



ISSN Print: 2394-7489  
ISSN Online: 2394-7497  
IJADS 2020; 6(2): 25-29  
© 2020 IJADS  
[www.oraljournal.com](http://www.oraljournal.com)  
Received: 16-02-2020  
Accepted: 20-03-2020

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## Platelet rich fibrin in regenerative endodontics: An update

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### Abstract

Endodontic therapy has enabled the rehabilitation of numerous teeth over the years. The revitalization of the teeth or replacement of the diseased and nonvital pulp with healthy pulp tissue remains as the most desired outcome of endodontic treatment. Regenerative endodontic procedures require the use of appropriate scaffolds to provide a spatially correct position of cell location, regulate differentiation, proliferation, or metabolism of the stem cells. Platelet-rich fibrin is one such scaffold which is currently gaining popularity in the field of regenerative endodontics. To ensure a successful and predictable outcome of regenerative endodontic procedure, it is of vital importance to have thorough and precise knowledge about the scaffolds used. This review provides an insight and an update about the use of platelet-rich fibrin in regenerative endodontic procedures, its benefits and limitations.

**Keywords:** Regenerative endodontics, platelet rich fibrin, revitalization, scaffold

### Introduction

One of the most exciting developments in dentistry today is regeneration, and at the vanguard of this innovative research are endodontists. Regenerative endodontics restores the healthy state of root canals, allowing for the continued development of the root and surrounding tissue by utilising the concept of tissue engineering.

Iwaya *et al.* first used the term “revascularisation”<sup>[1]</sup> However, the term revitalisation replaced revascularisation as a more befitting term since the tissues regenerated in the canal space were not exclusively blood vessels but also hard and soft tissues. The term ‘regenerative endodontics’ was adopted by the American Association of Endodontists in 2007, based on a tissue engineering concept. Regenerative endodontics involves the regeneration of the pulp tissues damaged by infection, trauma or developmental anomalies by utilising the concept of tissue engineering triad, i.e. stem cells, scaffolds and bioactive growth factors<sup>[2]</sup>.

An essential prerequisite for any regenerative treatment is the presence of a scaffold which provides biological and mechanical support to the stem cells. The scaffold forms a three-dimensional replica of the extracellular matrix creating an environment that allows the cells to migrate, proliferate and differentiate<sup>[3]</sup>.

A recent trend in the domain of regenerative endodontics involves the use of autologous platelet concentrates as scaffolds for regeneration which have shown promising clinical and radiographic results<sup>[4-8]</sup>. Platelet-rich plasma (PRP) and platelet rich fibrin (PRF) are two concentrated sources of platelets that are in use currently. Platelets contain a concentrated suspension of growth factors that act as bioactive surgical additives when applied locally to induce wound healing<sup>[9, 10]</sup>.

The first generation of platelet concentrate includes platelet rich plasma which could improve wound healing when there is destruction of parenchymal tissues of the organs. PRP has been utilised as a bioscaffold in RET clinically due to its regenerative potential<sup>[11]</sup>.

Choukroun *et al.* developed PRF, a second-generation platelet concentrate in 2001. PRF has shown considerable advantages over PRP in its application in regenerative endodontics<sup>[10]</sup>.

The following review attempts to highlight the various prospects of PRF and their clinical applications in regenerative endodontics.

### What is PRF?

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate where autologous platelets and leucocytes form a complex fibrin matrix <sup>[10, 12]</sup> which promotes the healing of soft and hard tissue and are in use as tissue-engineering scaffolds for endodontics <sup>[13]</sup>.

### Classification

Platelet-rich fibrin is classified into two types according to the leukocyte content:

1. Pure PRF or leukocyte-poor PRF
2. Leukocyte-rich PRF (also called advanced PRF or Choukroun's PRF) <sup>[12]</sup>

### Preparation of PRF

The preparation of PRF should follow a standardised protocol in order to obtain adequate amount and quality of the fibrin matrix, leukocytes, platelets and growth factors. The technique for preparation of PRF followed today is the one provided by Choukran *et al.* The equipment necessary for PRF preparation includes a PC-02 table centrifuge and blood collection kit containing a 24 gauge butterfly needle and 9ml blood collection tubes. A whole venous blood sample (around 5ml) is withdrawn without anticoagulant in 10-mL tubes and is centrifuged immediately at 3000 rpm for 10 minutes. The centrifugation process causes blood to contact with the test tube wall, leading to activation of platelets and initiation of the coagulation cascade. Centrifugation is done immediately at 3000 rpm for 10 minutes. Within a few minutes most platelets of the blood sample in contact with the tube walls get activated due to the absence of any anticoagulants resulting in the initiation of the coagulation cascade.

The resultant products will consist of three layers:

- **Topmost layer:** Platelet-poor plasma (straw-coloured)
- **Middle layer:** PRF clot
- **Bottom layer:** Red blood cells

The circulating thrombin transforms the fibrinogen which is concentrated initially in the higher part of the tube into fibrin. A fibrin clot is thus formed in the middle of the tube, between the red blood cells at the bottom and acellular plasma at the top. The platelets are trapped in the fibrin clot <sup>[13]</sup>.

It is removed from the test tube using surgical tweezers and separated from the other layers with the help of sterile scissors.

The PRF is then squeezed between sterile gauze pads to obtain a membranous film which can be packed into the root canals with ease <sup>[14]</sup>.

Performing this technique quickly can help in achieving a clinically usable PRF. In the absence of an anticoagulant, the coagulation of the blood samples begins almost immediately upon contact with the glass tube. This PRF preparation technique can fail if the time required to collect and centrifuge the blood is overly long. The polymerisation of the fibrin within the tube can occur diffusely, and only a small blood clot having no consistency can be obtained <sup>[15]</sup>.

### Components of PRF

Platelet-rich fibrin consists of a myriad of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor  $\beta$ 1 (TGF  $\beta$ 1), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), Fibroblast growth factor, exhibiting various potent local properties such as cell migration, attachment, proliferation, differentiation.

The various PRF growth factors play the following roles:

- **Interleukin 1:** Key mediator of inflammation control & stimulates T-helper lymphocytes.
- **Interleukin 6:** Activates B lymphocytes, stimulates secretion of antibodies.
- **Interleukin 4:** Supports proliferation and differentiation of activated B cells, supports healing by moderating inflammation.
- **Tumour necrosis factor-alpha:** Activates monocytes, stimulates remodelling capacities of fibroblasts
- **Cytokine vascular endothelial growth factor:** Promotes angiogenesis
- **Platelet-derived growth factors:** Regulates migration, proliferation and survival of mesenchymal cell lineages.
- **Insulin-like growth factor:** Cell multiplication mediator in apoptosis, exerts chemotactic effects towards human osteoblasts <sup>[16]</sup>.
- **Transforming growth factor  $\beta$ 1:** Stimulates proliferation of fibroblasts and periodontal ligament cells, enhances collagen synthesis.
- **Vascular endothelial growth factor:** maintains the integrity of the endothelial cell lining of the blood vessel and promotes neoangiogenesis during the wound healing.
- **Fibroblast growth factor:** Regulates ectodermal derived cells and shows chemotactic and mitogenic actions on periodontal ligament fibroblast cells <sup>[17]</sup>.

**Table 1:** Comparison of PRF with PRP <sup>[8, 17, 18]</sup>

PRP	PRF
Anticoagulant used- Bovine thrombin and calcium chloride	No anticoagulant
Two spin centrifugation (soft spin done at 1300 rpm for 10 minutes, followed by hard spin, done at 2000 rpm for 10 minutes)	Single centrifugation (centrifuged at 2700-3000 rpm for 12 minutes)
Preparation is labour intensive	Simple and cost-effective
Drastic activation and rapid polymerisation due to the addition of thrombin for the conversion of fibrinogen to fibrin leads to a dense network of monofibers which is deficient in cytokine concentration	Flexible three-dimensional fibrin network which supports cytokine enmeshment and cellular migration due to slow physiological polymerisation.
Slower healing. Shows limited bone and dentine regeneration	Faster and stronger healing kinetics
Inhibits differentiation of BMSC	Shows proliferation and differentiation of BMSCs
Maximum release of morphogens occurs before the actual cell ingrowth, and there are fewer signalling molecules for osteoblasts and odontoblasts from the surrounding tissues	Releases its growth factors steadily with the peak level reaching at 14 days corresponding to the growth pattern of periapical tissues
Fibrin matrix susceptible to washout in the surgical field	Stronger stable fibrin matrix

### PRF in revascularisation

Shivshankar *et al.* conducted a triple-blind randomised clinical trial to evaluate the effect of PRP, PRF and induced bleeding in the revascularisation of teeth with necrotic pulp and an open apex. They concluded that the three groups showed similar root lengthening and lateral wall thickening; however, PRP was better than PRF and induced bleeding technique concerning the periapical wound healing when used in the regenerative endodontic procedures <sup>[19]</sup>. This is in contrast with the study done by Narang *et al.*, in which PRF was referred to have given excellent results on the grounds of periapical healing <sup>[8]</sup>. Shivshakar *et al.* have attributed their

results to the liquid consistency of PRP which could have enabled its unimpeded access to the periapex, unlike PRF, which has a gel-like consistency, thereby delivering the maximum amount of growth factors to hasten the wound healing process.

Nageh *et al.* evaluated the pulp sensibility in mature necrotic teeth using a modified regenerative endodontic procedure by inducing bleeding in root canals and using platelet-rich fibrin (PRF). They found a highly significant difference between the baseline and 12 months follow up period with regards to the tooth sensibility. The nerve regeneration achieved is attributed to PRF being a rich source of various growth factors enrolled in neurogenesis<sup>[20]</sup>.

Bakhtiar *et al.* in a case series performed root canal revascularisation using PRF on four immature teeth with necrotic pulps all of which displayed resolution of the periapical lesions, further root development, and apical closure after 18 months<sup>[21]</sup>.

Similar studies by various authors have displayed the efficacy and successful outcome of treatment while using PRF along with revascularisation<sup>[22-24]</sup>.

The success of these cases can be credited potentially to the use of PRF which causes human dental pulp cell proliferation and increases protein expression of osteoprotegerin (OPG) and alkaline phosphatase (ALP) activity, which are markers of osteoblastic differentiation.<sup>[25]</sup> Some human dental pulp cells in the apical papilla remain vital despite the presence of large periapical lesions. The Hertwig's epithelial root sheath promotes the differentiation of these cells into odontoblast like cells following the regression of the inflammation<sup>[16]</sup>.

Ulusoy *et al.* compared the clinical and radiographic performance of REPs using platelet-rich plasma (PRP), platelet-rich fibrin (PRF), a platelet pellet (PP), and an induced blood clot (BC) and concluded that PRP, PRF, and PP can yield similar clinical and radiographic outcomes to BC without the need for prior apical bleeding and with significantly less tendency for root canal obliteration<sup>[9]</sup>.

According to a retrospective controlled cohort study conducted by Hongbing LV *et al.* tooth revascularisation/revitalisation using PRF as a scaffold achieved similar outcomes to the technique of inducing periapical bleeding concerning the healing of the periapical lesion, continued root formation and resolution of clinical signs and symptoms<sup>[14]</sup>.

A recent approach to improve the prognosis of treatment is to combine the use of PRF as a scaffold along with provocation of periapical bleeding in the treatment protocol. Following the induction of bleeding from the periapical area, the patients centrifuged blood is used to fill the remaining canal space. Various studies have also shown a favourable outcome while using this protocol<sup>[20, 21]</sup>. The reason for this favourable outcome could be a synergistic effect when PRF and blood clot are in use together. The stem cell population in a periapically induced blood clot is higher than that of PRF, which is obtained from the peripheral blood.<sup>[26]</sup> On the other hand, PRF contains a higher concentration of platelets which may continuously release different growth factors, thus aiding in tissue regeneration<sup>[14]</sup>.

Mittal *et al.* compared the regenerative potential of PRF and artificial scaffolds (commercially available collagen, placentex, and chitosan) in necrotic immature permanent teeth. They concluded that PRF and collagen are better scaffolds than placentex and chitosan for inducing apexogenesis in immature necrotic permanent teeth<sup>[27]</sup>.

Miron *et al.* conducted a systematic review in which they

evaluated 7 *in vitro*, 11 *in vivo* and 31 clinical studies. 85.7% of the *in vitro* and 100% of the *in Vivo* studies demonstrated a statistically significant advantage of combining PRF to the regenerative therapies. 27 of the 31 (87%) clinical studies supported the use of PRF for the regeneration of tissues and wound healing for various procedures in medicine and dentistry<sup>[28]</sup>.

### Action of PRF in healing and tissue regeneration

A crucial stage in healing and tissue regeneration is angiogenesis. PRF serves as an essential guide for angiogenesis. The 3-dimensional structure of the fibrin gel and the simultaneous action of cytokines trapped in the meshes explains the angiogenesis property of the fibrin matrix<sup>[29]</sup>.

The fibrin gel also contains key angiogenesis soluble factors such as fibroblast growth factor basic (FGFb), vascular endothelial growth factor (VEGF), angiopoietin and platelet-derived growth factor.<sup>[30]</sup> Thus, the fibrin binding of numerous different growth factors explains the induction of direct fibrin angiogenesis.<sup>[28, 31]</sup> Fibrin also stimulates  $\alpha v \beta 3$  integrin expression by the endothelial cells, which a vital phase in angiogenesis<sup>[29]</sup>.

During hemostasis and healing, the fibrin clot traps the circulating stem cells brought to the injured site due to initial neovascularisation. Within the fibrin matrix, these cells converge on a secretory phenotype which allows the vascular and tissue restoration<sup>[29, 32]</sup>.

### Limitations of PRF

- Can be used only in limited volumes. An autologous blood sample is used to obtain PRF; hence, the quantities produced are low. This fact limits the use of PRF for general surgeries.
- Tissue banks for PRF are unfeasible. PRF membranes are highly specific to the donor and cannot form an allogenic graft tissue.<sup>[15]</sup>
- Cannot be stored as it will result in shrinkage due to dehydration and alteration of the structural integrity as well as decreased growth factor content in PRF.<sup>[33]</sup>

### Leukocyte-Platelet Rich Fibrin

L-PRF is a blood derivative that is obtained by centrifuging the patient's own blood, which contains autologous platelets, growth factors, cytokines, and leukocytes that play a essential role in tissue regeneration, which enables extracellular matrix synthesis, cell proliferation and differentiation, angiogenesis, and occurrence of chemotaxis. L-PRF consists of close combination of cytokines contained in a fibrin network, glucan chains, and structural glycoproteins and is considered as the second generation of platelet concentrates<sup>[34]</sup>.

### Advanced PRF

Choukroun *et al.* produced an improved PRF form which contains greater number of white blood cells and named it advanced platelet-rich fibrin (A-PRF). Leukocytes have been shown to be very important immunocytes capable of directing various cell types in the healing process of the wound. The fact that high centrifugal forces shift cell populations to the bottom of collection tubes, it has recently been assumed that an increase in leukocyte counts in the PRF matrix can be achieved by reducing the centrifugal g-force. Since then, an increment of total leukocyte count has been observed in the PRF matrix constructs (now called advanced PRF or A-PRF) by decreasing centrifugal g-force. Having said that, in

accordance to this hypothesis, the release of several growth factors in A-PRF was found significantly higher compared with L-PRF and PRP<sup>[34]</sup>.

#### Clinical application of PRF in regenerative procedures

- PRF can be used as an apical plug in apexification procedures following trauma or in cases of resorption.
- Pulpal floor perforation.
- As a scaffold for dentin pulp regeneration in immature and mature teeth.

#### Conclusion

This review enlightens the applications and various aspects of PRF in regenerative endodontics.

Although PRF belongs to a new generation of platelet concentrates, it is in the first place a fibrin technology. Indeed, the biologic activity of the fibrin molecule is enough in itself to account for the significant cicatricial capacity of the PRF. And the slow polymerization mode confers to the PRF membrane a particularly favorable physiologic architecture to support the healing process.

Apart from its application in various disciplines of dentistry PRF is also used all over the world in a various medical field as well.

The results obtained from PRF are quite promising but further studies are required to support its use and clinical efficacy and long term stability.

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