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ROLE OF PLATELET-RICH FIBRIN IN PERIODONTAL REGENERATION

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ABSTRACT

Platelet-rich fibrin (PRF) 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 biochemical modifications. The PRF clot forms a strong natural fibrin matrix, which concentrates almost all the platelets and growth factors of the blood harvest Platelet rich fibrin (PRF) is believed to be a natural alternative with accepted results and minimal risks. PRF has a lot of advantages and indications, because of its minimally invasive technique with low risks and favorable clinical results. PRF can be used as a resorbable membrane because it is a fibrin matrix in which platelet cytokines, growth factors, and cells are trapped and may be released after a certain time. Autologous PRF is a healing biomaterial, and applied in various disciplines of dentistry. The following review attempts to summarize the relevant literature regarding the technique of using PRF, including its preparation, advantages, and disadvantages of using it in clinical applications.

Keywords: Periodontal regeneration, Platelets, Growth factors

INTRODUCTION

Periodontal disease is a complex, multifactorial disease characterized by the loss of connective tissue attachment with destruction of periodontal tissues. The main goal of periodontal treatment is to stop the inflammatory process, prevent its progression and to regenerate the lost periodontal tissues. Periodontal regeneration is involving biologic sequela like cell adhesion, migration, proliferation, and differentiation in an organized sequence [1]. This procedures include soft and hard tissue grafts, root biomodifications, guided tissue regeneration [2]. In fact, the regenerative periodontal therapies have a limited periodontal restoration [3]. The healing of periodontal tissue include interactions between epithelial, fibroblasts, osteoblasts cells, periodontal ligament cells. The end result is fibrin formation, platelet aggregation, and release of several growth factors into tissues from platelets [4]. In fact, cytokines and growth factors in platelets are responsible for inflammation which resulted in wound healing [5]. Fibrin, fibronectin and vitronectin are secreted by platelets and act as a matrix for the adhesion molecules and connective tissue. [6]. To

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promote periodontal tissue repair, platelets can be used to aid in regeneration. PRF are used to promote the speed of periodontal healing via regulation the inflammatory process [2]. It is known that platelets play an important role in hemostasis.

Choukroun et al in 2000 was the first who used PRF [7]. It 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 any artificial biochemical modifications. It can be used in oral and maxillofacial surgery, and is considered as a new generation of platelet concentrate. It consists of a matrix of autologous fibrin [3] and has many advantages over platelets rich plasma (PRP), which include easy in preparation and no need for chemical addition to the blood, which makes it entirely autologous preparation [8]. Several studies show rapid wound healing with the use of it [9,10]. It does not need second surgical site and procedure as in case of autogenous graft. Its complexity in preparation and risk of cross-infection make their use is still confused. In addition, concentrated platelet-rich plasma (cPRP) was prepared with a less complex production protocol. Healing is a complicated process involving cellular organization, chemical signals, and the extracellular matrix for tissue repair [11]. Platelets' regenerative concept was introduced in the 70's [12], they contain growth factors which increase collagen production, cell mitosis, blood vessels growth, recruitment of other cells that migrate to the site of injury, and cell differentiation induction [8]. **Whitman et al in 1997** [13], were a pioneer to introduce the use of platelet-rich plasma in oral surgical procedures, proving great advantages because it increases osteoprogenitor cells in both the host bone and bone graft. However, using it also presents risk because bovine thrombin, which is used to handle PRP, may generate antibodies to factors V, XI, and thrombin that could cause coagulopathies that may affect its efficacy [8]. Formation of platelet concentrates lead to the formation of fibrin adhesive-concentrated platelet-rich plasma (cPRP); because of legal restrictions on blood handling procedures, another family of platelet concentrate was introduced in France-platelet-rich fibrin (PRF) [14]. PRF prolongs the physiologic wound healing. This results in a condensed mesh of fibrin that is saturated with cytokines, growth factors in a ratio of 1 to 4. PRF increases the healing process and optimizes bone grafting results [15,16]. It can result in the regeneration of bone and can be used in conjunction with either a bone substitute or alone [17-19]. The PRF was produced by centrifuging a patient's blood for 10 minutes without the addition of an anticoagulant. Because of the centrifuge process, blood coagulation occurs and separates into three distinct layers. The bottom layer is a red blood cell (RBC) layer that is removed while the top layer is a cell free layer that is also unused. The middle layer is a mesh network which contains most of the platelets and fibrin. [6] Once separated from the clot, the PRF is ready to be used. This layer can be shaped into a plug and compressed into a membrane or depending on what treatment is needed. [Fig 1].

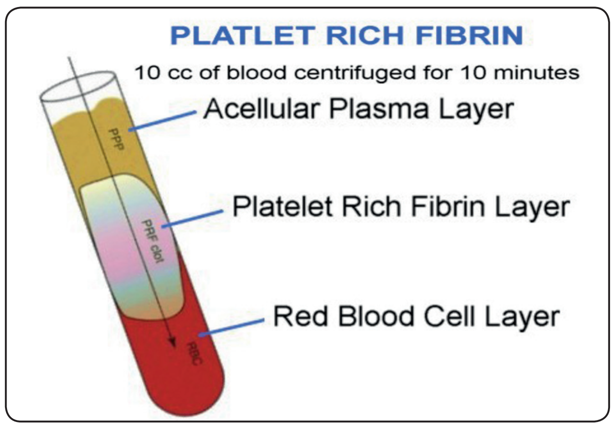

Fig. (1) Test tube showing platelet-rich fibrin after centrifugation

Classification of platelet concentrates

According to **Ehrenfest et al. 2010,** the current classification (2009), platelet concentrates classified into 4 groups based on the presence of leucocytes and fibrin architecture [20]:

a) Pure PRP/Leucocyte-poor PRP: Absence of Leucocytes and low density of fibrin network.

b) Leucocyte and platelet-rich plasma: Presence of Leucocytes and low-density fibrin network.

c) Pure platelet-rich fibrin PPRF/Leucocyte-poor PRF: Without leucocytes but with high-density fibrin network.

d) Leucocyte and Platelet-Rich Fibrin: With leucocytes but with high-density fibrin network.

Architecture and composition of the PRF membrane

Fibronectin and Vitronectin are key proteins that play a strategic role in the adhesion and migration of the platelets. The firmness of fibrin clot results from the slow release of the fibronectin over a period of seven days. On the other hand, vitronectin is released from the PRF membrane only during the first four hours. Although platelet growth factors play an important role in the biology and functioning of PRF, the fibrin architecture and leukocyte content are two key parameters that have not been considered in detail [21]. PRB and PRF are mainly derived from platelet [Table 1].

TABLE (1) Comparison of platelet Concentrates

Sample	Red Blood Cell (RBC) (%)	Platelet (%)	White blood Cells (%)
Blood Clot	95	5	1
Platelet Rich Plasma (PRP)	4	95	1
Platelet Rich Fibrin (PRF)	2	97	1

PRF and Periodontal Regeneration

The main goal of periodontal treatment is to stop and control the periodontal infection and to regenerate all tissues of the periodontium (Periodontal ligament, Bone, Cementum, and Connective tissue) [22]. In fact, growth factors are used recently in the promotion of periodontal regeneration and healing, growth factors include Platelet Derived Growth factor (PDGF) as one of the important factors [Table 2] . The use of PRF in the management of intrabony defects has shown significant results when compared with open flap debridement alone[23-25].

TABLE (2) The main growth factors

Growth factors	Source	Action
Insulin Growth factor (IGF)	Osteoblast, Macrophages	Regulate cell growth Enhances healing
Platelet Derived Growth factor (PDGF)	Platelets, Macrophages	Stimulates angiogenesis Stimulate proliferation of mesenchymal stem cells
Epidermal growth factor (EGF)	Platelets	Stimulates angiogenesis Stimulate proliferation of myoblasts
Transforming growth factor (TGF)	Platelets, Lymphocytes	Proliferation of osteoblasts Stimulates angiogenesis
Keratinocyte growth factor (KGF)	Platelets	Growth of Keratinocytes
Basic fibroblast growth factor (bFGF)	Platelets	Stimulates angiogenesis Stimulate proliferation of myoblasts
Vascular Endothelial growth factor (VEGF)	Endothelial cells	Initiates angiogenesis

Yu-Chao **et al in 2011** reported that the use of PRF as a grafting material seems to be an effective for regenerative treatment for periodontal intrabony defects [26]. **Thorat et al in 2011** showed a significant reduction in probing depth and clinical attachment level gain when comparing the clinical and radiological effectiveness of autologous PRF gel in the treatment of intra-bony defects of chronic periodontitis patients with conventional periodontal flap surgery alone when compared with baseline and 9 months [10]. However, there was more probing depth reduction (4.56 ± 0.37) and gain of clinical attachment (3.69 ± 0.44) in the PRF treated group. The percentage of intra bony defect fill in the PRF group (46.92%) was higher than the conventionally treated subjects (28.66%); suggesting that the various growth factors present in the PRF may increase regeneration [23]. **Panda et al in 2016** reported that PRF can be used effectively alone as a regenerative material, in conjunction with open flap surgery [25]. **Lekovic** et al in 2012. showed that treatment of intra-bony defects with PRF results in significant improvements of pocket depth, clinical attachment level and defect fill compared with conventional treatment [23]. PRF has great potential for surgical wound healing and can be used in surgical treatment of intra-bony defects. In fact, we need more studies to assess the histology of the regenerated tissue while using PRF.

PRF and Regeneration of Peri-Implant Bone Defects

Platelet concentrates may help for the regeneration of peri-implant bone defects and they may improve osseointegration[27]. Three specific situations can be encountered, the first situation concerns the peri-implantitis also called de-osseointegration, the second are discovered during implant placement, when there is inadequate bone for implantation [27]. The last situation of peri-implant bone defects can be encountered during an immediate post-avulsion or post-extraction implantation procedure [28]. **Lee et al** in 2012 reported that, in animal model, that peri-implant defect sized 3.0 × 5.0 mm (width × length) was successfully repaired by the application of PRF alone in the bony defect [29]. Only limited in vivo studies have been carried out on the effects of PRF on regeneration of peri-implant bone defects. There is a need for further studies to evaluate the effect of PRF applied for use in bone defects in humans.

PRF and Gingival Recession

Kumar et al in 2013 reported that the autogenous platelet concentrates graft (PCG) or subepithelial connective tissue graft (SCTG), covered by a coronally positioned flap, were effective in the treatment of shallow gingival recession defects (≥ 2mm) with significant root coverage (87% and 80% for SCTG and PCG, respectively) at 12 months postoperatively [30].

In fact, the root coverage procedures aimed to improve esthetics, minimize hypersensitivity. Coronally positioned flap, with subepithelial connective tissue is the most effective plastic procedure. **Aroca** et al in 2009 reported that PRF membrane increased gain in width of keratinized gingiva at the test sites at 6 months compared to the modified coronally advanced flap alone [31]. Recently, to improve the efficiency of the root coverage treatments and reduce the morbidity of the techniques (second surgical donor site…), various alternative subistitutes are used such as the PRF. **Jankovic et al in 2012** proved that, the use of PRF membrane in gingival recession treatment provided acceptable clinical results at 6 months compared to connective tissue graft (CTG) treated gingival recessions [32]. No difference could be found between PRF and CTG procedures in gingival recession's therapy, except for greater gain in keratinized tissue [32].

The advantages of PRF membrane as graft material are related to the absence of a donor site surgical procedure and minimum patient discomfort during the early wound healing period. Further studies are necessary to assess the histology of the regenerated tissue [30] .PRF have some degree of advantages and disadvantages (table 3)

In summery PRF is a complicated compound of strong fibrin matrix as a bridgeable membrane with growth factors released after at least 1 week [33]. In addition, PRF can considered as a reservoir of many growth factors that play a major role in periodontal repair processes. It was reported that PRF retards epithelial cell proliferation in vitro, but has a strong positive effect on the proliferation of gingival fibroblasts, periodontal ligament fibroblasts, and osteoblasts[34]. In addition, PRF suggests the pivots for new periodontal attachment formation through activation of phosphorylated extracellular signal regulated protein kinase, osteoprotegerin and

TABLE (3) Advantages and disadvantages of PRF.

Advantages	Disadvantages
No biochemical handling of blood	Insufficient autologous blood
Simple	Need immediate handling
Less coast	
Anticoagulants not required	
Bovine thrombin not required	
Slow polymerization resulting in favorable healing	
Immune system supported by PRF	
PRF promotes hemostasis	

alkaline phosphatase[35]. Moreover, PRF showed antimicrobial effects[36]. These regenerative potential and antibacterial effects of PRF may be effective in periodontal surgery. It was reported that, PRF can be used alone as grafting material for periodontal regenerative therapy. At 6 months after surgery, the outcomes showed a probing depth and clinical attachment gain in the periodontal osseous defects and radiographic density increase[37]. A study by **Chang in 2011** for the application of PRF with synthetic bone graft for periodontal infrabony defects reported that, there is clinical attachment gain and pocket reduction with minor gingival recession. There was more dense bone formation in the grafted teeth after 1 year of follow-up. Application of PRF in combination with synthetic bone graft was first used for the treatment of perioeendo combined intrabony defect with the achievement of probing depth reduction, clinical attachment gain, increase of gingival thickness, and increase of periapical bone density over a 6-month period [38]. **Uraz et al in 2015**, reported that PRF allowed treatment of gingival recession with adequate wound healing, highly root coverage, in conjunction with more gingival tissue thickness [39]. Recently, it was demonstrated that, the beneficial effect of PRF in intrabony defects, furcation invasion, and periodontal plastic surgery [40].

CONCLUSION

Management of periodontal defects has a wide variety and new techniques are developed. Current therapeutic techniques can promote the stimulation of tissue formation after dental surgical procedures. The use of PRF stimulates the bone regeneration; increasing the volume of the bone and the overlying gingival tissue. PRF when used in conjunction with many dental procedures provides favorable results. Autogenous PRF can decrease or eliminate the risk of disease transmission. In vitro and in vivo studies have demonstrated safe and favorable effects on hard and soft tissue healing in periodontal surgery. Current evidence based dentistry shows that PRF can be routinely used in periodontal regenerative surgery, with good biological effects and satisfactory clinical results under correct manipulation.

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