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Clinical evaluation of platelet-rich plasma and bioactive glass in the treatment of intra-bony defects

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Abstract

Background: There are limited numbers of studies focused on the using of platelet-rich plasma (PRP) combined with different types of bone substitutes in intra-bony defects.

Aim: The purpose of this study was to evaluate the effect of bioactive glass graft material (BG) with and without PRP on the clinical healing of intra-bony defects.

Materials and Methods: Twenty-nine intra-bony defects were randomly treated with either PRP/BG or BG alone. Clinical parameters were recorded at baseline and repeated 9 months after surgery and surgical reentries were also performed.

Results: The results showed that both treatment modalities were effective. Pocket depth reduction of 3.60 ± 0.51 mm, clinical attachment gain of 3.3 ± 1.77 mm and defect fill of 3.47 ± 0.53 mm were noted in the PRP/BG group, with 3.29 ± 1.68, 2.86 ± 1.56 and 3.36 ± 0.55 mm improvements, respectively, noted for the BG group. None of the differences between the two treatment modalities were statistically significant.

Conclusions: It is suggested that both PRP/BG combination and BG alone are effective in the treatment of intra-bony defects. The results also showed that using PRP with BG has no additional benefit in the reduction of pocket depth, clinical attachment gain and defect fill.

Key words: bioactive glass; intra-bony defect; platelet rich plasma; regenerative treatment

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The treatment modalities for intra-bony defects include guided tissue regeneration (GTR), autografts, allografts, alloplasts, growth factors and combination of these techniques as well as osseous resective surgery (Gottlow 1993, Salama et al. 1994, Zamet et al. 1997, Cortellini et al. 1998, Laurell et al. 1998, Parashis et al. 1998, Carnevale & Kaldahl 2000, Nevins et al. 2003). Although the use of intra-oral autogenous bone graft is a well accepted treatment option in periodontal community, limited availability of donor sites, requirement for an additional surgery to obtain the graft material are the limitations of this technique. Because the use of an allograft such as freeze-dried bone has the risk of disease transmission (Low et al. 1997), alloplastic bone substitutes are being widely used in clinical practices.

Among various subgroups of alloplastic bone grafts bioactive glass (BG) is a kind of bioactive ceramic (Anderegg et al. 1999) consisting of SiO_2, CaO, Na_2O and P_2O_5. It has been suggested that the bioactive glasses bond to bone without an intervening fibrous connective tissue interface (Schepers et al. 1991). In a histological study, Schepers & Ducheyne (1997) reported that narrow-size (300–355 μm) BG has osteostimulatory effect besides its osteoconductive properties. It was demonstrated that BG had an antibacterial effect against subgingival and supragingival bacteria (Alan et al. 2001). Moreover, in soft and hard tissue measurements no significant differences were reported between demineralized freeze-dried bone allografts (DFDBA) and BG grafted sites (Lovelace et al. 1998).

Growth factors are a class of natural biologic mediators having local and systemic effects, which regulate cell migration, attachment, proliferation, differentiation and promote extracellular matrix accumulation via binding to

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specific cell-surface receptors (AAP Position Paper 1996). Many growth factors are deposited in the extracellular matrix where they are released during matrix degradation and they act as a part of a complex network of signals with mutual effects during tissue remodelling and regeneration. Post-natal therapeutic application of growth factors for repair of damaged tissue or an organ is used to accomplish regeneration or generation of tissue by reinducing the developmental process that had created this organ or body part during foetal or post-natal growth (Schliephake 2002). Platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and insulin-like growth factor (IGF) may be available for this purpose (Cromack et al. 1990, Lynch et al. 1991a, b, Rutherford et al. 1992, Wang et al. 1994, Howell et al. 1997).

Platelets contain high concentrations of PDGF and TGF-β in their α granules and the preparation of platelet-rich plasma (PRP) seems to be an appropriate and economical method to obtain these growth factors autogenously. Marx et al. (1998) and Okuda et al. (2003) reported that PRP contains a concentration of platelets and growth factors, PDGF and TGF-β. PRP has been successfully used in many recent studies and favourable clinical outcomes have been reported following the incorporation of PRP gel in the surgical procedures of the maxillofacial region, sinus augmentation, mandibular reconstruction, implant placement and intra-bony defect treatment (Marx et al. 1998, Anitua 1999, de Obarrio et al. 2000, Kassolis et al. 2000, Camargo et al. 2002, Lekovic et al. 2002, Petrungaro 2002). However, there are limited numbers of studies focused on the application of PRP in combination with alloplastic graft materials, evaluating the treatment outcomes in intra-bony defects (Okuda et al. 2005). Therefore, the aim of the present clinical study was to evaluate the additional effect of PRP on the treatment of intra-bony defects by comparing PRP/BG and only BG.

Material and Methods

Study population

Twenty-nine systemically healthy patients (16 females and 13 males, mean age 36.03 ± 12.02 years) with moderate to advanced chronic periodontitis were referred to Department of Periodontology, Faculty of Dentistry, Hacettepe University for periodontal treatment and were recruited for the study. The study design and consent were approved by the Faculty of Medicine, Ethical Committee of Medical, Surgical and Drug Research, Hacettepe University. Informed consent was obtained from each patient following the information about the treatment plan. The hygienic conditions of the patients, after initial therapy including oral-hygiene instructions and four quadrants of scaling and root planning, were evaluated.

Criteria for inclusion in the study were as follows: (1) no systemic diseases, (2) having a good level of oral hygiene [plaque index (PI) < 1 Löe 1967], (3) mobility < 1 mm in total, (4) radiographic evidence of vertical alveolar bone loss at the mesial aspect of the tooth, (5) presence of a mesial inter-proximal probing pocket depth $\geqslant 6$ mm following initial therapy, (6) no prosthetic restoration or endodontic treatment on the related tooth, (7) any medications affecting the coagulation mechanism. Five patients in the test and four patients in the control group were smokers (six to 10 cigarettes per day).

Patients included in the study were divided into two groups randomly by the flip of a coin. The test group included of 15 patients treated with PRP/BG, whereas the control group included 14 patients treated with BG (Unigraft 200–420 μm, 40–70 mesh, Unicare Biomedical Inc. Santa Ana, CA, USA) only.

Clinical recordings

Clinical examinations were made at baseline and 9 months after the surgical procedure. PI (Silness & Löe 1964), gingival index (GI) (Löe & Silness 1963) and bleeding on probing (BOP) (Ainamo & Bay 1975) were recorded for all sites. The following clinical parameters were recorded using customized acrylic stents with guiding grooves and the cemento-enamel junction was used as a reference point: probing depth (PD), gingival recession (GR) and the clinical attachment level (CAL). After debridement of surgical site, the distances between cemento-enamel junction and base of the defect (CEJ–BD), cemento-enamel junction and crest of the defect, (CEJ–CD) and intra-bony defect depth (IDD) were recorded intra-surgically. The measurement taken at mesio-buccal sites on each tooth to be treated is considered for statistical evaluation. Measurements were performed with a Williams probe to the nearest millimetre. All clinical and intra-surgical measurements were performed by a single examiner (author A. B.) at baseline and 9 months after the surgical procedure without knowledge of the treatment groups.

Preparation of PRP with BG

The PRP preparation for the test group started 30 min. before surgery. Nine millilitres of whole blood was drawn by venipuncture of the antecubital vein and collected into two 4.5 ml Vacutainer blood collection tubes (ref no. 367714) obtained from Becton–Dickinson Vacutainer Systems (Beliver Industrial Estate, Plymouth, UK). These tubes were made of siliconized glass, containing 0.105 mol/l buffered sodium citrate. The tubes were initially centrifuged at 200 *g* for 10 min. and the plasma part was separated from the red blood cells (RBCs). The whole plasma portion and the top layer of the RBCs, which include fresh platelets attending blood circulation, were transferred to a polypropylene tube. Second centrifuge procedure was performed at 250 *g* for 10 min. leaving the PRP at the bottom of the tube. The upper portion of the plasma, namely platelet-poor plasma (PPP), was discarded. An aliquot of the venous blood from each PRP preparation was diluted by adding saline solution at a ratio of 1:5 platelets and counted by a haematology analyzer (Coulter® GEN.S Beckmann Coulter Inc. Fullerton, CA, USA). The platelet concentrations were increased 3.5 ± 2.6 times. Finally 0.5 ml of PRP, 0.3 ml 0.025 M $CaCl_2$ and the blood—harvested from the surgical site just after the incision—mixed were in the vial containing the graft and left for gelation. In the control group BG was mixed with four to six drops saline as per the manufacturer's instructions.

Surgical procedure

One surgeon performed all surgeries (BD). Following local anaesthesia, intra-crevicular incisions were performed, extending to the neighbouring teeth. Then, full-thickness flaps were raised vestibularly and orally. Extreme care was taken to preserve the marginal gingiva and inter-dental tissue to achieve

better closure of the grafted sites. No conditioning of the root surfaces was performed. Defect debridement and root planning were carried out carefully with hand and ultrasonic instruments to remove subgingival plaque, calculus and inflammatory granulation tissue. Intra-surgical measurements were then recorded, and PRP/BG or only BG was placed into the test and control sites (Fig. 1). Care was taken not to overfill the defects. After grafting, flaps were re-positioned to their original levels and periodontal dressing was placed (Voco pac, VOCO Gmbh, Cuxhaven, Germany), and amoxicillin 1000 mg every 12 h for 7 days was prescribed. Naproxen sodium 550 mg every 12 h was also prescribed to achieve an analgesic and anti-inflammatory effect. Patients rinsed with 0.12% chlorhexidine gluconate mouth rinse twice daily for the first 4 weeks. Sutures were removed 2 weeks following surgery. Patients were instructed not to brush or floss the surgical area for 4 weeks and each patient was then placed on monthly recall visits, including supragingival tooth cleaning, until reentry.

Nine months after the initial surgery, all clinical measurements were repeated and re-entry surgeries were performed. Re-entries consisted of buccal and lingual mucoperiosteal flaps and removal of all soft tissues present in the bony defects.

Statistical analysis

Mean values (mean ± standard error) were reported for each parameter. These data were statistically evaluated by a commercially available software program (GraphPad Software Inc. San Diego, CA, USA). Comparisons of clinical parameters between the test and control groups at baseline and 9 months post-surgery were performed utilizing the unpaired *t*-test. Mc Nemar test was applied to analyze BOP at baseline and 9 months post-surgery. For all analysis $p<0.05$ was considered statistically significant. Smoking status was ignored due to the small number of smokers.

Results

All 29 patients completed the study. Experimental and control sites healed uneventfully. The distribution of patients and defects is as shown in Table 1.

Mean PI, GI and BOP scores at baseline and 9 months are shown in Table 2. There were no statistically significant differences between the test and control groups at baseline ($p>0.05$). At 9 months, mean PI, GI and BOP scores in both groups decreased significantly when compared with baseline. In both groups the number of BOP positive teeth was 4 ($p<0.05$). The differences between the test and control groups were not significant at 9 months postoperatively ($p>0.05$) (Table 2).

Mean clinical measurements for PRP/BG and BG groups at baseline and at 9 months are shown in Table 3. The differences between the test and control groups at baseline for PD, GR and CAL parameters were not statistically significant ($p>0.05$); however, both groups showed strong significant changes for PD and CAL between baseline and 9 months ($p<0.001$). Clinical attachment gain was 3.13 ± 0.46 mm for the test group and 2.86 ± 0.42 mm for the control group. GR was − 0.47 ± 0.19 mm for the test group and − 0.43 ± 0.25 mm for the control group, both of which were

Table 1. Patient ages, tooth locations, gender, and number of osseous walls

Characteristics	PRP/BG ($N=15$)	BG ($N=14$)
Age (mean ± SD)	37.87 ± 14.16	34.07 ± 9.34
Male	7	6
Female	8	8
Maxilla	10	6
Mandible	5	8
Anterior	4	0
Posterior	11	14
Osseous walls		
1	5	3
2	8	8
3	2	3

PRP, platelet-rich plasma; BG, bioactive glass.

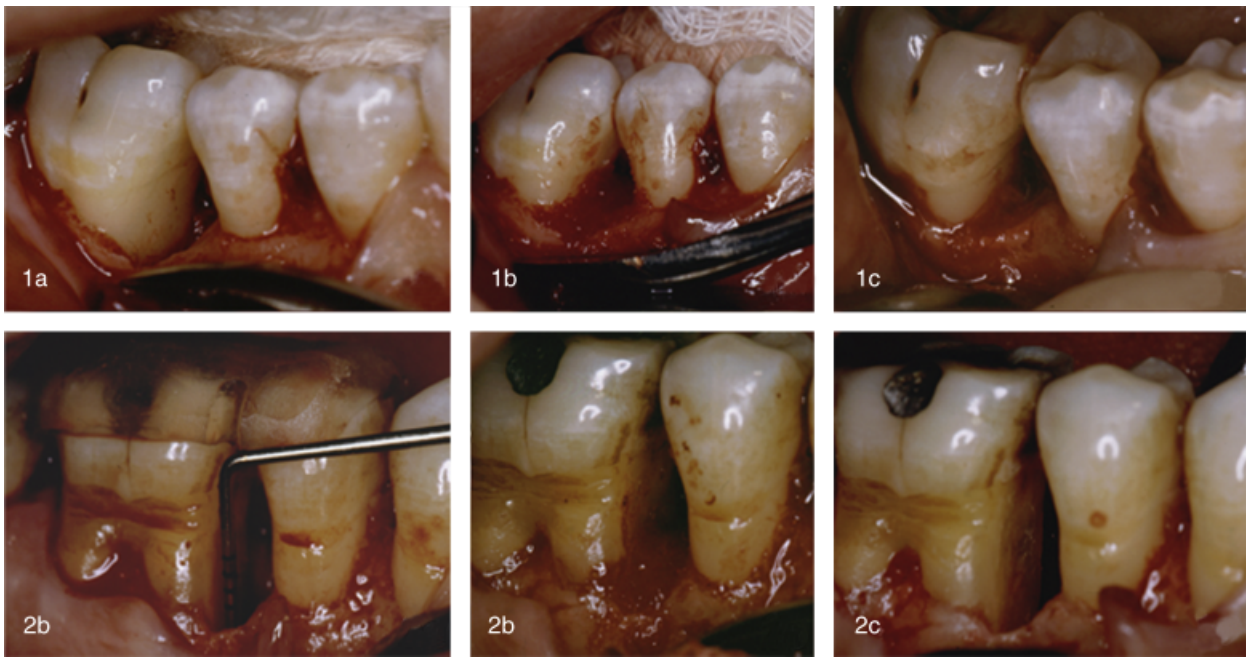

Fig. 1. Control group, the defect (1a) filled with bioactive glass grafts (1b) and 9 months after the surgical procedure (1c). Test group, the defect (2a) filled with alloplastic bone grafts and platelet rich plasma combination (2b) and 9 months after the surgical procedure (2c).

Table 2. Mean PI, GI and BOP values (mean ± SE) at baseline and 9 months

	Baseline	9 months	*p* value
PI			
PRP/BG ($n = 15$)	0.50 ± 0.10	0.13 ± 0.04	$p < 0.05$
BG ($n = 14$)	0.64 ± 0.15	0.23 ± 0.08	$p < 0.05$
p value	NS	NS	
GI			
PRP/BG	0.92 ± 0.09	0.25 ± 0.05	$p < 0.001$
BG	0.93 ± 0.15	0.34 ± 0.08	$p < 0.05$
p value	NS	NS	
BOP*			
PRP/BG	12/15	4/15	$p < 0.05$
BG	11/14	4/14	$p < 0.05$
p value	NS	NS	

*Number of positive sites for BOP.
NS, not significant; PI, plaque index; GI, gingival index; BOP, bleeding on probing; PRP, platelet-rich plasma; BG, bioactive glass.

Table 3. Mean ± SE clinical measurements at baseline and 9 months

	Baseline	9 months	*p* value	Δ Baseline to 9 months
PD (mm)				
PRP/BG ($n = 15$)	7.80 ± 0.28	4.20 ± 0.49	$p < 0.001$	3.60 ± 0.51
BG ($n = 14$)	8.36 ± 0.53	5.07 ± 0.45	$p < 0.001$	3.28 ± 0.45
p value	NS	NS		NS
CAL (mm)				
PRP/BG	8.53 ± 0.42	5.40 ± 0.50	$p < 0.001$	3.13 ± 0.46
BG	9.07 ± 0.57	6.21 ± 0.58	$p < 0.05$	2.86 ± 0.42
p value	NS	NS		NS
GR (mm)				
PRP/BG	0.73 ± 0.30	1.20 ± 0.35	NS	− 0.47 ± 0.19
BG	0.72 ± 0.38	1.14 ± 0.40	NS	− 0.43 ± 0.25
p value	NS	NS		NS

NS, not significant; PD, pocket depth; GR, gingival recession; CAL clinical attachment level; PRP, platelet-rich plasma; BG, bioactive glass.

Table 4. Mean ± SE intra-surgical measurements at baseline and 9 months

	Baseline	9 months	*p* value	Δ Baseline to 9 months
CEJ–BD (mm)				
PRP/BG ($n = 15$)	9.07 ± 0.47	5.93 ± 0.56	$p < 0.001$	3.00 ± 0.55
BG ($n = 14$)	9.64 ± 0.61	6.50 ± 0.57	$p < 0.001$	3.14 ± 0.45
p value	NS	NS		NS
CEJ–CD (mm)				
PRP/BG	3.80 ± 0.42	4.13 ± 0.46	NS	− 0.33 ± 0.19
BG	3.50 ± 0.34	3.71 ± 0.41	NS	− 0.21 ± 0.15
p value	NS	NS		NS
IDD (mm)				
PRP/BG	5.27 ± 0.42	1.80 ± 0.56	$p < 0.001$	3.47 ± 0.53
BG	6.14 ± 0.48	2.78 ± 0.59	$p < 0.001$	3.36 ± 0.55
p value	NS	NS		NS

NS, not significant; CEJ, cemento-enamel junction; BD, base of the defect; CD, crest of the defect; IDD, intrabony defect depth; PRP, platelet-rich plasma; BG, bioactive glass.

not statistically significant ($p > 0.05$). At 9 months, there was no significant change between the study groups for PD, GR and CAL ($p > 0.05$).

Table 4 shows mean intra-surgical measurements for the test and control groups at baseline and 9 months. The comparison of the two groups shows no difference between the test and control groups for CEJ–BD, CEJ–CD and IDD at baseline ($p > 0.05$). When the values at baseline and 9 months were compared within groups, the mean changes of CEJ–BD in the test and control groups were 3.00 ± 0.55 and 3.14 ± 0.45 mm, respectively ($p < 0.001$). IDD changes were 3.47 ± 0.53 mm for the test group and 3.36 ± 0.55 mm for the control group, both statistically significant ($p < 0.001$). At 9 months following surgery, crestal bone resorption was minimal in both groups ($p > 0.05$). The differences between the study groups for CEJ–BD, CEJ–CD and IDD parameters were not statistically significant at 9 months ($p > 0.05$).

Discussion

This study compared PRP/BG combination with BG to investigate the effectiveness of PRP with a synthetic graft material. Patients were seen on a monthly basis in order to maintain the hygienic conditions. Cortellini et al. (1999) demonstrated that monthly periodic controls enhanced patient cooperation and infection control. In our study, significant differences were observed in both groups for PI, GI and BOP before and after treatment, but differences were not significant between the groups at baseline and 9 months.

The clinical response of the BG-treated group in this study was comparable with previously published studies using BG as a graft material. Low et al. (1997) treated 17 defects on 12 patients and reported a 3.33 mm pocket reduction and a 1.92 mm attachment gain. Another study (Froum et al. 1998) compared bioactive glass graft material and open-flap debridement in the treatment of 59 intra-bony defects in 16 patients, and the results were evaluated at 12-months reentry. In the grafted group, a 4.26 mm pocket depth reduction, a 2.96 mm attachment level gain, 1.29 mm GR and a 3.28 mm defect fill were observed. Lovelace et al. (1998) used bioactive glass and DFDBA in 15 patients and suggested that bioactive glass was capable of producing similar results to that of DFDBA at 6 months. Zamet et al. (1997) concluded that this bioactive glass is effective as an adjunct to conventional surgery in the treatment of intra-bony defects. However, it was suggested that results failed to demonstrate statistically significant better clinical results than surgery alone or DFDBA grafting and also there was no histological evidence in humans that BG may promote true periodontal regeneration (Karring et al. (2003). Nevins et al. (2000) reported on five human intra-

bony defects that were treated with bioactive glass. Histological analysis confirmed the new formation of root cementum and connective tissue attachment at only one tooth. In the present study, clinical data demonstrated improvement when compared with baseline data, but we did not make any comparisons with open-flap debridement.

There are only a few studies comparing the clinical effects of PRP/graft combination with a graft material alone. In one of these studies (Hanna et al. 2004), 13 bilateral defects were treated with PRP/bovine-derived xenograft (BDX) or BDX alone. The authors reported a 3.54 and 2.53 mm pocket depth reduction with the test and control groups, respectively. The clinical attachment gain was 3.15 mm for the test and 2.31 mm for the control group and the differences were reported to be significant. Okuda et al. (2005) reported the treatment of 70 patients with PRP/porous hydroxyapatite (HA) or HA with saline. They demonstrated a mean CAL gain of 3.4 ± 1.7 mm and a mean defect fill 3.5 ± 1.5 mm in their test group and concluded that adding PRP to HA led to a significantly more favourable clinical improvement in the treatment of intra-bony periodontal defects. Results of the present study demonstrated a mean CAL gain of 3.1 ± 0.5 mm and a mean defect fill of 3.5 ± 0.5 mm in the PRP/BG group. The BG group, also, showed a mean CAL gain of 2.9 ± 0.4 and a mean defect fill of 3.4 ± 0.6 and there was no statistically significant difference between the groups. This may be because of using different graft material and/or study design. The explanations of the reasons for the lack of additive effect of PRP will be speculative due to the limitations of the present study in which we did not test/detect the potential mechanisms of PRP for bone formation. Number of participants in this study (15 test, 14 control unpaired defects) may be relatively small, but it is in the acceptable range for a certain amount of clinical periodontal regenerative studies in humans (Lekovic et al. 2002). Based on the literature, in deeper defects (4 mm or more), a greater CAL gain is achieved (Cortellini et al. 1998, Cortellini & Tonetti 2005). In this study, the intra-bony component of the bony defects was 5.27 ± 0.42 mm for the test group and 6.14 ± 0.48 mm for control group.

Authors follow various methods for PRP preparation (Marx et al. 1998, Kassolis et al. 2000, Landesberg et al. 2000, Dugrillon et al. 2002, Gonshor 2002, Robiony et al. 2002, Weibrich & Kleis 2002, Su et al. 2004). Because periodontal defects are small in size, obtaining a large amount of blood from patients for PRP preparation is unnecessary; hence, we used only 9 ml of venous blood. Landesberg et al. (2000) reported that two centrifugal forces of 200 *g* for 10 min. provide the maximum increase at platelet number and Dugrillon et al. (2002) stated that an increased amount of *g* force decreases the amount of growth factor instead of increasing it. There are also differences in the last step of PRP preparation, which includes addition of an agent to start gelation and activation of platelets. Some authors (Whitman et al. 1997, Marx et al. 1998, Anitua 1999, Landesberg et al. 2000, Sonnleitner et al. 2000) suggest different agents such as bovine thrombin or fibrin adhesive, whereas others (Kassolis et al. 2000, Gonshor 2002, Robiony et al. 2002) demonstrated the utilization of patient's own blood as we performed in our study. We did not observe any gelation problems with the test group in our study. Su et al. (2004) prepared gels using human thrombin and bovine thrombin and reported that concentrations of PDGF and TGF were significantly higher when human thrombin was used. Although bovine thrombin has been proven to be safe to activate PRP, some clinicians may want to avoid its use like in this present study (Gonshor 2002). However, the number of platelets in PRP is another important issue in the literature about PRP, Christgau et al. (2006a) showed only a weak correlation between the platelet counts or the growth factor levels and the clinical and radiographic regeneration outcomes.

The results of our study demonstrate that both PRP/BG and BG are effective treatment modalities, but mixing BG with PRP does not have an additional effect on the clinical parameters for intra-bony defects in humans. In the present study, we observed that PRP facilitates bone graft application and contributes to soft tissue healing. In a review, authors investigated the studies, in which fibrin sealant and biomaterials are used in combination and reported that fibrin sealants improve the surgical handling of biomaterials and widen their field of application in bone surgery (Le Guennehec et al. 2004).

There are some studies reporting that PRP does not have an additional effect. Froum et al. (2002) tested the efficacy of PRP in three bilateral sinus graft cases with inorganic bovine bone grafts that contained minimal or no autogenous bone and reported that PRP addition did not make a difference in vital bone production and bone–implant contact. In another study (Wiltfang et al. 2003), sinus floor elevations were performed and β-tricalcium phosphate was either mixed with PRP or used alone. Authors suggested that PRP would only result in accelerated bone formation if target cells were present. Wiltfang et al. (2004) also performed another study in an animal model and investigated the influence of PRP on the regeneration of bony defects. They concluded that PRP did not significantly increase the amount of re-ossification when combined with β-tricalcium phosphate. The authors also stated that, using PRP and xenogenic bone substitutes might cause adverse effects. Most recently, other studies have shown that PRP did not have additional influence on periodontal and bone regeneration (Christgau et al. 2006a, b, Klongnoi et al. 2006, Döri et al. 2007)

According to the results of this study, PRP/BG combination and BG alone are effective in treating intra-bony defects in patients with advanced periodontitis. The addition of PRP to a bioactive glass graft material does not make significant improvements on the investigated clinical parameters. Because there is no research related with PRP and BG, it is not possible to compare the results directly. Further clinical and histological studies should be undertaken to examine the use of bioactive ceramics in combination with PRP.

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Clinical Relevance

Scientific rationale for the study: Bioactive glass graft material (BG) has been used to fill periodontal intra-bony defects. Several studies have indicated the beneficial effects of PRP on bone healing and the possible promotion of periodontal regeneration. This study was carried out to evaluate the influence of PRP in treating periodontal intra-bony defects using BG.

Principal findings: Results from this research showed both treatment modalities were effective in improving clinical parameters to a significant extent. However, PRP has failed to additionally improve the clinical outcome.

Practical implications: The potential influence of PRP on periodontal regeneration remains unclear.