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REVIEW ARTICLE

Platelet Concentrates: A New Alternative to Bone Regeneration

Shruti Chhabra, Naveen Chhabra, Puja Vaid

ABSTRACT

Platelets significantly promote soft and hard tissue healing owing to the abundance of growth factors present in them. These growth factors enhance the rate of wound healing by aiding in cell proliferation, differentiation, chemotaxis and angiogenesis. Thus using platelet concentrates is a simple way of enriching a natural blood clot with growth factors. The objective of this review article is to discuss the evolution of different platelet concentrates and their clinical implications.

Keywords: Platelets, Platelet growth factors, Platelet rich plasma, Platelet rich fibrin.

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INTRODUCTION

Wound healing is a physiological process involving a cascade of events to restore and replace the function of a damaged tissue by cellular migration, proliferation and differentiation, increased collagen production and initiation of vascular ingrowth. Many cell types, growth factors and other proteins interact with one another to bring about timely and efficient repair of wounds.[1]

Platelets form the hemostatic plug by aggregating and adhering to exposed subendothelium thus promoting blood clotting. They also aid in recruiting leukocytes and progenitor cells to sites of vascular injury and inflammation. Tissue repair is aided by cell proliferation and differentiation, chemotaxis, angiogenesis induced by growth factors produced by the patelets.[2]

Using platelet concentrate is a simple means to enrich natural blood clot with growth factors which may lead to a more rapid and denser regenerate. This article is designed to highlight the expanded role of platelets in nonhemostatic events and the evolution of platelet concentrates in various forms.

EVOLUTION

Fibrin Glue

Owing to the search for improved hemostatic agents and surgical adhesives, fibrin glue (alternatively referred to as fibrin sealant or fibrin gel) was developed in 1970. It is classically described as a two component mixture in which concentrated fibrinogen (source random donor or single donor cryoprecipitate), factor XIII and fibronectin are added to thrombin, calcium chloride and an inhibitor of fibrinolysis to form a fibrin clot.[3] The mechanism of action of fibrin adhesives reproduces the last stages of coagulation during which fibrinogen is converted into fibrin.

Shortcomings

The risk of transmission of virus, like human immunodeficiency virus (HIV). There is at least one documented case of HIV transmission from using a cryoprecipitate based form of fibrin glue.[4]

Autologous Fibrin Adhesives

In lieu of the increased risks associated with the use of fibrin glue, its marketing was prohibited and attempts at the development of autologous fibrin adhesives increased. In 1994, autologous fibrin adhesive was described by Tayapongsak et al,[5] in which patient's blood is harvested 1 to 3 weeks before the intervention and requires separating one unit of whole blood into red blood cell component and the plasma fraction for use as a cryoprecipitate which is thawed over 24 hours before being ready to use.

Shortcomings

- Extremely long and complex protocols.
- Clerical error by the blood bank places the patient at risk for potential transfusion reaction or infectious disease complication.
- Patients have to meet the blood bank's criteria for weight, hemoglobin concentration, age and general health status. Failure to do so disqualifies patient from its usage.

Platelet Rich Plasma

Platelet rich plasma (PRP) is a modification of autologous fibrin adhesive which requires autologous blood collection in the immediate preoperative period and processing in the centrifugation machine using a variable speed cell salvage system (Figs 1 and 2) which is then mixed with bovine thrombin and calcium chloride (Fig. 3) at the time of application. This results in activation and gelling of platelet concentrate.[6]

It is an autologous concentration of human platelets in a small volume of plasma. A natural blood clot contains 95%

Fig. 1: Digital centrifugal machine

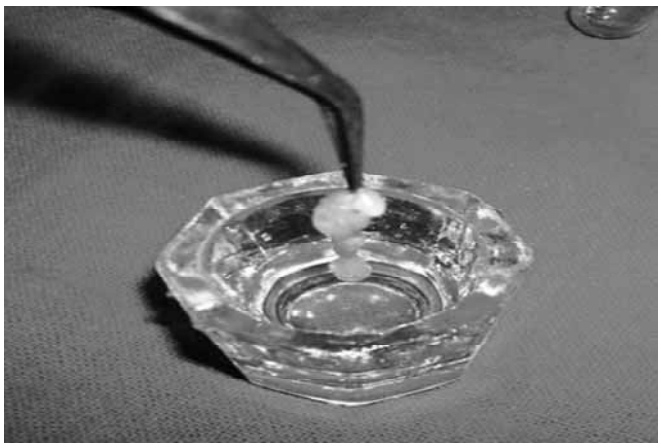

Fig. 3: Platelet rich plasma gel formed by mixing PRP with bovine thrombin and calcium chloride

Fig. 2: Swing out head

red blood cells, 5% platelets, less than 1% white blood cells and numerous amounts of fibrin strands, whereas PRP blood clot contains 4% red blood cells, 95% platelets and 1% white blood cells. As PRP is a concentration of platelets, it is also a concentration of growth factors proved to be actively secreted by activated platelets to initiate wound healing. These growth factors are summarized in Table 1.[7]

Platelet rich plasma is more than just a platelet concentrate. As these concentrated platelets are suspended in a small volume of plasma, it also contains the three proteins in blood fibrin, fibronectin and vitronectin. These proteins act as cell adhesion molecules for osteoconduction and epithelial migration.

Table 1: Growth factors released from platelets

Growth factor	*Source cells*	*Target*	*Action*
PDGF	• Platelets • Macrophages • Monocytes • Endothelial cells • Smooth muscle cells	• Fibroblasts • Smooth muscle cells • Glial cells • Macrophages/ neutrophils	• Stimulates chemotaxis/mitogenesis in fibroblast/glial/ smooth muscle cells • Regulates collagenase secretion/collagen synthesis • Stimulates macrophage/neutrophil chemotaxis
TGF-β	• Platelets • Macrophages • Monocytes • Neutrophils • T lymphocytes	• Fibroblasts • Marrow stem cells • Endothelial cells • Epithelial cells • Preosteoblasts	• Stimulates endothelial, fibroblastic and osteoblastic mitogenesis • Regulates collagen synthesis/collagenase secretion • Regulates mitogenic effects of other growth factors • Stimulates endothelial chemotaxis and angiogenesis
PDEGF	• Platelets • Macrophages • Monocytes	• Fibroblasts • Endothelial cells • Epithelial cells	• Stimulates endothelial chemotaxis/angiogenesis • Regulates collagenase secretion; stimulates epithelial/mesenchymal mitogenesis
PDAF	• Platelets • Endothelial cells	• Endothelial cells	• Increases angiogenesis and vessel permeability • Stimulates mitogenesis for endothelial cells
IGF-1	• Osteoblasts • Macrophages • Monocytes • Chondrocytes	• Fibroblasts • Osteoblasts • Chondrocytes	• Stimulates cartilage growth, bone matrix formation and replication of preosteoblasts and osteoblasts • Acts as an autocrine and paracrine factor • In combination with PDGF can enhance the rate and quality of wound healing
PF-4	• Platelets	• Fibroblasts • Neutrophils	• Chemoattractant for neutrophils and fibroblasts • Potent antiheparin agent

PDGF: Platelet-derived growth factor; TGF-β: Transforming growth factor-beta; PDEGF: Platelet-derived epidermal growth factor; PDAF: Platelet-derived angiogenesis factor; IGF-1: Insulin-like growth factor 1; PF-4: Platelet factor-4

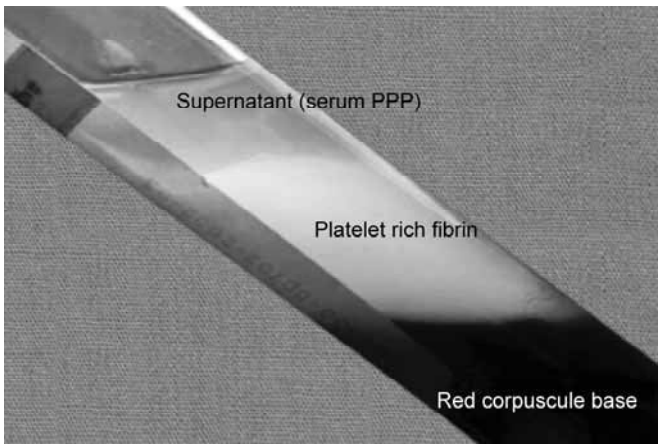

Fig. 4: Resultant product

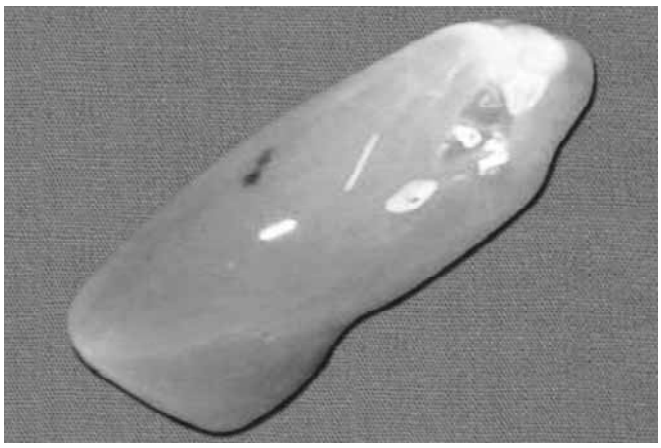

Fig. 5: Platelet rich fibrin obtained

Shortcomings

- The use of bovine thrombin puts the patient at risk of life-threatening coagulopathies associated with the development of antibodies to factor V, XI and thrombin.[8]
- Higher concentration of thrombin impedes cell migration during bone healing.
- It mediates only the early aspects of bone repair process through an osteopromotive mechanism. Thrombin activation of PRP causes 81% of total TGF-β and PDGF-AB to be released within the first day with insignificant release in the following healing period.

Platelet Rich Fibrin

Platelet rich fibrin (PRF) is a second generation platelet concentrate first developed in France by Choukron et al in 2001, prepared from centrifuged autologous blood. It is a fibrin clot rich in platelets without addition of bovine thrombin, calcium chloride or anticoagulant (Figs 4 and 5) during preparation thus eliminating the risks associated with the use of thrombin.[9]

Platelet rich fibrin is derived from a natural and progressive polymerization occurring during centrifugation. A progressive or relatively slow polymerization mode may increase incorporation of the circulating cytokines in the fibrin meshes which are then released in a relatively long-term and controllable way which in turn will help in soft tissue healing and accelerated bone regeneration.[10]

The absence of anticoagulant activates most platelets of the blood sample in contact with the tube walls and the release of the coagulation cascade in few minutes. Therefore, the speed of blood collection and transfer to the centrifuge is important, as with delay, the fibrin will polymerize in a diffuse way in the tube and only a small blood clot without consistency will be obtained.

Shortcomings

- Low platelet counts may be a limiting factor.
- Care is required in patients with known thrombotic risk factors.
- Parallel use of antiplatelet drugs like aspirin could limit its efficacy.
- The source being autologous blood, it can be used in limited quantity.

THERAPEUTIC USES

Fibrin Glue/Autologous Fibrin Adhesives[11]

1. Hemostatic agent in soft tissue deficits.
2. Replacement for suture material in the split thickness skin graft procedure.
3. In reapproximation of comminuted bone fragments in complicated fractures.
4. In dural closure.
5. In microneural and microvascular anastomoses.

Platelet Rich Plasma/Platelet Rich Fibrin

1. Maxillofacial surgery and bone grafts (filling of cystic cavities, in sinus lift surgeries, alveolar cleft palate repair, ridge augmentations, socket preservation).[12]
2. Dental implant surgery
3. Orthopedic surgery and bone reconstruction
4. Facial plastic and cosmetic surgery
5. Skin ulcers
6. Eye surgery—retinal hole repair
7. Sports medicine—cartilage and tendon repair.

Uses of PRF over PRP

1. The improved mechanical properties of PRF over conventional PRP translate it into a biologic matrix that is easy to handle and implant in a wide variety of tissue repair applications with an added advantage, where otherwise PRP is indicated.
2. Platelet rich fibrin has increased modulus of elasticity in comparison to PRP. This property imparts it better pliability and drapability, allowing it to closely conform to a wide variety of irregular surgical sites and surfaces similar to split thickness skin autografts.

3. Platelet rich fibrin can easily be sutured to the surgical site, thus advantageous for use in situations where PRP can easily be washed out as during an operation as in arthroscopic joint repair procedures.

CONCLUSION

Uneventful and enhanced wound healing is desirable and critical in improving quality of life after surgery. The production of a dense, cross-linked, sturdy PRF made of intact platelets and fibrin by high-speed centrifugation in the absence of exogenous thrombin, yields an ideal scaffold for use in tissue repair. The use of PRF seems to be one of the most promising methods to enhance healing in a controllable and long-term way. In summary, these are still early days of periodontal tissue regeneration and more recent developments in basic science indicate that these approaches are unquestionably practical and, given their promise, worth exploring.[13] Further studies using a large number of donors are currently underway to confirm the viability, growth factor release and biological response of the platelets within and released from PRF.

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