Platelet Rich Plasma a Boon for Periodontal Regeneration: A Review

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Platelet rich plasma (PRP) is the component of blood that is rich in platelets. When put in the wound site, it accelerates the healing by using body’s natural healing responses. The aim was to review the concepts of PRP and its applications in the dental field. MEDLINE, Google Scholar and EMBASE was searched using terms PRP, platelet concentrates, autologous platelet gel, plasma very rich in platelets. It has been substantiated in the literature that the PRP has an ability to enhance the regenerative process of the human body by using patient’s own blood. The application of PRP offers the dental patient something that is safe from outside disease transmission or immunogenic reactions.

Keywords: Fibronectin, Platelet rich plasma, Platelets, Transforming growth factor

INTRODUCTION

Platelet rich plasma (PRP)/platelet concentrates/autologous platelet gel/plasma very rich in platelets is exactly what its name suggests. The substance is a by-product of blood (plasma) that is rich in platelets. It contains platelets, coagulation factors and plasma proteins. PRP may be stored at room temperature (25-26°C) up till 8 h. PRP provides the benefit in the form of accelerated healing potential. In order for it to provide maximum healing potential, it should be able to extract the maximum amount of platelets that can release desired growth factors. Scientific evidence for enhanced bone and soft tissue healing has been demonstrated using platelet concentrate with viable platelet levels increased 300-600% above baseline levels. The increased amount of growth factors will enhance the healing potential of the injury site. PRP is simple and easily available source of growth factors to enhance bone and soft tissue healing. It is derived from methods to concentrate autologous platelets that can be used for the purpose of supporting and accelerating the healing potential of the surgical wounds.1,5

BIOLOGY OF PRP

Blood clot is the primary requisite for initiating all the soft tissue healing processes and bone regeneration activities of all the natural wounds. It is the starting point of the healing process.

PRP is a simple strategy to concentrate platelets or enrichment of the natural blood clot that forms in normal surgical wounds for accelerated complete healing. A natural blood clot contains 95% red blood cells (RBCs), 5% platelets and 1% white blood cells (WBCs) and many fibrin strands. A PRP blood clot is composed of 4% RBCs, 95% platelets, and 1% WBCs.

BIOLOGY OF PLATELETS

Platelets are the smallest corpuscular components of human blood (diameter 2-4 microns). Number varies from 150,000 to 300,000/mm³ of blood. The origin of platelets is the bone marrow, where megakaryocytes, as the result of mitotic proliferation of a progenitor cell - liberate platelets as the end product of the protrusions of their membrane and cytoplasm. The typical shape of resting platelets is discoid and upon activation they undergo a transition to a globular form with pseudopodia. They do not have nucleus for replication and will die off in 8-9 days. They actively extrude the growth factors involved in wound healing. These growth factors, also called cytokines are small proteins, each of 25,000 Daltons molecular weight. They are stored in α granules of the platelets. In response to platelet to platelet aggregation or platelet to connective tissue contact, due to injury or surgery, the cell membrane of the platelet is activated to release these granules. They then release growth factors via active extrusion through the cell membrane. All the growth factors are not released by platelet disruption or fragmentation. Instead, these growth factors are completely extruded through the cell membrane and make them active growth factors.

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COMPONENTS OF PRP

The specific components of PRP are:
- Platelet derived growth factor (PDGF)
- Transforming growth factors (TGFs)

Both of these are contained in the alpha-granules of platelets:
- Fibronectin
- Vitronectin

These are called cell adhesion molecules found in plasma:
- Fibrin.

Platelet-derived growth factor PDGF is the evolutionary sentinel growth factor that triggers the wound healing process. It exists in three dimeric forms:
- PDGF-AA
- PDGF-BB
- PDGF-AB.

Each form is active, but the specific role of each one has not yet been determined. On its release in the active form, it binds to a specific kinase receptor on the target cell. These receptors are transmembrane receptors. The PDGF occupation of the extra membrane portion of the receptor site causes activation in the sub-membrane intracytoplasmic areas. Specifically, this activation causes a high-energy phosphate bond activation of a single protein bound to the cytoplasmic projection of the transmembrane receptor. When the high-energy phosphate activates this signal, it also cleaved off the transmembrane receptor. This activated signal protein then floats within the cytoplasm and reaches the nucleus. Within the nucleus, this signaling protein will activate the expression of various genes.

FUNCTIONS

- Stimulate cell replication of stem cells for healing
- Stimulate cell replication of endothelial cells
- Promote the migration of perivascular healing
- To modulate the effects of other growth factors.

TGFs-beta the so-called superfamily of TGFs number about 47 and includes bone-specific morphogen growth factors that number 13 and known as bone morphogenetic proteins. The types of TGF found in platelets are TGF beta-1 (β1) and TGF beta-2, that are the most generic connective tissue growth factors involved in matrix formation. TGF β1 and β2 are about 25,000 Daltons of molecular weight, are found in the alpha-granules of platelets and the mechanism of activation is the same as that described for PDGF. Cells that are activated by TGFβ1 or β2 include fibroblasts, endothelial cells, osteoprogenitor cells, chondroprogenitor cells, and mesenchymal stem cells on activation of fibroblasts, collagen will be produced. An endothelial cell will be stimulated to produce new capillaries. A chondroprogenitor 51 cell will further differentiate and produce the matrix for cartilage. A mesenchymal stem cell will be stimulated to produce a variety of wound healing cells needed for completion of healing.

Fibronectin and Vronectin

Both of these are called cell adhesion molecules. Cellular proliferation and migration that occurs in bone and cartilage healing in which cells move to new positions to lay down their products like bone or cartilage. Related to bone, this is termed osteoconduction. These cells move via a process of endocytosis and are transported through the cytoplasm to their front end where they are re-incorporated into the cell membrane surface on the front end, and the cell moves in a creeping fashion. Fibronectin and vitronectin also provide grip to cells as they move.

Fibrin

Fibrin is derived from plasma and provides cell mobility in the wound. The role of fibrin, which is cross-linked protein derived from the fibrinogen in plasma, is not only to serve as a scaffold or surface for cellular migration, but to entrap platelets. It entraps platelets along with RBCs. This will lead to a random distribution of platelets and growth factors throughout the wound.

PRP Procurement

PRP is processed from autologous blood based on numerous centrifugation and cell 66 separator principles. The cell separator withdraws 400-450 ml of autologous blood through a central vein catheter at a rate of 50 ml/min. (This sample is then placed into a centrifuge at a speed of 5600 rpm, to separate the blood into RBCs, point-to-point protocol [PPP] and PRP). Before the blood is placed in a centrifuge, sodium citrate dextrose is added to the blood at a ratio of 1.5 for the purpose of anticoagulation through calcium binding.

Now, the sample is placed in the centrifuge and centrifuged at 5600 rpm to yield three basic layers according to density. The least dense layer which is PPP is about 45% of the sample, middle layer consists of RBCs and is about 40% of the sample of the lower layer is the PRP that makes up around 15% of the sample. It is also called the buffy coat because of its white or buffy appearance. The PPP component is acellular plasma, which accounts for about 200 ml of not and is returned back to the patient.

The RBC component accounts for 180 ml and is also returned to the patient. The PRP is plasma with a concentrated number of platelets and WBCs, which accounts for about 70 ml of volume. Both PPP and PRP are plasma fractions.
Preparation of PRP Gel for Clinical Use

- 10 ml syringe
- 7 ml PRP
- 1 ml calcium chloride (activator)
- 1 ml air (mixing bubble)

For the preparation of activator 1 ml CaCl₂+ 1000 units of topical bovine thrombin. The CaCl₂ and thrombin initiate the coagulation process and easy handling. For each mix, CaCl₂ uses a 10 ml syringe to prevent coagulation of remaining PRP. Each mix draws 7 ml PRP+ 1 ml CaCl₂+ 1 ml air respectively. It is then agitated for 6-10 s to initiate clotting and is immediately used onto the graft site or added to particulate graft. It can also be gelled into a membrane that can be placed into a surgical site.

Clinical Applications of PRP in Dentistry
Bone grafting for dental implants that includes:

- Inlay and onlay grafts
- Sinus lift procedures
- Ridge augmentation procedures
- Closure of cleft lip and palate defects
- Repair of bone defects created by removal of teeth or small cysts
- Repair of fistulas between the sinus cavity and mouth.

Advantages of PRP

- Safety-PRP is a by-product of the patient’s blood, therefore, disease transmission is not an issue
- Convenience-PRP can be generated in the dental office while the patients can undergo an outpatient surgical procedure
- Faster healing-the super saturation of the wound with PRP, and thus growth factors produce an increase of tissue synthesis and thus faster tissue regeneration
- Cost effectiveness-since PRP harvesting is done with 55 cc of autogenous blood; the patient does not have to incur the expenses of the harvesting procedure
- Ease of the use-PRP is easy to handle and actually improves the ease of application of bone substitute materials and bone grafting products by making them more gel-like.

Contraindications for Use of PRP
Patients with bleeding or hematological diseases.

Adverse Effects and Limitations

- Interposition of fibrin glue between opposed nerve bundles has been observed to impede nerve regeneration
- Does not impede rapid arterial or venous hemorrhage
- Does not replace good surgical techniques.

Role of PRP in Periodontal Regeneration

With the bone and soft tissue regeneration becoming more evident in many areas of dentistry, it is important to employ methods for enhancing regeneration procedures. Regenerative procedures are important for periodontal regeneration to support a healthy dentoalveolar complex and to enhance bone for dental implant placement. The PRP obtained offers up to 2.16 times increase in the maturation rate and substantially a greater density of a bone graft procedure. Soft tissue healing is also substantially improved through the application of PRP, by increasing collagen content; promoting angiogenesis and increasing early wound strength. Sequence of bone regeneration to understand how PRP affects bone regeneration, the sequence of regeneration should be made clear. During a bone grafting procedure, platelets become entrapped in a graft clot and degranulate within hours, releasing PDGF and TGF-β.¹⁶⁻¹⁸

PDGF binds with endothelial cells to initiate capillary ingrowth, and TGF-β binds to osteoblasts and stem cells to mitosis and to stimulate osteoid production. Initially, macrophages are attracted to the graft site with the help of an oxygen gradient of 30-40 mm Hg. These macrophages then drive the remaining bone regeneration and healing process. The lifespan of platelets in a wound and their influence on growth factors are <5 days; therefore, bone regeneration is extended by two mechanisms. The first mechanism is the stem cell increase into osteoblasts, which can then produce TGF-β. The second mechanism for bone regeneration extension is from macrophage replacement of platelets. By day 14, complete vascularization of the graft is seen. Stem cells have differentiated into osteoblasts and osteoid is being laid down. Early bone formation is occurring at 4-6 weeks leads to woven bone is formed. During phase two modeling, lamellar bone is formed, representing a more organized bone, which in turn matures via functional loading with stresses placed on it.

Role of PRP in Regeneration

Through the application of PRP in the bone graft wound site, a substantial increase in the platelet count is offered. This increases the availability for platelets to create the cascade system via PDGF and TGF-β. The average platelet count in an individual’s blood is between 111,000 and 523,000. By concentrating the platelets to PRP, the average platelet count increases to a range of 595,000-11000,000, with an average increase of 33.8%. Platelets, which are in the graft site for <5 days, allow the body to efficiently begin a cascade of reactions using growth factors. It can be considered that PRP jump-starts the cascade of regenerative events leading to the formation of a mature graft site. The important factors affecting periodontal regeneration are PDGF and TGF-β.

PDGF

It is a chemoattractant for fibroblasts, leukocytes and smooth muscle cells. Acting synergistically with insulin-like
growth factor (IGF)-I it promotes general protein synthesis and extracellular matrix and collagenase. TGF-β induces biological responses from PDGF. It induces synthesis of fibronectin and Type I, III, V collagens, inhibitors of metalloproteinases and stimulates osteoblast activity. All these are likely to come into play in periodontal regeneration. Lynch et al. (1989) tested the effect of growth factors on periodontal repair in naturally occurring periodontitis in beagle dogs; they found that the combined use of PDGF and IGF results in improved bone regeneration as compared to controls. Periodontal ligament was formed, and no ankylosis was observed. When PDGF and IGF are used together, these factors may enhance regeneration of both hard and soft tissue components of the attachment apparatus.

**TGF-β**

Several studies have shown that TGF-β regulates osteoblastic and osteoblastic activity leading to bone and cartilage formation. TGF-β appears to have several biological effects, which could enhance and facilitate the growth and regeneration of periodontal tissue.19,20

**CONCLUSION**

The ability to enhance the regenerative process of the human body by using autogenous blood is now available and is substantiated in the literature. The application of PRP offers the dental patient something that is safe from outside disease transmission or immunogenic reactions. This PRP can be easily done in the dental office and can be used for various surgical procedures. The growth factor enhancement is especially applicable for patients whose healing is impaired such as the elderly. PRP appears to enhance both hard tissue and soft tissue healing through concentrated platelets and growth factors such as PDGF and TGF-β.

**REFERENCES**


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