

## REVIEW ARTICLE

### PLATELET RICH FIBRIN: A PROMISING INNOVATION IN REGENERATIVE THERAPY

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**ABSTRACT:** Platelets can play a crucial role in regenerative therapy as they are reservoirs of growth factors and cytokines which are the key factors for regeneration of the bone and maturation of the soft tissue. Platelet-rich fibrin (PRF) was first described by Choukroun et al. in France. It has been referred to as a second-generation platelet concentrate, which has been shown to have several advantages over traditionally prepared PRP. Platelet-rich fibrin (PRF) is autologous platelet concentrates prepared from patient's own blood. It is a natural fibrin-based biomaterial prepared from an anticoagulant-free blood harvest without any artificial biochemical modification that allows obtaining fibrin membranes enriched with platelets and growth factors. Evidence from the literature suggests the potential role of PRF in regeneration and tissue engineering. The slow polymerisation during centrifugation and fibrin-based structure makes PRF a better healing biomaterial than PRP and other fibrin adhesives. The purpose of this review article is to describe the novel second-generation platelet concentrate PRF, which is an improvement over the traditionally prepared PRP for use in regenerative dentistry.

**KEYWORDS:** Growth factors, platelet rich fibrin, platelet rich plasma, regeneration, tissue engineering.

**INTRODUCTION:** Regenerative medicine holds promise for the restoration of tissues and organs damaged by disease, trauma, cancer, or congenital deformity. Regenerative medicine can perhaps be best defined as the use of a combination of cells, engineering materials, and suitable biochemical factors to improve or replace biological functions in an effort to effect the advancement of medicine.

The basis for regenerative medicine is the utilization of tissue engineering therapies. Probably the first definition of tissue engineering was by Langer and Vacanti who stated it was "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function."<sup>1</sup> MacArthur and Oreffo defined tissue engineering as "understanding the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use."<sup>2</sup>

The term tissue engineering was originally coined to denote the construction in the laboratory of a device containing viable cells and biologic mediators (e.g., growth factors and adhesins) in a synthetic or biologic matrix, which could be implanted in patients to facilitate regeneration of particular tissues.

The role of tissue oxygenation in wound healing became the focal point in the 1980s. Tissue oxygenation enhances phagocytic and bactericidal ability of host immune cells and supports collagen as well as other protein synthetic events. The importance of growth factors in enhancing wound healing has become the focus of research in the present day. In addition, a link has been established between tissue oxygenation and growth factors.<sup>3</sup>

## REVIEW ARTICLE

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Macrophage stimulation causes the release of angiogenic and other growth factors that support wound healing and resist infection.<sup>4</sup> In general, tissue engineering combines three key elements, namely scaffolds (Collagen, bone mineral), signaling molecules (Growth factors), and cells (Osteoblasts, fibroblasts). Tissue engineering has been redefined presently as the relatively new, highly promising field of reconstructive biology, which draws on the recent advances in medicine and surgery, molecular and cellular biology, polymer chemistry, and physiology.<sup>5</sup>

Bone graft materials commonly used are demineralized freeze-dried bone allograft (DFDBA) and freeze-dried bone allograft (FDBA). The osteoinductive properties of DFDBA have made it the grafting material of choice as compared to FDBA, xenografts, and alloplasts. However, the osteoinductive potential of DFDBA procured from different bone banks or from different batches of the same bank may vary highly. The bioactivity of DFDBA seems to be dependent on the age of the donor; the younger the donor the more osteoinductive the graft material.<sup>6</sup> This controversy as well as concerns about disease transmission has pushed clinicians toward using xenografts and alloplastic materials. Although these materials are biocompatible and are osteoconductive in nature, clinical outcomes are unpredictable. The problem that arises next is how to improve clinical outcomes by improving the properties of these grafts. Some commonly used materials in regenerative procedures include guided tissue regeneration, guided bone regeneration, distraction osteogenesis and more recently introduced emdogain and preclinical trials on use of fibroblast growth factor 2 (FGF2) for periodontal regeneration.

In the past two decades, an increased understanding of the physiological roles of platelets in wound healing and after tissue injury has led to the idea of using platelets as therapeutic tools. Platelet-Rich Plasma (PRP) consists of a limited volume of plasma enriched with platelets, which is obtained from the patient. The use of PRP as a potentially ideal scaffold for regenerative therapy and has been documented in the literature. However, the use of bovine thrombin for the activation of Platelet Rich Plasma (PRP) has been an issue of controversy which led to the development of the second generation platelet concentrate known as Platelet Rich Fibrin (PRF) which is totally autologous in nature. It is very simple and inexpensive. PRF contains platelets, growth factors, and cytokines that might enhance the healing potential of both soft and hard tissues.

**EVOLUTION OF PLATELET CONCENTRATES:** Platelets are small, irregularly shaped anuclear cells, 2-4  $\mu\text{m}$  in diameter, which are derived from fragmentation of precursor megakaryocytes. The average life span of a platelet is between 8 and 12 days. Platelets play a fundamental role in hemostasis and are a natural source of growth factors. Growth factors stored in the  $\alpha$ -granules of platelets include platelet derived growth factor, insulin-like growth factor, vascular endothelial growth factor, and transforming growth factor- $\beta$ .

The release of growth factors is triggered by the activation of platelets, which may be initiated by a variety of substances or stimuli, such as thrombin, calcium chloride, collagen or adenosine 5c-diphosphate. In addition to these growth factors, PRP contains fibrinogen and a number of adhesive glycoproteins that support cell migration.

In general, platelet concentrates are blood-derived products used for the prevention and treatment of hemorrhages due to serious thrombocytopenia of the central origin. Platelet concentrates have been developed to be used as bioactive surgical additives that are applied locally to promote wound healing stems from the use of fibrin adhesives. Since 1990, medical science has

## REVIEW ARTICLE

recognized several components in blood, which are a part of the natural healing process; when added to wounded tissues or surgical sites, they have the potential to accelerate healing.

Fibrin glue was originally described in 1970 and is formed by polymerizing fibrinogen with thrombin and calcium. It was originally prepared using donor plasma; however, because of the low concentration of fibrinogen in plasma, the stability and quality of fibrin glue were low.

These adhesives can be obtained autologously from the patient or can be obtained commercially. These products are heat-treated, thus immensely reducing, but not entirely eliminating, the risk of disease transmission. Therefore, the commercially available adhesives constitute an infinitely small risk of disease transmission.<sup>7,8</sup>

Growth factor	Source cells	Target	Biologic action
Platelet-derived growth factor	Platelets, macrophages, monocytes, endothelial cells, smooth muscle cells	Fibroblasts, smooth muscle cells, glial cells, macrophages, neutrophils	Stimulates DNA and protein synthesis in osseous tissues; mitogenic effects on mesenchymal cells; angiogenic effect on endothelial cells
Transforming growth factor $\beta$	Platelets, T-lymphocytes, macrophages/monocytes, neutrophils	Fibroblasts, marrow stem cells, endothelial cells, epithelial cells, preosteoblasts	Stimulates angiogenesis; enhanced woven bone formation; stimulate matrix synthesis in most culture systems; chemotactic effect on osteoblastic cells; stimulates endothelial chemotaxis; stimulates bone formation by inhibitory effect on osteoclasts
Platelet-derived angiogenesis factor	Platelets, endothelial cells	Endothelial cells	Mitogenic effect on endothelial cells; increased angiogenesis and vessel permeability
Insulin-like growth factor 1	Osteoblasts, macrophages, monocytes, chondrocytes	Fibroblasts, osteoblasts, chondroblasts	Stimulates proliferation of osteoblasts and matrix synthesis; increases expression of bone matrix proteins, such as osteocalcin; in combination with PDGF it enhances the rate and quality of wound healing
Platelet factor 4	Platelets	Fibroblasts, neutrophils	Chemoattractant for neutrophils and fibroblasts

PDGF - platelet-derived growth factor, TGF- $\beta$  - transforming growth factor  $\beta$ , PDAF - platelet-derived angiogenesis factor, IGF-1 - insulin-like growth factor -1, PF-4 - platelet factor - 4

### PROPERTIES OF PLATELET CONCENTRATES:

1. Increase tissue vascularity through increased angiogenesis.
2. Enhancing collagen synthesis.
3. Enhancing osteogenesis.
4. Increasing the rate of epithelial, and granulation tissue production.
5. Antimicrobial effect.
6. Reaction with other material: PRP does not react or interfere with any other restorative material glass ionomer cements or composite resin used as filling material are not affected by it.
7. Biocompatibility: PRP offers a biologically active substance with the release of growth factor.
8. Tissue regeneration: PRP allows regeneration of tissue with the release of growth factors.

Platelet rich plasma gel (PRP gel) is an autologous modification of fibrin glue obtained from autologous blood used to deliver growth factors in high concentrations. It is an autologous concentration of human platelets in a small volume of plasma, mimics coagulation cascade, leading to formation of fibrin clot, which consolidates and adheres to application site. Its biocompatible and biodegradable properties prevent tissue necrosis, extensive fibrosis and promote healing.

PRP contains high concentration of platelets and native concentration of fibrinogen. The alpha granules of platelets include a high concentration of factors, which are released on activation of

## REVIEW ARTICLE

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platelets by adding calcium chloride and thrombin to PRP. The growth factors are diverse group of polypeptides that have important roles in the regulation of growth and development of a variety of tissues. PRP obtained from autologous blood is used to deliver growth factors in high concentrations to the site of bone defect or a region requiring augmentation.

A blood clot is the center focus of initiating any soft-tissue healing and bone regeneration. In all natural wounds, a blood clot forms and starts the healing process. PRP is a simple strategy to concentrate platelets or enrich natural blood clot, which forms in normal surgical wounds, to initiate a more rapid and complete healing process. A natural blood clot contains 95% red blood cells, 5% platelets, less than 1% white blood cells, and numerous amounts of fibrin strands. A PRP blood clot contains 4% red blood cells, 95% platelets, and 1% white blood cells.<sup>9</sup>

Sanchez et al. have elaborated on the potential risks associated with the use of PRP. The preparation of PRP involves the isolation of PRP after which gel formation is accelerated using calcium chloride and bovine thrombin. It has been discovered that the use of bovine thrombin may be associated with the development of antibodies to the factors V, XI and thrombin, resulting in the risk of life-threatening coagulopathies. Bovine thrombin preparations have been shown to contain factor V, which could result in the stimulation of the immune system when challenged with a foreign protein.<sup>10</sup>

Other methods for safer preparation of PRP include the utilization of recombinant human thrombin, autologous thrombin or perhaps extrapurified thrombin. Landesberg et al. have suggested that alternative methods of activating PRP need to be studied and made available to the dental community.<sup>11</sup>

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.

The purpose of this review article is to describe a novel second-generation platelet concentrate called PRF, which is an improvement over the traditionally prepared PRP for use in regenerative dentistry.

**PLATELET RICH FIBRIN:** PRF was first developed in France by Choukroun et al. in 2001.<sup>12</sup> This second-generation platelet concentrate eliminated the risks associated with the use of bovine thrombin.

Platelet-rich fibrin (PRF) 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 biochemical modifications.

The PRF clot forms a strong natural fibrin matrix, which concentrates almost all the platelets and growth factors of the blood harvest and shows a complex architecture as a healing matrix with unique mechanical properties which makes it distinct from other platelet concentrates.<sup>13, 14, 15</sup>

PRF is superior to other platelet concentrates like PRP due to its ease and inexpensive method of preparation and also it does not need any addition of exogenous compounds like bovine thrombin and calcium chloride. It is advantageous than autogenous graft also because an autograft requires a second surgical site and procedure. Thus PRF has emerged as one of the promising regenerative materials.

## REVIEW ARTICLE

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**PREPARATION OF PRF:** The protocol for PRF preparation is very simple and simulates that of PRP. It includes collection of whole venous blood (Around 5 ml) in each of the two sterile tubes (6ml) without anticoagulant and the tubes are then placed in a centrifugal machine at 3,000 revolutions per minute (rpm) for 10 min, after which it settles into the following three layers: Upper straw-colored acellular plasma, red-colored lower fraction containing red blood cells (RBCs), and the middle fraction containing the fibrin clot. The upper straw-colored layer is then removed and middle fraction is collected, 2 mm below to the lower dividing line, which is the PRF. The mechanism involved in this is; the fibrinogen concentrated in upper part of the tube, combines with circulating thrombin due to centrifugation to form fibrin.

A fibrin clot is then formed in the middle between the red corpuscles at bottom and acellular plasma at the top. The middle part is platelets trapped massively in fibrin meshes. The success of this technique entirely depends on time gap between the blood collection and its transfer to the centrifuge and it should be done in less time. The blood sample without anticoagulant, starts to coagulate almost immediately upon contact with the glass, and it decreases the time of centrifugation to concentrate fibrinogen. Following proper protocol and quick handling is the only way to obtain a clinically usable PRF clot charged with serum and platelets. Resistant autologous fibrin membranes may be available by driving out the fluids trapped in fibrin matrix.

Because of the absence of an anticoagulant, blood begins to coagulate as soon as it comes in contact with the glass surface. Therefore, for successful preparation of PRF, speedy blood collection and immediate centrifugation, before the clotting cascade is initiated, is absolutely essential. PRF can be obtained in the form of a membrane by squeezing out the fluids in the fibrin clot.

PRF also contains physiologically available thrombin that results in slow polymerization of fibrinogen into fibrin which results in a physiologic architecture that is favorable to wound healing. The cytokines which are present in platelet concentrates play an important role in wound healing.

The structural configuration of PRF with respect to cytokine incorporation in fibrin meshes is different from that present in PRP. The natural polymerization in PRF results in increased incorporation of the circulating cytokines in the fibrin meshes (Intrinsic cytokines). These intrinsic cytokines will be having an increased lifespan and they will be released and used only at the time of initial cicatricial matrix remodeling which creates a long term effect.

Another added advantage of PRF is the presence of natural fibrin network which protects the growth factors from proteolysis. PRF also favors the development of micro-vascularization leading to a more efficient cell migration

PRF has a dense fibrin network with leukocytes, cytokines, structural glycoproteins and also growth factors such as transforming growth factor  $\beta$ 1, platelet-derived growth factor, vascular endothelial growth factor and glycoproteins such as thrombospondin-1.<sup>16</sup> Leukocytes that are concentrated in PRF scaffold play an important role in growth factor release, immune regulation, anti-infectious activities and matrix remodeling during wound healing.<sup>17</sup>

The slow polymerization mode of PRF and cicatricial capacity creates a physiologic architecture favorable for wound healing<sup>18</sup>

**PRF IN TISSUE ENGINEERING:** The a-granules present in platelets contain growth factors like platelet derived factor (PDGF), transforming growth factor-b (TGF-b), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF).<sup>19</sup>

## REVIEW ARTICLE

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Platelet derived growth factor (PDGF) has an important role in periodontal regeneration and wound healing and receptor for PDGF is present on gingiva, periodontal ligament and cementum and it activates fibroblasts and osteoblasts promoting protein synthesis.<sup>20</sup> PDGF also functions as a chemo attractant for fibroblasts and osteoblasts in gingiva and periodontal ligament resulting in their activation.

PRF promotes angiogenesis because as it has low thrombin level optimal for the migration of endothelial cells and fibroblasts. PRF entraps circulating stem cells due to its unique fibrin structure. This property of PRF finds application in healing of large osseous defects where there is migration of stem cells differentiating into osteoblast phenotype.

PRF also helps in facilitating adhesion and spreading of cells, regulates gene expression of growth factors, growth factor receptors, proteins, and determines the outcome of a cell's response to growth factors due to the presence of collagen, fibronectin, elastin, other non-collagenous proteins, and proteoglycan in the extracellular matrix of PRF.<sup>21,22</sup>

The use of PRF as a tissue engineering scaffold was investigated by many researchers for the past few years. In a study by 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.<sup>21</sup>

PRF has immune functions like chemotaxis as leukocytes present in PRF degranulates during activation and releases cytokines like IL-1, IL-4, IL-6 and TNF- $\alpha$ . PRF also contains anti-inflammatory cytokine such as IL-4 which requires further research<sup>15</sup>

Thus PRF is a potential tool in tissue engineering but clinical aspects of PRF in this field requires further investigation.

**CLINICAL APPLICATION:** In oral and maxillofacial surgery to improve bone healing in implant dentistry. The most common encountered problems are lack of adequate bone and proximity to anatomic structures at the implantation site and recent advancements of PRF usage in surgical procedures can predictably combat such difficulties. In combination with freeze-dried bone allograft (FDBA) in sinus floor elevation to enhance bone regeneration.

In various bone reconstruction procedures PRF could provide a possible new bone. Mazor et al., stated that use of PRF as the sole filling material during a simultaneous sinus lift and implantation procedure had stabilized a good amount of regenerated bone in the subsinus cavity up to the tip of implants in a case series through a radiological and histological evaluation at after 6 months from the surgery.<sup>23</sup>

PRF membranes protects the surgical site; promotes soft tissue healing; and when its fragments mixes with graft material, it functions as a "biological connector" between the different elements of graft and acts as a matrix which supports neoangiogenesis, capture of stem cells, and migration of osteoprogenitor cells to the center of graft.

PRF plugs can also be used in treating the residual extraction sockets. Use of autologous PRF in extracted socket filling after immediate bone augmentation using titanium membranes applied to the socket walls and primary closure was found to be feasible and safe with adequate bone filling after 8 weeks or above for implant fixation.

Anil kumar et al., has reported PRF as a potential novel root coverage approach for treating gingival recession in mandibular anterior teeth using combined laterally positioned flap technique

## REVIEW ARTICLE

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and PRF membrane. Combined use of PRF and bone graft with good results has also been reported for combined periodontic-endodontic furcation defect.<sup>24</sup>

Aroca et al., in the 6 month of their randomized clinical trial, concluded that addition of a PRF membrane positioned under the MCAF (Modified coronally advanced flap) provided inferior root coverage, but an additional gain in gingival/mucosal thickness (GTH) at 6 months compared to conventional therapy.<sup>25</sup>

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.

PRF membrane has been used as a barrier membrane over a large bony defect to maintain a confined space for the purpose of guided tissue regeneration. PRF in conjunction with Hydroxyapatite crystals can accelerates the resorption of the graft crystals and induce the rapid rate of bone formation.

Combination of PRF as a matrix and MTA as an apical barrier is considered as a good option for creating artificial root end barrie

**DRAWBACKS OF PRF:** The main shortcoming of PRF is its preparation and storage.

The clinical benefit of PRF depends on time interval between speed of handling between blood collection and centrifugation as PRF is prepared without any addition anticoagulants.

PRF storage after preparation. PRF membranes should be used immediately after preparation as it will shrink resulting in dehydration altering the structural integrity of PRF.

Dehydration also results in the decreased growth factor content in PRF and leukocyte viability will be adversely affected altering its biologic properties.

PRF when stored in refrigerator can result in risk of bacterial contamination of the membranes. These limitations with the use of PRF can be circumvented by sticking onto a standard protocol for preparation and preservation.

**CONCLUSION:** PRF represents a new revolutionary step in the platelet gel therapeutic concept. PRF eliminates the redundant process of adding anticoagulant as well as the need to neutralize it. The addition of bovine-derived thrombin to promote conversion of fibrinogen to fibrin in PRP is also eliminated. The elimination of these steps considerably reduces biochemical handling of blood as well as risks associated with the use of bovine-derived thrombin.

The platelets and leukocyte cytokines are important biomaterial, and the fibrin matrix supporting them is very helpful in constituting the determining the elements responsible for therapeutic potential of PRF. Cytokines are immediately used and destroyed in a healing wound. There exists a harmony between cytokines and their supporting fibrin matrix.

PRF can be used in conjunction with bone grafts, which offers several advantages including promoting wound healing, bone growth and maturation, graft stabilization, wound sealing and hemostasis, and improving the handling properties of graft materials.

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## REVIEW ARTICLE

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## REVIEW ARTICLE

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