Review Article

Platelet-Rich Fibrin - A Biofuel for Periodontal and Tissue Regeneration: A Review Article

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Abstract: The ultimate goal of periodontal therapy remains the complete regeneration of those periodontal tissues lost to the destructive inflammatory immune response, or to trauma. The development of bioactive surgical additives to regulate the inflammation and increase the speed of healing process is one of the great challenges in clinical research. Various platelets concentrates have been studied including the platelet-rich plasma. The growth factors present in platelets are important to guide the regenerating cells to the area of healing. The short duration of cytokine release and poor mechanical properties have resulted in the search of a new material with adequate properties for clinical application and ease of preparation. Hence, Platelet-rich fibrin (PRF) is one such material that holds on to these factors enmeshed in the fibrin network resulting in their sustained release over a period of time that can accelerate the wound healing process. With this knowledge, research has been carried out for a past few years for the clinical application of PRF. This autologous scaffold provides the much needed bio-chemical mediators which has the potential for enhancing reconstruction of the periodontium. This review focuses on the properties and various applications of PRF in the field of dentistry and tries to understand as to why PRF would be an important link to reach predictable periodontal regeneration.

Keywords: Periodontal regeneration, PRF, Platelet concentrates, Platelet growth factors, Wound healing, Bone regeneration, Tissue engineering.

INTRODUCTION

Periodontal disease is defined as a complex, multifactorial disease characterized by the loss of connective tissue attachment with destruction of periodontal tissues. The aim of periodontal therapy is to eliminate inflammatory process, prevent the progression of periodontal disease and also to regenerate the lost periodontal tissues. Periodontal regeneration is a complex multifactorial process involving biological events like cell adhesion, migration, proliferation, and differentiation in an orchestrated sequence[1]. Periodontal regenerative procedures include soft tissue grafts, bone grafts, root biomodifications, guided tissue regeneration, and combinations of these procedures[2]. The concept of tissue engineering has brought about a drastic improvement in the healing process of tissues. Hence the pivotal goal in periodontal and maxillofacial tissue regeneration is to reconstruct the defects which lead to the search of a biofuel[3]. Among the rich sources of autologous growth factors are various generations of platelet concentrates that are currently in use. Platelet-rich plasma (PRP), the first generation concentrate, has been used alone and in combination with grafting materials and barrier membranes in the management of periodontal and surgical defects[4,5]. However, the effects of platelet rich plasma on bone regeneration have been limited.

PRF is a second- generation platelet concentrate widely used to accelerate soft and hard tissue healing and is a strictly autologous fibrin matrix containing a large quantity of platelet and leukocyte cytokines[6]. Ross et al. were amongst the pioneers who first described a growth factor from platelets[7]. Growth factors are released after activation from the platelets trapped within fibrin matrix and have been shown to stimulate the mitogenic response in the periosteum for bone repair during normal wound healing[7]. Choukroun's PRF has been the latest development among the platelet concentrates[8]. This paper intends to review the potential of PRF in the field of Periodontal and Tissue regeneration.

Historical Background of Platelet Concentrates: The world of medicine was acquainted with the regenerative potential of platelets when Ross et al[9] in 1974 introduced the regenerative potential of platelets by discussing their role in wound healing.

The alpha granules of platelets contain various mitogenic factors such as Platelet Derived Growth Factor, Vascular

Endothelial Growth Factor and Transforming Growth Factor-β (Fig 1).

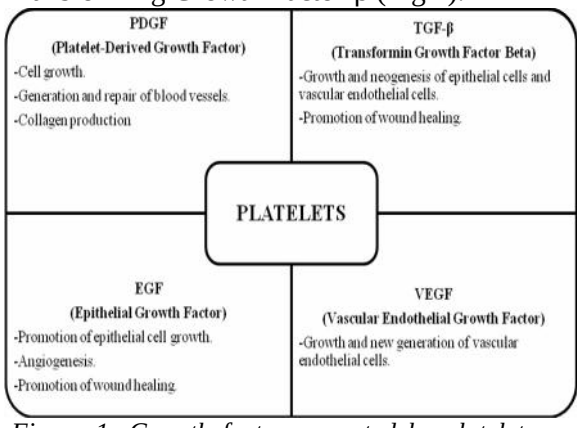

Figure 1: Growth factors secreted by platelets including platelet-derived growth factor, transforming growth factor beta, epithelial growth factor, and vascular endothelial growth factor. (Annals of Burns and Fire disasters-vol. XXV- n. 4- December 2012).

This storage pool of growth factors proteins is vital to initial wound healing. Upon connective tissue contact, as occurs in injury or surgery, the cell membrane of the platelet is "activated" to release these alpha granules. Active proteins are thus secreted which bind to transmembrane receptors of the target cells to activate intracellular signalling proteins.This results in expression of a gene sequence that directs cellular proliferation, collagen synthesis and osteiod production[10]. Platelets are used as powerful tools for periodontal regeneration for the past two decades due to the key role of platelets in wound healing process. Although the use of fibrin adhesives is well documented from the past 30 years[11,12] their use is still controversial due to the complexity in preparation and risk of cross- infection.

Later, concentrated platelet-rich plasma (cPRP) was developed with a less complex production protocol. It is prepared from the patient's own blood and is activated by the addition of thrombin and calcium. The structure consists of a three dimensional biocompatible fibrin scaffold with a limited volume of plasma enriched in platelets. When PRP is activated the growth factors and proteins are released to the local environment, accelerating postoperative wound healing and tissue repair[13]. But there are certain risks associated with use of PRP[14].

The presence of bovine thrombin in PRP can result in the development of antibodies to the clotting factors V, XI and thrombin which can adversely affect the coagulation process. In addition, bovine thrombin preparation contain clotting factor V which can result in immune system activation when challenged with a foreign protein. Other drawbacks about the use of PRP include legal restrictions on handling the blood and also controversies in the literature regarding the benefits and clinical outcome of use of PRP. All these have led to the generation of a new family of platelet concentrate called platelet-rich fibrin which overcomes many of the limitations of PRP. PRF is a potent autologous regenerative material with many clinical applications in the field of periodontics as it accelerates both soft tissue and hard tissue healing.

Role of Platelet Concentrates

Application of fibrin adhesives in surgical management of hemostasis is well documented since early 1900s.

Fabbro et al.[15] summarized the ideal role of platelet concentrates as:

1. Augmentation of tissue healing: By increased proliferation of connective tissue progenitors that stimulate fibroblast and osteoblast activity and enhance osteogenesis[16].
2. Anti- microbial activity: Against bacterial species involved in oral infections[17,18].
3. Modification of host defence mechanism: By delivery of signaling peptides that attract macrophage cells[19].
4. Modification of immune reaction: by releasing leukocytes that synthesize interleukins[20].

Role of Platelets in Periodontal Wound Healing: Platelets play a key role in wound healing and hence wound healing after periodontal treatment can be accelerated by the use of platelet concentrates. The wound healing process initiated by the formation of blood clot and after tissue injury in periodontal surgery causes adherence and aggregation of platelets favouring the

formation of thrombin and fibrin. In addition, there is release of certain substances from platelets that promote tissue repair, angiogenesis, inflammation and immune response. Platelets also contain biologically active proteins and the binding of these secreted proteins within a developing fibrin mesh to the extracellular matrix can create chemotactic gradients favouring the recruitment of the stem cells, stimulating cell migration, differentiation, and promoting repair. Thus, the use of autologous platelet concentrates is a promising application in the field of periodontal regeneration and can be of help in clinical situations requiring rapid healing[21].

CLASSIFICATION OF PLATELET CONCENTRATES[22]

Proposed by Ehrenfestet al. (2009) , four main families of preparations are defined, depending on their cell content and fibrin architecture[23]:-

1. Pure Platelet- Rich Plasma (P-PRP) or leukocyte- poor PRP products are preparations without leukocytes and with a low- density fibrin network after activation.
2. Leucocyte and PRP (L-PRP) products are the preparations with leukocytes and a low-density fibrin network after activation.
3. Pure platelet- rich fibrin (P-PRF) or leucocyte –poor platelet- rich fibrin preparations are without leucocytes and with a high- density fibrin network. These products only exist in a strongly activated gel form, and cannot be injected or used like traditional fibrin glues.
4. Leucocyte- and platelet-rich fibrin (L-PRF) or second- generation PRP products preparations with leucocytes and with a high- density fibrin network.

Platelet Rich Plasma (PRP): Platelet-rich plasma was introduced for the first time by Marx et al. in 1998[16.]The data reported by Marx suggested that PRP addition accelerated the rate and degree of bone formation[16]. PRP was developed to combine the fibrin sealant properties with growth factor effect of platelets, thus providing an ideal growth factor delivery system at the site of injury. These growth factors exhibit chemotactic and mitogenic properties that promote and modulate cellular functions involved in tissue healing, regeneration, and cell proliferation[24].

Clinical Applications - (PRP)[25]

1. In sinus lift procedures, PRP accelerates the healing and reduces the healing time with stable bone gain.
2. Ridge augmentation can be achieved with the use of PRP.
3. Socket preservation to maintain the alveolar bone height is possible.
4. Intrabony defects or osseous defects have shown bone fill with the use of PRP.
5. Can also be used in jaw reconstruction surgeries.
6. Also used in Soft tissue procedures like gingival grafts, sub-epithelial grafts, and so forth, because of the property of PRP of accelerating soft tissue healing.

Limitations[26]

1. Lack of uniformity in PRP preparation protocol as different platelet concentrations have different storage time.
2. Release of growth factors for a shorter period of time.
3. Antibodies to bovine factor Va may cross react with human factor Va and may produce coagulopathies and rare bleeding episodes.

Platelet Rich Fibrin (PRF): PRF (platelet-rich fibrin) was first developed in France by Choukroun et al. in 2001, for use in the field of oral and maxillofacial surgery.[27] PRF is classified as a second generation platelet concentrate as it is prepared as a natural concentrate without the addition of any anticoagulants or bovine thrombin or any other gelifying agent.[28,29] PRF is often called Choukroun's PRF as there are other platelet concentrates with similar names such as Vivostat PRF (considered a pure platelet-rich plasma) or Fibrinet PRF (without leukocytes). Choukroun's platelet- rich fibrin (PRF) is a leukocyte and platelet- rich fibrin biomaterial[23] with a specific composition and three-dimensional architecture. PRF has a dense fibrin network

with leukocytes, cytokines, structural glycoproteins[30]and also growth factors such as transforming growth factor β_1, platelet-derived growth factor, vascular endothelial growth factor and glycoproteins such as thrombospondin-1 during ≥ 7 day.[31] Leukocytes that are concentrated in PRF scaffold play an important role in growth factor release[31], immune regulation, anti-infectious activities[32], and matrix remodelling during wound healing. The slow polymerization mode of PRF and cicatricial capacity creates a physiologic architecture favourable for wound healing.

The crux of PRF synthesis lies in the attempts to accumulate platelets and release cytokines in a fibrin clot. The PRF clot is yielded by a natural polymerization process during centrifugation, and its natural fibrin architecture seems responsible for a slow release of growth factors and matrix glycoproteins during ≥7 days[32]. PRF clot concentrates 97% of platelets and >50% of leukocytes in a specific three dimensional distribution[33].

Preparation of PRF: Preparation of PRF follows the protocol developed by Choukroun et al. in Nice, France.[33]The protocol for PRF preparation is very simple; however it has to be manufactured just prior to its application. Requirements: 1. Table centrifuge, 2. Ten ml dry glass test tube (without anticoagulant), 3. Blood collection armamentarium.

The main advantages in PRF preparation are the single- stage centrifugation and absence of bovine thrombin. The blood obtained from the subject is placed into the test tube and centrifuged immediately for 10 minutes at 3000 rpm[34] or 2700 rpm for 12 minutes with similar findings.[35]

The steps involved are as follows (Fig 2):

1. Blood specimen is collected or drawn from the patient.
2. The blood specimen is placed in the centrifuge and is allowed to spin immediately for the stipulated time.
3. Following this, the blood sample settles into various layers.

The absence of any anticoagulant, grants the activation of platelets to set off a coagulation cascade. Due to the absence of the anticoagulant, the blood coagulates immediately upon contact with the glass tube. Initially, fibrinogen occupies the upper part of the tube, only till the circulating thrombin transforms it into a fibrin network[6].

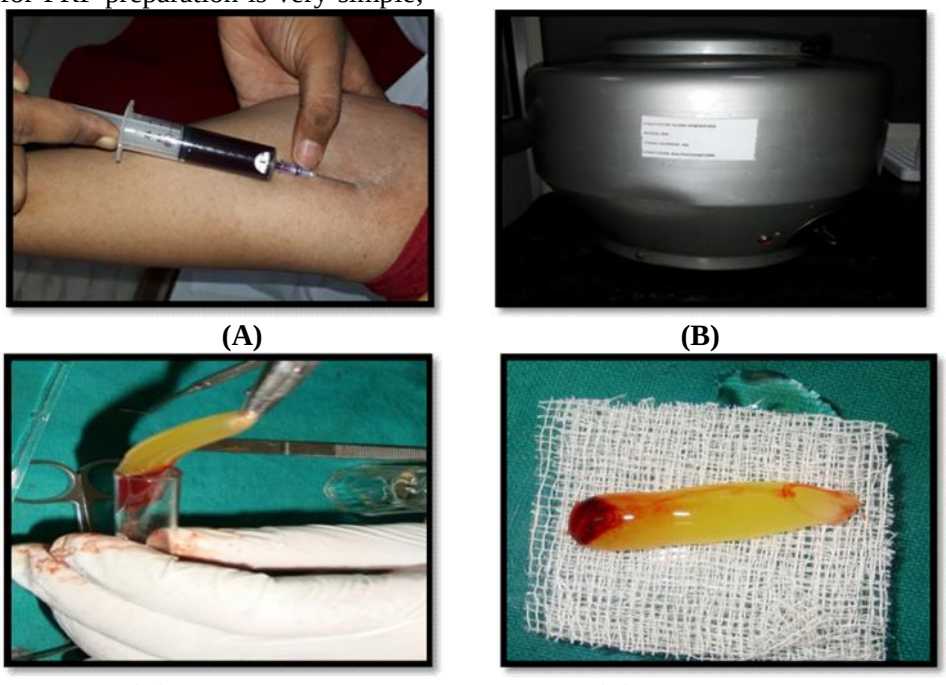

Figure 2: *Preparation of PRF GEL. A. Collection of blood sample, B. Centrifuge, C. Retrieval of PRF with the help of artery forcep, and D. PRF Gel.*

The layers that are formed are as follows:

a) The lower fraction containing the RBCs.
b) The middle fraction containing the fibrin clot.
c) The upper fraction containing the straw-coloured acellular plasma.

The upper portion of the test tube containing acellular plasma will be removed. The middle portion containing the fibrin clot is then removed from the lower part containing the red blood cells. The natural and progressive polymerization results in a fibrin clot formation with substantial embedding of platelets and leukocyte growth factors into the fibrin matrix[35].

PRF Gel: The clot can be squeezed between two gauge pieces to obtain an inexpensive autologous fibrin gel[6]. The serum exudate expressed from the clot is rich in proteins such as vitronectin and fibronectin[36]. This exudate may be used to hydrate graft materials, rinse the surgical site, and store autologous graft[6].

PRF Membrane: The PRF Box is commercially available to prepare the PRF membrane. The PRF clot is placed on the grid in the PRF box and covered with compressor lid which squeezes out the fluid from the clot. The membranes formed using this method had constant thickness which remain hydrated for several hours and have recovered the serum exudates expressed from the fibrin clots.

Why use PRF?

PRF is an adjunct to the natural healing process and has been the following effects:

a) The fibrin clot acts as a support through its mechanical properties, which involved the protection of graft materials and also acts as a biological connector between the bone particles.
b) The fibrin network is also engaged in cellular migration, mainly for the endothelial cells necessary for the neoangiogenesis, vascularization, and survival of the graft.
c) The process of healing is carried along and aided by the persistent release of various growth factors that include PDGF, TGF-β and IGF-1.
d) The presence of leukocytes and various cytokines enables the self-regulation of the infectious and inflammatory processes.

Phases of Wound Healing

Wound healing consists of three phases:

I. Inflammatory phase(1-4 days) (substrate- preparation phase)
II. The proliferation phase(2-22 days) (collagen- building phase)
    a. Epithelization
    b. Angiogenesis
    c. Granulation tissue formation
    d. Collagen deposition
III. Maturation(remodelling phase) (6-12 months)
    a. Collagen maturation and contraction

ROLE OF PRF IN WOUND HEALING:-

1. Prolonged release of growth factors at the wound site.
2. Proliferation of fibroblasts and osteoblasts.
3. Promote angiogenesis.
4. Induces collagen synthesis.
5. Mechanical adhesion by fibrin.
6. Trapping of circulating stem cells.
7. Regulation of immunity.

Clinical implications of PRF

Extraoral Clinical Applications: Use of PRF in periodontology and oral and maxillofacial surgery has been largely described. PRF membrane functionalized by incorporation alkaline phosphatise induces the mineralization of PRF. Thus, PRF can also be a suitable material for bone replacement[36].

1. PRF promotes dentinogenesis by stimulating cell proliferation and differentiation of dental pulp cells[37].
2. Healing of severe non-healing lower-extremity ulcers[38].
3. Repair articular cartilage defects[39].
4. Application in facial plastic surgery such as Nasolabial folds, Facial volumization, Superficial rhytides, Acne scars, Rhinoplasty, Facial estheticlipostructure, Autologous fat

transfer, Rhytidectomy, Depressed scar and Dermal augmentation. [40,41]

Intra Oral Applications: In recent times a lot of research has been done on PRF numerous cases have been reported regarding the use PRF clot and PRF membranes.

In Oral and Maxillofacial Surgery:-

1. Filling material in avulsion sockets, bony defects etc.
2. Bone augmentation in sinus lifts for posterior maxilla augmentation for implants, bony defects.
3. Ridge preservation.
4. Guided bone regeneration.
5. Filling of cystic cavity.

In Periodontics:-

1. PRF membrane has been used for root coverage with single and multiple teeth recession.
2. Regenerative procedures in treatment of 3-walled osseous defect.
3. In the treatment of combined periodontic endodontic lesion.
4. Treatment of furcation defect.
5. PRF enhances palatal wound healing after free gingival graft.
6. Guided tissue regeneration.
7. Periapical lesions.

In Endodontics:-

1. In treatment of open apex:
   a. For regeneration of pulp-dentin complex.
   b. In combination with MTA to create root end barriers in apexification procedures to prevent extrusion of material.
2. In regenerative pulpotomy.
3. To fill in bony defect.

In Tissue Engineering:

The use of PRF as a tissue engineering scaffold was investigated by many researches for the past few years[42]. In a study by Gassling et al. 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. Thus, PRF is a potential tool in tissue engineering but clinical aspects of PRF in this field requires further investigation[43].

Advantages of PRF over PRP (Dohan et al.)[43]

i. No use of anticoagulants.
ii. Slow natural polymerization.
iii. 3D fibrin network forming a matrix aiding in cytokine retention for extended periods.
iv. Formulation of a PRF membrane that possesses elasticity and flexibility.
v. Simple and cost effective.
vi. Completely autogenous.
vii. Extended growth factor release for 7 days.
viii. PRF help in hemostasis.
ix. In-expensive.
x. No requirement of any additive constituent such as bovine thrombin.
xi. Act as an 'immune regulation node'.
xii. Has anti-inflammatory effects.
xiii. No associated infections.

Shortcomings of PRF:

I. Rapid use of the PRF without delay or short handling time.
II. Low quantity of PRF is obtained.
III. PRF possesses the circulating immune cells and antigenic molecules that prevent its use as an allogenic material[44].
IV. Also, there is an increased risk of transmitting infectious agents.

Future directions: In the future more studies should be carried out to correlate the clinical outcome of PRF with its biological mechanisms which opens novel applications of this autologous platelet concentrate. There are only limited studies in the literature on the effect of PRF on cell proliferation and other biologic effects. Therefore, more studies should be conducted which open newer strategies for the use of this platelet concentrate.

CONCLUSION: PRF by Choukroun's technique is a simple and inexpensive derivative for the successful regeneration of periodontal tissues. The main advantage is that PRF preparation utilizes the patient's own blood reducing or eliminating disease transmission through blood. The use of PRF as an adjunct in wound healing, during periodontal regeneration has been successful

for the correction of osseous defects in periodontics, oral and maxillofacial surgery and implant dentistry. In the future, more studies and clinical trials are needed to investigate potential applications of PRF in the field of periodontal regeneration and tissue engineering and to extend its clinical applications.

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How to cite this article: Amaranath J, Das N, Gupta R, Gupta I. Platelet-Rich Fibrin - A Biofuel for Periodontal and Tissue Regeneration: A Review Article. Rama Univ J Dent Sci 2017 June;4(2):14-22.

Sources of support: Nil **Conflict of Interest**: None declared