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Platelet-Rich Fibrin: Role in Periodontal and Pulpal Regeneration

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ABSTRACT
Platelets are reservoirs of growth factors and cytokines and play a crucial role in wound healing and regeneration of tissues. Literature review suggests an important role of platelet concentrates in periodontal and pulpal regeneration. Platelet-rich fibrin is a second generation platelet concentrate which contains platelets and growth factors in the form of fibrin membranes prepared from the patient's own blood free of any anticoagulant or other artificial modifiers. This article briefly describes the role of platelet-rich fibrin in periodontal and pulpal regeneration.
Keywords: *Platelet-rich fibrin, Platelet concentrates, Regeneration.*

INTRODUCTION

Wound healing is a normal biologic process that occurs in human body to restore the structure and function of diseased or injured tissue. It is the interaction of a complex cascade of cellular events and involves four overlapping phases: haemostasis, inflammation, proliferation and tissue remodelling.[1] Platelets are specialized blood cells that play a key role in physiologic as well as pathologic processes of haemostasis, inflammation, wound healing, host defence, thrombosis, tumor metastasis etc.[2]Platelet concentrates are currently used in different fields of medicine and dentistry, on surgical or wounded sites in order to stimulate and accelerate healing. This review article outlines the applications of platelet-rich fibrin in regenerative dentistry.

PLATELET CONCENTRATES

Platelets, the smallest of human blood cells, are produced by differentiation of megakaryocytes. Activation of platelets is important for platelet function and includes a complex interplay of adhesion, signalling molecules, and release of bioactive factors.[2] Platelets remain suspended in the liquid plasma when whole blood is centrifuged at a low centrifugal force and protocols for the preparation of platelet concentrates is based on this characteristic.[2] In transfusion medicine, platelet concentrates were originally used for the treatment and prevention of haemorrhage due to severe thrombopenia.

Based on the presence of leukocytes and fibrin architecture platelet concentrates can be generally classified into four groups:[3,4]

1. Pure Platelet-Rich Plasma (P-PRP) or Leukocyte-Poor Platelet-Rich products are preparations without leukocytes and with a low density fibrin network after activation. Used as liquid solutions or in an activated gel form.
2. Leukocyte-and Platelet-Rich Plasma (L-PRP)products are preparations with leukocytes and with a low density fibrin network after activation. Also used in two forms - liquid solution or activated gel.
3. Pure Platelet-Rich Fibrin (P-PRF) or Leukocyte-Poor Platelet-Rich Fibrin are preparations without leukocytes and with a high-density fibrin network. Used in strongly activated gel form.
4. Leukocyte- and Platelet-Rich Fibrin (L-PRF) products are preparations with leukocytes and with a high-density fibrin network. Also used in strongly activated gel form.

The most commonlyplatelet concentrate is platelet-rich plasma(PRP).The preparation of PRP often requires the use of specialised equipment, chemicals and animal-derivedadditives which increases the risk for complications secondaryto allergic reactions.[5] This led to the production of platelet-rich fibrin (PRF), a platelet concentrate which neither contained additives nor required specialised armamentarium for preparation.

PLATELET-RICH FIBRIN

Platelet-rich fibrin is a secondgeneration platelet concentrate and is often referred to as Choukroun's PRF after its inventor.PRF was developed in France by Joseph Choukroun *et al.*[6] in 2001. They used PRF to improve bone healing in cases of implants.[7] Choukroun's PRF is a leukocyte and platelet-rich fibrin biomaterial[3] with a specific composition and three-dimensional architecture.[8] PRF contains platelets and growth factors in the form of fibrin membranes. It is prepared from the patient's own blood and is free of anticoagulant or any other additives. Activation of platelets trapped within fibrin matrix leads to growth factor release and havebeen shown to stimulate mitogenic response in the periosteum for bone repair during normal wound healing.[7]

PRF: PREPARATION PROTOCOL

The classical technique for PRF preparation was invented by Choukroun.[6,9] It is the current technique of PRF preparation authorized by the French Health Ministry, where PRF is prepared without using an anticoagulant during blood harvesting or bovine thrombin during gelling.[8, 9]

PRF preparation requires an adequate table centrifuge and collection kit includinga 24 gauge butterfly needle and 10 mL blood collection tubes. A blood sample is taken without anticoagulant in 10 mL tubes and are immediately centrifuged at 3000 rpm for 10 minutes. The absence of anticoagulant allows activation of the majority of platelets contained in the sample to trigger a coagulation cascade within a few minutes. Fibrinogen concentrates in the upper part of the tube, until the effect of the circulating thrombin transforms it into a fibrin network. This results in a fibrin clot containing the platelets located in the middle of the tube, just between the red blood cell layer at the bottom and acellular plasma at the top. The clot is removed from the tube and the attached red blood cells scraped off and discarded.PRF can also be prepared in the form of a membrane by compression between two sterile gauzes or in a specific tool.[9]

ROLE OF PRF IN PERIODONTAL AND PULPAL REGENERATION

Platelet concentrates provide an ideal base for wound healing and regeneration of tissues due to its fibrin sealant properties as well as growth factors present in platelets.[7] The α-granules of platelets contain various growth factors like transforming growth factor (TGF β_1, TGF β_2), platelet-derived growth factor (PDGF),basic fibroblast growth factor (bFGF),insulin-like growth factor(IGF-I,IGF-II), epidermal growth factor (EGF),vascular endothelial growth factor (VEGF) etc. Concentrated platelets can accelerate

tissue regeneration by acting as a reservoir for autologous growth factors.[10]

The regenerative potential of platelets was introduced in 1974 when Ross *et al*.described the release of growth factor from platelets.[11]PRF has become a valuable adjunct to surgery in both the medical and dental fields through its combination of high efficiency platelet and leukocyte collection in a stable matrix, along with activation of growth factors and preservation of tissue repairing cytokines.The application of PRF in fields of plastic surgery, oral and maxillofacial surgery, implant surgery and periodontal and endodontic therapy has demonstrated successful and rapid results in terms of bone regeneration.[12]

The ultimate goal of periodontal therapy is regeneration of tissues destroyed by periodontal disease. Over the years, various modalities have been tried for management of osseous defects resulting from the periodontal disease process. Recently, the attention has shifted towards use of growth factors to regulate various cell-stromal interactions involved in periodontal regeneration. These growth factors are the vital biologic mediators that can regulate the proliferation, chemotaxis and differentiation of the locally derived progenitor cells in the defect site.[13]Combination of autologous PRF and the commercially available bone grafts holds a promising potential for periodontal regeneration. Management of furcation defects[14], gingival recessions[15] and intra bony defects[16,17] with the help of PRF have shown promising results. PRF has also been used in sinus lift procedures[18] and as a scaffold for human periosteal cells in vitro[19], in the field of tissue engineering.

The combination therapy using platelet-rich fibrin with demineralised bone matrix has been found to be an effective grafting modality for the management of intrabony osseous defects.[12]PRF has been shown to be an effective modality of therapy in the regenerative treatment of degree II mandibular furcations.[14] A combination of PRF gel, hydroxyapatite (HA) graft and guided tissue regeneration (GTR) membrane in a large periapical lesion with intrabony defect resulted in faster healing. The use of PRF in conjunction with HA crystals might have accelerated the resorption of the graft crystals and would have induced the rapid rate of bone formation.[20] The use of PRF as a potential novel root coverage approach has been reported by Anil Kumar*et al.*[15] for covering localised gingival recession in mandibular anterior teeth using combined laterally positioned flap technique and PRF membrane.

Gassling *et al.* reported that PRF appears to be superior to collagen as a scaffold for human periosteal cell proliferation and PRF membranes can be used for in vitro cultivation of periosteal cells for bone tissue engineering.[21]PRF promotes angiogenesis because of low thrombin level optimal for the migration of endothelial cells and fibroblasts. PRF entraps circulating stem cells due to its unique fibrin structure and this property of PRF finds application in healing of large osseous defects.[8]

Regenerative endodontics is the formation and delivery of tissues to replace pulp that has been traumatized or diseased or is absent.[22]

Regenerative endodontics has been mostly focused on immature teeth as they have a greater chance for pulpal regeneration.To achieve regeneration three main elements- source of cells, growth factors and other tissue-inducing mediators and a scaffold, or a three dimensional tissue structure that regulates the release of the growth factors, are required. Thus, regenerative endodontic techniques will possibly involve some combination of disinfection or debridement of infected root canal systems with apical enlargement to permit revascularization and use of adult stem cells, scaffolds, and growth factors.

Hargreaves *et al.*[23] suggested that platelet concentrates may be a promising material for endodontics as they possess the characteristics required to achieve regeneration. Shivashankar *et al.*[24], Khetarpal *et al.*[25] and Rudagi & Rudagi[26] used PRF in combination with mineral trioxide aggregate (MTA) in managing cases with open apexes and found accelerated periapical healing

and apical bone formation. Shivashankar *et al.*[24] concluded that revitalization of necrotic infected immature tooth is possible under conditions of total canal disinfection and PRF is an ideal biomaterial for pulp-dentin complex regeneration. Use of MTA and PRF for the repair of the perforation defect and Grade II furcation has resulted in long term results with regeneration of the lost periodontium in furcation area.[27] The osteoconductive and osteoinductive properties of platelet-rich fibrin were used to stimulate pulpal and periodontal regeneration in an avulsed maxillary incisor.[28] PRF entails a prospective research as a potential scaffold for regenerative endodontic therapy.

DRAWBACKS OF PRF

The main disadvantage of PRF is its preparation and storage. The clinical benefit of PRF depends on time interval between blood collection and centrifugation, as PRF is prepared without addition of anticoagulants. PRF membranes should be used immediately after preparation to prevent shrinkage due to dehydration altering the structural integrity of PRF. Dehydration can also lead to decrease in growth factor content. Storage in refrigerator can result in risk of bacterial contamination of the membranes. All these limitations with the use of PRF can be prevented by following a standard protocol for preparation and preservation.[8]

CONCLUSION

Various studies have demonstrated promising results related to the use of PRF alone or in combination with other biomaterials. PRF is an ideal biomaterial for pulp-dentin complex regeneration as well as regeneration of periodontal tissues. The main advantage of PRF preparation is that it utilizes the patient's own blood, thus reducing the chance for disease transmission through blood. Its several advantages makes it possible for use in different fields of reconstructive and regenerative medicine and dentistry.

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