Review Article

Contemporary Platelet Concentrates in Periodontics

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Abstract

Platelets are natural reservoirs of growth factors and cytokines that play a critical role, in the formation, maturation, and repair of soft and hard tissues. Platelet concentrates (PCs) are derived from centrifuged blood and are named according to their biological characteristics, such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor. They have come a long way from fibrin adhesives to new generation PRF'S. PRP is a PCs that have been used widely to accelerate soft-tissue and hard-tissue healing. PRF belongs to a new generation of PCs geared to simplified preparation without biochemical blood handling. PCs have become popular in dentistry as a regenerative therapy since they are autologous in origin, and they deliver a high concentration of platelets, growth factors, and leukocytes. At present, PC is widely used for sinus floor elevation, alveolar ridge preservation, periodontal bone defects, guided bone regeneration, and treatment of gingival recessions.

Keywords: Gingival recession, Growth factors, Platelet concentrates, Platelet-rich plasma, Platelet-rich fibrin, Regeneration.

Introduction

One pivotal discovery that has fueled the quest in regenerative science and tissue engineering has been the role that growth factors play in the process of tissue repair and formation.[1] Multifaceted and newly emerging local delivery of growth factor to the periodontium is much closer and readily available therapeutic measure for clinical purposes than the cell transplantation or gene therapy. It has the capability to become a dynamic tool subsequently for regenerative periodontal medicine.[2] A broad range of vehicles are being explored and implied to deliver the growth factors efficiently and perform their intended function.[2] However, majority of the vehicles are not commercially available and are not widely used for patients due to several drawbacks like loss of bioactivity, limited control overdose administration, non-targeted delivery, and/or lack of availability.[3]

Platelets contain numerous growth factors such as TGF-b, vascular endothelial growth factors (VEGF), and platelet-derived growth factor (PDGF) that play crucial role in tissue healing. Platelet concentrates (PCs) are often used for different surgical therapies in medical and dental fields to enhance bone and soft-tissue healing by placing supraphysiological concentrations of autologous platelets at the site of tissue damage.[3] The objective of all these technologies is to extract all the elements from a blood sample that could be used to improve healing and promote tissue regeneration. PC has evolved from its initial application of fibrin glue to recent proposals like third-generation platelet-rich fibrin (PRF's), Alb-PRF, and Bio-PRF. All PC have countless applications favorably in periodontics and implantology. Nevertheless, the method of preparation, standing time, transfer process, and other variables such as G-force and temperature of centrifuge are the different characteristics for the diverse results that are being reported in clinical research.[4]

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Advancements in PCs (Table 1)

PC's has evolved from using the fibrinogen as a native surgical adhesive and hemostatic agent in the 19th century to the contemporary PCs that play a crucial role in the wound healing and regeneration.[5]

Platelets and their Growth Factors[6-8]

Platelets are cytoplasmic fragments of megakaryocytes formed in the marrow and are round or oval, approximately 2 μm in diameter. Platelets contain high quantities of key growth

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factors which are involved in cell proliferation and matrix remodeling. Sequestered platelets contain different growth factors (Figure 1) in their alpha granules. Apart from platelets, the growth factors are even released from numerous cells such as macrophages, smooth muscle cells, fibroblasts, monocytes, endothelial cells, and other immune cells to act upon their respective target sites to perform actions.

Table 1: PCs Advancements

Year	Events
1954	Term PRP is given by KINGSLEY
1970	FIBRIN GLUE was introduced by MATRAS
1979	Gelatin platelet – gel foam
1986	Knighton *et al*. – platelet-derived wound healing factors (PDWHF)
1988, 1990	Kingsley *et al*. and Knighton *et al*. – platelet-derived wound healing formula (PDWHF)
1997	Whitman *et al*. termed fibrin gel as platelet gel
1998	Marx *et al*. – PRP
2000	Choukroun *et al*. – based on the strong fibrin gel polymerization-labeled it as PRF
2006	Sacco introduced a new concept of CGF
2006, 2008	Everts has given, platelet-leucocyte-gel
2009	Dohan *et al*. proposed the classification of platelet concentrates
2010	Sohn introduced the concept of sticky bone
2012	Mishra *et al*. proposed a new classification of platelet concentrates
2012	Tunali *et al*. introduced T-PRF
2014	Choukroun introduced an advanced PRF (A-PRF)
2015	Mourao *et al*. described the preparation of I-PRF
2019	Bio-prf
2020	Alb-prf

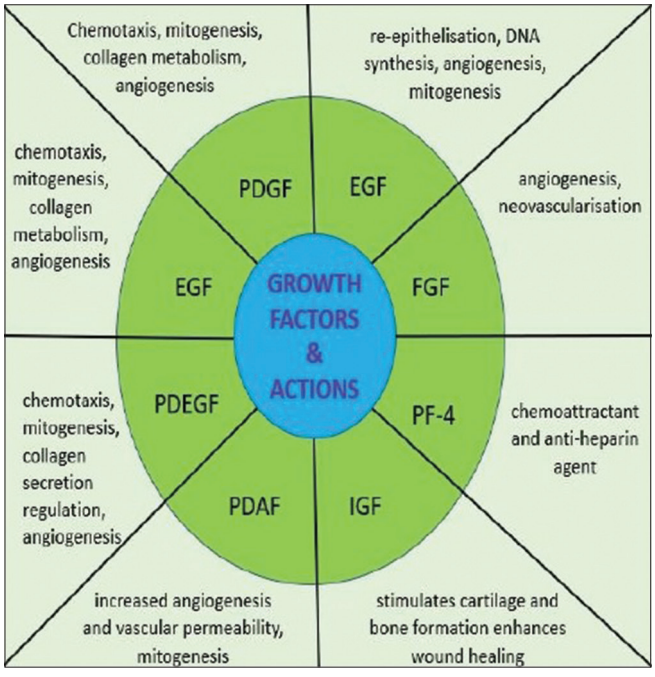

Figure 1: Growth factors and their actions

Beside growth factors platelets also possess proteins such as fibronectin, osteocalcin, thrombospondins, fibrin, and other cellular components.

Classification of PCs[9-11]

The advances of PCs are often termed under the wordplay between platelet-rich plasma (PRP) as first-generation PC and PRF as second-generation PC. The antiquity of these products was always linked with perplexity, mostly related to the lack of consistent terminology, characterization, and classification of the PCs that were in the trail for the past few decades.[12] Different techniques (Table 2) fabricate divergent PCs with distinct biological capabilities and uses. For coherent clinical understanding, Ehrenfest *et al*.[9-11] have classified PCs into four major categories:

I. Pure PRP
II. Leucocyte-rich PRP
III. Pure PRF
IV. Leucocyte-rich PRF (L-PRF).[13]

Recently, many next generations and membranes were introduced which has many advantages on comparison with the previous generations.

New Generation Prfs

T PRF-Tunali *et al*. (2012) developed a modified autologous L-PRF protocol using titanium test tubes instead of glass test tubes, in which under microscopy study showed a thicker and better-organized fibrin network in T PRF samples compared to L PRF, and histomorphometric analysis showed that fibrin network in T PRF covered a significantly larger area than the later.[14] A-PRF-Ghanaati *et al*., in his study, has shown that by decreasing the rpm and increasing the centrifugation time (1500 rpm, 14 min) observed an enhanced presence of neutrophilic granulocytes in the clot of A-PRF and it appeared to be an ideal provider of autologous cells (especially neutrophils and macrophages), thus enabling mutual stimulation, thereby creating a synergistic relationship in the interest of tissue regeneration.[15]

I PRF-Agrawal *et al*. stated that the main difference between i-PRF from solid PRF is the decrease in rpm and centrifugation time. i-PRF is the liquid variety of PRF which may accelerate the wound-healing processes with increased vascularization. The benefits of i-PRF show slow and sustained release of growth factors, by releasing the expression of transforming growth factor-β and collagen-1 mRNA, along with cell migration.[16,19]

BIO PRF-Miron *et al*., with the help of horizontal centrifugation, discovered BIO PRF that had a significant increase in both the number and concentration of platelets and leukocytes (up to 3.5× higher for either solid/liquid PRF.[17]

ALB PRF-Fujioka-Kobayashi *et al*. after centrifugation heated the obtained platelet poor plasma to create the denatured albumin which aided in the release of growth factors from the ALB PRF at very slow pace.[18]

Table 2: PCs Preparation protocols

Platelet concentrate type	Method (automated/manual)	Description
Fibrin adhesives	Tisseel from Baxter Healthcare.	The operating mode of fibrin adhesives reproduces the last stages of the enzymatic cascades of coagulation during which the fibrinogen is converted into fibrin in the presence of thrombin, factor XIII, fibronectin, and calcium ions.[5]
P-PRP	Cell separator/plasmapheresis PRP (Automated) Weibrich *et al.* Vivostat PRF (Automated)	PRP is collected by a discontinuous method where a patient is connected to a machine continuously around 300 ml PRP can be collected through differential ultracentrifugation (300 g). When PRP is obtained from a blood bag of 450 ml, 40 ml-PRP is Obtained. Sophisticated technology, expensive, cumbersome (Automated)[9,11]
	Anitua's PRGF (Manual)	Citrated blood 5 ml-collected in test tube and centrifuged at 460 g/8 min. Platelet poor layer is discarded to PRGF, and Cacl2 is added to obtain unstable PRGF gel after 15 min and has to be used immediately. (Manual)[9,11,21]
L-PRP	PCC System by 31 and Smart-PRep PRP (Automated) Magellan APS system Christensen *et al*. Gravitational Platelet Separation system (GPS) PRP (Automated)	Two compartment system based on Curasan manual principle[9,12] A cell separator with an optical reader is available. Multi-functional system Another variation of two chambers
	Curasan and Friadenet-Schutze PRP (Manual) Platelex (Slovakia) Regenmethod (Manual)	Both these techniques employ a classical method of two stage centrifuge. First soft spin (2400 rpm/10 min) that gives three layers. PPP and buffy coat are transferred to another tube and after a hard spin, the PPP (3600 rpm/15 min) is discarded leaving behind PRP. Depending on the technique of collecting buffy coat, one can randomly get either P-PRP or L-PRP.[9]
		Specific jellifying agents are used.[9]
P-PRF	Fibrinet PRFM (Manual)	Consists of two tubes, one for blood collection and another for PRFM Clotting. Around 9 ml of blood is collected in a tube containing tri sodium citrate anticoagulant and a separator gel and centrifuged for 6 min at high speed. Buffy coat and PPP are transferred in a second tube containing cacl2 and centrifuged for 15 min and then a stable PRFM clot can be collected.[9,10]
L-PRF	Choukroun's PRF (Manual) Choukroun *et al*. Intra spin (Manual)	Considered a second-generation platelet concentrate obtained by the natural process without any anticoagulants or jellifying agents. Venous blood was collected and centrifuged at low-speed yielding an RBC layer, PRF clot in the middle, and acellular plasma top layer.[10]
		Only FDA-approved kit for PRF. Employs 9 ml glass coated plastic tube centrifuged at room temperature at 2700 rpm for 12 min. Contains an expression kit to compress the clot to make PRF membranes.[13]
		Non-FDA-approved centrifuge to produce L-PRF.
CGF	Sacco	Altered centrifugation speed (2400–2700) for isolation of much larger denser fibrin matrix with increased growth factors. Demonstrates the presence of TGF- b, VEGF, and CD34.[14]
Sticky bone	Sohn	Autologous fibrin glue mixed with bone graft.[14] The sticky bone is a moldable mass containing platelets and leucocytes in its fibrin network, has adequate physical properties to prevent the micro and macro movement of the grafted bone and prevents the ingrowth of soft tissue in the graft.
T-PRF	Tunali *et al.*	Ti tubes were used for collection and centrifugation instead of glass tubes.[14] The centrifugation protocol is similar to that followed to obtain L-PRF (2800 rpm, 12 min). The fibrin structure of T-PRF is woven and thicker.
A-PRF	Advanced PRF process, France	Reduced centrifugation (1500 rpm, 14 min) G force aids in earlier vascularization, faster soft-tissue growth, more cytokines and release of BMP'S[15]
I-PRF	Maurao *et al*.	10 ml whole blood without anticoagulant centrifuged at 700 rpm for 3 min.[15,19]
		Blood was collected in a 9 ml tube without any additive and centrifuged for 2 min at 3300 rpm, the resultant orange color fluids in the tubes are i-PRF.[15,19]
Bio-PRF	Horizontal centrifugation system-Miron *et al*.;	No additives are used to form a super clot with increased levels of regenerative cells and growth factors.[17]
Alb-PRF	Masako *et al.*	Peripheral blood 9 ml is collected in a plastic tube is centrifuged at 700 g for 8 min, platelet poor plasma layer is heated at 75°c for 10 min to create denatured albumin (Alb-gel)[18]

Uses of PCs[20]

- For accelerated hard- and soft-tissue healing and also for bone healing in implant surgery
- PRF can also be used as a protective barrier membrane to seal off and promote healing of oroantral communications following extractions and to close a palatal connective tissue harvesting site
- For bone augmentation and Sinus lifts – as the sole material, or in combination with graft materials
- Using a mix of PRF with a bone graft, in bone defects and peri implant defects, or, in cases of immediate implants, covering it with several PRF layers
- In periodontics to correct intra-bony defects, gingival recession, guided bone regeneration, periapical lesions, also as a vestibuloplasty wound bandage, etc

- It has also been used for regeneration in open apex, regenerative pulpotomies, periapical surgeries, etc
- In tissue engineering, for *in vitro* cultivation of human periosteal cells for bone, pulp revascularization
- In multiple extractions to preserve the alveolar ridge (extraction socket preservation)
- Bone regeneration around immediate implants, inside the alveolar defects, and periodontal/peri-implant defects
- In the membrane form, it could be useful for small otologic surgery, plastic surgeries, etc.

Discussion

PCs are the novel thriving versatile components in periodontal regeneration either when they are used alone or in fusion with other biomaterials. There are many technological advancements in preparing and understanding the different types of platelets concentrates from random single spin centrifugation to fully automated commercially available systems. Regardless of consonance brought up in the effective antihemorrhagic surgical techniques, finding hemostatic agents remain an interminable problem. Over a long period, fibrin adhesives[6] have been criticized, because they are blood-derived products produced by pharmaceutic industries (e.g., Tisseel from Baxter Healthcare), they constituted an infinitely small viral contamination risk and are currently being marketed in the US. More simplified tools inherent to the production of autologous fibrin adhesives have recently been developed with the evolution of similar technologies such as cPRP-type PCs.

The early in the age plasma rich in growth factors was used with autologous grafts to treat the severe defects.[21] The addition of PRP with various other grafts such as BPBM and DFDBA improved the bone fill in defects compared to control groups exhibiting the effectiveness and ability of PRP to regenerate the bone supportively with grafts.[22,23] Hou *et al*., in their systematic review and meta-analysis, concluded that PRP may be beneficial as an adjunct to conventional grafting procedures. However, PRP when combined with regenerative procedures such as GTR the beneficial effect of PRP in the treatment of intrabony defects is negligible.[24] Arbildo *et al*., in their systematic review and meta-analysis, concluded that PRP shows positive clinical outcomes (PPD and CAL) for treating IBD when used alone or in combination with other regenerative materials.[25]

Castro *et al*., in their systematic review and meta-analysis with the most accepted protocols of centrifugation (3000 rpm/10 min. or 2,700 rpm/12 min.), stated that L-PRF showed favorable biological effects in terms of hard- and soft-tissue healing along with minimal post-operative discomfort.[27] Furthermore, PRF in combination with other biomaterials or drugs, stem cells, and the design of engineered structures based on it, can have remarkable results in bone regeneration.[26] Similarly, bone graft in combination with PRF showed better clinical and radiographic outcomes when compared to PRF alone in the treatment of IBD.[28] Pepelassi *et al*., in their systematic review, concluded that there are significant clinical and radiographic supplemental effects of L-PRF to OFD and to osseous grafting in periodontal endosseous defects (IBD and Furcation defects) of systemically healthy non-smokers, as compared without L-PRF.[29] Panda *et al*., in their systematic review, stated that autologous PCs in the treatment of furcation defects may be beneficial when used as an adjunct to open flap debridement alone and additional grafting procedures.[30] Tarallo *et al*., in their systematic review and meta-analysis, stated that PRF demonstrated better results than OFD alone in furcation treatment.[31]

The function of PRP was to stimulate cell replication of stem cells for healing, stimulate cell replication of endothelial cells, promote the migration of perivascular healing, and modulate the effect of other growth factors. The discovery of PCs even aided in attaining better clinical outcomes in treating gingival recessions. The treatment of gingival recessions using subepithelial connective tissue grafts has numerous limitations, including restricted supply in multiple recessions, post-operative morbidity (donor site), and increased surgical time**.** According to Ali *et al*., non-surgical treatment of gingival recessions by PC injections has improved root coverage in contrast to surgery, as it aids in soft-tissue healing by increasing collagen content, promoting angiogenesis, and increasing early wound strength.[32]

Miguel Augusto Rodas *et al*., in his systematic review and meta-analysis, stated that PRF is an important aid in the wound healing process. PRF membranes are a promising alternative to gingival autogenous grafts, for root coverage procedures.[33] PRF is a autogenous material that, in a single medium, provides a mesh that acts as a platform containing judicious cells for tissue proliferation, and molecules that stimulate reconstruction and regeneration. Additional molecules, like VEGF, act as an ardent stimulator of angiogenesis, likely increasing blood supply, hastening matrix synthesis thereby enhancing wound healing process. The PCs also had several productive features, like relatively simple procurement and economical. Furthermore, they reduce post-operative symptoms.[33,34]

In contrast to that, Moraschini *et al*., in their systematic review and meta-analysis, concluded that the use of prf membranes did not improve parameters such as rc, ktw, or cal in the treatment of gingival recessions compared to the other treatment approaches and also stated that ctg revealed favorable results of the ktw compared to prf, which might be attributed to the fact of faster deterioration of the prf membranes, with the successive decrease in the release of growth factors, which could influence initial endurance of periodontal tissues to withstand intraoral constraints compared to autogenous connective tissue grafts, in the treatment of gingival recessions.[34] T-PRF and i-PRF have higher cell migration rates. They increase the release of PDGF and TGF-β, with more collagen production, thereby demonstrating the safety and efficacy of T-PRF and i-PRF in the treatment of gingival recession.[35,36]

Miron *et al*., in their systematic review and meta-analysis, stated that the use of CAF for the use of CAF/PRF showed

statistically significantly higher rRC without marked changes in KMW. When CAF/CTG was compared with CAF/PRF, CTG group resulted insignificantly better rRC and KMW when compared with PRF group. On that account, from a clinical stance in cases with inadequate KMW, the use of CTG should be opted over PRF.[37]

PCs may not completely act as soul role players in successful implant therapy, but they provide beneficial effects when used adjunctively, which was in accordance with study conducted by Ergun *et al*. with Non-PRP and PRP application during implant placement followed by ISQ values evaluation.[38] Toffler *et al*. conducted a study on healing for localized sinus augmentation using a crestal approach in combination PRF and stated that PCs demonstrated high degree of safety and success during implant placement.[41] Stähil *et al*., in his systematic review, concluded that PRP in sinus floor elevation and ridge preservation combined with grafting materials might transiently improve bone regeneration and bone healing and also stated that it might reduce post-operative pain and swelling.[39] Strauss *et al*., in their systematic review (2018), stated that PRF might enhance implant stability during osseointegration, may reduce alveolar bone resorption and when combined with bone grafting did not show any effect in sinus floor elevation.[40]

Conclusion

PCs in their everyday utilization showed promising clinical effects. In spite of having better clinical edge, constructive actions are still lacking. Novel advances including modern PCs such as t-Prf, a-prf, i-prf, bio-prf, alb-prf, CGF, sticky bone, and approaches have been reported, but no longitudinal trails have been done to prove their amelioration over traditional prp and prf. However, various studies included and discussed in this review that has limitations such as risk of bias and flexibility in obtaining PCs due to the different protocols currently in prevailing and scope of different systems that are commercially available. Hence, it is also recommended to carry out multiple well-designed rcts based on based on ethnicity, age, and gender to eliminate risk of heterogeneity, which can influence the framework and quality of PCs. Further data and documentation of research in terms of both animal and human histological confirmation is necessary to verify whether PCs actually has any precedence to true periodontal regeneration.

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