure from normality was observed. Group means and standard errors based on defect site means are reported. Wald's tests were used for multiple comparisons and the level of significance was set at 5%. The analysis was performed using the statistical package Stata for Windows (Stata 9.2, Stata Corporation, College Station, TX, USA). Intra- and inter-examiner reliabilities were assessed by re-examining 19 and 10 patients, respectively. The overall κ was 0.92 and 0.76 for the intra- and inter-examiner reliabilities, respectively, showing good reproducibility of the examiners.

Results

One subject discontinued the study after the surgery was completed due to circumstances unrelated to the study protocol; thus, the number of participants completing the study were as follows: 19 subjects received the GTR/bone graft combination and 20 subjects received the bone grafting control protocol.

There were no relevant differences between the GTR and control groups relative to gender and age distribution (Table 1). Similarly, defect sites were similarly distributed among the maxillary and mandibular and anterior and posterior teeth (incisors/canines and pre-molars).

Complete gingival wound closure for primary intention healing was accomplished for all defect sites. Nevertheless, the bioresorbable PLA device became exposed within 1 week in five patients (28%), within 2 weeks in 16 patients (84%), and within 3 weeks in 17 patients (89%). No other adverse reactions or relevant clinical findings other than gingival recession were observed.

Patients in both treatment groups exhibited consistent and high oral hygiene standards as evidenced by low plaque and gingival indices (Table 3). Nevertheless, bleeding-on-probing scores were consistently high comparing pre-surgery with 9-month post-treatment observations, although the control group showed a statistically significant decrease from pre- to

Table 3. Oral hygiene standards and gingival health (means ± SE)

	Pre-surgery	9 months	Δ Pre – 9 Months	*p*-value
GTR ($N = 19$)				
Plaque index	0.47 ± 0.11	0.55 ± 0.14	– 0.08 ± 0.14	0.58
Gingival index	0.87 ± 0.12	0.55 ± 0.13	0.32 ± 0.13	0.02
Bleeding on probing (%)	86.84 ± 6.36	92.11 ± 4.24	– 5.26 ± 7.44	0.48
Control ($N = 20$)				
Plaque index	0.48 ± 0.10	0.58 ± 0.13	– 0.10 ± 0.13	0.44
Gingival index	0.93 ± 0.08	0.48 ± 0.13	0.45 ± 0.16	0.006
Bleeding on probing (%)	98.50 ± 2.47	82.50 ± 6.48	15.00 ± 7.25	0.045

GTR, guided tissue regeneration.

Table 4. Oral hygiene standards and gingival health – GTR *versus* control (means ± SE)

	GTR Δ Pre – 9 months	Control Δ Pre – 9 months	*p*-value
Plaque index	– 0.08 ± 0.14	– 0.10 ± 0.13	0.91
Gingival index	0.32 ± 0.13	0.45 ± 0.16	0.52
Bleeding on probing	– 5.26 ± 7.44	15.00 ± 7.25	0.06

GTR, guided tissue regeneration.

Table 5. Defect site characteristics and treatment effects (means ± SE in mm)

	Pre-surgery	9 months	Δ Pre – 9 months	*p*-value
GTR ($N = 19$)				
Gingival recession	1.29 ± 0.27	2.32 ± 0.33	1.03 ± 0.20	< 0.001
Probing depth	7.08 ± 0.30	4.39 ± 0.32	2.68 ± 0.34	< 0.001
Attachment level	8.37 ± 0.49	6.71 ± 0.44	1.66 ± 0.33	< 0.001
Probing bone level	9.47 ± 0.52	8.29 ± 0.51	1.18 ± 0.38	0.003
Control ($N = 20$)				
Gingival recession	1.56 ± 0.27	2.21 ± 0.34	0.64 ± 0.22	0.007
Probing depth	7.10 ± 0.33	4.67 ± 0.29	2.44 ± 0.35	< 0.001
Attachment level	8.56 ± 0.49	6.87 ± 0.52	1.69 ± 0.46	< 0.001
Probing bone level	9.21 ± 0.50	8.05 ± 0.57	1.15 ± 0.48	0.02

GTR, guided tissue regeneration.

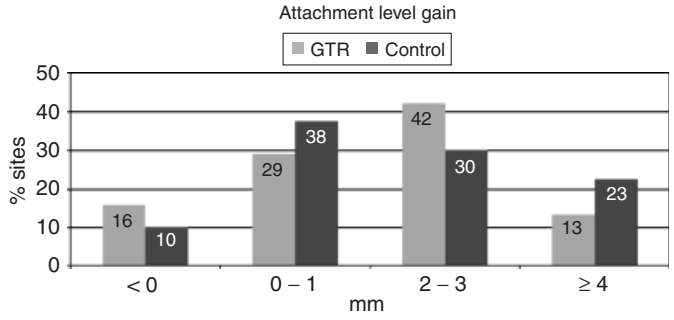

Fig. 2. Frequency distribution of attachment-level gain among defect sites treated with the guided tissue regeneration (GTR) and the control protocol.

post-treatment (98% *versus* 82%; $p = 0.045$). In all, there were no statistically significant or other relevant differences between the treatment groups for the oral hygiene or gingival health parameters (Table 4).

There was a statistically significant shift in gingival recession, probing depth, clinical attachment, and probing bone level from pre- to post-treatment (Table 5). Gingival recession increase averaged (± SE) 1.03 ± 0.20 *versus* 0.64 ± 0.22 mm for the GTR and control groups, respectively ($p = 0.20$; Table 6). Similarly, the corresponding observations for probing depth reduction (2.68 ± 0.34 *versus* 2.44 ± 0.35 mm), attachment level gain (1.66 ± 0.33 *versus* 1.69 ± 0.46 mm), and probing bone level gain (1.18 ± 0.38 *versus* 1.15 ± 0.48 mm) did not show statistically significant differences between the treatments. Moreover, there were no significant changes in tooth mobility over time for the control (from 0.80 ± 0.14 to 0.85 ± 0.18, $p = 0.80$) and GTR groups (from 0.95 ± 0.18 to 0.90 ± 0.17, $p = 0.71$), and no significant differences were observed between the groups ($p = 0.67$).

Reviewing the distribution of sites gaining clinical attachment and alveolar bone, it becomes evident that there were no remarkable or statistically significant differences between the GTR and the control protocol; approximately 55% of the GTR sites and 53% of the control sites exhibited attachment-level improvements ⩾2 mm ($p = 0.46$; Fig. 2). The corresponding assessments for probing bone-level improvements were 55% and 40% ($p = 0.11$; Fig. 3). There were also no remarkable differences in residual probing depths between the treatment protocols; approximately 20% of the sites exhibited a probing depth ⩽3 mm, 60% probing depths of 4 or 5 mm, and 20% probing depths equal to or exceeding 6 mm at the 9-month observation ($p = 0.90$; Fig. 4).

Discussion

The objective of this randomized-controlled clinical trial was to evaluate the adjunctive effect of GTR using a bioresorbable PLA barrier device when combined with autogenous bone grafting in the treatment of deep intra-bony periodontal defects. Oral hygiene standards and gingival health, gingival, periodontal, and alveolar bone changes were monitored over a 9-month healing interval. The results demonstrated significant and similar improvements for both treatment protocols including probing depths, clinical attachment, and alveolar bone levels. Apparently, the GTR protocol did not provide additional value to the procedure. In other words, there were limited non-significant differences between defect sites receiving the bioresorbable barrier device and those that did not.

A parallel-group design was used to compare treatments in systemically healthy subjects exhibiting periodontal

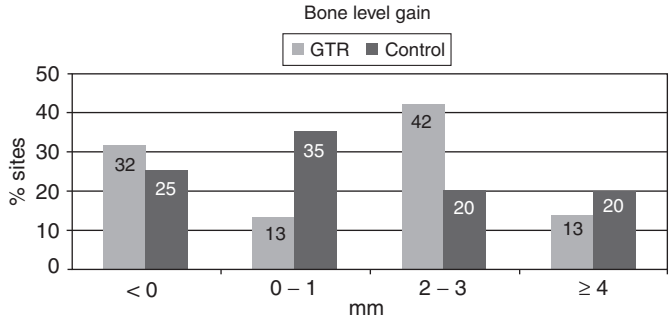

Fig. 3. Frequency distribution of bone-level gain among defect sites treated with the guided tissue regeneration (GTR) and the control protocol.

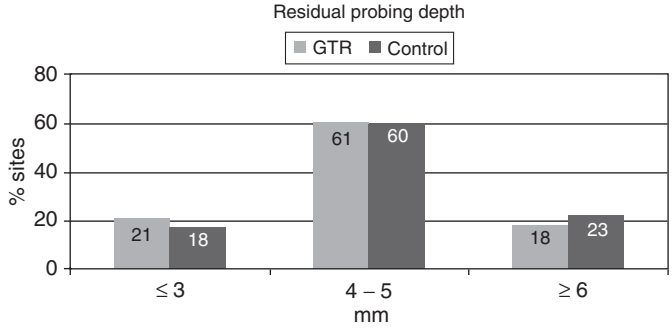

Fig. 4. Frequency distribution of residual probing depth among defect sites treated with the guided tissue regeneration (GTR) and the control protocol.

Table 6. Treatments effects – GTR *versus* control (means ± SE in mm)

	GTR Δ Pre – 9 months	Control Δ Pre – 9 months	*p*-value
Gingival recession	1.03 ± 0.20	0.64 ± 0.22	0.20
Probing depth	2.68 ± 0.34	2.44 ± 0.35	0.61
Attachment level	1.66 ± 0.33	1.69 ± 0.46	0.95
Probing bone level	1.18 ± 0.38	1.15 ± 0.48	0.96

GTR, guided tissue regeneration.

intra-bony defects. This study design is well suited for this type of clinical trials because defect configuration may be balanced more easily between treatments compared with a split-mouth design in which one has to accept more readily the inherent variability in the location and morphology of periodontal defects within subjects (Selvig et al. 1993, Haney et al. 1995). Regarding sample size, the present sample was estimated to have enough power to show an additional effect of 1 mm with the adjunct use of GTR. The dropout of one subject did not jeopardize the study power because it was within the limits of the sample size calculation.

Primary intention healing appears to be critical for the successful outcome of GTR procedures (Haney et al. 1993, Sigurdsson et al. 1994, Wikesjö et al. 2003b). Incomplete wound closure or suture-line dehiscencies developed during the early healing sequence, resulting in bacterial colonization of the barrier device (Selvig et al. 1992) and development of an inflammatory lesion rather than a regenerate underneath the device (Haney et al. 1993, Sigurdsson et al. 1994, Wikesjö et al. 2003b). Lack of device coverage or gradual exposure during healing is not uncommon in clinical practice also under stringent research conditions involving accomplished clinicians (Trombelli et al. 1997, Machtei 2001, Sanz et al. 2004). Indeed, clinical studies have shown that defect sites with exposed GTR devices generally exhibit limited, if any, improvements (Selvig et al. 1992, Trombelli et al. 1997, Machtei 2001, Sanz et al. 2004). For example, Trombelli et al. (1997) reported that 66% of 38 patients experienced device exposure at intra-bony defects treated with an occlusive ePTFE device, probing bone-level gain averaging 2.2 ± 2.3 mm for exposed sites *versus* 4.1 ± 2.3 mm for unexposed sites. Machtei (2001), in a systematic review, reported 46% exposures of 309 sites from studies predominantly evaluating bioresorbable barrier devices and observed statistically significant smaller attachment-level gains in exposed compared with unexposed sites. Sanz et al. (2004) reported on 32 patients treated with a bioresorbable GTR device, stating ''all cases treated with GTR presented at least one surgical complication, mostly membrane exposure''. The clinical outcomes following GTR in this study appeared to be generally inferior to that previously reported from this experienced research group. In the present study, 28% of the PLA membranes were or became exposed within a week, 84% within 2 weeks, and 89% within 3 weeks; however, no adverse effect on the healing could be discerned at the 9-month registrations. Perhaps the autologous bone graft overcame any unfavourable consequences of device exposure or provided an environment that made clinical detection of eventual deleterious effects treacherous compared with that when an intra-bony defect is not filled with a bone graft or biomaterial.

Biologic evaluations using occlusive and porous barrier devices have shown that space provision but not tissue occlusion is essential for periodontal regeneration (Wikesjö et al. 2003b, c). Other biologic evaluations have shown that implanted bone biomaterials may compromise periodontal wound healing (Trombelli et al. 1999). The biomaterial may in fact obturate the defect site to migration and proliferation of critical tissue resources from the periodontal ligament but also alveolar bone. It is not inconceivable that healing events under provisions for primary intention healing could have been different between the GTR and the control group in the present study. The use of autologous bone may augment outcomes through osteogenic and/or osteoconductive pathways whereas GTR devices are intended to provide an environment conducive to express the innate potential for periodontal regeneration. This study failed to demonstrate an added effect of GTR to autologous bone grafting. Perhaps the bone graft obturated the defect

site to periodontal regeneration; perhaps the regenerative potential was exhausted for either technology; or perhaps the GTR device exerted an effect eventually compromised by device exposure.

The present study demonstrated clinical improvements similar to that reported for several other treatment concepts including biologic constructs, autologous bone grafts, bone biomaterials, and GTR as stand-alone protocols or in combinations (Schallhorn et al. 1970, Stahl et al. 1983, Renvert et al. 1985, Bowers et al. 1989, Becker & Becker 1993, Cortellini et al. 1995, Mellado et al. 1995, Choi et al. 1996, Nygaard-Østby et al. 1996, Tonetti et al. 2002, Sanz et al. 2004, Nevins et al. 2005). Some studies/treatments demonstrate somewhat greater numerical improvements than others. However, differences in outcomes may rather relate to defect location and configuration, surgical technique, and post-surgery protocol than experimental variation. Evaluation and data presentation also play a role in such comparisons. Only deep intra-bony defects have a substantial clinical regenerative potential in absolute measures. Thus, popular side-by-side comparisons of treatment effects between studies may not be entirely meaningful in the present and other settings.

The GTR device in the present study was based on a PLA polymer technology. Bioresorbable polymers are well-described technologies used to manufacture devices for fracture fixation and drug delivery (Langer 1990, Hollinger & Leong 1996, Rokkanen et al. 2000). These implantable devices biodegrade by hydrolysis to their monomers that are metabolized. Orthopaedic devices such as pins, plates, rods, and bolts based on PLA technologies are known to induce adverse reactions including osteolytic processes as late as 5 years post-implantation (Weiler et al. 1996, Bostman & Pihlajamaki 2000a, b, Mosier-LaClair et al. 2001). Pre-clinical studies have shown accumulations of multinucleated giant cells and associated resorption of newly formed and resident bone when biomaterials based on PLA technologies have been implanted into periodontal defects (Wikesjö & Nilvéus 1990, Sigurdsson et al. 1996). Similar reactions have been observed in human biopsies from periodontal or alveolar sites treated with PLA devices for GTR (Tatakis & Trombelli 1999, Schmitz et al. 2000). The specific GTR device used in the present clinical study was evaluated in a rat calvarial model (Polimeni et al. 2007). Young-adult male Sprague–Dawley rats were surgically implanted with the device, or served as sham-surgery or non-operated controls. Control animals showed no signs of bone formation or resorption or signs of inflammatory reactions in the adjoining tissues. In contrast, extensive amounts of residual biomaterial, associated foreign body reactions, and bone resorption were observed in animals receiving the PLA device over the entire 12-month healing interval. The present clinical study provided no indication of adverse events experienced with the above PLA technologies. Perhaps exposure of the device to the oral milieu accelerated its elimination through biodegradation and/or sequestration such that adverse effects could not develop, much less be clinically appreciated.

Conclusions

The results suggest that GTR using the bioresorbable PLA barrier device does not provide additional value to reconstructive surgery including autogenous bone grafting in intra-bony periodontal defects.

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Clinical Relevance

Scientific rationale for the study: Histologic cases and clinical studies may suggest that autogenous bone grafts have a potential to stimulate regeneration of periodontal structures. Few, if any, reports have concerned the effect of autogenous bone grafts combined with GTR. The objective of this randomized-controlled clinical trial was to evaluate the adjunctive effect of GTR using a bioresorbable PLA barrier device when combined with autogenous bone grafts in the treatment of deep intra-bony periodontal defects.

Principal findings and practical implications: The results suggest that GTR using the bioresorbable PLA barrier device does not provide additional value to reconstructive surgery including autogenous bone grafts in intra-bony periodontal defects.