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The Effect of PRP (Platelet-Rich Plasma) on Reconstruction of Mandibular and Maxillary Bone Defects: A Review of Recent Experimental Studies on Humans and Animals

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Abstract: During the last 10 years, several scientists around the world investigate the effect of growth factors on the reconstruction of mandibular and maxillary bone. The aim of these studies is the use of safer materials and techniques that could promise a good result. Platelet in Platelet-Rich Plasma (PRP) contain a very big amount of growth factors as PDGF, TGF-β, VEGF and IGF. The aim of this study, is the review of the results of several researches that are based on the potential of PRP to enhance bone healing at humans and animals, mainly in combination with graft materials. In this study results of the most important studies, based on the use of PRP, are exposed and analyzed. These findings are controversial. Some researchers insist on the positive effect of PRP on bone augmentation, while others do not support the use of PRP as a technique with certain advantages. It is important for researchers to consecrate some certain protocols about studies transaction, homogeneity of the samples, PRP preparation, PRP use and the evaluation of the results. In addition to the above mentioned, physical, biological and biochemical properties of growth factors must be identified to offer the opportunity of good and long-lasting treatment. Overall, PRP application is very promising, especially for the treatment of no totally healthy patients whose condition requires fast ant safe procedures of bone and other tissue healing.

Key words: Growth factors, bone augmentation, bone regeneration, bone healing, platelet-rich plasma

INTRODUCTION

Nowadays, one of the biggest problems which has to be solved during oral surgery procedures, is bone augmentation of mandible and maxilla. A large and stable volume of bone must be created to give surgeons the opportunity to place implants safely and with good prognosis. Resorption of the alveolar ridge, unavoidably takes place after teeth extractions. This resorption, additionally to the presence of systemic diseases, the patients' age and the disadvantageous anatomic features of the surgical region (for example, extensive plunges of sinus cavity into the posterior maxillary bone) make the operation difficult and in many cases impossible (Carlsson and Persson, 1967; Atwood, 1963). Immediate loading of implants after extractions, has been recommended as a means to minimize bone loss and shorten the time of the prosthetic treatment (Lang *et al*., 1994; Rosenquist and Grenthe, 1996). Unfortunately, immediate implantation is often associated with a residual bone defect between the implant neck and the bone walls. As has been previously reported (Becker *et al*., 1998; Landsberg, 1997), large gaps may jeopardize the success of such implant procedures. These gaps may cause cell migration from the connective and epithelial tissue into the gap, possibly preventing osseointegration.

Various techniques, including the use of barrier membranes and graft material (as guided bone and guided tissue augmentation), have been proposed for the management of these defects (Becker *et al*., 1990). The technique of Platelet-Rich Plasma (PRP) is an easy and effective way to obtain a big amount of growth factors. α-granules in platelets have abundant growth factors that when secreted, are responsible for crucial steps during tissue regeneration; increasing cell-mitosis, increasing collagen matrix production (which acts osteoconductively), recruiting other cells to the wound, initiating vascular in-growth and inducing cell differentation (Ouyang and Qiao, 2006). PRP is an autologous concentration of platelets in plasma, developed by gradient density centrifugation (Whitman *et al*., 1997). It contains many factors, such as PDGF (Platelet-Derived

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Growth Factor), TGF-β (Transforming Growth Factor-β) and VEGF (Vascular Endothelial Growth Factor). It has been reported a significant enhancement of bone and soft tissue healing when PRP is used in ophthalmologic surgery, cardiac surgery, bone surgery, cosmetic surgery and in oral and maxillofacial surgery (Whitman *et al*., 1997; Kassolis and Reynolds, 2005; Philippart *et al*., 2005). Furthermore, it is concluded by studies on animals and humans that growth factors can induce the migration, attachment, proliferation and differentiation of periodontal progenitor cells (Ouyang and Qiao, 2006). Consequently, they promote bone production and bone formation by stimulating the osteoblasts and angiogenesis by stimulating the endothelial vascular cells (Ouyang and Qiao, 2006). It is widely believed that vascular system and bone production are two vital factors for successful bone healing. For this reason, scientists continuously search the relationship between the use of growth factors and bone formation. They try to find a way for qualitative and quantitative bone production, which can promise a long-lasting result that allows implants placement without abortions.

The local application of Platelet-Rich Plasma (PRP) to achieve bone regeneration in oral and maxillofacial surgery was firstly described by Marx *et al*. (1998). This team indicated that the group treated with supplementation of growth factors, obtained by mixing autologous PRP with bone graft, had better bone healing and higher bone density than the control group. In another use of PRP to enhance successfully bone regeneration and improve soft tissue healing in fresh extraction sites was observed (Anitua, 1999). Kassolis *et al*. (2000) used PRP with freeze-dried bone allografts in sinus floor elevation and alveolar ridge augmentation with good postoperative results. But, although, the clinical advantages of PRP use have been highlighted by Marx (2004), Anitua (1999), Kassolis *et al*. (2000), the exact activity of PRP on bone processes is still unknown today (Consolo *et al*., 2007). Furthermore, there are many studies that do not suggest PRP as an effective factor for bone reconstruction (Froum *et al*., 2002; Shanaman *et al*., 2001; Aghaloo *et al*., 2002).

The aim of this study is to provide the results of several studies that evaluated the regenerative potential of PRP on bone defects in humans and animals and to give some information about the biological characteristics of growth factors which are secreted by platelets.

MATERIALS AND METHODS

The effect of platelet-rich plasma on healing of maxillary and mandibular bone, in humans and animals, has been investigated from many scientists but with controversial results. As it has been referred, Marx (2004) first described bone activity in patients with mandibular defects 5 cm or greater, who had received cancellous bone grafts with or without PRP. The researchers found that 2, 4 and 6 months post-grafting the PRP sites were more mature than the non-PRP sites. At 6 months, histology showed greater trabecular bone area with the PRP grafts. The model for increased bone formation that they proposed suggested that the released Transforming Growth Factor-β (TGF-β) and Platelet Derived Growth Factor (PDGF) resulted in the stimulation of stem cells and osteoblast progenitor cells to divide and/or differentiate and initiate bone formation while also inducing endothelial cell mitosis and subsequent angiogenesis. According to Gerard *et al*. (2006), who searched the effect of PRP combined with autologous bone graft in a dog model, PRP appeared to enhance early autologous graft healing but, after 2 months, at the 3-and 6-month time points, this activity is no longer significant. The early enhanced healing occurred increasing the amount of non-viable grafted bone that was removed by increasing the amount of new bone that was formed. This is expectable because increased amounts of growth factors stimulate both osteoblasts and osteoclasts. PRP did not change the rate at which new bone was formed and no increase in trabecular density was realized in these grafts.

A second study (Thor *et al*., 2007) on a sample of 11 patients who were subjected to sinus augmentation with particulated autogenous bone bilaterally with the addition of PRP in one side, showed that significantly more new bone was formed at PRP-treated sites compared to controls after 3 months of healing, but after 6 months, this effect could no longer be observed. This indicated that PRP has a rather low regenerative capacity but may influence the early phase of bone healing. According to Pierce *et al*. (1989) the direct effect of PRP decreases after only a few days. This is in accordance to the results of another experiment on a rabbit model, which describes that the most influential time in which PRP would exert its effect is the very early healing period, as the lifespan of a platelet in a wound and the period of the direct influence of its growth factors is less than 5 days (Butterfield *et al*., 2005). In this study, is also shown that a moderate number of new blood vessels entering the PRP-enhanced graft were present in the 14 day specimen, but this was not subjectively different from the non-PRP side. Consolo *et al*. (2007) after the use of PRP in combination with autologous graft for sinus floor augmentation to 16 patients with a mean age of about 50 years, indicated a certain regenerative potential of PRP when used with autologous bone. Unfortunately, the effect of this

enhancement of bone reconstruction appeared to be restricted to shorter treatment times. A progressive extinguishment of the PRP activity is recorded after an interval longer than 6-7 months. They also showed that bone was much denser after the application of PRP. This conclusion agrees with the results obtained by Rodriguez *et al.* (2003), who achieved a mean densitometry value increase of 35% in the site treated with PRP and Bio-Oss, 4 months after surgery.

There are many researches based on PRP's effect on peri-implant hard and soft tissues with positive or no significant results. Kim *et al.* (2002a) reported on the use of PRP in conjunction with dentin-plaster of Paris around implants placed in the iliac crest of dogs at 6 and 12 weeks. They reported that PRP enhanced bone contact with implants. Fontana *et al.* (2004) agree with these findings and indicated that a greater volume of peri-implant bone was observed when PRP was used. Another study that acclaims the application of PRP mixed with allograft (DFDBA) to peri-implant tissues, shows that PDGF, mainly combined with autogenous graft, can accelerate mineralization by as much as 40% during the 1st year (Kim *et al*., 2002b). Negative results come from the experiments of (Vasconcelos *et al.* (2007) and Casati *et al.* (2007) after the application of PRP in combination with Guided Bone Regeneration (GBR) on dog models. They did not found any significant effect on peri-implant defects. Furthermore, it must be reported that the salutary effect on bone regeneration was attributed to the titanium membrane which was placed under the mucosa-periosteum flap. Membrane protected the fibrin clot against mechanic traumas, excluding soft tissue cells from invading into the defect and left osteoblasts to produce new bone without any bulk. Except from all the above mentioned, it must be referred that a meta-analysis of studies looking at the use of PRP in conjunction with implants in humans, concluded that there is a lack of scientific evidence to support the use of PRP in combination with bone grafts during augmentation procedures (Sanchez *et al*., 2003).

There are many parameters that are related to the biological behavior of PRP and consequently of growth factors. In a study, the researchers searched the difference in effect between activated (with thrombin and $CaCl_2$) PRP and non-activated PRP (Nikolidakis *et al*., 2008). They showed that PRP-gel (activated PRP) had no significant effect on the early cortical bone response to the Ca-P coated implants, while PRP in a liquid form (without any activation) showed a tendency to increase bone apposition to roughened titanium implants. A possible explanation from these researchers for this difference can be the mechanical trauma as caused by the pressure after application of the gel PRP.

PRP has a very viscous, jelly-like consistency, which can result in additional pressure on the drill walls of the already tightly fitting implant. As a consequence, the healing process at the bone-implant interface includes an extensive resorption phase due to pressure and necrosis of interfacial bone. Additionally, their results indicate that the concentrated platelets in PRP do not absolutely require exogenous thrombin for releasing growth factors and stimulating cells. Contrary conclusions come from Lekovic *et al.* (2003), Marx (2004) and Eawase *et al.* (2005), who recommend the activation of PRP. They refer that the sticky characteristic of PRP preparation works as a haemostatic agent and stabilizes the graft material and the blood clot. In addition, the preparation of PRP is simple and rapid. Because of its sticky characteristic, PRP improves the handling properties of the graft material and may be helpful to shorten the operating time.

A special study (Messora *et al*., 2008), based on 32 rats whose bone defects had been treated with PRP application, concluded that PRP placed in the defects and covered by Platelet-Poor Plasma (PPP) before suturing, significantly enhanced bone healing. PPP, which is the upper part of plasma after centrifugation (PRP is the middle one), has a firmer consistency than PRP. The presence of fibronectin, fibrin and factor XIII (Tayapongsak *et al*., 1994) may have increased stability and healing of the flap over the surgical defect. In addition, PPP may have also contributed to a greater bioavailability of the growth factors present in PRP.

Another important issue that must be analyzed is the appropriate concentration of platelets in PRP. The most valid results come from Weibrich *et al.* (2004), who placed PRP in peri-implant bone defects and concluded that a concentration of 1.000.000 platelets μL^{-1} is the most productive concentration for bone healing. They also found that at lower concentrations, the effect is suboptimal, while higher concentrations might have a parodoxically inhibitory effect. A concentration-regulated anti-mitogenic effect of TGF-β has been reported previously (Floege *et al*., 1991; Pollard, 2001). Weibrich *et al.* (2004) conclusions are confirmed by other studies that found that the most regenerative concen-tration of platelets in PRP, in both humans and animals, is 1.000.000 plat μL^{-1} (Marx *et al*., 1998; Kim *et al*., 2002b). Generally speaking, it must be claimed that more studies, especially on humans and under stable experimental conditions and evaluating protocols are required for such a conclusion.

RESULTS AND DISCUSSION

Investigators continuously strive to improve bone grafting techniques and to provide the means to obtain a faster and denser bony regeneration. Thus, placement of oral implants would be much more predictable and safe. The use of PRP is an example of such a technique. Its use is based on the potential of the plasma to release multiple wound-healing growth factors and cytokines, which are responsible for increasing cell mitosis, increasing collagen production, recruiting other cells to the site of injury, initiating vascular in-growth and inducing cell differentiation. Released growth factors such as Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor β (TGF-β) and Epithelial Growth Factor (EGF) have been shown to have an osteo-regenerative effect because of their pro-angiogenic activity and differentiation effects on osteoblasts (Casati *et al*., 2007). It is generally, believed that sufficient vascularity of the surgical site and production of new bone are the 2 most vital factors for successful implant-prosthetic treatment. In addition, to the above mentioned, bone healing depends on many parameters as the size of the bone defect, the stability of the flap, the mechanical and biological characteristics of bone graft materials, the surgical handlings, the age and the physical condition of each patient (Roussy *et al*., 2007). Consequently, PRP technique is able to provide good results only if these parameters are optimal. On the other hand, there are many factors associated with the technique of PRP that are not studied adequately, such as the choice of the anticoagulant and the activator, the speed of centrifugation and the amount of time between activation of the PRP and its clinical use (Messora *et al*., 2008; Efeoglu *et al*., 2004). Furthermore, as the regenerative potency of PRP undoubtedly depends on its growth factors levels, it must be referred that the appropriate GF levels are not known yet. Recent studies observed differences in GF levels even in PRP samples with the same concentration of platelets (Lartineau *et al*., 2004; Frechette *et al*., 2005). Thus, more studies are required to find the levels of growth factors that would provide the best supplement in bone reconstruction. Vasconcelos *et al*. (2007) have also reported that the exact identification and the combinations of growth factors are not completely investigated. Additionally, there are no certain data that implicate the positive or negative influence of PRP activation with thrombin and $CaCl_2$. The results of several studies about this issue are controversial too (Nikolidakis *et al*., 2008; Lekovic *et al*., 2003; Marx, 2004; Eawase *et al*., 2005). Another characteristic of PRP which must be widely investigated is the influential time in which its growth factors would exert their effect. Some scientists found that this influential time is up to 6 or 7 months (Marx *et al*., 1998; Consolo *et al*., 2007), while others concluded that the effect of PRP lasts for approximately 2 months (Gerard *et al*., 2006; Thor *et al*., 2007) of even only for a few days (Pierce *et al*., 1989; Butterfield *et al*., 2005). Taking into consideration that the main part of osteogenesis takes place in the first month after surgical procedure (Raghoebar *et al*., 2005) and bone is removed and formed with more fast rate for the first 6-7 months, it is obvious that if the effect of PRP lasts for up to 6-7 months, it's use can be considered as serviceable. Reversely, if PRP action lasts for only a few days, it can be concluded that this technique is not so beneficial as many believe. Consequently, it is obvious that more studies are needed to ensure certain data about the actual duration of PRP's effect which simultaneously indicates the duration of the regenerative potency of platelets growth factors.

As it has been previously mentioned, 1.000.000 platelets μL^{-1} is considered as the most productive concentration of platelets in PRP (Marx *et al*., 1998; Kim *et al*., 2002b; Weibrich *et al*., 2004). Trully, it is difficult to predict the final concentration of platelets into the surgical region, because of the bleeding from the bone. Bleeding from the gap might dilute the PRP and consequently the concentration of platelets would be <1.000.000 plat μL^{-1}. In addition, as bleeding from the bone can supply the graft with platelets when it is packed in the gap, the bone graft used without PRP will be mixed with some platelets (You *et al*., 2007). Thus, more basic research into the optimal concentration of PRP within grafts is necessary to adequately capitalize on the ability of platelet growth factors to enhance bone formation in a graft.

One of the well-known characteristics of PRP is related to his physical condition after activation with thrombin and $CaCl_2$ and is called the sticky characteristic. The sticky activated PRP acts as haemostatic factor and stabilizes the graft material and the blood clot. Additionally, coagulated PRP improves the handling properties of the bone graft material, which is combined with PRP and consequently shortens the operative time and the mechanical trauma from surgical procedure (Lekovic *et al*., 2003; Marx, 2004; Eawase *et al*., 2005). Furthermore, some researchers suggest that PRP may acts as a biological membrane in the treated defects, exerting a guided tissue regeneration effect, impeding the apical migration of epithelial cells and connective tissue cells from the flap and helping osteoblasts to product bone freely (Messora *et al*., 2008). Gerard *et al*. (2006) indicated that PRP acts as a biologic adhesive agent that holds the

bone particles together, thereby making manipulation of the graft material much easier. Also, the addition of PRP invokes a pre-consolidated type of property to the graft that resists movement during closure of the facial cover flap over the graft and during the postoperative course (Gerard *et al*., 2006). These indications seem to be true, but they need to be further investigated to be widely accepted.

The potential of PRP to promote soft and hard tissue healing is accepted without doubt. It is obvious even only by referring the biological characteristics of released growth factors and their effect on human tissues (haaemostasis, creation of new vascularity, production of collagen matrix, migration, proliferation and differentation of epithelial and osteoproductive cells). Although, PRP's regenerative effect is accepted, researchers have to be more specific by setting certain protocols that most studies will follow (surgical procedure, selection of the human or animal sample, centrifugation speed, PRP activation, more studies based on humans, stable and defined data processing methods). Furthermore, physical, biological and biochemical features of platelets and growth factors need to be well-investigated (growth factors levels and platelets concentration, interactions between the growth factors, influential time after their placement into the bone defect).

According to all the above mentioned, more studies based on PRP technique would offer the opportunity for safer use of PRP and consequently, for predictable regenerative procedures. In the final analysis, the surgeon might wish to use PRP in patients for whom jump starting a bone graft would be recommended (Gerard *et al*., 2006). Such patients include those with radiated tissue beds, where an intra-operative inadvertent perforation of mucosa occurs, or in patients with compromised systemic comorbidity, such as diabetes mellitus, or even in patients with severe periodontic diseases where prognosis for a stable result is controversial.

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