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Platelet-rich fibrin: Current trends in periodontal regeneration

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ABSTRACT

Autologous platelet concentrates (APCs) have witnessed a sharp rise in popularity in recent years due to their low cost and ability to promote tissue neoangiogenesis. Platelet-rich fibrin (PRF) is a platelet concentrate (PC) generated from the patient's blood without anticoagulants. PRF is a platelet-based condensation of suspended growth factors. It also has a substantial fibrin network, many leukocytes, cytokines, and glycoproteins and is used for tissue and bone regeneration. PRF plays a substantial role in wound healing. Based on the leucocyte and fibrin concentrations of PCs. Dohan Ehrenfest categorized PCs into four groups. L-PRF was used in the clot formation to fill the defect and in the membrane cover. Since then, studies, technological advances and manufacturing protocols have created newer forms and enhanced their potential as regenerative materials in numerous disciplines. In endosseous and furcation deformities, new APC varieties are being explored as biological mediators of regeneration. A computerized search of the PubMed and Google Scholar databases was performed to select relevant articles from 2006 to 2022. Screening of English language systematic reviews, meta-analyses, original research, and narrative reviews were considered in synthesizing this review. Primary subject headings like PRF, platelet-rich plasma, PCs, growth factors and PRF, periodontal regeneration and PCs were combined using Boolean 'and' with secondary terms like types, preparation, furcation, recession and intrabony defects.

Introduction

Periodontal disease is an inflammatory condition that destroys supporting structures, resulting in tooth loss. Periodontal therapy mainly aims at regenerating lost periodontal tissues. Several autologous and synthetic biomaterials enhance soft tissue and bone restoration. Autologous biomaterials occurring naturally [such as autologous platelet concentrates (PC)] refer to those present within the body and act as messengers for repair, regeneration, and healing (1). Synthetic biomaterials (alloplastic) possess a few disadvantages, such as foreign body reaction and avascularity (1-3).

Platelets and fibrin are two well-known autologous biomaterials that promote wound healing and regeneration. Research has been conducted in various fields to develop blood-derived products like PCs. Due to its excellent regeneration characteristics, platelet-rich fibrin (PRF) has demonstrated promising outcomes. This review describes the history, features, and current concepts regarding the function of PRF regeneration of the periodontium.

Methods

A computerized search of the PubMed and Google Scholar databases was performed to select relevant articles from 2006

to 2022. Screening of English language systematic reviews, meta-analyses, original research, and narrative reviews were considered in synthesizing this review. Primary subject headings like PRF, platelet-rich plasma (PRP), PCs, growth factors and PRF, periodontal regeneration and PCs were combined using Boolean 'and' with secondary terms like types, preparation, furcation, recession and intrabony defects (IBDs).

Historical background-from fibrin glue to PCs

Due to its known properties of wound healing and regeneration, blood-derived products have been widely used in the medical field for the past 40 years (1,4). The use of fibrin glue and sealants for topical hemostasis, soft tissue healing, and as melting agents for synthetic bone substitutes grew in the 1970s (3). It was created by combining donor plasma fibrinogen, factor XIII, and fibronectin with thrombin and calcium, which causes fibrinogen to polymerize (1,3). However, there were several drawbacks such as the suboptimal stability of fibrin glue due to low concentration of fibrinogen, low resistance to physical stress, expensive processing and more importantly the risk of cross-infection and viral transmissions (5). Since these products were made from human blood in blood banks, some countries had legally restricted their use due to the risk of contamination (6). Hence, many experiments using patient blood were conducted to test various methods to obtain autologous fibrin glues.

Hematology is where the concept of PCs initially emerged (1). It is an evolution of fibrin glue technology (6). In its initial stages, PCs were used to treat patients with severe thrombocytopenia to prevent hemorrhage (7). However, its usage spread to the areas of regeneration and wound healing. The multiple functions of platelets and the widespread availability of numerous growth factors and cytokines help in regeneration. Platelets produce fibrin, fibronectin, and vitronectin which provide the matrix for connective tissue and cell migration (2).

Ross et al. (3) described platelet regeneration capacity in early 1974. First-generation PC, PRP, was used in oral and maxillofacial surgery by Whitman, Berry, and Green (1997) (8) and Marx and associates (1998) (9). Combining the properties of growth factors generated by platelets and the characteristics of fibrin glue results in enhanced healing and regeneration effects of PRP (7). Due to the availability of several different systems for procuring PRP, a uniform protocol for PRP preparation needs to be revised. However, in most techniques, the patient's blood is mixed with an anticoagulant before being centrifuged to separate the blood into layers based on weight, including red blood cells (RBCs), leukocytes, platelets, and plasma (6,7). After its procurement, the stability of PRP is maintained for 8 hours, which eradicates its potential to transmit diseases or cause immunogenic reactions. Platelets start releasing growth factors within the first 10 min of PRP activation. Hence, PRP should be administered during the first ten minutes of its activation since 95% of growth factor release occurs within one hour (10). There are several drawbacks of PRP, depending on several variables, namely PC, leukocyte count, activator type, and time of fibrin scaffold placement after clotting; the characteristics of PRP can vary (1). Also, the poor handling properties due to its liquid nature, lack of uniformity in preparation protocol, and brief release of growth factors limit the clinical advantages (1). Incorporating bovine thrombin in PRP can cause the coagulation factors V, XI, and thrombin to be the target of antibodies, showing a negative impact on the coagulation process (2). Also, there are legal restrictions on handling blood, thereby paving the way for PRF (1,2).

Given the drawbacks mentioned above, Choukroun et al. (11) developed PRF in France, a second-generation PC rich in leucocytes and platelets in a fibrin network (also referred to as Choukroun's PRF). PRF is a robust regenerative biomaterial that was found to accelerate tissue healing and hence has several applications in periodontics (11).

Platelet concentrate classification

1. PCs were categorized into the following groups by Dohan et al. (5) in 2009 based on the leukocyte content and fibrin structures (Figure 1) (10,12).
2. The PAW (platelet activation, white blood cells) categorization system established by De Long et al. (13) was based on the activation method, white blood cell and neutrophil content, and platelet number.
3. Mishra et al. (14) proposed another classification, confined to PRP and applicable only to sports medicine centered on the presence or absence of leukocytes. Four different forms of PRP were identified to determine whether PRP

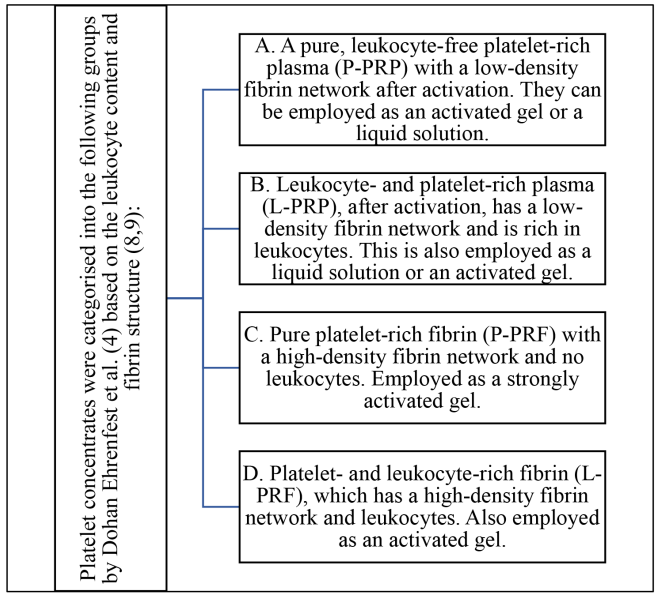


Figure 1. Platelet concentrate classification
PRP: Platelet-rich plasma, PRF: Platelet-rich fibrin

is activated. In addition, other classifications are proposed by various authors (15-18). However, no agreement on classification systems has yet been reached.

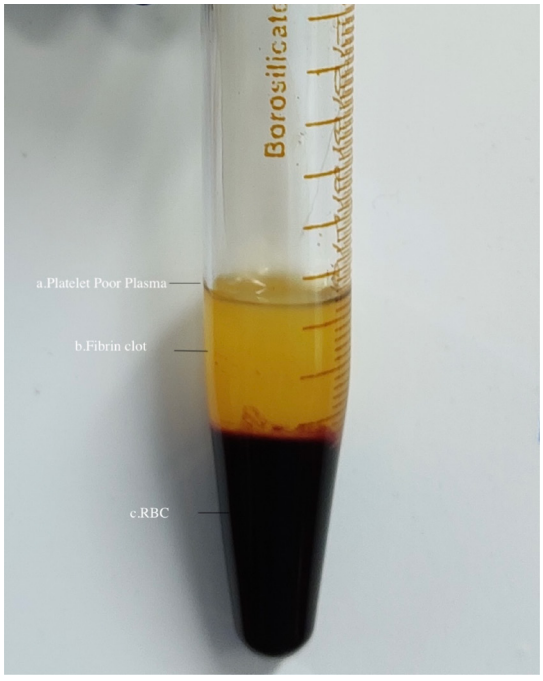
Preparation of PRF

Unlike PRP, no anticoagulant is used; therefore, there is no need for animal thrombin or calcium for fibrin polymerization. A PC-02 table centrifuge and a blood collection kit with a 24 gauge butterfly needle and 10 mL blood collection tubes are necessary to prepare PRF.

Protocol

5 mL of venous blood in each sterile tube was collected. It was centrifuged for 10 minutes at 3000 rpm (19). After the process, the whole blood is divided into three layers (12): a layer of platelet-poor plasma (PPP) on top, a fibrin clot with platelets and leukocytes in the middle (L-PRF) and RBCs at the bottom of the tube (Picture 1).

Plastic tubes were coated with silica and silicon to activate the coagulation process. Without anticoagulants, the platelets in contact with the inner walls become activated, progressively activating the coagulation cascade. In the beginning, fibrinogen exists at the top portion of the tube. Later, following centrifugation, thrombin is activated and converted to fibrin, forming a fibrin clot. The speed of blood collection and transfer to the centrifuge is crucial to the success of this procedure (19). The adhering RBCs were scraped off the fibrin clot obtained after centrifugation and discarded. By pressing out the fluids in the fibrin clot, L-PRF can also be transformed into the shape of a membrane.



Picture 1. Blood layers after centrifugation. a) Platelet-poor plasma. b) Fibrin clot. c) Red blood cells

PRF techniques/protocols and types

With the advance in research, several modifications in the preparation protocol of PRF were devised to enhance its wound healing and regeneration potential (Figure 2).

Periodontal regeneration with PRF

PRF is a platelet-based consolidation of suspended growth factors. It also has a substantial fibrin network, abundant leukocytes, cytokines, glycoproteins, and several other components. The platelets contain granules that release cytokines and other factors such as serotonin, von Willebrand factor, factor V, osteonectin, and antimicrobial proteins; they cause homeostasis and enhance the clearance of pathogens. Leukocytes in PRF function in wound healing and regeneration. They also have anti-inflammatory, anti-nociceptive (20,21) and cell proliferation differentiation properties (12). PRF contains abundant growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), fibroblast growth factor, and vascular endothelial growth factor (VEGF). VEGF is involved in various functions like osteoblast proliferation, collagen production, and angiogenesis. The Fibrin matrix promotes the invasion of various inflammatory, endothelial, and other cells. This matrix can also capture glycosaminoglycans enhancing cell migration and healing (12). They also contain stem cells, such as human bone mesenchymal stem cells that are stimulated when they come into contact with L-PRF (5,12).

In contrast to PRP, which has a rigid network, PRF has a thin, elastic fibrin network that promotes improved cytokine entrapment and cellular motility (2). The PRF matrix contains glycosaminoglycans like hyaluronic acid and heparin, which has a strong affinity for small peptides like cytokines, promoting cell migration and enhancing healing (5). PRF also promoted micro vascularization and increased cell migration (2). Furthermore, due to a natural fibrin network, there is no proteolysis of growth factors. All these properties make PRF a better healing biomaterial.

Hence, abundant growth factors in PRF have indicated its use in various regenerative and wound-healing procedures. The fundamental goal of periodontal therapy is to regenerate lost periodontal structures to restore health, function, and esthetics. As a result, the use of PRF in treating soft tissue healing, gingival recessions, IBDs, and furcation defects has gained popularity in periodontics. Also, the benefits are abundant, such as a simple process of preparation application and a cost-effective method. There is no addition of bovine thrombin and anticoagulants, and the PRF membrane is elastic and flexible owing to its three-dimensional structure, enhancing cellular migration and proliferation. PRF has certain demerits; since autologous blood is used, it is a challenge to get more significant amounts. Hence, its utility in general surgery is limited. The period between

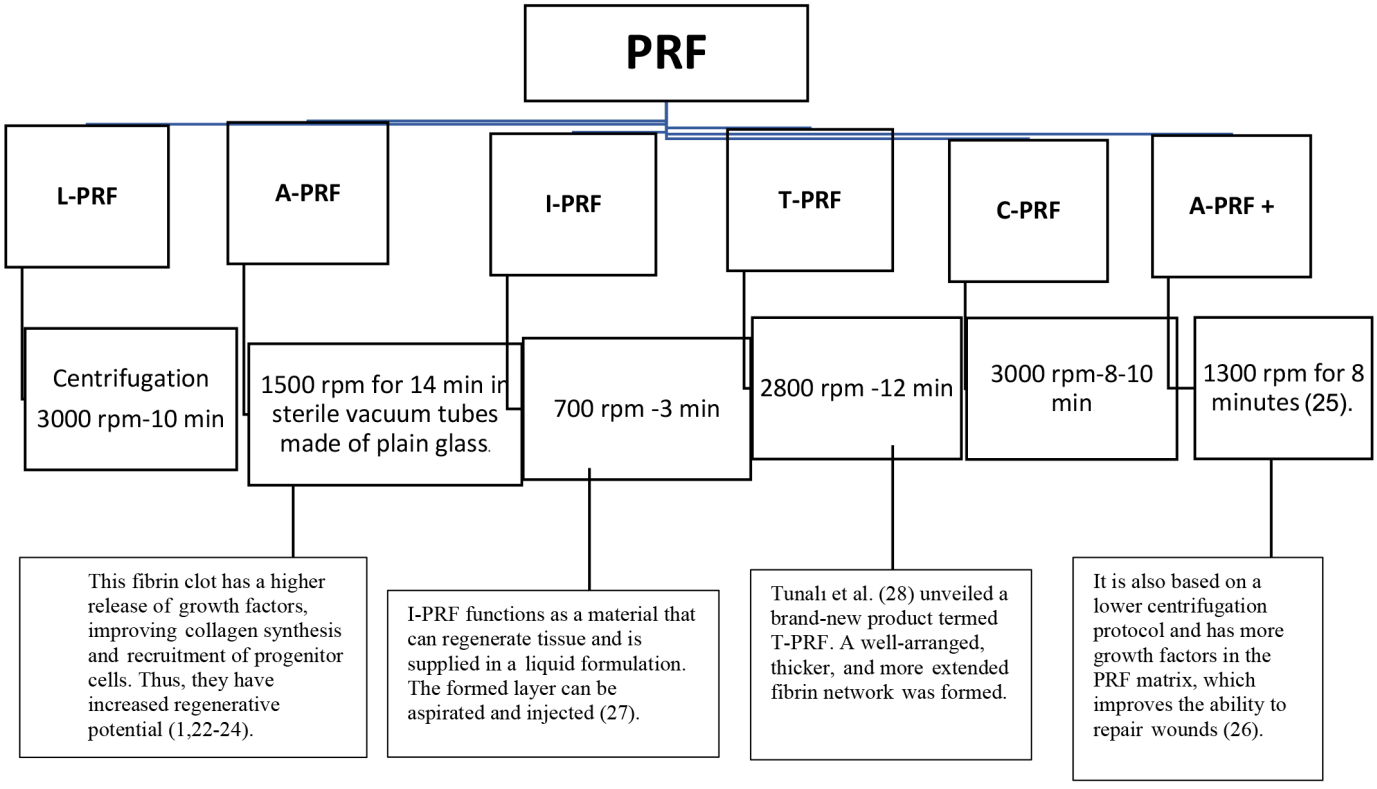


Figure 2. PRF techniques/protocols and types
PRF: Platelet-rich fibrin

blood collection and centrifugation impacts the success of the procedure. It is donor-specific since it comprises immune cells and highly antigenic components. If not used immediately, the PRF membrane shrinks, resulting in the loss of structural integrity and leukocyte viability. Also, there is a risk of bacterial contamination when stored.

The role of PRF in the regeneration of IBD

It has been demonstrated that PRF enhances bone-forming cell proliferation, differentiation, migration, and mineralization during bone formation. Several mechanisms have been suggested for bone formation through the use of PRF. The macrophages in PRF can directly promote osteogenesis. It encourages the propagation of growth factors, periodontal ligament cells, and osteoblasts, inducing osteoprotegerin production and proliferation of osteoblasts. After activation, platelets and leukocytes release cytokines that promote bone regeneration. Also, the TGF-β1, present in PRF stimulates collagen and fibronectin synthesis, promoting bone regeneration. VEGF promotes angiogenesis, which is required for skeletal development. PDGFs and IGF-1 promote osteoblast proliferation and differentiation (29).

Recently, the application of PRF for treating IBD was compared to other available modalities in a recent systematic review by Miron et al. (30). They obtained comparable outcomes using open flap debridement (OFD)/PRF and OFD/bone grafts (BG). Chen et al. (31) conveyed that the benefits of OFD+PRF are more significant than that of BG+PRF, considering radiographic bone fill and depth reduction as the primary outcomes.

The role of PRF in recession coverage (RC)

There is improved soft tissue healing because PRF membranes gradually and continuously release growth factors like VEGF, encouraging angiogenesis and accelerating tissue repair and regeneration by cell migration and repopulation in the injured site (32). When PRF was used with a coronally advanced flap for RC procedures, there was a decrease in matrix metalloproteinase-8 and interleukin beta levels but an increase in tissue inhibitors of metalloproteinase-1 levels at ten days. As a result, the initial stages of the process result in increased periodontal wound healing (33).

According to a few studies, PRF significantly enhances patient-reported outcome measures, such as postoperative pain observation and discomfort (34,35). The use of PRF was not superior to alternative treatments for Miller Class I and II gingival recessions, according to a systematic review by Moraschini and Barboza Edos (36) regarding root coverage, keratinized mucosa width, or clinical attachment level.

The role of PRF in furcation defects

Because of the furcation location and the roots' uneven morphology, the biofilm is very challenging to access for oral hygiene procedures. Along with other well-known patient-related factors, including age, gender, smoking habit, and diabetes, the degree of furcation involvement is a risk factor for tooth loss. Several reconstructive periodontal surgical procedures and materials are used to treat these areas. Regenerative treatments are aimed at bone, cementum, and periodontal ligament regeneration in the furcation. When PRF is used, the growth factors stored in the granules are activated and released, aiding in bone regeneration (37). A systematic review and meta-analysis by Pepelassi and Deligianni (38) L-PRF demonstrated a significant clinical and radiographic additive effectiveness of OFD and osseous graft in teeth with furcation involvement. Also, in two- or three-walled periodontal endosseous defects in systemically healthy non-smokers, compared to those without L-PRF (38). PRF demonstrated better results than OFD alone in furcation treatment; however, it has fewer advantages as an adjunct to osseous graft. There is scarce literature available for any definitive conclusion regarding the combined effect of osseous graft and PRF. Also, the furcation defect studied was either maxillary or mandibular furcation with the variability of bone architecture and complexity of the furcation access.

Other uses of PRF

PRF has several other applications in other procedures, such as socket preservation - The regenerative potential in socket preservation and following the tooth extraction is beneficial. However, more evidence is required to confirm its effectiveness (39). In implant dentistry - PRF addition to the implant surface has been shown to increase the bone-implant contact and enhance bone regeneration to enhance healing, osseointegration, and thereby the stability of implants. This could reduce the treatment time interval between implant placement and loading.

Furthermore, it improves soft tissue thickness to increase stability and minimize marginal bone loss and mucogingival surgery (40). PRF in the form of a membrane is beneficial in the palatal donor sites while harvesting free gingival grafts. The growth factors in PRF positively influence angiogenesis, cellular proliferation, and mitogenesis of wound-healing cells at the surgical site, thereby promoting fast healing (41).

Recent advances

Albumin gel platelet-rich fibrin

One of the significant challenges faced with PRF was its 10-14 days period of resorption *in vivo*. To overcome this drawback, Kawase et al. (42) introduced a heat compression technique for PRF membranes used for guided tissue regeneration. However, this leads to a poor regeneration capacity as no cells or growth factors can withstand denaturation. Hence, a new technique was developed that reintroduces the platelet-rich layer from the buffy coat into heated PPP (albumin gel) after cooling (43).

Albumin gel platelet-rich fibrin (Alb-PRF) enhanced cell migration and proliferation, biocompatibility, the release of seven key growth factors, and collagen synthesis. Centrifugation was done in plastic tubes at 700 g for 8 min. The process involved in producing the albumin gel comprised collecting the PPP layer and subjecting it to a 10-minute heating at a temperature of 75 degrees Celsius. This was allowed to cool down for 10 min at room temperature. The PRF's higher cell and growth factor content and albumin gel's low resorption properties are combined in this procedure (44).

BIO-PRF (horizontal centrifugation protocol) / C-PRF

Liquid PRF tubes were used in the Bio-PRF horizontal centrifuge to create C-PRF. 3000×g centrifugation protocol (C-PRF protocol) for 5-8 minutes. The following benefits are observed using horizontal centrifugation;

A) It enables an improved cellular separation by allowing cells to travel easily throughout the blood layers. Compared to traditional approaches, there is a considerable increase in leukocyte and PC.

B) It is known as a "gentle centrifugation" because the cells along the back wall of centrifugation tubes sustain less damage when low forces are used to manufacture it (45).

Conclusion

For periodontal regenerative procedures, a range of surgical techniques, biomaterials, and BGs have been employed individually and in combination. PRF derived from autologous blood acts as a scaffold containing growth factors and living cells that potentiate wound healing and tissue regeneration. With its low cost, ease of preparation, and handling, PRF and its variants have emerged as potential regenerative materials with various applications in periodontics and other disciplines.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.S.J., N.S., Design: D.S.J., N.S., Data Collection or Processing: D.S.J., N.S., Literature Search: D.S.J., N.S., Writing: D.S.J., N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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