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Platelet concentrates: An Asset in Periodontology and Oral Implantology -The richest of resources in nature, lie in the nature itself

[1]Dr. Farah Shaikh, Post Graduate, Department of Periodontology and Implantology, M.A Rangoonwala College of Dental Sciences and Research Centre, Pune

[2]Dr. Sangeeta Muglikar, Professor and HOD, Department of Periodontology and Implantology, M.A.Rangoonwala College of Dental Sciences and Research Institute Pune

[3]Dr. Mahavish Khan, Post Graduate, Department of Periodontology and Implantology, M.A Rangoonwala College of Dental Sciences and Research Centre, Pune

[4]Dr. Bhagyashree Jabade, Senior Lecturer, Department of Periodontology and Implantology, M.A Rangoonwala College of Dental Sciences and Research Centre, Pune

[5]Dr. Zeba Nandrekar, Post Graduate, Department of Periodontology and Implantology, M.A Rangoonwala College of Dental Sciences and Research Centre, Pune

Corresponding Author: Dr. Farah Shaikh, Post Graduate, Department of Periodontology and Implantology, M.A Rangoonwala College of Dental Sciences and Research Centre, Pune

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Abstract

Platelets are the blood cells known to play an important role in hemostasis, addition to this, platelets were shown to be involved in a variety of pathophysiological responses. Platelet concentrates, have evolved and have come a long way in Periodontal regeneration. Platelet concentrates have been widely utilized in many fields of medicine owing to their ability to rapidly stimulate vascularization of tissues. This article is meant to review the aspects of platelet concentrates in the field of periodontology and oral implantology.

Keywords: Platelet concentrates, platelet-rich plasma, platelet-rich fibrin, platelets, PRP, PRF

Introduction:

Periodontitis is a complex, inflammatory disease of the supporting tissues of the teeth, resulting in progressive destruction of periodontal ligament and alveolar bone thus causing loss of connective attachment. Periodontal therapy urges to eliminate inflammatory process, progression of the disease and in regeneration of the lost periodontal tissue.(1)

Periodontal regeneration is a complex process which involves various biologic events like cell adhesion, migration, proliferation and differentiation in a sequence.[2] Periodontal regeneration is a huge step up in restoring the architecture and function of the periodontium by using various techniques which includes soft tissue grafts, bone grafts, root biomodifications, guided tissue regeneration, and combinations of these techniques.[3]

Platelets contain biologically active proteins that binds to developing fibrin mesh or to the extracellular matrix. The proteins, thus, create a chemotactic gradient for recruitment of stem cells. These stem cells undergo differentiation, and promote healing by regeneration. Hence, the use of autologous platelet concentrates (platelet rich plasma and platelet rich fibrin) opens a promising treatment option in the field of periodontal regeneration, especially in clinical situations demanding rapid healing.[4]

Platelet and its significance

Platelets are the second-most corpuscles found in the blood. Platelets are biconvex discoid shaped. They are from megakaryocytes. Their lifespan is about 7 and 10 days, and the normal peripheral blood concentration is 150-450 × 109 /L. Dimensions of approximately 2.0-4.0 by 0.5 µm and a mean volume of 7-11 fl.[5]

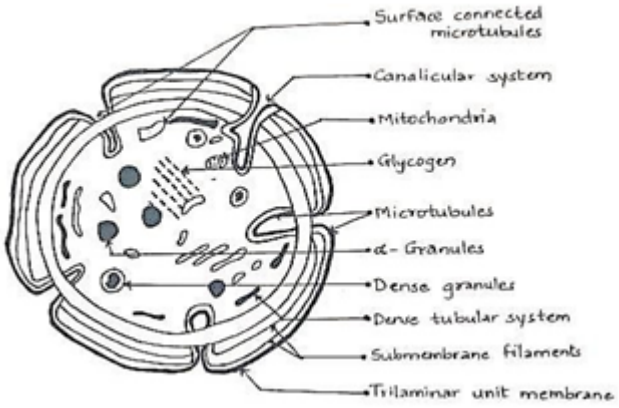


Fig.1: Ultrastructure of Platelet Platelets plays a significant role in inflammation and wound healing due to presence of cytokines and various growth factors that are responsible for cell proliferation, cell differentiation, induction, collagen synthesis, and vascularization. These factors includes: Platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF)(12) (Table-1).

Ross *et al (*1974) introduced the regenerative potential of platelets. Initially the application of platelet concentrates was limited to treatment and prevention of hemorrhage. Its scope in medical field has expanded and evolved to a more refined concept of tissue regeneration such as active biomaterials and Platelet concentrates such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) which are derived from patient's own blood.

Growth factor /Molecule	Action
PDGF	Stimulates chemotaxis/ mitogenesis in fibroblast/smooth muscle cells; Regulates collagenase secretion/collagen synthesis.
TGFβ	Stimulates/inhibits endothelial, fibroblastic and osteoblastic mitogenesis; regulates collagen synthesis/collagenase secretion; stimulates endothelial chemotaxis and angiogenesis.
EGF	Stimulates endothelial chemotaxis /angiogenesis; regulates collagenase secretion; epithelial /mesenchymal mitogenesis.

bFGF	Increases angiogenesis, epithelization and fibroblastic mitogenesis.
VEGF	Stimulates angiogenis; migration and mitosis of endothelial cells; chemotactic for macrophages and granulocytes; vasodilation.
IGF	Stimulates cartilage growth, bone matrix formation, Replication of preosteoblast and osteoblast; act as anautocrine and paracrine factors; enhances rate and quality of wound healing.
RANTES	Recruitment of monocytes and Tcells
Fibrinogen , Vitronectin	Activated platelets and with ECM components enhances platelet adhesion and local aggregation; stimulates attachment and proliferation of osteoblasts and fibroblasts; enhances angiogenesis
vWF, PECAM GPs, P-Selectin	Ensures a stable anchorage with sub endo the lial matrix by direct interaction with collagen.
Fibronectin Thrombospondin1	Bone mineralization, cell-matrix interactions, and collagen binding
Other Chemokines	Attract leukocytes and activate other platelets, regulate inflammatory pathways.

Evolution of platelet concentrates: [6]

Platelet concentrates have come a long way since its first appearance as fibrin glue, which was used as surgical adjuvants for more than 40 years to the most recently introduced to A- PRF,T-PRF and i-PRF. Fibrin glue was prepared from high concentrations of thrombin and fibrinogen. The evolution of platelet concentrates was a result of evolution in its preparation protocol. The milestones in the evolution of platelet concentrates are illustrated in Table 2.

Table 2: Milestones in the evolution of Platelet Concentrates

Year	Milestones
1954	Kingsley first used the term platelet-rich plasma (PRP)
1970	Matras introduced “Fibrin glue”
1986	Knighton et al demonstrated that platelet concentrate promoted healing andtermed it as platelet-derived wound healing factors (PDWHF)
1997-1998	Whitman and Marx introduced Platelet-rich Plasma (PRP)
1999	Plasma rich in growth factors(PRGF) was developed by Anitua and Co workers
2001	Choukroun et al introduced Platelet rich fibrin (PRF) assecond generation plateletconcentrate
2006	Sacco introduced concenrated growth factors (CGF) a newconcept which were larger, richer and denser than PRF
2009	Dohan Ehrenfest et al proposed first classification of platelet
2010	Sohn introduced the sticky bone concept (autologousfibrin glue mixed withbone graft)

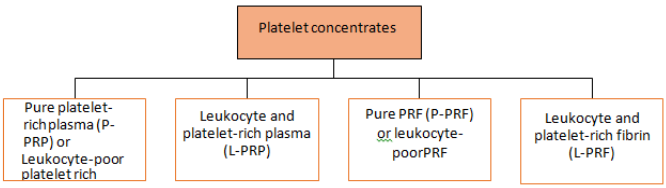
2014	Choukroun et al introduced advanced PRF(A-PRF) Tunalı et al introduced Titanium prepared PRF (T-PRF)
2015	Mourao et al described the preparation of injectable PRF (i-PRF)

Classification: [8][10]

Proposed by Dohan Ehrenfest et al, 2009

Classified Based on 2 key parameters-	1) Presence of cell content (mostly leukocytes)
	2) Fibrin architecture.

This classification included 4 main categories of products:



Sohn, 2010 Introduced the concept of sticky bone.

Modifications of platelet rich fibrin-

1. Advanced platelet rich fibrin (A-PRF) (Choukroun ,2014)
2. Titanium prepared platelet rich fibrin (T-PRF) (Tunali et al, 2015)
3. Injectable PRF (i-PRF) (Mourao et al, 2015).

Types	Parameters	Available as	Usage
Pure Platelet-Rich Plasma (P-PRP) or Leukocyte-Poor Platelet-Rich Plasma	Without leukocytes, low-density fibrin afteractivation.	Injectable liquid. activated gel form.	Placed/ injected on wound or surgical site.
Leukocyte-and Platelet-Rich Plasma (L-PRP)	With leukocytes, Low-density fibrin afteractivation.	Injectable liquid. activated gel form commercial or experimental systems	Placed/ injected on wound or surgical site. Minimal handling of the blood samples and maximum standardization of preparations.
Pure Platelet-Rich Fibrin (P- PRF) or Leukocyte-Poor Platelet-Rich Fibrin	Without leukocytes, high- density fibrin	Strongly activated gel form	Handled like fibrin membranes/solid materials for other applications. Cannot be injected/ used like traditional fibrin glues.
Leukocyte and Platelet- Rich Fibrin (L-PRF)	With leukocytes, high-density fibrin Open-access technique based on the concept of one-step centrifugation of blood without anticoagulant and without blood activator	Only exist in strongly activated gel form	Strong fibrin matrix- handled like real solid material for many applications. Cannot be injected.

Platelet-Rich Plasma(PRP):[8][9]

Platelet-rich plasma is a first-generation platelet concentrate. Platelet rich plasma (PRP), were introduced in the 1998 in dentistry by Whitman and Marx. PRP serves as a reservoir for growth factors that promote wound healing and tissue regeneration. (Marx al 1998 and Kassolis JD et al 2000)

Platelet-Rich Plasma (PRP)
Preparation of PRP: Double centrifugation of autologous blood is done consisted of soft spin (1300 rpm - 10 minutes) followed by hard spin (2000 rpm -10 minutes) after that PRP collected at the bottom part of tube. **Step 1**: In first centrifugation, the tube is centrifuged at 1300 rpm and allows the blood to separatein 3 distinct layers: The red blood cells constitute 55% of total volume are at the base of the tube, platelet-poor plasma (PPP) constitutes 40% of total volume, and between them middle layer of platelets concentrations (PRP) that constitutes only 5% of total volume and presents as buffy coat. The upper-part without anticoagulant is transferred to another sterile tube. **Step 2:** This second tube undergoes another centrifugation performed at 2000 rpm which is a bit longer and faster which again results in distinct layers: some residual red blood corpuscles trapped at the bottom of the tube, acellular plasma (PPP) for 80% of total volume and between them platelet concentrates (PRP).

Clinical applications	a. Periodontal regeneration- Root coverage procedures b. Clinical conditions requiring good bone fill along with gain in clinical attachment c. Gingival recession d. Intra bony defects e. In combination with bone graft f. Sinus Lift Procedures g. Ridge Augmentations h. Socket Preservation i. Soft Tissue Procedures.
Systematic review andmeta-analysis	**Panda et al** systematically evaluated the clinical and radiological outcomes of the additive efficacy of autologous platelet concentrates in treatment of intrabony defects when used alone and along with other regenerative procedures. PRP was foundto be effective when used as an adjunct to grafting materials, but ineffective when used in combination with guided tissue regeneration procedures.
Advantages	a. PRP enhances rapid regeneration by bringing cytokines and growth factorsto site. b. Free from concerns over transmissible disease. c. Convenient and economical for patient.
Disadvantages	a. Preparation protocol of PRP lacks standardization. b. Although never reported, the addition of bovine thrombin to the platelet concentrate could cause adverse reactions such as systemic lupus erythematosus. These disadvantages have reduced the usage of PRP and led to evolution of "second generation PRP" coined as Platelet rich fibrin which is purely an autologous human thrombin.

Platelet-Rich Fibrin: [8][9]

Platelet-Rich Fibrin is an autologous fibrin-based biomaterial derived from human blood. It was first developed in 2001 in France by Joseph Choukroun et al.[9] It is a promising biomaterial as it accelerates soft- and hard-tissue healing.

PRF produces proliferation of fibroblasts and osteoblasts, causes prolonged release of growth factors at the wound site, promotes angiogenesis, induces collagen synthesis, acts as a guide in wound coverage, provides mechanical adhesion by fibrin and traps circulating stem cells. Hence PRF plays a key role in wound healing. A main advantage of PRF is that it follows a very simple preparation protocol developed by Choukroun et al which requires neither anticoagulant nor bovine thrombin. Preparation of PRF:(Fig:3) Blood sample is collected without anticoagulant in tubes and immediately centrifuged at 3000rpm for 10 minutes, following this the blood sample settles in three distinct layers:

- Uppermost layer - straw-colored acellular plasma,
- In the middle - PRF clot
- At the base - Red blood cells. (Fig-2)

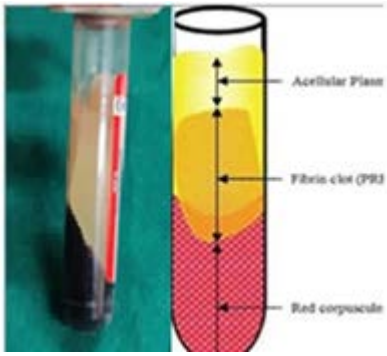


Fig: 2: Layers of PRF

Formation of PRF Membrane

The PRF clot is placed between two sterile gauzes or in a specific PRF tool, where in the clot is compressed and transformed into an inexpensive autologous fibrin membrane as suggested by Mazor et al. Three main components of PRF:

- Host cells
- Three-dimensional fibrin matrix
- Growth factors in PRF which act together and play a key role in faster and powerful tissue regeneration.

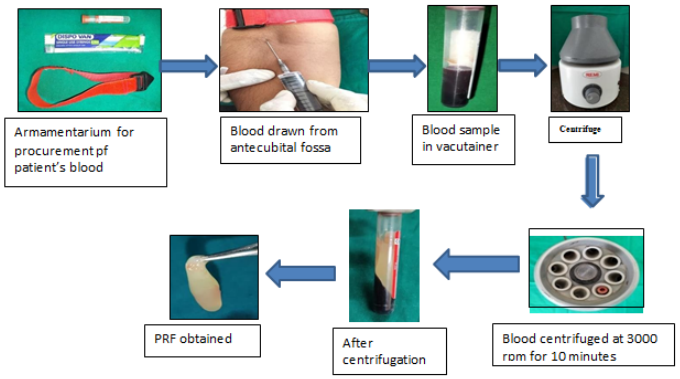


Fig: 3 Preparation of PRF

The PRF fibrin network which is an autologous leukocyte-platelet-rich fibrin matrix, composedof tetra molecular structure with platelets, cytokines, and stem cells within it and acts as a biodegradable scaffold that serves as a reservoir of growth factors and cytokinesthat has sustain release over 10-14 days period. Thus PRF serves all important criteria for tissue regeneration.

Advantages of PRF[6]	Disadvantages of PRF[6]
Simple technique with single-step centrifugation.	depends directly on blood collection and handling, and transfer time to a centrifuge
Autologous blood sample, involving minimal blood manipulation	Size of PRF limited by volume of blood drawn
No requirement anticoagulant or bovine thrombin	Preparation of PRF requires glass coatedtubes to achieve polymerization
Can be used by itself or in combination with bonegrafts	PRF membranes need to be used immediately after preparation as they shrink due to dehydration
More efficient with less controversies compared to PRP	
Requires minimal experience formanipulation	
Inexpensive and quick alternative	

Recent Advances in PRF [(11)]

There have been various evolutions in platelet concentrates by various techniques, modification in centrifugation protocol, by enhancing biological actions and clinical applications. Various modifications within the conventional protocol like the advanced PRF, inject able PRF, PRF lysate andTitanium-prepared PRF.

Advanced PRF

PRF and L-PRF are produced at a speed of 3000 rpm and 2700 rpm respectively for 12 minutes in sterile glass based plastic tubes. Choukroun et al modified preparation protocol for PRF to produce APRF, by reducing the

centrifuge speed (1500 rpm) and more time (14 minutes) in sterile vacuum glass tubes (A-PRF10 tubes). By lower centrifugation protocol, incorporated monocytes with the PRF, even distribution of platelets, neutrophils. Hence it was named Advanced PRF.

Advanced PRF+

By further reducing centrifugation time (1300 rpm) to 8 minutes, Fujioka-Kobayashi(2016) suggested another modification of A-PRF, called as APRF+. The A-PRF+ demonstrated high no. of leukocytes and growth factors (PDGF, TGF- β1, EGF and IGF).

Injectable PRF

One of the latest developments in the PRF is the production of injectable PRF (i-PRF). Choukroun et al modified preparation protocol for PRF to produce i-PRF, by reducing the centrifuge speed (700 rpm) for 3-4 minutes in sterile plastic tubes. Mixing the bone graft withi-PRF results in the formation of a well agglutinated "Sticky Bone".

PRF Lysate

After PRF preparation, it is incubated at 37°C in a humidified atmosphere and the exudate collectedhas been referred to as PRF lysate. It is a reservoir of several growth factors including PDGF, TGF, VEGF & EGF. It is used to o reverse the damage caused by chronic UV radiation exposure to human dermal fibroblasts.

Titanium-PRF

A newer method was investigated by the usage of various materials for blood processing during PRF preparation. Tunali & co-workers used titanium tubes to produce PRF and called it T-PRF. The centrifugation protocol was similar to Choukroun's method. T-PRF produced a well polymerized andorganized fibrin framework.

Clinical Application of PRF

Uses of Platelet Rich Fibrin in Regenerative Dentistry

Periodontal regeneration[11]

- Repair of Intrabony and Furcation Defects
- Soft tissues regeneration
- Guided bone regeneration

Figure 4: Root coverage Procedure

Plastic periodontal procedures

- Soft-tissue root coverage
- In treatment of Muco Gingival Recessions by Utilizing The Fibrin Assisted Soft Tissue Promotion (FASTP) Technique

PRF as an Adjunct to Implant Dentistry[6]

- An injectable-PRF (i-PRF) for adequate graft stability
- In Management and Preservation of Extraction Sockets
- As an adjuvant with immediate implant placement
- Treatment of Peri-implant osseous defects
- In Peri-implant tissue healing
- Alveolar Ridge augmentation

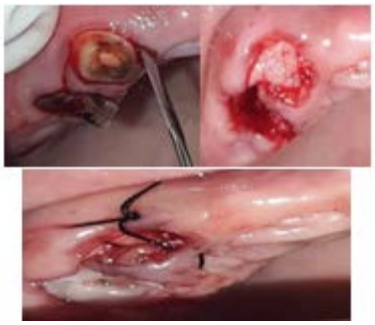


Figure 5: Socket Preservation using PRF

Figure 6: PRF around implant

Used in Endodontics

- As a scaffold for dentin pulp regeneration

- Apical plug in Apexification.
- PRF along with tricalcium phosphate (TCP) bone graft in treating periapical cysts

Use of Platelet Rich Fibrin in Other fields of Medicine

- For regeneration of chronic leg ulcers
- For cartilage (knee) regeneration
- Ligaments and tendons regeneration
- In Sports Medicine
- For skin regeneration
- In orthopedic medicine

PRF in Facial Aesthetics and Rejuvenation

- i-PRF injections with a derma rollers
- i-PRF injections with a derma pen
- i-PRF and PRF for mesotherapy by syringe injections
- Platelet concentrate during the vampire technique
- Augmentation techniques with PRF matrix and i-PRF—combination Therapies
- Rejuvenation of nasolabial fold with PRF and i-PRF
- Use of PRF and i-PRF for lip augmentation
- PDO threads using PRF and i-PRF

Strauss et al (2018) reported that the use of PRF would increase implant stability by reducing alveolar bone resorption and also would reduce postoperative pain and enhance woundhealing after implant therapy. A meta-analysis by Li et al (2019) proved that the synergistic application of PRF and 1%alendronate provided better results during periodontal bone regeneration. Rodas et al (2020) reported in his systematic review and meta-analysis that PRF membranes are a promising alternative to Autogenous gingival grafts in the treatment of Miller class I and II gingival recessions.

Future Perspectives: [12]

- PRP and PRF proteomes characterization is highly desirable to enable more robust and predictable clinical outcomes.
- Platelet concentrates as controlled release devices, which will allow sustained delivery of these growth factor cocktails.
- Further studies on the effect of autologous platelet concentrates on stem cell behavior, proliferation and differentiation to be used for cell-based therapies.
- We need more data to find the proper therapeutic doses for platelet concentrates suitable for different clinical applications.
- Future clinical trials are necessary to further investigate the potential of utilizing platelet concentrates for soft tissue regenerative protocols in combination with various biomaterials, pharmaceutical agents or stem cells.

Platelets are being proposed to be used as carriers for loading drugs or biological therapies to specific target locations. Studies conducted on platelets have shown their capability of recognizing and interacting with tumour cells. So, development of new drug delivery systems and therapeutic strategies could be of use in management of tumours as this might help to minimize the side effects of chemotherapy such as cytotoxicity and non-specific targeting. Zhen Gu and collaborators generated PD-1-expressing platelets to use it as post-surgery consolidation treatment in tumours. This could accumulate within the tumour surgical wound enhancing its anti-tumour immune response thus eliminating the residual tumour cells which could result in relapse of the tumour locally and distally. One of the most abundant cell-derived microparticle are Platelet-derived microparticle (PMPs or platelet “dust”) which are produced by platelets upon activation. Various studies on

this microparticle suggest its role as modulators of immune system as well as its role in various diseases. These microparticle have gained attention as potential diagnostic markers when used for detection of rheumatoid arthritis and cardiovascular diseases. The use of advanced delivery systems such as liposomes for encapsulating the platelet concentrates has proved advantageous due to its biocompatibility, low immunogenicity, protection of growth factors against enzymatic degradation, and long-term bioavailability as well as ease of surface modification for selective targeted delivery. In-vitro studies have shown favorable results for enhanced bone regeneration when biodegradable scaffolds such as calcium phosphates and poly lactic-co-glycolic acid were combined with biopolymers such as hyaluronic acid and gelatin for encapsulating PRP.

Conclusion

Various in vitro and in vivo studies have demonstrated safe and promising results associated with the use of PRF alone or in combination with other biomaterials. Its various advantages and potential indications to be used both in medicine and dentistry.

Platelet concentrates are a biggest asset of nature and a unique ingress of tissue engineering within the field of dentistry.

PRF technology is in its preliminary stage, and is growing popularity in dentistry. The effectiveness of these platelet concentrates in periodontal regenerative procedures should be evaluated in long–term randomized control studies comprising of enormous samples to affirm the advantages and the hidden potential of PRF as an autologous biomaterial to promote hard and soft tissue healing and regeneration.

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