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Role Of Platelet Derivatives In Dentistry

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Abstract
Autologous Platelet Concentrates (Apcs) Are Blood Derivatives Prepared From The Patient's Own Blood In Which The Activated Platelets Become Trapped Within A Fibrin Matrix Scaffold And Release Growth Factors And Cytokines Involved In The Key Processes Of Tissue Regeneration. The Forms Of Apc Include The Platelet-Rich Plasma (Prp), Platelet-Rich Fibrin (Prf) And Concentrated Growth Factor (Cgf). The Use Of Autologous Hematological Components Has Become A Highly Attractive Therapeutic Tool In Many Areas Of Medical And Dental Fields For The Past 2 Decades For The Treatment Of Various Debilitations. These Platelet Concentrates Have Shown To Be Of Great Promise In The Field Of Dentistry, Starting From Implantology, Sinus Lifting Procedures, Treating Of Endodontic And Periodontal Lesions To Regenerative Procedures And Also In Temporomandibular Disorders And Some Oral Lesions. This Novel Technique Can Be Used As An Adjunct To Conventional Treatment Modalities In Dentistry. This Review Article Focuses On The Different Types Of Platelet Concentrates And Their Clinical Application In Various Fields Of Dentistry.

Keywords: *Autologous Platelet Concentrates, Growth Factors, Platelet Rich Fibrin, Platelet Rich Plasma, L-Prp, Tissue Regeneration, Temporomandibular Disorders, Lllt.*

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I. INTRODUCTION

Platelets are cellular fragments which are anucleate, disc shaped cells obtained from megakaryocytes in the bone marrow; they are specific secretory elements that release the contents of their intracellular granules in response to activation. These platelets were discovered by Bizzozero in the 19th century[1] and after which Wright discovered that megakaryocytes are platelet precursors.[2]

Platelets play role in the synthesized proteins and the pattern of the peptide synthesis changes in response to cellular activation.[3] Platelets consist of a wide variety of protein molecules, among them there are high presence of signaling, membrane proteins, protein processing, cytoskeleton regulatory proteins, cytokines, and other bioactive peptides that activate and regulate basic aspects of wound healing.[3]

Autologous platelet concentrates (APCs) are produced by the centrifugation of venous blood at different speeds and the use or non-use of thrombin and anticoagulant. As a result of these processing protocols, a fibrin clot is formed that contains platelets and leukocytes.[4]

The main generations of APCs are platelet-rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF). Due to the unique biological properties of the platelet derivatives in wound healing their use in the clinical scenario has increased to support the healing processes in different pathological conditions.

The description of PRP and its concepts were first started in the field of hematology.[5] In the 1970s, hematologists infused PRP intravenously in case of platelet deficits.[6] Later, PRP started to be used in maxillofacial surgery as PRF. Fibrin has the capability of adherence and homeostatic properties, and PRP has anti-inflammatory properties which stimulates cell proliferation.[7]

In the field of dentistry, these platelet derivatives have a wide variety of applications starting from wound healing to bone formation, and also as an adjunctive treatment for Temporomandibular disorders (TMDs) and some oral lesions.

II. BIOLOGY OF PLATELETS AND THEIR DERIVATIVES

All blood cells are derived from a pluripotent stem cells, which differentiates into different cell lines. Each of these cell series consists of progenitors that can divide and mature.[8]

Platelets are long cell fragments which are 2.5μm in its length, develops from megakaryocytes and controlled by thrombopoietin. The complete count of platelet is 150,000 to 450000 platelet/ μL.[9] They lack nuclei but contains other cell organelles and have a life span of 8-10 days.

Platelets are the first constituent of the blood to arrive at the site of tissue injury and to specifically activate the early inflammatory phase of the healing process.[10] They play a major role in aggregation, clot formation, homeostasis through cell membrane adherence, and release of substances to promote tissue repair and which influences the reactivity of blood vessels and the blood cells are involved in angiogenesis, regeneration, and inflammation.[11] These platelet secretory granules consists of growth factors (GFs), signaling molecules, cytokines, integrins, coagulation proteins, adhesion molecules, which are formed in megakaryocytes. There are three major storage compartments in platelets they include

- Alpha granules,
- Dense granules, and
- Lysosomes.[12]

Platelets are rich in alpha granules and they contain adhesive proteins.[9]

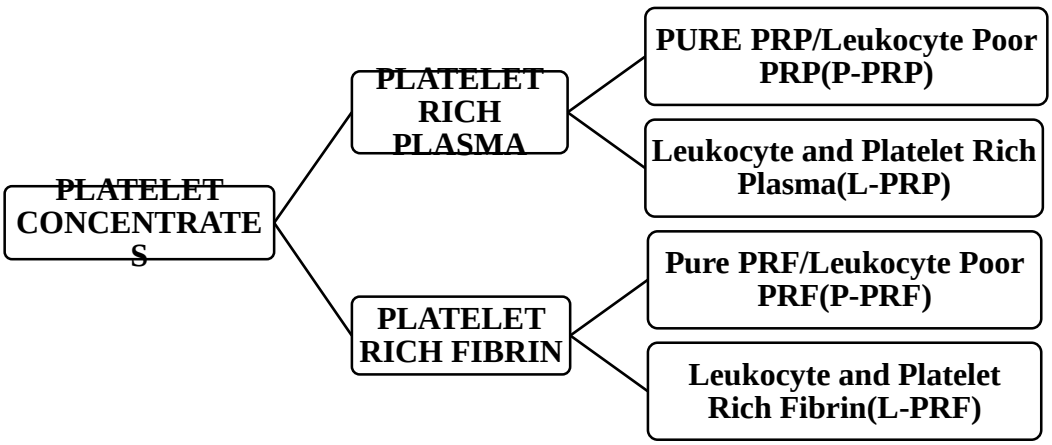
Alpha granules influence the wound healing process through several types of growth factors including the following:

- Platelet-derived growth factor (PDGF)
- Epithelial growth factor (EGF)
- Vascular endothelial growth factor (VEGF)
- Endothelial cell growth factor (ECGF)
- Fibroblast growth factor (FGF)
- Transforming growth factor beta (TGFβ) and
- Insulin-like growth factor (IGF).

These growth factors chemotactically recruit and activate the stem cells as well as induce the mitogenesis and differentiation. In contrast, dense granules promote tissue regeneration by secreting mediators such as serotonin and histamine, which increase vessels permeability and tissue perfusion.[13] Over the years, several platelet-rich blood derivative formulations have been explored.

III. CLASSIFICATION OF PLATELET CONCENTRATES[13]

The classification given in (2009), platelet concentrates can be generally classified into four groups based on the presence of leukocytes and fibrin architecture (Ehrenfest et al. 2010, Ehrenfest et al. 2014):



1) Pure PRP/Leucocyte-poor PRP: Absence of Leukocytes and low density of fibrin network after activation. Used in two forms - liquid solution or activated gel.
2) Leucocyte and platelet-rich plasma: Presence of Leukocytes and low-density fibrin network after activation. Also used in two forms - liquid solution or activated gel.
3) Pure platelet-rich fibrin PPRF/Leukocyte-poor PRF: Without leukocytes but with high-density fibrin network. Used in strongly activated gel form.
4) Leucocyte and Platelet-Rich Fibrin: With leukocytes but with high-density fibrin network. Also used in strongly activated gel form.

PLATELET RICH PLASMA

The first-generation platelet concentrates include plasma (PRP) and platelet rich growth factors (PRGF). PRP was introduced by Marx[14]. It is defined as high concentration of autologous platelets in a small volume of autologous plasma[15].

PRP plays a vital role in wound healing. The process of wound-healing can be divided into three stages: biochemical activation, cellular activation and cellular response. First, the conversion of the mechanical injury into biochemical signals occurs. Hageman factor in the serum triggers this cascade. As a result of the disruption of microcirculation, the plasma comes in contact with tissue proteins and the basement membrane, activation of the Hageman factor and platelets also occurs. The clotting cascade allows fibrin to facilitate homeostasis, and it activates thrombin. Thrombin, calcium chloride and ADP trigger the activation of platelets, thereby release of alpha granules from platelets occurs, with the subsequent secretion of a large variety of growth and differentiation factors.[16]

PRP is used clinically to deliver growth factors in high concentrations to the site of bone defect or a region requiring augmentation.[17] However, the method of preparation of PRP is technique sensitive and time consuming. It requires the use of bovine thrombin for the activation of PRP and release growth factors at the site of placement. [18-20]

PRGF (platelet rich growth factors) were developed by Anitua in 2001 [21] to overcome the disadvantages. He simplified the method of preparation of PRP and replaced the use of bovine thrombin with calcium chloride. PRGF releases growth factors and bioactive proteins at localized injected sites which stimulates tissue regeneration.

PLATELET RICH FIBRIN

PRF is a second generation concentrate which was first developed by Choukroun in France in 2001, prepared without the addition of any anticoagulants.

PRF contains autologous leukocyte-platelet-rich fibrin matrix[22,23], composed of tetra molecular structure, with cytokines, platelets, and stem cells within it [24,25] which acts as a biodegradable scaffold [26] that favors the development of microvascularization and lead to migration of epithelial cell to its surface. [24,28] PRF may serve as a vehicle in carrying cells involved in tissue regeneration [26] and seems to have a sustained release of growth factors [28] in a period between 1 and 4 weeks, stimulating the environment for wound healing in a significant amount of time. It has a complex architecture of strong fibrin matrix with favorable mechanical properties and is slowly remodeled, similar to blood clot. [29] PRF is advantageous as it is a simplified and efficient method of preparation technique, obtained by autologous blood sample,[25] no use of bovine thrombin reducing the chances of cross infection, slow natural polymerization which results in physiologic thrombin concentration and flexible 3-D structure of PRF which is more favorable to cytokine enmeshment and cellular migration.[16] Its chief advantages include ease of preparation and lack of biochemical handling of blood, which makes this preparation strictly autologous.

PREPARATION OF PLATELET DERIVATIVES

The classic method of PRP preparation involves two sequential centrifugation steps namely, separation and concentration spins. The first spin (separation spin) pellets plasma, leukocytes (neutrophils, lymphocytes, and monocytes), and platelets, from erythrocytes. The second spin (concentration spin) collects concentrated platelets in a small volume of plasma (designated as PRP). PRP can be activated by various compounds, such as autologous thrombin or calcium chloride, which induces the formation of a PRP gel.[30] The activation process not only forms a fibrin gel for platelet attachment and adhesion, but also initiates degranulation, resulting in the release of bioactive substances. Large number of leukocytes may be present in the final PRP preparation, which is referred as leukocyte-rich PRP (L-PRP) and can potentiate PRP action.[14] If an anticoagulant is not added, platelet-rich fibrin (PRF) is formed, which consists of a fibrin matrix, platelet-derived cytokines, growth factors, and entrapped leukocytes devoid of erythrocytes.[31] The advantages of using PRF include ease of preparation, no addition of biochemical reagents or anticoagulants, ease of application, and capacity for more sustained release of bioactive factors.[32]

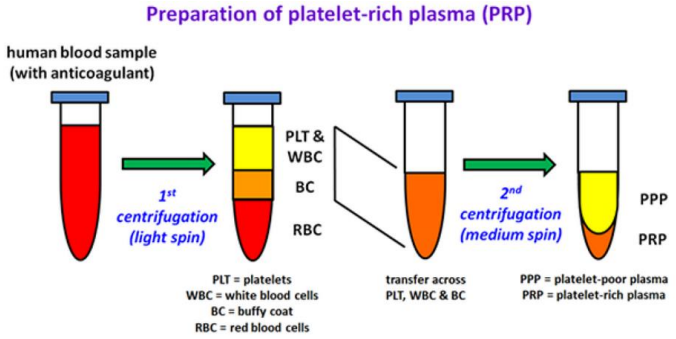


Figure 1: Preparation of PRP

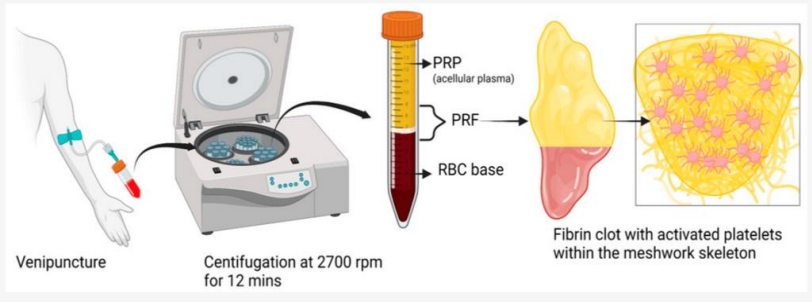


Figure 2. Schematic representation of PRF preparation

Blood products	PRF (2004)	PRGF (2001)	PRP (1998)
Protocol	Easy	Complex	Very complex
Speed-rate	Fast	Very Slow	Slow
Reproducibility	No Bias	Possible Bias	Possible Bias
Use of anticoagulants	No	Yes	Yes
Amount obtainable	Good	Poor	Enough
Costs of the protocol	Low	High	Moderate
Amount of fibrin obtainable	High	Low	Low
Speed of fibrin formation	Physiological	High	High
Fibrin morphology	Trimolecular	Tetramolecular	Tetramolecular
Leukocytes amount	65%	0%	0-50%
Immunomodulatory properties	Yes	No	Poor
Neo-angiogenic potential	+++++	++	+
Osteoconductive potential (scaffolding)	High	Poor	Poor
Mechanical properties (sol-gel-membrane)	Good	Poor	Enough
Presence of MSCs	Yes	Yes	Yes

Table 1: Overview table comparing the main three blood products and their characteristics. Table modified from Giannini et al. 34 PRP, platelet-rich plasma; PRGF, plasma rich in growth factors; PRF, platelet rich fibrin.

Clinical Implementation in Oral and Maxillofacial surgery

- The use of PRF in Oral and Maxillofacial surgery has many applications such as socket preservation, sinus lift and bone augmentation. PRF also influences on the postoperative pain and swelling. In a study done by Singh et al[35] in 2012 they took 20 patients and Ozgul et al[36] in 2015 performed a study on 56 patients underwent bilateral extraction of the third molars followed by the application of PRF into only one extraction pocket (study site), while the other site was left untreated. The results showed that there was less pain and that soft tissue healing was better in the PRF pocket.
- A systematic review and Meta-analysi done by Bao MZ and Liu W etal [37] in 2021 on Application of platelet-rich fibrin on mandibular third molar extraction they concluded that there are only limited clinical evidence in application of PRF after mandibular third molar extraction which could reduce pain, swelling, trismus and the occurrence of dry socket and promote soft tissue healing.
- PRF can also be used as an adjuvant in patients on anticoagulant therapy as it stimulates coagulation pathway along with thrombospondin an helps in wound closure.[38]
- In sinus lift procedures and implantation, Choukroun et al in 2006 [39] evaluated the use of autologous PRF in combination with freeze-dried bone allograft (FDBA). The results showed improved bone healing,

enhancement of bone regeneration and decreased healing time prior to implant placement. PRF is a simple and inexpensive biomaterial in systematic use during sinus lift.

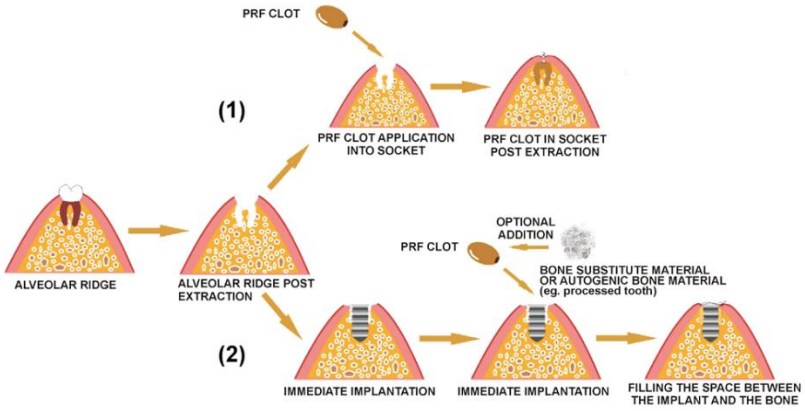
- 

Figure 3[40]- Appilactions of PRF in oral and maxillofacial surgeries

Implant placement surgeries

- After an extraction, the wound area goes through many physiological processes, such as bone resorption and gingival remodeling.[41,42] It has been proposed to place an implant soon after the extraction to protect the osseous complex. Healing of the bone next to the implant starts with the formation of a fibrin clot. The implant surface activates the platelets stuck to the fibrin.
- Many authors have claimed that platelets are an excellent source of the growth factors, and the application of PRF leads to better bone regeneration and faster osseointegration of titanium implants.[43,44].
- Various plasma derivatives have been used in during implant placement and in the treatment of peri-implant bone defects (after peri-implantitis, during implantation in an insufficient bone volume or during immediate post-extraction or post-avulsion implantation), the sinus lift procedures and various complex implant-supported treatments.

Periodontics

- PRF preparations showed compelling data in various in vitro and clinical studies. They are utilized in various procedures such as management of infrabony defects, gingival recession, furcation defects, extraction socket preservation, and accelerated healing of wounds.[45]
- Simonpieri et al in 2009 [46] used PRF membranes for regeneration of both the bone volume and gingival tissue using the concept of "natural bone Regeneration" (NBR).
- Anil kumar et al in 2009 [47] also reported the use of Platelet rich fibrin membrane for root coverage in localised gingival recession in mandibular anterior teeth using combined laterally positioned flap technique.
- In a systematic review and meta-analysis done by Richard J.Miron etal [48] in 2021 on use of platelet-rich fibrin for the treatment of periodontal intrabony defects. They concluded that Open Flap Debridement (OFD)/PRF leads to statistically significant clinical improvements in Probing depth (PD) reduction, Clinical attachment level (CAL) gain, and Radiographic bone fill (RBF) when compared to Open Flap Debridement alone.

Endodontics

- PRF can be used in regenerative endodontics as it could release growth factors with its own biological scaffold. This could be attributed to study conducted by Huang et al in 2010, who reported that PRF promotes dentinogenesis by stimulating proliferation of human dental pulp cells. It also enhances odontoblasts differentiation by increasing the protein expression of Osteoprotegerin (OPG) and Alkaline Phosphatase (ALP) activity.[49]
- PRF is ideal for the revascularization of immature permanent teeth with necrotic pulps by providing a scaffold rich in growth factors, enhancing cellular proliferation and differentiation. It acts as a matrix for tissue ingrowth.[50]
- Evidence of progressive thickening of dentinal walls, root lengthening, regression in the periapical lesion, and apical closure was reported by Shivashankar et al in 2010, following the use of PRF on a tooth with pulpal necrosis and open apex.[51]

Oral medicine

Oral Submucous Fibrosis

- A study done by Amer Sabih Hydri etal[52] in 2019 they compared Triamcinolone and Platelet Rich Plasma Injection (I -PRF) for Improving Trismus in Oral Submucous Fibrosis and they concluded that Intraoral injection of platelet rich plasma was more effective than Triamcinolone in improving trismus due to OSMF.

Lichen planus

- Platelet-rich fibrin can be used in symptomatic lichen planus, in a study they compared triamcinolone acetonide and PRF as injective therapy was done by Bennardo et al [53] in 2021 reported a mean decrease of 59.8% in the lesion size for PRF-treated sites and of 59.2% for triamniconole acetonoide-treated sites and the authors stated that PRF had effectiveness similar to that of triamcinolone acetonide.
- Ebru SAGLAM etal[54] in 2021 used injectable platelet-rich fibrin in erosive oral lichen planus cases and the effects of i-PRF with those of corticosteroids was compared, both the methods decreased pain and lesion size similarly, and both increased satisfaction. They concluded that the use of i-PRF may be considered an option in cases refractory to topical corticosteroid therapy.
- Shankar A etal [55] in 2021 used the Combination of LLLT and i-PRF for the treatment of Oral Lichen Planus which showed a drastic improvement in the Patient and changed his Quality of Life. The results of these synergistic treatment modalities, LLLT and i-PRF have been promising but more studies are required to prove its potential.
- In the treatment of oral mucosal lesions by scalpel excision PRF membrane can be used for grafting. Himani Pathak etal [56] in 2015 used prf membrane in 26 sites and results of study suggested that PRF membrane is a successful coverage agent that aids in healing of superficial oral mucosal wounds.

Temporomandibular disorders

- In a Scoping Review on i-PRF Administration to Temporomandibular Joint Cavities was done by Marcin Sielski etal [57] in 2023, they concluded that supplementing the temporomandibular joint rinsing with i-PRF administration further relieves pain and improves mandible mobility. The lack of RCTs on the intra-articular administration of I-PRF as a stand-alone procedure encourage further research.

Pedodontics

Mittal et al [58] in 2019 used PRF in Apexogenesis of Young Permanent Teeth and he evaluated the regenerative ability of PRF and artificial scaffolds in dying incomplete root development of permanent teeth, and observed that PRF and collagen are superior scaffolds to chitosan and placentrex for apexogenesis.

PRF is used as a Pulp Capping Material in a study done by Bakshi et al in 2017 [59], PRF showed promising results when used as a direct pulp capping medicament, compared with MTA. Dou et al in 2020 [60] conducted a study to investigate the effect of Ca (OH) 2, MTA, iRoot BP, PRF and CGF are potential pulp-capping materials for vital pulp therapy.

Prosthodontics

Platelet aggregates are also used in bone remodeling process due to presence of many growth factors and osteogenic proteins and can be used for the ridge augmentation procedures.

PRGF can be used in patients with denture-induced fibrous hyperplasia as it accelerates wound re-epithelialization, reduction of bleeding and other signs of inflammation.[61]

Moussa et al. studied the effects of covering palatal autogenous blocks with L-PRF membranes on bone augmentation outcomes and reported significantly greater bone graft resorption in the absence of L- PRF membranes at 4 months.[62]

IV. CONCLUSION

The applications of these platelet concentrates are boon in the field of dentistry as it is an autologous biomaterial which is used as both liguid and gel form. Major advantage of this biomaterial is that it is very economical, user friendly, technique of extraction of the plate concentrate is also easier. It has wider applications in many conditions ranging from implant placement, promotes wound healing, extraction socket, infra bony defects and also in some oral lesions. Clinical outcomes of these applications are tremendous hence many prospective studies should be carried out to validate the utility of this biomaterial.

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