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Platelet Rich Plasma in Reconstructive Periodontal Therapy

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1. Introduction

1.1 Regenerative periodontal therapy

The goal of periodontal therapy is to improve periodontal health and thereby to satisfy the patient's esthetic and functional needs or demands. To achieve this goal, most periodontal treatments aim to reduce probing depths and maintain or improve attachment levels and these parameters are used as surrogates of improved tooth retention. Conventional periodontal therapy includes non-surgical treatment as well as a variety of surgical approaches. In such treatments, histologic analysis revealed that periodontal healing occurs with repair rather than regeneration (Listgarten & Rosenberg, 1979). In repair, long junctional epithelium exists between the treated root surface and alveolar bone (Caton & Greenstein, 1993). However, over the last three decades, the major goal of periodontal therapy has been shifted from repair to reconstruction of periodontal tissues thereby reversing the damage to the periodontium caused by the disease process.

"True periodontal regeneration" is the reformation of a functionally oriented periodontal ligament with collagen fibers inserting in both regrown alveolar bone and reformed cementum over a previously diseased root surface. The first evolutionary stage of periodontal regeneration focused on using a variety of bone graft materials. A number of techniques and autogenic, allogenic, xenogenic and alloplastic bone graft materials have been used for regeneration purpose (Brunswold & Mellonig, 1993). Although significant clinical improvements in terms of probing depth reduction, attachment and bone gains were obtained, the results of the histological studies reported that new attachment achieved by bone grafts was usually a result of the formation of long junctional epithelium with slight or no new connective tissue attachment and negligible new cementum formation. Since these techniques have had limited success, more effective regenerative approaches have been suggested that utilize tissue-engineering techniques.

The concept of tissue engineering in periodontics began with guided tissue regeneration (GTR), a mechanical approach utilizing nonresorbable or bioabsorbable membranes to regenerate periodontal defects. GTR is a technique in which the placement of an occlusive membrane guides progenitor cells, residing in the periodontal ligament to repopulate the osseous defects in order to form new tooth supporting tissues (Nyman et al., 1982). The evidence, in fact, demonstrated that treatment of two- and three- wall intrabony defects with GTR has yielded successful clinical results in numerous studies and could promote

periodontal regeneration in terms of true new attachment with nonresorbable as well as bioabsorbable barrier membranes (Cortellini & Tonetti, 2000). Since the improvement of the fibrous attachment level seems to be easier to obtain than a corresponding improvement in bone level with the utilization of GTR technique, it is utmost important that the space underneath the barrier must be preserved for an adequate period of time during healing for complete periodontal regeneration to occur. On the other hand, in cases where the membrane collapsed into the defects, reduced amounts of bone were formed due to the lack of space for progenitor cell population. In the light of the above, bone grafting technique has been an option in creating a space for the regenerating tissues underneath the membranes and also suggests the use of additional osteoconductive and/or partially osteoinductive properties of the graft materials. Combined usage of bone graft materials with GTR technique generally resulted in similar or more bone gain with the reported GTR studies alone (Paolantonio, 2002; Nygaard-Ostby et al., 2008). Although GTR and combined techniques successfully promote regrowth of the destroyed periodontium, application of the method is often difficult while there is substantial variation in clinical predictability, degree of efficacy, and histologic outcomes.

Shortcomings associated with GTR and advances in molecular/developmental biology set the ground for a new concept in periodontal regeneration by emphasizing the importance of biologic mediators.

Enamel matrix protein is one of the biologic mediators used for regeneration purpose. The discovery of the presence of the enamel matrix layer between the peripheral dentin and the developing cementum, periodontal ligament and alveolar bone formation, has provided the fundamental concept for enamel matrix protein derivative (EMD)-supported tissue engineering in regenerative periodontal therapy. General conclusions about the clinical relevance of EMD are limited by the high level of heterogeneity across the studies. Some studies have reported superior effects of EMD, other studies failed to present any additional effects (Trombelli, 2005). Histological data indicate that the application of EMD on the diseased root surfaces enhances the formation of a new connective tissue attachment (i.e. new cementum with inserting collagen fibers) and of new alveolar bone (Bosshardt, 2008). However, it has been suggested that there exists a possible limitation to the regenerative capability of EMD, related to its semi-fluid consistency and lack of space making effect (Mellonig, 1999). Therefore, combining EMD with a graft material, will overcome the problem of flap collapse and space maintenance when using it alone. Thus, more recently prominence has been given to the use of EMD in combination with graft materials (Scheyer et al., 2002; Bosshardt, 2008). While bone grafts intended to promote bone formation, their combination with EMD would designate a biological effect on the cascade of events leading to periodontal regeneration. Some studies indicate that the clinical outcomes of EMD may be improved when used in combination with bone grafts with respect to EMD alone (Kuru et al., 2006; Yılmaz et al., 2010b). In contrast, limited evidence seems to demonstrate no additional effect of EMD over the regenerative potential of the bone grafts (Scheyer et al., 2002).

2. Polypeptide growth factors

Recently, there has been a tremendous interest in polypeptide growth factors (PGFs) as another biologic mediator in periodontal regeneration (Giannobile, 1996). They are an enchanting group of agents in regeneration because of their regulatory effects on

proliferation and differentiation of cells from bone and connective tissues. PGFs have the ability to regulate biological events including cell adhesion, migration, proliferation and differentiation. Among all PGFs, platelet derived growth factor (PDGF) and transforming growth factor-β (TGF-β) have been studied most extensively. PDGF and TGF-β have been shown to promote cell growth and differentiation *in vitro* and periodontal regeneration in animals (Lynch et al., 1991; Rutherford et al., 1992, Sporn & Roberts, 1992). However, human studies concerning the effects of PGFs on periodontal regeneration *in vivo* are limited. In these studies, PDGF has been shown to exert a substantial effect on periodontal regeneration as measured by attachment gain and bone fill in human intrabony and furcation defects (Howell et al., 1997; Camelo et al., 2003). Although promising results have been obtained, the routine use of PDGF and TGF-β as therapeutic agents for periodontal regeneration is not reality yet. Recently, a convenient approach to obtain not only these PGFs but also epithelial growth factor, vascular endothelial growth factor, insulin-like growth factor-1, basic fibroblast growth factor, hepatocyte growth factor is the use of autologous platelets.

3. What is platelet rich plasma?

Platelet rich plasma (PRP) is a preparation, serving as an autologous source of highly concentrated doses of platelets. The term PRP includes a high concentration of platelets obtained by a single or double step centrifugation of autologous blood (Tamimi et al., 2007). PRP preparations have also been designated as 'platelet pellet', 'autologous platelet concentrate' or 'platelet gel' (Marx, 2001).

Although it is not well clarified, PRP presents its effects through enhancement of soft and hard tissue healing processes. Since the actual amount of regenerated tissue and the course of soft tissue healing are dependent on the individual healing potential, which is significantly influenced by the presence and amount of the PGFs naturally available in the wound, the increased local concentrations of PGFs with the application of PRP in periodontal wound site enhance the healing outcome (Christgau et al., 2006a). In the early stages of the healing process, PGFs within PRP attract undifferentiated mesenchymal cells within the fibrin matrix and trigger cell division. Proliferation of connective tissue progenitors, stimulation of fibroblasts and osteoblast activity and angiogenesis are crucial steps in healing process and regeneration and it is assumed that local delivery of PRP seems to be responsible for all these cascade of events (Marx et al., 1998; Cheung & Griffin, 2004).

3.1 Preparation of platelet rich plasma

PRP can be easily prepared from patient's own blood by centrifugation and separated into three fractions: platelet-poor plasma (PPP) (fibrin glue or adhesive); PRP; and red blood cells. Platelets are enriched by 338% in the PRP preparation. PPP is the upper layer obtained after blood centrifugation in which platelet counts are negligible and is composed of acellular plasma containing fibrinogen and plasmatic growth factors. PRP is the bottom layer and is a volume of autologous plasma that has a platelet concentration approximately 3-4 times higher than baseline levels (150000-450000/μl).

Different procedures have been established for the preparation of PRP including Curasan PRP kit (Curasan, Kleinostheim, Germany), platelet concentration collection system (3i/Implant Innovations, Palm Beach Gardens, FL) and Smart PreP (Harvest Technologies Corp., Plymouth, MA, USA). A variety of factors influence the reliability of these systems including cell separator used, centrifugation steps, amount of blood collected

preoperatively, baseline platelet concentration, amount of platelet concentrate obtained, final platelet concentration, type of blood anticoagulant and platelet activator used (Del Fabbro et al., 2010). Any of these factors may play a major role in PRP activation and affect the expected outcome in terms of biologic properties. Smart PreP is an FDA approved system in which PRP, PPP and autologous thrombin can be obtained. The unique property of the system is its autologous thrombin that is not present in any of the other systems which is an important step in the activation of release of PGFs from platelets. Since the activator of the system is autologous, there is no risk of disease transmission.

When PRP is taken into account for use in clinical practice, clinicians may encounter with several issues, including the clinician's proficiency in drawing the necessary blood, the cost of the procedure, the efficacy of centrifugation machine in obtaining appropriate concentrations of platelets, extra time and steps to prepare the coagulated PRP for its actual use. The centrifugation process is considered to be critical since different platelet counts correspond to the differences in centrifugation machines and techniques (Hanna et al., 2004; Weibrich et al., 2002, 2003). The PRP processed by means of Smart PreP system, ensures high percentages of platelet concentration with less blood drawn from the patient and with less complex procedures. In this system, for the PRP preparation, one hour before surgery, 20 ml of blood was drawn from the patient through a venipuncture in the antecubital vein. The drawn blood was mixed with 2ml of anticoagulant solution and was then processed through a centrifuge to obtain 3ml of the PRP according to the manufacturer's instructions. Immediately before application, this PRP was mixed with autologous thrombin. For the preparation of autologous thrombin, 10 ml of blood was also drawn from the antecubital vein. The drawn blood was mixed with 1ml of anticoagulant solution and following 45 minutes of incubation period, was centrifuged to obtain 1ml of autologous thrombin. A delivery syringe was used to mix the PRP with autologous thrombin (Yılmaz et al., 2007, 2009, 2010a, 2011).

3.2 The use of platelet rich plasma in the treatment of periodontal intrabony defects

During the last decade, there has been an increasing interest on the use of PRP in intraoral therapy including periodontal defects. The effectiveness of PRP in combination with different types of grafting materials, with or without EMD/GTR membranes, has been evaluated in regenerative periodontal therapy. Review of the literature reveals that, mostly, PRP is combined with bone grafts in the treatment of intrabony defects. Since the space maintenance of the defect is a crucial factor in periodontal regeneration, PRP's gel-like consistency may complicate the healing leading to flap collapse. Yılmaz et al. (unpublished data), evaluated the clinical and radiographic results of PRP alone in the treatment of intrabony defects. The authors concluded that successful results were obtained only in narrow and deep defects (Figures 1a-f).

Studies comparing the treatment of intrabony defects with PRP combined with different types of bone grafts with or without GTR to open flap debridement, GTR or grafts alone demonstrated significantly greater clinical attachment gain and defect fill following the combination approach (De Obarrio et al., 2000; Camargo et al., 2002; Lekovic et al., 2002; Hanna et al., 2004; Okuda et al., 2005; Quyang & Qiao, 2006). On the other hand, very recent controlled clinical studies demonstrated similar results when PRP, bone grafts and EMD/GTR were compared to bone grafts and GTR (Camargo et al., 2009; Christgau et al., 2006b; Papli&Chen, 2007; Yassıbağ-Berkman et al., 2007; Piemontese et al., 2008; Döri et al., 2007a, 2007b, 2008a, 2008b, 2009; Harnack et al., 2009). Although it is difficult to draw

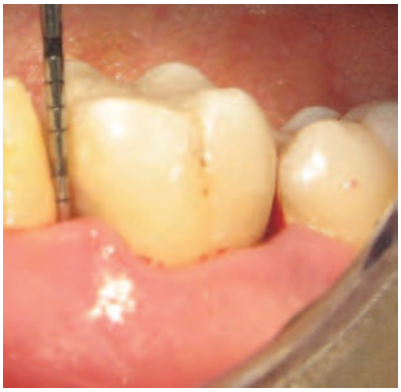

Fig. 1. (a) Initial clinical view of the intrabony defect and probing depth

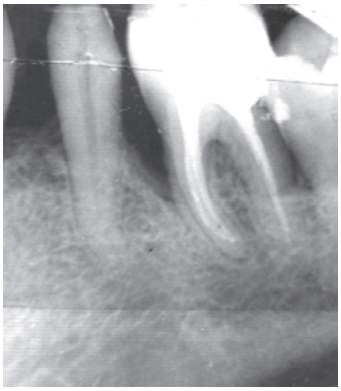

Fig. 1. (b) Initial radiographic view of the intrabony defect

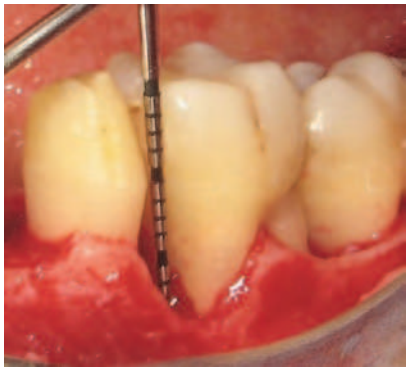

Fig. 1. (c) Intrasurgical measurement of the intrabony defect

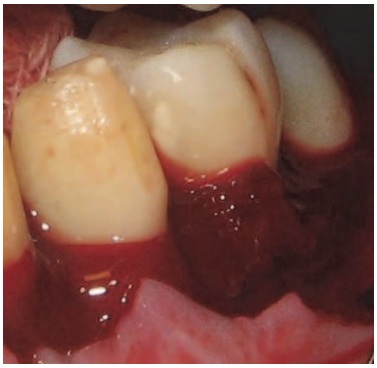

Fig. 1. (d) Application of PRP alone

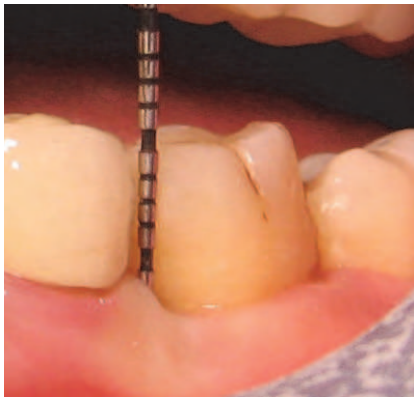

Fig. 1. (e) 12-months clinical view of the intrabony defect and probing depth

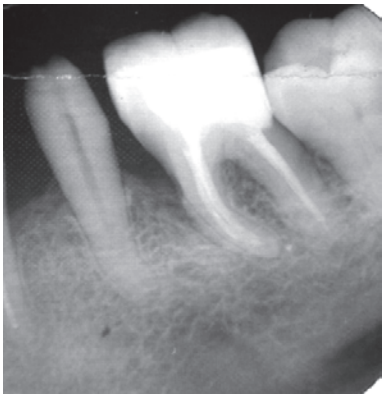

Fig. 1. (f) 12-months radiographic view of the intrabony defect

general conclusions and conflicting results exist, the pre-clinical and clinical data of PRP seems to be promising.

The clinical researches on PRP and their contradictional statements warrant further investigations to contribute to the PRP-supported regenerative therapy. In this process, trials evaluating the efficacy of PRP in combination with different regenerative materials can still add valuable information for the clinician in decision making regarding effective and predictable treatment alternatives for periodontal regeneration. Therefore a series of studies have been performed on the effect of PRP in the treatment of periodontal intrabony defects by Yılmaz et al. (2007, 2009, 2010a, 2011).

In these studies, outcome variables were soft and hard tissue measurements. For all patients, the following clinical parameters were recorded preoperatively and at 12 months postoperatively by the same calibrated examiner. A calibration exercise was carried out to obtain acceptable intra-examiner reproducibility (Sculean et al., 2005). Intraexaminer calibration was performed as follows: five patients, not included in the study, with at least four teeth of probing depth ≥5 mm on at least one aspect of each tooth, were evaluated by the examiner on two seperate sessions with 48 h interval. The examiner was accepted as calibrated if measurements at baseline and at 48 h were similar to the millimeter at ≥90%. Plaque index was measured according to Silness & Löe (1964) and sulcus bleeding index according to Mühlemann & Son (1971). Probing depth, relative attachment level, marginal recession and probing bone level were measured to the nearest millimeter with a calibrated periodontal probe (PCP 15 UNC, Hu-Friedy, Chicago, IL, USA) using an individual occlusal stent as a reference point for probe placement. Occlusal stents for positioning measuring probes were fabricated with cold-cured acrylic resin on a cast model obtained from an alginate impression. It was produced so that it covered the occlusal surfaces of the tooth being treated and the occlusal surfaces of at least one tooth in the mesial and distal directions. It was also extended apically on the buccal and lingual surfaces to cover the coronal third of the teeth. Six grooves were placed so that the post-surgical measurements could be at the same position and angulation as those made prior to surgery. Probing depth was the distance between the free gingival margin and the probeable bottom of the pocket, relative attachment level was the distance between the probeable bottom of the pocket and the edge of the stent, recession was the distance between the free gingival margin and the edge of the stent and probing bone level was the distance between the probeable bone crest and the edge of the stent (Figure 2).

Probing bone level was measured under local anesthesia by transgingival probing (sounding). The probe was forced through the soft tissue toward the bone until definite resistance was met (Kersten et al., 1992). Plaque index was evaluated at 4 periodontal sites (mesio-buccal, mid-buccal, disto-buccal, mid-lingual) whereas other measurements were made at 6 points (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual). Measurements where the edge of the stents was taken as the reference point were relative values (relative attachment level, recession, probing bone level) to evaluate the attachment loss/gain, marginal soft tissue level change, and clinical bone loss/gain.

Pre-operative and 12-month post-operative intra-oral radiographs were taken by the paralleling technique using a film holder device (RWT® Standard Film Holder System; bite blocks, indicator arms, aiming rings; Kentzler-Kaschner Dental GmbH, Ellwagen/Jagst, Germany) for the evaluation of radiographic bone level connected to an acrylic dental splint (individual) to achieve identical film placement at each evaluation with the aim of standardization. The film holder was coupled to the X-ray tube via an adapter (RWT®

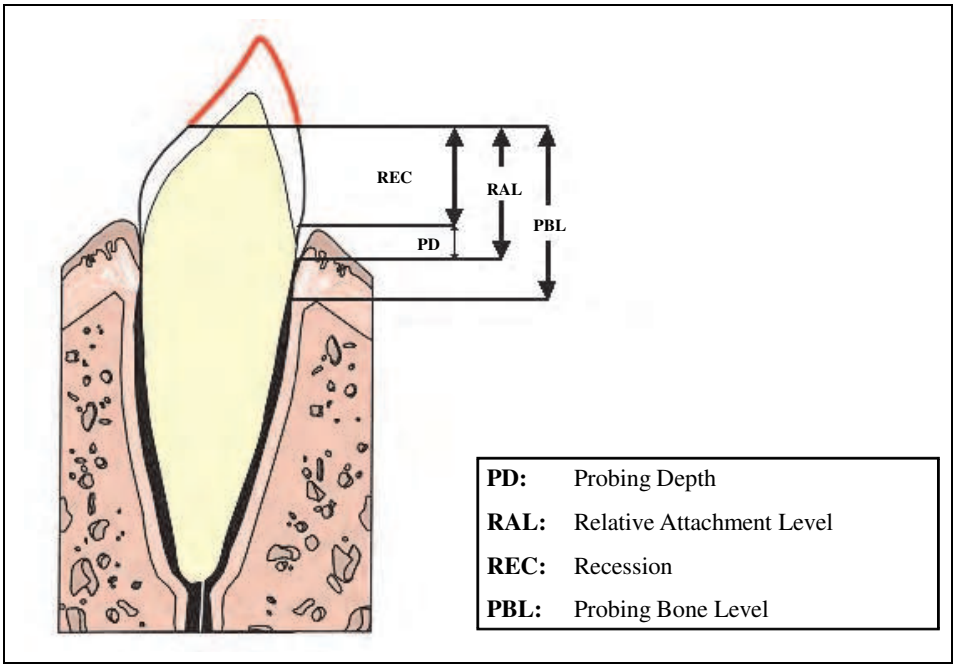

Fig. 2. Clinical measurements

Standard Film Holder System; aiming rings; Kentzler-Kaschner Dental GmbH, Ellwagen/Jagst, Germany). Pre- and post-operative radiograph pairs were independently assessed on a light box by 3 experienced clinicians who were not told which radiograph was which. The mode (most frequent) count was accepted. When measuring radiographic bone level, the 3 investigators were blinded with respect to the clinical measurements and had to reach agreement in terms of the location of both anatomical and bone loss landmarks. Radiographic measurements were obtained utilizing an adhesive millimeter grid (X-ray Grid, 3-4 cm, Meyer Haake GmbH, Oberursel, Germany). The differences between pre- and post-operative radiographic bone level measurements were considered as the radiographic bone loss/gain.

Besides these clinical and radiographic measurements, during operations, distance from the edge of the occlusal stent to the bottom of the defect (A) and distance from the edge of the stent to the most coronal extension of the alveolar bone crest (B) were measured. The intrabony component of the defects was defined as A-B (Figure 3).

The pioneering study was a case report evaluating the clinical, radiographic and re-entry results of a generalized aggressive periodontitis patient with wide intrabony periodontal defects treated with combined PRP and bovine derived xenograft (BDX) (Yılmaz et al., 2007). At 12 months postoperatively, clinical and radiographic measurements together with re-entry results showed marked improvements from baseline with increased stabilization of whole dentition including the hopeless teeth. In the light of this report, the authors emphasized that the surgical technique together with the materials used may be a possible solution for extensive bone loss in patients with generalized aggressive periodontitis (Figures 4a-g).

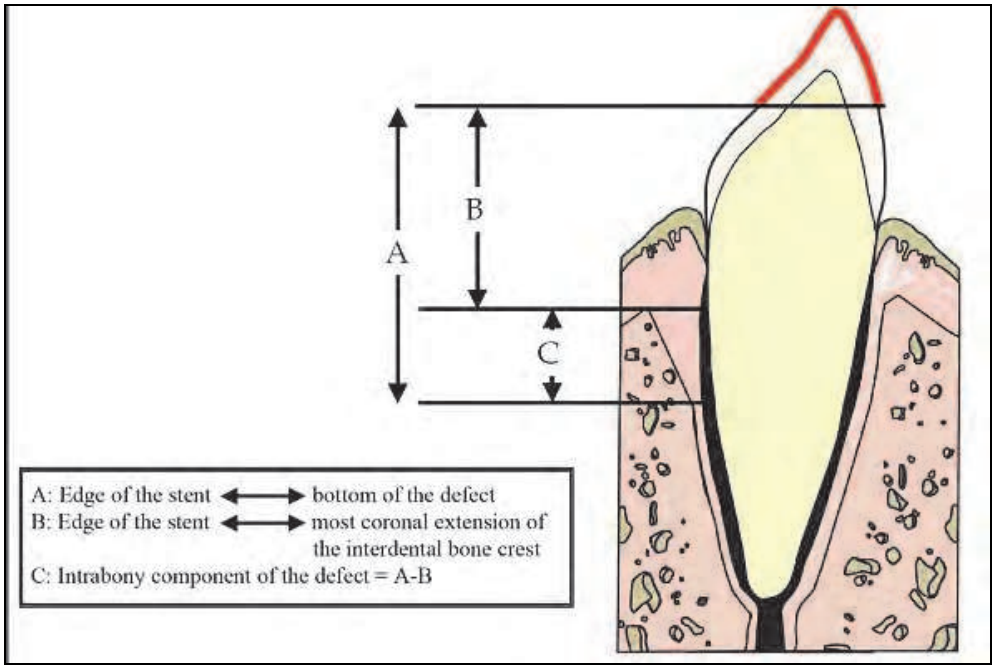

Fig. 3. Intrasurgical measurements

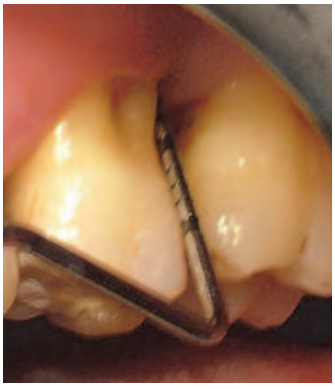

Fig. 4. (a) Initial clinical view of the intrabony defect and probing depth

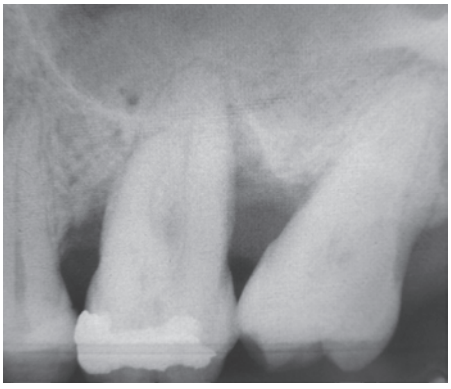

Fig. 4. (b) Initial radiographic view of the intrabony defect

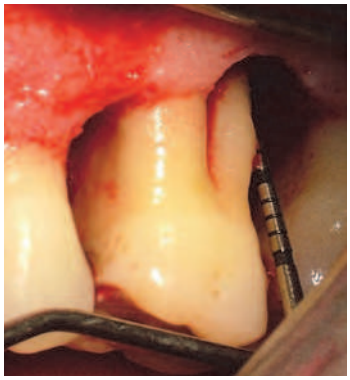

Fig. 4. (c) Intrasurgical measurement of the intrabony defect

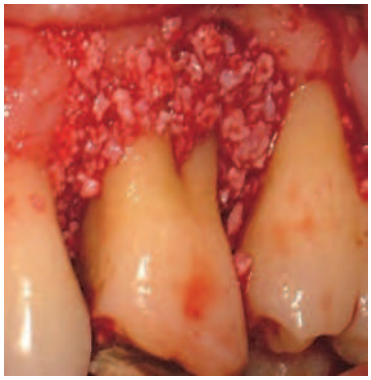

Fig. 4. (d) Application of PRP and BDX combination

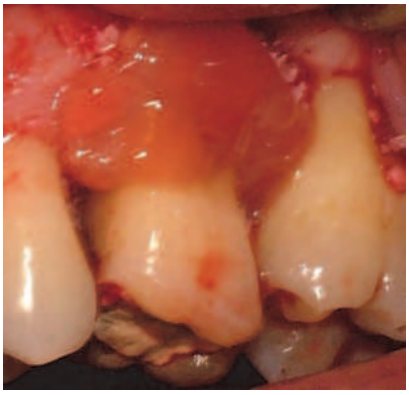

Fig. 4. (e) Application of PRP

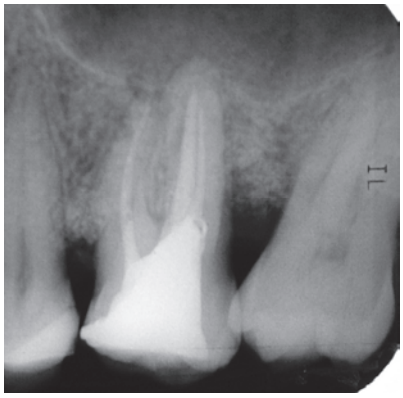

Fig. 4. (f) 12-months radiographic view of the intrabony defect

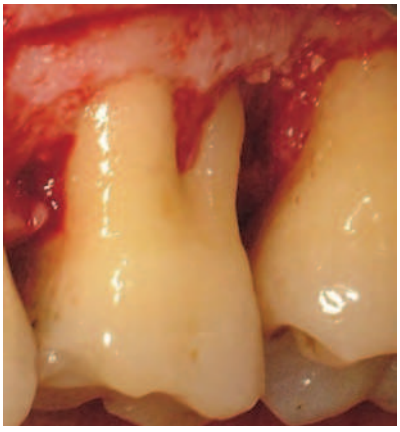

Fig. 4. (g) Re-entry at 12-months

The consecutive study investigated the effectiveness of PRP and BDX combination in the treatment of deep intrabony defects with an emphasis on the evaluation of early wound healing (Yılmaz et al., 2009). A total of 85 intrabony defects with an intrabony component of ≥3mm were selected in 20 advanced chronic periodontitis patients. Defects were surgically treated with PRP/BDX. At baseline and 12 months after surgery, the following parameters were recorded: plaque and sulcus bleeding indices, probing depth, relative attachment level, marginal recession, probing bone and radiographic bone levels. Postoperative healing was evaluated by an early healing index at 1 and 2 weeks after surgery. At 12 months, all clinical and radiographic parameters were improved ($p<0.001$). The mean changes at 12 months were: probing depth reduction of 4.78±1.20 mm, attachment gain of 4.24±1.03 mm, recession of 0.54±0.34 mm, clinical bone gain of 3.75±0.97 mm, and radiographic bone gain of 3.79±1.02 mm, respectively. Two weeks after surgery, primary closure was maintained in 95% of the defect sites. Treatment with a combination of PRP and BDX leads to a significantly favorable clinical and radiographic improvement in deep intrabony periodontal defects (Figures 5a-h).

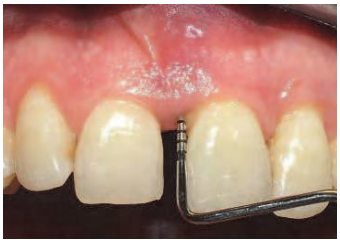

Fig. 5. (a) Initial clinical view of the intrabony defect and probing depth

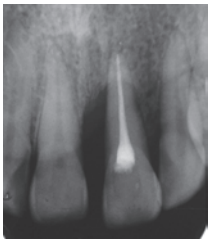

Fig. 5. (b) Initial radiographic view of the intrabony defect

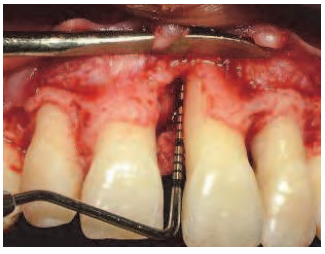

Fig. 5. (c) Intrasurgical measurement of the intrabony defect

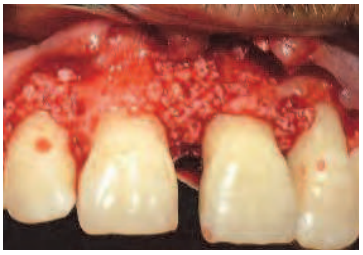

Fig. 5. (d) Application of PRP and BDX combination

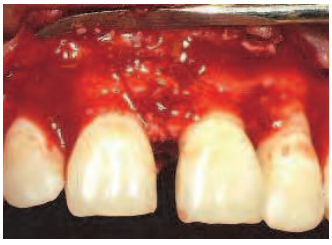

Fig. 5. (e) Application of PRP

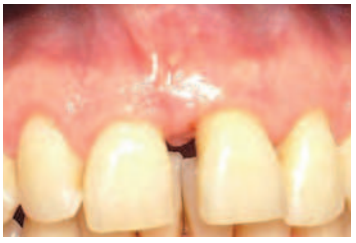

Fig. 5. (f) 12-months clinical view of the intrabony defect

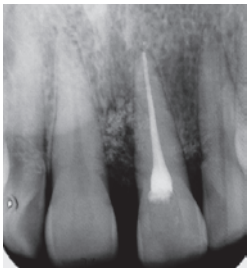

Fig. 5. (g) 12-months radiographic view of the intrabony defect

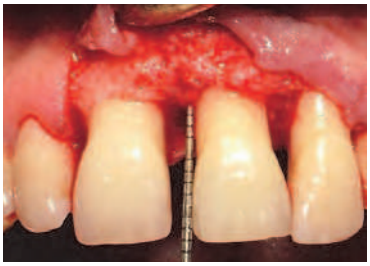

Fig. 5. (h) Re-entry at 12-months

The most common environmental risk factor jeopardizing the outcomes of periodontal regenerative therapy is smoking. Smokers showed a significantly less favourable response compared with non-smokers after regenerative procedures (Tonetti et al., 1995; Trombelli & Scabbia, 1997; Trombelli et al., 1997; Zucchelli et al., 2002; Stavropoulos et al., 2004). The precise mechanisms by which smoking interferes with periodontal regenerative healing are not completely understood. It can be hypothesized that any substance that might jeopardize the function of cells capable of periodontal regeneration could also impair tissue repair and regeneration (Balaji, 2008). Smoking byproducts such as nicotine and cotinine may inhibit the attachment, proliferation and chemotaxis of human periodontal ligament fibroblasts (Giannopoulou et al., 1999; James et al., 1999). In the literature, there is a body of clinical evidence supporting the negative influence of smoking on the outcome of regenerative procedures, mostly GTR (Tonetti et al., 1995; Trombelli & Scabbia, 1997; Trombelli et al., 1997; Zucchelli et al., 2002; Stavropoulos et al., 2004). However, there are no data on the effect of smoking status on the clinical and radiographic outcomes of a procedure based on the usage of PRP in intrabony defects. In order to clarify this issue, the healing response of intrabony defects following regenerative treatment with PRP/BDX was evaluated in smokers and non-smokers (Yılmaz et al., 2010a). A total of 24 advanced chronic periodontitis patients, 12 smokers and 12 non-smokers, with 113 intrabony defects with an intrabony component of ≥3mm were included in this study. Defects were surgically treated with PRP/BDX. At baseline and 12 months after surgery, plaque and sulcus bleeding indices, probing depth, relative attachment level, marginal recession, probing and radiographic bone levels were recorded. Considering the soft tissue measurements, smokers and non-smokers presented a mean probing depth reduction of 3.97±0.76 mm and 4.63±0.52 mm, recession of 0.76±0.44 mm and 0.50±0.12 mm and attachment gain of 3.26±0.42 mm and 4.06±0.40 mm, respectively. Evaluation of the hard tissue findings revealed that the mean clinical and radiographic bone gains in smokers and non-smokers were 2.83±0.47 mm and 3.63±0.38 mm, 2.98±0.38 mm and 3.67±0.48 mm, respectively. Inter-group differences for probing depth reduction ($p<0.05$), attachment ($p<0.001$), clinical ($p<0.001$) and radiographic bone gains ($p<0.001$) were found to be significant between smokers and non-smokers. These results emphasized that treatment outcome following PRP/BDX application in intrabony defects is impaired with smoking.

All patients participating in these studies tolerated the surgical procedures well. No complications such as infection, abscess formation and tissue necrosis were observed at any treated site. Additionally, an early healing index representing the early wound healing was evaluated (Wachtel et al., 2003). This index not only differentiates different degrees of

exposure, but also records the amount of fibrin formation when complete closure is present. Clinical experience has shown that the most rapid and uneventful healing is associated with no or minimal fibrin formation. In all patients, at 1 and 2 weeks, almost all sites were completely closed. It has been reported that biological, physical and chemical properties of PRP may effect the wound healing (Okuda et al., 2003). During the early stages of wound healing, PGFs lead to a cellular and molecular events that result in wound healing in an orchestrated manner (Wikesjö et al., 1992). The effects of PGFs on cells and high content of fibrinogen (fibrin glue) that promotes a favorable scaffold for cellular migration are essential steps in the regeneration of periodontal defects. The PRP preparation presents a sticky characteristic, which works as a hemostatic and stabilizing agent and may aid the immobilization of the blood clot and bone graft in the defect area (Kawase et al., 2003). Blood clot immobilization has been suggested to be an important event in the early phases of wound healing in periodontal regenerative procedures (Polson & Proye, 1983). Moreover, establishing nontension primary wound closure of various soft tissue flaps is paramount for optimal postoperative wound healing (Kuru et al., 2006). Regenerative surgical procedures that require clinical flap manipulation also require excellence in suturing. When the proper suture technique is used, primary intention healing occurs. Accurate apposition of surgical flaps is significant to patient comfort, blood clot stabilization and prevention of unnecessary bone destruction. Interrupted suture techniques achieve excellent clinical results when used for wound closure with tension-free flaps. In these studies, interrupted sutures were used and flaps were placed back to their original places. The sutures were free of tension, obtaining a complete coverage of the intrabony defects. Collectively, the enhanced wound healing potential of PRP and primary wound closure may explain the improved early healing index results found in these studies. A shortcoming encountered with the currently available modalities of periodontal regenerative therapy is limited predictability. Even though the various modalities of osseous grafting, GTR, and, in particular, the combination of both, have been shown to be effective in promoting clinical and histologic periodontal regeneration, complete restoration of the attachment apparatus in every treated defect is still not a reality (Cortellini & Tonetti, 2000). Furthermore, it is very difficult and expensive to use such materials when full mouth bone defects are present. The ability to incorporate PGFs into the periodontal wound healing site with the application of PRP provides a promising approach to reach the established regenerative goals (Christgau et al., 2006a, 2006b). It is also possible to treat multiple intrabony defects in the same mouth with PRP prepared with the blood drawn from the same patient. Bone grafts as autografts, allografts, xenografts and synthetic materials have been shown to improve attachment levels and promote defect fill in humans (Garret, 1996). However, they usually result in the development of a long junctional epithelium between the root surface and gingival connective tissue (Caton & Zander, 1976). Therefore, while materials intended to promote bone formation play an important role in periodontal therapy, their combination with agents like PRP, capable of enhancing cell-mediated phenomena in periodontal wound healing has the potential to optimize the outcome of periodontal regeneration.

Smoking, as a risk factor, affects the results of regenerative periodontal therapy with PRP/BDX (Yılmaz et al., 2010a). Smokers presented less favourable soft and hard tissue healing when compared to non-smokers. This result may be attributed to the hypothesis that there may be a differential susceptibility of PRP to the negative effects of smoking (due to nicotine and its cytotoxic and vasoactive effects). In the literature, PRP was accepted as a practical source for PGFs required in regenerative procedures (Marx et al., 1998). Therefore,

any factor that might jeopardize the regenerative potential of PRP by adversely affecting PGF production could also influence the regenerative outcomes (Balaji, 2008). It has been reported that smoking down-regulates hydroxyproline and collagen production (Jorgensen et al., 1998). Hydroxyproline and collagen are essential for the production and maintenance of connective tissue. The presence of nicotine on root surfaces in smokers has also been documented (Cuff et al., 1989). This nicotine can be stored in fibroblasts, which alters fibroblast function and proliferation (Peacock et al., 1993; Tipton & Dabbous, 1995). When fibroblasts are exposed to nicotine, cellular changes can occur (Hanes et al., 1991). This altered function of fibroblasts due to nicotine exposure could also be the cause of the poor periodontal wound healing. These combined effects of smoking may lead to less favourable outcomes following regenerative periodontal procedures.

3.3 Platelet rich plasma versus platelet poor plasma

Few studies have attempted to evaluate the effects of PPP which is poor in platelets. An animal experimental study provides an evidence of the positive role of PPP as a potential osteoinductive biologic tissue adhesive (Abiraman et al., 2002). In a recent animal study, it has been shown that PPP enhances bone formation based on radiographic and histologic findings (Findikcioglu et al., 2009). It has also been demonstrated that PPP is capable of stimulating osteoblastic proliferation, increasing DNA synthesis and performing a mitogenic effect of osteoblasts/periodontal ligament cells (Hamdan et al., 2009; Findikcioglu et al., 2009). Despite the fact that pre-clinical data appear promising, only one clinical study is available in the literature for the use of PPP in the treatment of intrabony defects. In this study, the healing outcomes of intrabony defects following treatment with PRP versus PPP combined with BDX were assessed (Yılmaz et al., 2011). Using a split mouth design, a total of 79 intrabony defects with an intrabony component of ≥3 mm in 20 patients were treated either with PRP/BDX or PPP/BDX. At baseline and 12 months after surgery, plaque and sulcus bleeding indices, probing depth, relative attachment level, recession, probing and radiographic bone levels were recorded. After 12 months, PRP/BDX and PPP/BDX groups, presented a mean probing depth reduction of 3.87±0.86 mm and 3.76±0.80 mm, recession of 1.35±0.68 mm and 1.58±0.54 mm, attachment gain of 2.51±0.97 mm and 2.18±0.87 mm, clinical bone gain of 2.18±0.86 mm and 2.09±0.89 mm, and radiographic bone gain of 2.11±0.87 mm and 2.19±0.96 mm, respectively. Inter-group differences were found to be insignificant. These results suggest that the outcomes of the treatment following PRP/BDX and PPP/BDX applications in intrabony defects are similar. When the platelet counts are taken into consideration, plasma poor in platelets, seems to demonstrate similar clinical efficacy as the plasma rich in platelets (Figures 6a-h).

PRP is an application of tissue engineering and can be considered as a storage vehicle for growth factors. However, previously demonstrated platelet count related actions may not solely reflect the mechanism of PRP and additional components of PRP and PPP also may have important biological activities during healing. It was suggested that PRP contains high concentrations of several growth factors such as PDGF and TGF-β, which may strongly modulate the regeneration process (Kawase et al., 2005; Christgau et al., 2006a). On the other hand, there may have been sufficient amounts of PGFs naturally occuring in the periodontal wound. Platelet activation in response to tissue damage during surgical periodontal procedures forms a platelet plug and blood clot to provide hemostasis and secretion of biologically active proteins. Thus, the therapeutical local application of PRP might have a

little effect on the periodontal wound healing in terms of growth factor content (Christgau et al., 2006a). Other than growth factors, it was also suggested that because of its fibrinogen content PRP reacts with thrombin to induce fibrin clot formation (Camargo et al., 2005). This

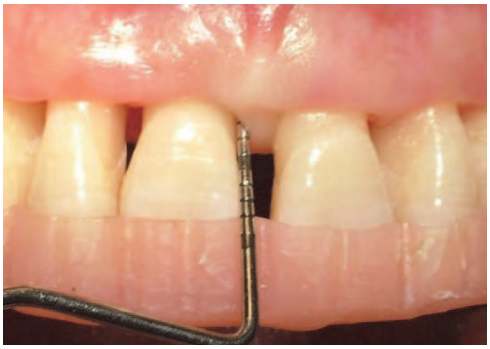

Fig. 6. (a) Initial clinical view of the intrabony defect and probing depth

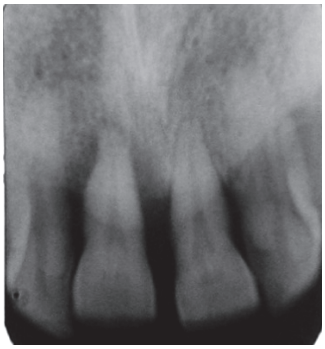

Fig. 6. (b) Initial radiographic view of the intrabony defect

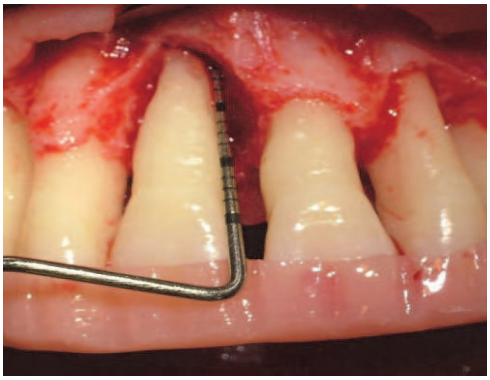

Fig. 6. (c) Intrasurgical measurement of the intrabony defect

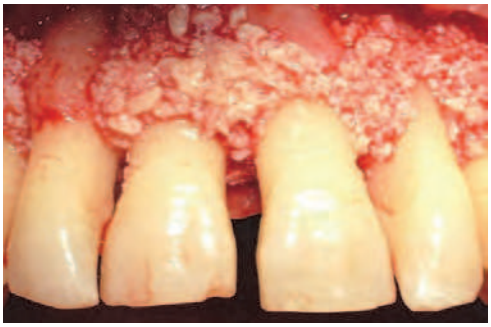

Fig. 6. (d) Application of PPP and BDX combination

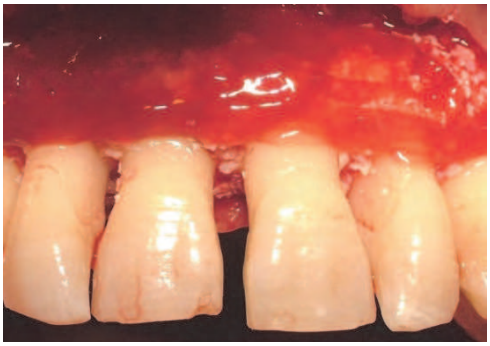

Fig. 6. (e) Application of PPP

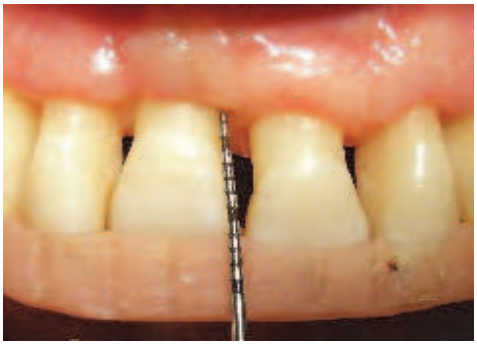

Fig. 6. (f) 12-months clinical view of the intrabony defect

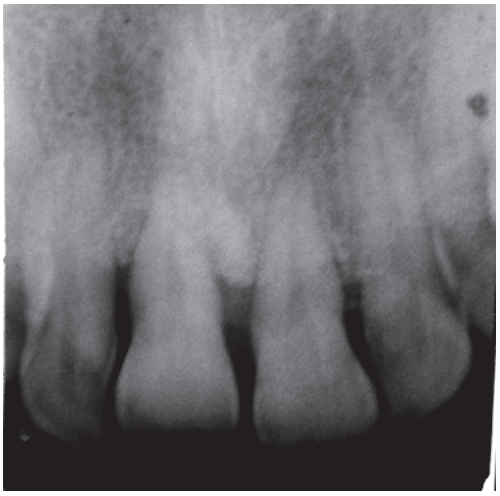

Fig. 6. (g) 12-months radiographic view of the intrabony defect

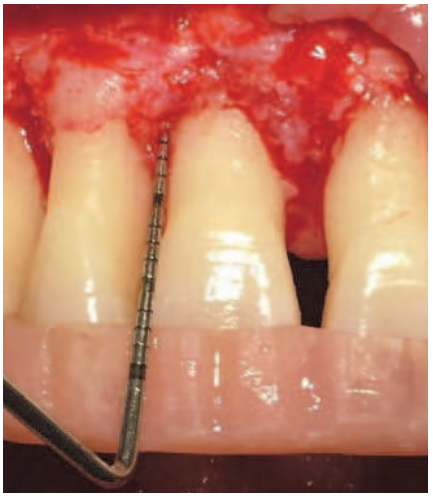

Fig. 6. (h) Re-entry at 12-months

reaction is capable of upregulating collagen synthesis in the extracellular matrix and provides a scaffold for cellular migration and adhesion (Camargo et al., 2005). PPP contains much more fibrinogen than PRP (Gosain & Lyon, 2002). It is of interest to note that this fibrinogen has firmer consistency that leads to its biologic sealant activity and adhesive potential (Gosain & Lyon, 2002). These features may have contributed to the similar clinical healing results obtained in both groups. Apart from the aforementioned knowledge, Creeper et al. (2009) stated that both PRP and PPP are capable of inducing differentiation of the periodontal ligament cells and osteoblasts that are critical for periodontal and bone regeneration and PPP also contains certain growth factors comparable to those found in PRP.

4. Conclusion

Although complete periodontal regeneration is unpredictable with any regenerative therapy currently used, the use of spesific biomaterials/biologicals show strong potential in improving clinical results in periodontal defects. Part of the problem is that it is still unclear how periodontal disease effects the supporting bone's regenerative potential and what specific biologic factors are involved. In recent years, however, clinicians have begun to learn much more about how periodontal regeneration works on a cellular and molecular level. This is a key step to developing strategies and materials that allow clinicians to promote periodontal regeneration predictably. As more is learned about the biologic process of periodontal wound healing and regeneration, new materials and techniques, are expected to make the task of periodontal regeneration even more predictable. It is likely that some combination of techniques may eventually prove to yield the best results. Overall, reconstruction of lost periodontal tissues with these new approaches results with functionally and esthetically acceptable teeth not only for the dentist but also for the patient.

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