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Platelet rich plasma: A new era of regeneration

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Abstract---Platelet-rich plasma (PRP) has been a breakthrough in the stimulation and acceleration of bone and soft tissue healing. It represents a relatively new biotechnology that is part of the growing interest in tissue engineering and cellular therapy today. Because of its newness, there is a potential for misunderstanding, misuse, and application of what the practitioner may incorrectly think is PRP. The purpose of this paper is to discuss the definition of PRP, its safety, its proper development, and its most efficacious means of application.

Keywords---platelet-rich plasma, bone grafts, regeneration.

Introduction

For years, the search to achieve predictable periodontal regeneration is going on. Although bone grafts may contain osteoconductive, osteogenic or osteoinductive properties, their usefulness and predictability are limited due to difficulty in obtaining an adequate amount of specific size or shape of bone and its frequent inability to functionally integrate into the bony defects. To overcome this drawback, in the past decade there has been an intensive effort in the field of cell and molecular biology in an attempt to better understand the mechanisms of polypeptide growth and differentiation factors (GFs) in the repair and regeneration

of tissues and their pleiotropic effects on wound repair in nearly all tissues, including the periodontium.¹

What is PRP

Platelet-rich plasma (PRP) is defined as a platelet pool found in non-coagulated and centrifuged blood.² PRP is an autologous concentration of human platelets in a small volume of plasma.³ It was first introduced to the oral surgery community by Whitman et al in 1997⁴

Components of PRP

GFs (table-1) Such as platelet-derived growth factor (PDGF-A, PDGF-B, PDGF), transforming growth factor-beta (TGF- β), vascular endothelial growth factor (VEGF), epithelial growth factor, insulin-like growth factors (IGFs), epidermal growth factor (EGF), and epithelial cell growth factor (ECGF) as well as three blood proteins are known to act as cell adhesion molecules for osteoconduction and as a matrix for bone, connective tissue, and epithelial migration: fibrin, fibronectin, and vitronectin, WBC & phagocytic cells, native fibrogen concentration, vasoactive and chemotactic agents, High concentration of platelets.^{5,6,7,8} Marx^{2,3} proposed that a PRP concentrate should approximate 400% (4X) of the peripheral blood platelet count.

Mechanism of action of PRP

PRP accelerates osteogenesis by releasing GFs at the local site. PRP brings about: early consolidation of the graft, speeds up mineralization, improves trabecular bone density. PRP also accelerates endothelial, epithelial, and epidermal regeneration. PRP stimulates angiogenesis, enhances collagen synthesis, promotes enhanced soft tissue wound healing, decreases dermal scarring, enhances hemostatic response and reverses the inhibition of wound healing caused by glucocorticoids.⁸

PRP works via the degranulation of the alpha granules in platelets, which contains the synthesized and prepacked GFs such as platelet derived growth factor (PDGF-A, PDGF-B), transforming growth factors-beta (TGF- β), vascular endothelial growth factor (VEGF), epithelial growth factor, insulin-like growth factors (IGFs), epidermal growth factor (EGF), and epithelial cell growth factor (ECGF) as well as three blood proteins known to act as cell adhesion molecules for osteoconduction and as a matrix for bone, connective tissue: fibrin, fibronectin, and vitronectin. (repeat of the sentences marked in yellow keep any one of them)³ The active secretion of these GFs is initiated by the clotting process of blood and begins within 10 minutes after clotting. More than 95% of the presynthesized GFs (short forms for the word GF should not be included) are secreted within 1 hour. Therefore, PRP must be developed in an anticoagulated state and should be used on the graft, flap, or wound within 10 minutes of clot initiation. The secreted GFs immediately bind to the external surface of cell membranes of cells in the graft, flap, or wound via transmembrane receptors. These transmembrane receptors in turn induce an activation of an endogenous internal signal protein, which causes

the expression of a normal gene sequence of the cell such as the cellular proliferation, matrix formation, osteoid production, collagen synthesis, etc

Safety with PRP

Being an autogenous preparation, PRP is inherently safe and therefore free from concerns over transmissible diseases. However, PRP is no different in a substrate than the blood clot that forms in every wound and therefore could not support bacterial growth any more than any other blood clot. In fact, PRP has a pH of 6.5-6.7 compared with a mature blood clot of 7.0-7.2. It has thus been counter-suggested that PRP actually inhibits bacterial growth.³

Preparation of PRP

When 20ml of autologous blood is used, 2ml of citrate dextrose A (anticoagulant) is placed in the syringe prior to blood withdrawal. To separate and concentrate platelets, device must use two centrifugations, called *spins*. The first spin known as "separation spin"/"hard spin" that separates the platelet poor plasma from the Red Blood Cells (RBCs) from rest of the whole blood (WBCs, platelets and plasma). This is followed by a second spin known as "concentration spin"/ "soft spin", which separates and compacts the platelets, WBCs and a small number of residual RBCs from the plasma after 95% or more of the RBCs have been separated and sequestered into another compartment of the canister. The platelets are found in a small "pellet" that has to be dispersed out evenly in the plasma before use. Calcium chloride and thrombin are subsequently added for re-calcification and initiation of clot formation just prior to its actual application. To clinically apply PRP, the anticoagulated PRP solution and the CaCl₂ -thrombin solution are placed into two syringes, which is then placed into an ejection assembly with a nozzle to combine the two solutions into what looks like a squirt gun. Upon pushing the lever of the ejection assembly, each solution is expressed in proportion of 10:1 through nozzle tip, which delivers PRP to the precise location, and clotting occurs within 6 to 10 seconds. Alternatively, the PRP can be activated in the cup receptacle by adding just two drops of the CaCl₂ -thrombin solution to it. It is important to note that more than 2 drops of the CaCl₂ -thrombin solution is counterproductive.⁷ PRP prepared from 8 to 10 ml of whole blood is sufficient for periodontal regenerative therapies. Procuring PRP with the help of a general purpose tabletop laboratory centrifuge is easy and cost effective.

Dental applications of PRP: (separate heading for periodontal usage and dental use)

Include sinus lift procedures, onlay grafts, particulate grafts, alveolar cleft palate repair, oral/nasal fistula repair, post-operative hemostasis of bone graft donor sites, continuity defects of the mandible and hemophiliacs undergoing surgery implant site preparation and in the treatment of periimplantitis. In periodontal surgery it has been used in mucogingival surgeries such as gingival grafting, crown lengthening and periodontal regeneration and in implants.⁸ PRP has further been used in distraction osteogenesis and for bone forming activity in extra skeletal sites. The proposed benefits of PRP in clinical use (sinus grafting as model) was reviewed by *Boyapati et al*⁹ PRP is proposed to improve handling of

particulate grafts, facilitate graft placement and stability, improve rate and quality of vascular ingrowth, increase bone regeneration, enhance soft tissue healing and present mitogenic effects on necessary cells. It is an inexpensive and readily available source of growth factors and a natural biologic sealant without the risk of disease transmission.

By virtue of the GFs present in it PRP can be expected to expedite healing of the soft tissue over the graft and thereby reduce the potential for sequestration of graft particles and hasten bone regeneration in the defect and cause the formation of the more dense bone even when the graft material does not contain any autogenous osteoprogenitor cells. In vitro, platelet membranes have been shown to stimulate the mitogenic activity of human trabecular bone cells, thus contributing to the regeneration of mineralized tissues. Combination of PRP and freeze-dried bone graft has been suggested as an alternative therapeutic method for implants placements.

In the context of periodontal regeneration using (grammar) bone grafts, treatment of periodontal defects relies as much on soft tissue wound healing as it does on regeneration. Therefore, PRP, which already has an established role and expanding applications in periodontal defects surgery, should be seriously considered for use in most cases. Specifically, several authors have shown superior bone regeneration in human intrabony defects when porous bovine bone is combined with PRP as compared with the use of porous bovine bone alone. Similarly, PRP produced improved results when combined with several graft materials as compared with the same graft materials without PRP, including calcium sulphate, tricalcium phosphate, allogeneic bone, autogenous bone, and composites of autogenous and allogenic bone. PRP in combination with bone allograft and guided tissue regeneration as periodontal therapy for intrabony defects in humans resulted in significant gain in clinical attachment and filling of the treated defects.⁸

PRP can be infused into resorbable barrier membranes to retard epithelial migration, as well as to provide localized growth factors to accelerate hard and soft tissue maturation. Use of PRP in periodontal plastic surgical procedure decreases the incidence of both intra-operative and postoperative bleeding and pain, aids in the initial stabilization of the transposed connective tissue at the recipient site and promotes a more rapid revascularization of the transposed connective tissue by delivering GFs specific for capillary formation directly to the graft, the root surfaces, and the undersurface of the flap. It decreases the potential for postoperative infection and/or graft sloughage as the PRP promotes a rapid uptake and maturation of the graft.¹⁰

The harvested full-thickness gingival graft (FGG) may be placed in activated PRP while the recipient site is being prepared. This will allow the GFs in PRP to be secreted and to attach themselves to the membranes of the cells in the graft, while the cell adhesion molecules coat the deep surface of the graft. Both of these mechanisms will facilitate adhesion of the graft to the recipient site and then promote the capillary and connective tissue ingrowth necessary for complete survival of the graft.⁸ A growing interest in periodontal plastic surgery has made Connective tissue grafts (CTG) a relatively common procedure. The connective

tissue is almost always harvested from the lateral palatal shelf opposite the premolars and molars. In contrast to FGG harvested from the same area, the CTG donor site is primarily closed and therefore has less postoperative bleeding and pain. Placing PRP in this donor site is thus optional since rich vascularity of the tissue and the use of a primary closure usually result in rapid and uncomplicated healing. However, like FGG, the CTG should be incubated in an activated PRP while the recipient site is prepared. This will allow the platelets to secrete their GFs that will attach to the membranes of the cells in the graft as the graft's collagen fibrils become coated with the cell adhesion molecules in PRP.

*Yen CA et al (2007)*¹¹ treated the palatal donor sites in CTG procedures with PRP to determine whether PRP accelerates CTG wound healing and maintain donor site thickness. PRP-treated recipient sites showed accelerated clinical healing compared to controls. PRP did not accelerate donor site clinical healing. PRP has the potential to shorten the treatment time for patients who need multiple CTG procedures. A technique recently developed for root coverage in cases where an excessive amount of root exposure has occurred is the use of two materials-allogenic human dermis (Alloderm, LifeCell) and PRP- with a coronally positioned flap to achieve a predictable outcome.

The need for the allogenic dermis to adhere to and be rapidly incorporated into the bone adjacent to the exposed roots is critical to the outcome of the procedure. PRP's cell adhesion molecules and GFs assist in the initial adherence and act as a scaffold for the rapid incorporation of the allogenic dermis to bone as well as to the coronally repositioned flap and promote capillary and connective tissue ingrowth respectively. Therefore, the composite of allogenic dermis, PRP, and a full-thickness mucoperiosteal flap heals to the repositioned location and achieves coverage even in the most advanced cases of root exposure.¹²

Conclusion

PRP, which already has an established role and expanding applications in various dental treatments, should be seriously considered for use in most cases. Applications of prp are limited only by the understanding and inventiveness of the surgeon.

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Table:1 some GFs released from platelets and their biologic actions^{6,7}

GFs	Source cells	Target	Biologic action
Platelet derived growth factor (PDGF)	Platelets, Monocytes, Endothelial cells	Fibroblasts, Smooth muscle cells, glial cells, Macrophage,	Stimulates DNA, protein synthesis in osseous tissues, mitogenic effect on mesenchymal cells, angiogenic effect on endothelial cells
transforming growth factors-beta (TGF-β)	Platelets, Monocytes, Endothelial cells	Fibroblasts, Marrow stem cells, Endothelial cells, Epithelial cells, Preosteoblasts	enhances woven bone formation, stimulates matrix synthesis, chemotactic effect on osteoblasts, stimulates angiogenesis, endothelial chemotaxis, bone formation by inhibitory effect on osteoclasts
PDAF	Platelets, Endothelial cells	Endothelial Cells	Mitogenic effect; increased angiogenesis and vascular permeability
insulin-like growth factors (IGF)	Macrophages, osteoblasts, monocytes, chondrocytes	Fibroblasts, osteoblasts, chondroblasts	Stimulates proliferation of osteoblasts and matrix synthesis; increases expression of bone matrix proteins, in combination with PDGF it enhances the rate and quality of bone healing
PF-4	platelets	Fibroblasts, neutrophils	Chemoattractant for neutrophils and fibroblasts