Platelet Rich Plasma: Review of Literature

[1]Gholam-Ali Gholami *[2]Mohammad Mohammadi [3]Mohammadreza Abrishami

[1]Professor, Dept. of Periodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*[2]Assistant Professor, Dept. of Periodontics, Dental Oral Medicine Research Center, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran.
E-mail: m_mohammadi@kmu.ac.ir.
[3]Assistant Professor, Dept. of Periodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Objective: At present, growth factor-containing products such as enamel matrix derivatives, recombinant bone morphogenetic protein (rh-BMP), recombinant platelet derived growth factor and platelet rich plasma (PRP) have gained increasing attention. PRP is an autologous source of platelet growth factors used to enhance healing of soft and hard tissues. PRP has gained popularity due to its autologous nature, easy procurement and low cost.
Review of Literatures: This study focuses on procurement and clinical applications of PRP.
Conclusion: Controversy exists regarding the efficacy and applications of PRP and longitudinal studies are required to further elucidate this subject.
Key words: Bone graft, Platelet rich plasma, Soft tissue.
Please cite this article as:
Gholami GA, Mohammadi M, Abrishami MR. Platelet Rich Plasma: Review of Literature. J Dent Sch 2014; 32(3):176-186.
Received: 29.01.2013 Final Revision: 30.06.2013 Accepted: 03.07.2013

Introduction:

Dental implantation is the most commonly used technique for functional rehabilitation of an edentulous ridge. Implant treatments require adequate bone volume and density at the site of implantation.

Guided bone regeneration (GBR) is a surgical technique to improve the quality and quantity of bone in subjects with bone defects using autografts, allografts, xenografts and alloplastic materials. Bone autografts are the most ideal grafts to increase bone volume. However, they have some disadvantages such as the need for a secondary surgical site (donor site), longer duration of surgery, greater post-operative patient discomfort and limited graft volume (1).

Due to the risk of disease transmission when using demineralized freeze-dried bone allografts (DFDBA) and mineralized freeze-dried bone allografts (FDBA), use of xenografts and alloplasts has increased due to their relatively optimal biocompatibility, high osteoconductivity and to a lesser degree osteoinductivity (1). In order to minimize donor site trauma and not losing the osteoconductive property of autogenous bone, bone substitutes like hydroxy apatite (HA), tricalcium phosphate (TCP) and Bio-Oss in combination with autogenous bone have been suggested for bone grafting (2).

Graft maturation occurs within 6-12 months depending on the height and quality of the remaining crestal bone, percentage of autogenous bone in composite grafts and implant surface texture (when implants are placed in the grafted area) determined by the clinician (3).

It is beneficial for the patient to shorten this time period via enhancing the process of graft maturation. For example, when autogenous grafts are used alone, 4-6 months time is required for osseointegration of implant (in case of two-stage implant placement). Thus, the patient's waiting time until implant loading will be 10-12 months. As the result, osteoinductive materials have gained attention to enhance the process of maturation and improve the quality of

bone (3, 4). Growth factors are now used to enhance bone regeneration. These factors play a role in chemotaxis, mitogenesis and differentiation of cells involved in the process of bone formation due to having osteoinductive properties. These factors have the ability to induce the formation of periodontal ligament (PDL), bone and cement when used in periodontal lesions (5). Platelets have alpha granules containing growth factors and accumulate in the wound area in the cellular phase of wound healing. Thus, PRP has attracted attention to enhance the process of bone graft healing.

Platelet growth factors

Growth factors are polypeptides that play a role in the process of chemotaxis, differentiation, mitogenesis and metabolism of cells involved in wound healing. Growth factors present in platelet alpha granules are as follows (1, 5-7):

1. *Platelet-derived growth factor (PDGF):*
   Two-chain polypeptides contain di-sulfide bonds with a molecular weight of $27\text{-}30\times10^3$ Daltons. They also exist in macrophages, monocytes, smooth muscle cells and endothelial cells in addition to platelets. PDGF plays a role in bone protein synthesis as well as in bone resorption. It is a mitogenic factor for mesenchymal cells (fibroblasts and smooth muscle cells) and has chemotactic properties for fibroblasts, smooth muscle cells, macrophages and leukocytes. It also possesses angiogenic properties and induces collagen and extracellular matrix synthesis (8-10).
2. *Transforming growth factor B (TGF-B):*
   It is a two-chain polypeptide. The two chains are attached via di-sulfide bonds. Its molecular weight is 25,000 Daltons. Three different gene products of TGF-B are available namely TGF-B1, TGF-B2 and TGF-B3. TGF-B1 has the highest concentration in bone and platelets. TGF-B has autocrine and paracrine functions. Local effects of TGF-B on adjacent cells including fibroblasts, bone marrow stem cells, endothelial cells and preosteoblasts have been well documented. This growth factor plays a role in angiogenesis, and synthesis of fibronectin, glycosaminoglycans and collagen. One of its most important functions is chemotaxis and mitogenesis of pre-osteoblastic cells. Moreover, it inhibits the production of osteoclasts and prevents bone loss (11, 12).
3. *Platelet-derived epidermal growth factor (PDEGF):*
   This growth factor was the first growth factor detected by Cohen in 1962 (13). It induces the proliferation of keratinocytes and dermal fibroblasts and subsequently enhances wound healing.
4. *Platelet-derived angiogenesis factor (PDAF):*
   This polypeptide directly or indirectly stimulates vascular endothelial cells and is released in large amounts under hypoxic conditions (14).
5. *Insulin-like growth factor (IGF):*
   It is a single-chain polypeptide with 75,000 Daltons molecular weight. By its paracrine function, it induces the growth of cartilage, bone matrix formation and proliferation of osteoblasts and pre-osteoblasts. With its autocrine function, it increases the activity of alkaline phosphatase (ALP) in osteoblasts.
6. *Platelet factor-4:* With its anti-heparin potential, platelet factor 4 plays a chemotactic role for neutrophils and fibroblasts (15). The function of PRP is due to the presence of these growth factors.

What is PRP?

PRP is platelet-rich plasma also known as platelet concentrates (PCs), autogenous platelet gel (APG), plasma very rich in platelet (PVRP) and platelet rich growth factor (PRGF)(7).

PRP gel contains high concentrations of platelet and natural fibrinogen to a lesser extent (Figure 1). The properties of PRP are in fact based on

the production and release of several growth factors due to the activation of platelets. Release of growth factors occurs within 10 minutes from the onset of blood clot formation (16). By activation of platelets, their alpha granules are ruptured within 3-5 days. The released growth factors based on their half-life exert their primary proliferative effects maximally within 10 days (1, 7).

Normal blood platelet count is 15,000-44,000. In different PRP preparation systems, platelet concentration increases by 160-740% (17). Typically, to achieve the therapeutic effects of PRP, 400 to 500% increase in number of platelets (1,000,000/ml) is required (18, 19).

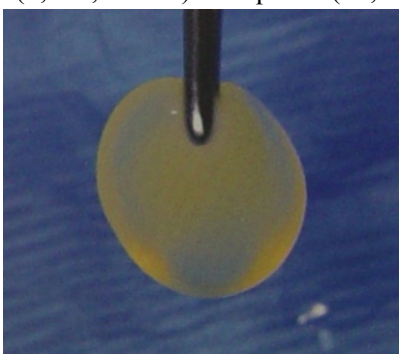

Figure 1- PRP gel

Figure 2- PRGF centrifugation

PRP preparation techniques:

PRP is basically prepared by centrifugation and isolation of blood components based on their molecular weight.

1. *General-purpose cell separator:* In this system, similar to ELMD-500, 450 ml of patient blood is collected in a blood collection bag containing citrate-phosphate-dextrose anticoagulant. Ethylenediamine tetra acetic acid (EDTA) is not used as an anticoagulant agent anymore because it disintegrates the platelets. Next, the blood is centrifuged in centrifugation tubes at 5,600 rpm (20, 21). By doing so, blood components are separated in three layers. Red blood cells precipitate at the bottom. The middle layer is composed of PRP and the platelet poor plasma (PPP) comprises the supernatant. The PPP is discarded and the remaining two layers are centrifuged at a low speed of 2400 rpm in order to isolate 30ml of PRP from the RBCs. In this process, PRP is prepared from patient blood within 30 minutes. In order to prepare PRP, fresh blood must be used within 6 hours after collection (1). Number of platelets in the prepared PRP must be at least 3 times their normal count in the plasma (4). The PRP prepared in this technique contains 500×10^3 to 10^6 platelets/ml (1). Using this technique, erythrocytes and the remaining PPP can be returned to the patient's circulation. With recent advances in technology, by using less volume of blood, higher platelet concentration is achieved and there is no need to return the RBCs and PPP to the patient's blood circulation.
2. *Platelet concentrating cell separator:* Due to the mentioned advantages, this technique has gained increasing popularity. Two of the cell separator systems namely HSPCS and 3i PCCS have been approved by the food and drug administration (FDA). However, different systems have been manufactured by different companies including Harvest SmartPrep®, Friadent-Schutze, Curasan and PRGF system (Figure 2)(1, 5, 22, 23). In these systems, larger volumes of patient blood are required to prepare PRP. Also, to prepare PRP gel, bovine thrombin is required. However, the PRGF system requires less amount of patient blood and there is no need for bovine thrombin. In this system, 5-40 ml of patient blood is collected in 5cc tubes

containing 3.8% trisodium citrate and centrifuged at 270G. By centrifugation, patient blood is separated into fractions as follows (from the bottom to the top)(Figure 3):

A. RBC layer
B. 0.2 ml of plasma very rich in growth factors (PVRGF) located immediately above the RBC layer
C. 0.3 ml of plasma rich in growth factor (PRGF)
D. 0.5 ml of plasma with growth factors (PGF)
E. 1 ml of plasma poor in growth factor (PPGF)(the most superficial layer)

In this technique, the time required for preparation of PRGF would be 10-15 minutes (5).

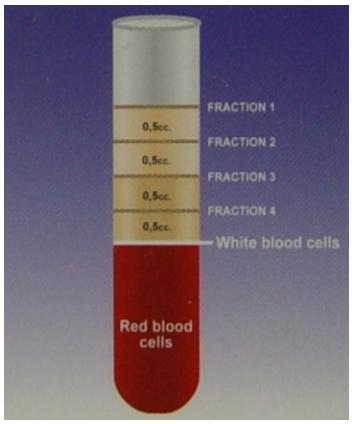

Figure 3- Separated layers following blood centrifugation at 270G in the PRGF system

Preparation of PRP for clinical application:

To prepare PRP gel, topical bovine thrombin (TBT) used to be applied; 6 ml of PRP, 1 ml of 10% calcium chloride, 1 ml of TBT and 1 ml of air were mixed and stirred for a few seconds in order for the process of coagulation and subsequent gelation to be initiated. But, reports were published regarding the production of antibodies against factors V, XI and thrombin increasing the risk of life threatening coagulopathies. By 2003, 32 patients were reported to develop TBT-related coagulopathies. Thus, highly pure thrombin was produced to decrease the concentration of factor V to less than 0.2 ug/ml (1). Landesberg, *et al*. (2000) invented a new technique to activate PRP using ITA gelling agent; but did not report the composition or mechanism of action of this material (21).

Marx (2000) suggested using recombinant human thrombin and autogenous thrombin (24). Kassolis, *et al*. (2000) used autogenous thrombin to activate PRP in the clinical setting (25).

In the PRGF system, manufactured by the Institute of Biotechnology in Spain, only 10% CaCl2 is used for the activation of platelets in PRGF. The manufacturer claims that this system does not need the use of thrombin (26).

Platelet rich fibrin was first introduced by Choukroun in France in 2001. The protocol of producing PRF is very simple. Blood sample is centrifuged in a 10cc tube without the anticoagulant at 3000 rpm for 10 minutes. Platelets become activated upon contact with the glass tube wall and release growth factors. Not using anticoagulants, thrombin and calcium chloride are among the advantages of PRF. Thus, in this technique, fast action is important for preparation of PRF (before blood coagulation) (27).

Clinical applications of PRP:

PRP is used alone or in combination with bone graft materials to regenerate hard tissue or as a barrier membrane for socket preservation (Figure 4), treatment of bone defects around immediate implants (Figure 5) or treatment of defects due to peri-implantitis (1).

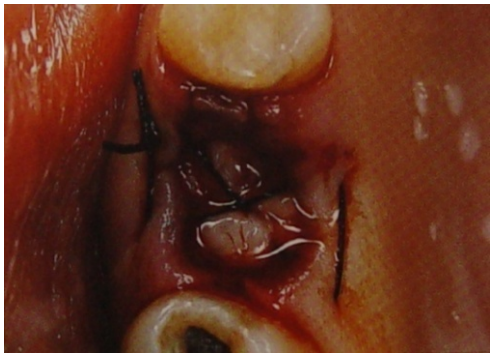

Figure 4A- Using PRGF gel for socket preservation (day of surgery)

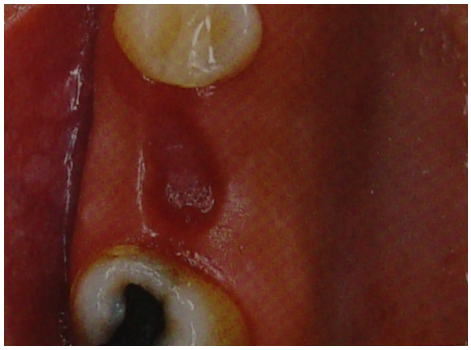

Figure 4B- Using PRGF gel for socket preservation (10 days post-operatively)

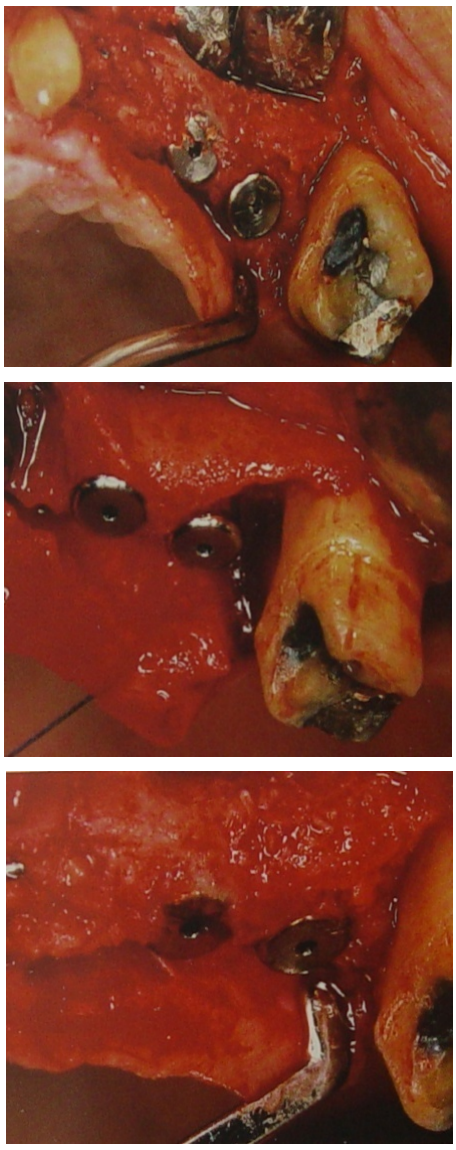

Figure 5- Using a mixture of autogenous bone and PRGF gel in a bone defect mesial to the maxillary first molar (top and middle, right and left sides); treatment outcome after 4 months (bottom, right side)

Marx, *et al*. reported the clinical outcome of PRP application in dentistry for the first time in 1998. In their study, PRP was used to improve the clinical outcome of cancelous bone marrow graft for mandibular regeneration after tumor resection. The results demonstrated increased rate and amount of new bone formation (28).

In 1999, Anitua used a combination of autogenous bone and PRP for socket grafting. They demonstrated better epithelialization and formation of more compact bone with well-organized trabeculae in the intervention group compared to the control group (using only autogenous bone)(26).

Kutkut, *et al*. (2012) in their study evaluated the efficacy of PRP for socket grafting and demonstrated a significant histomorphometric difference between the two groups of control (CollaPlug) and intervention (calcium sulfate in conjunction with PRP) ($p<0.05$). The percentage of newly formed bone was 66% in the intervention and 38% in the control group (29).

Suba, *et al*. (2004) in an animal study used a combination of PRP and Cerasorb in the test side and Cerasorb alone in the control side for socket grafting. The histological results demonstrated formation of high-density new bone at the test side after 6 weeks. After 12 weeks, moderate bone density at the test side and after 24 weeks, equal bone density at both sides was noted (30).

Simon, *et al*. (2009) demonstrated that platelet rich fibrin (PRF) in comparison with DFDBA along with membrane is the best option for socket preservation. Using PRF facilitates bone healing and decreases the complications related to the use of membrane (31).

When PRP is added to bone grafts, fibrin, fibronectin and other adhesion molecules form a scaffold with osteoconductive properties for bone growth. Addition of PRP gel to graft materials (autografts, allografts, xenografts and alloplasts) enriches the grafts with growth factors that accelerate new bone formation and

increase the quantity and quality of newly formed bone in sinus lifting, alveolar ridge augmentation, treatment of grade II furcation defects of the mandibular teeth and distraction steogenesis (1, 3, 5, 32, 33). Addition of PRP gel to graft materials gives them a putty-like consistency, facilitates their application to the respective site and increases graft stability (Figure 6) (5).

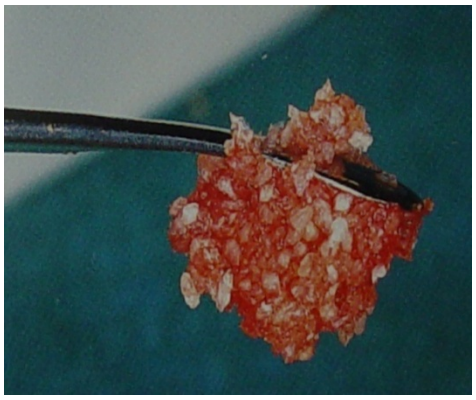

Figure 6- Putty-like consistency of the mixture of PRGF gel and bone graft materials

Using PRP facilitates soft tissue healing by speeding up revascularization, reepithelialization and cell proliferation after flap surgery (1). Thus, application of PRP to the flap margins or the tissue beneath the flap is recommended. Garg, *et al*. (2000) suggested using PRP-based resorbable membranes (34). Stenport, *et al*. (2011) reported that using PRP along with inlay or onlay grafts may affect bone formation in the grafted tissue (35). Torres, *et al*. (2010) evaluated the effect of application of PRP on exposure of titanium mesh. They demonstrated no exposure of titanium mesh in the PRP group and 27% exposure in the control group. Moreover, bone formation increased by using PRP (36).

PRP has also been used for repair of intra osseous periodontal defects (37-52). Pradeep, *et al*. (2012) evaluated the efficacy of PRP and PRF for treatment of three-wall bony defects due to chronic periodontitis. They demonstrated 55% bone healing in the two groups of PRP and PRF compared to the control group. Based on the results, PRP and PRF were not significantly different for treatment of 3-wall periodontal bone defects (39).

Sharma and Pradeep (2011) in their study evaluated the efficacy of PRF for treatment of grade II furcation defects in mandibular molars. Clinical and radiographic results reported the favorable efficacy of PRF for treatment of furcation defects compared to flap debridement alone. In their study, 5 out of 6 grade II furcation defects were converted to grade I as the result of PRF application (40).

Del Fabrro, *et al*. (2011) in a review study and meta-analysis evaluated the role of PRP in surgical periodontal treatments. The results showed that using PRP along with graft materials may have positive effects on the results of treatment of periodontal bone lesions but had no efficacy for GTR. Also, it was demonstrated that using PRP did not have any significant effect on gingival recession (38).

Powell, *et al*. (2009) evaluated the efficacy of PRP for wound healing following periodontal flap surgery in an animal study on mini pigs and demonstrated that using PRP had no effect on periodontal surgery wound integrity; histologically, no difference was noted between the two groups of periodontal flap alone and flap plus PRP (41).

Several studies have evaluated the use of PRP along with graft materials for sinus graft surgery (39-53). Mazor, *et al*. (2009) in their study evaluated the efficacy of using PRF alone for sinus augmentation and demonstrated that application of PRF alone for sinus augmentation simultaneous with implantation resulted in bone regeneration to the implant apex both radiographically and histologically. They recommended using PRF considering its low cost and easy procurement as a sinus augmentation technique especially when sinus membrane preservation is indicated (53). Riaz, *et al*. (2010) demonstrated that application of

PRP along with an allograft for sinus grafting was very efficient for increasing edentulous ridge height compared to the use of autogenous bone (54).

Arora, *et al*. (2010) in a systematic review stated that using PRP had no positive effect on the outcome of sinus grafting despite what is said theoretically regarding its effect on hard and soft tissues. But, working with graft materials is enhanced by using PRP (55).

DePoi, *et al*. (2008) used PRP for treatment of anoroantral fistula formed following sinus grafting and reported successful results (56).

Bae, *et al*, (2011) in a meta-analysis evaluated the efficacy of PRP for sinus grafting and demonstrated that implant success in the two groups of control (sinus grafting without PRP) and intervention (sinus grafting plus PRP) was not significantly different. New bone formation in the intervention group was significantly greater than in the control group. Bone-implant contact was not significantly different in the two groups (63). In another study, PRP was used in conjunction with piezoelectric alveolar ridge expansion technique (64). Lee, *et al*. (2007) used PRP for treatment of osteonecrosis due to the administration of oral bisphosphonates in 2 patients. The treatment outcome in both patients was successful considering complete resolution of pain and full coverage of exposed bone (65).

Conclusion:

PRP is widely used in surgical procedures for regeneration of hard and soft tissues. Using this gel in conjunction with graft materials enhances their application. Many studies have reported improved quality and quantity of newly formed bone due to its application. However, results in this respect are controversial.

Longitudinal studies are required to assess the efficacy of clinical application of PRP alone and in conjunction with graft materials. Meta-analyses are also recommended to determine the prognosis of regenerative procedures.

Conflict of Interest: "None Declared"

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