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Review Article

Periodontics

PERIODONTAL PERSPECTIVES OF AUTOLOGOUS BLOOD PREPARATIONS

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ABSTRACT

Periodontitis is an infectious disease of attachment apparatus. Untreated periodontitis leads to bone loss and attachment loss. Though several periodontal treatments are available, only some of them are regarded as truly regeneration. Regeneration is reconstitution of both hard and soft tissues in structure and function. Various modalities i.e. bone grafts and substitutes, guided tissue regeneration (GTR) membranes and polypeptide growth factors (PGFs) are used for periodontal regeneration. Platelet concentrates are richest source for polypeptide growth factors. This review highlights various platelet concentrates, and there clinical applications in the treatment of periodontal diseases.

KEYWORDS : Periodontitis, Growth factors, Platelet rich plasma, Fibrin tissue adhesive

Introduction: Periodontitis is an infectious disease causing destruction to periodontal tissues [1]. The goal of periodontal therapy is reconstitution of periodontium in structure and function. Periodontal regeneration requires series of biologic events i.e. migration, proliferation and differentiation of cells in the process of wound healing [2]. Platelets play a crucial role in hemostasis and wound healing. The α granules of platelets release platelet-derived growth factor (PDGF), transforming growth factor (TGFβ),and insulin-like growth factor (IGF-I).During activation, α granules fuses with platelet cell membrane releases growth factors. These growth factors bind to transmembrane receptors of target cells (Osteoblasts, fibroblasts, endothelial cells, and epithelial cells) leads to expression of various genes resulting cell proliferation, collagen synthesis and osteoid formation which results formation of soft and hard tissues of periodontium [2]

Platelet rich plasma (PRP): Marx first used PRP in the mandibular reconstruction defects [3] .It is a first generation platelet concentrates. It is a by-product of blood that is rich in platelets [4]. It contains platelets, coagulation factors and plasma proteins **(Fig.1)**. A natural human blood clot contains 95% red blood cells (RBCs), 5% platelets, less than 1% white blood cells (WBCs), whereas a PRP blood clot contains 4% RBCs, 95% platelets, and 1% WBCs [4]. It contains the maximum amount of platelets that can release desired growth factors (platelet derived growth factor (PDGF), transforming growth factors-β1 and -β2 (TGF-β1 and -β2) and insulin-like growth factor-1 [5] .The increased amount of growth factors will enhance soft and hard tissue healing process [5] .PRP contains Growth Factors (PDGF-AA, PDGF-BB, PDGF-AB & TGF), high concentration of platelets, phagocytes and fibrinogen. [6].The maturation rate during bone regenerative procedure is increased up to 2.16-times by PRP [6].The PRP production requires blood collection with anticoagulant, 2 steps of centrifugation, and using of calcium chloride and bovine thrombin for polymerization **(Fig.2)** [7]

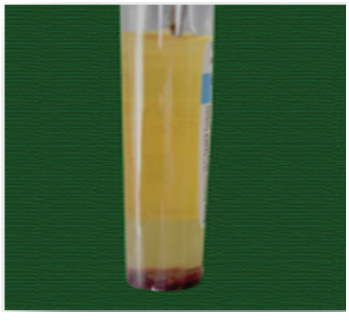


Fig.1: Platelet rich plasma

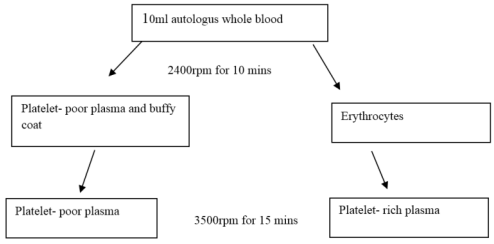


Fig.2: PRP protocol

Clinical implications, advantages, limitations and contraindications of PRP [6](Fig.3):

Clinical implications	Advantages	Limitations	Contraindications
1.Osseous defects 2. Sinus lift surgeries 3. Augmentation techniques 4. Peri-implant defects 5. Ridge preservation 6. Gingival recession 7.Healing of extraction wound	1. Safe autogenous preparation 2. Blood is collected at the time of preoperational	1. Presence of bovine thrombin which initiates allergic reaction 2. Lack of uniformity in PRP preparation protocols	1.Platelet disorders 2. Local infection at the site 3. Unwilling patient

Studies regard PRP application in different periodontal and implant surgical procedures: (Fig.4):

Treatment of	Positive Studies	Negative Studies
Infrabony defects(RCT)	Piemontese et al.2008[8],Kaushick BT et al. 2011[10]A.R. Pradeep et al.2012[13],Menzes et al.2012[14]],Hassan S et al. 2012[15] Kukreja BJ et al.2014 [16],Agarwal .A et al.2014 [17]	Dori et al.2007[7] ,Camargo et al.2009 [9], Harnack et al.2009 [10] ,Ozdemir B et al.2012 [12], Pinpe J et al. 2014 [18]
Gingival recession(RCT)	Jovovic et al.2013 [21]	Keceli. H et al.2008 [19], LeLafzi A et al. 2010 [20]
Sinus augmentation	Aiemetti et al.2008(RCT) [22] Torres et al.2009(RCT) [24], Khairy M et al. 2013(RCT)[25]	Schaff et al.2008(CS) [26]

RCT= Randomized clinical trial, CS= Case series

Positive Studies = Statistical significant difference between clinical parameters (PPD, CAL, Bone fill, Increase in keratinized width, root coverage, gingival thickness, bone formation around implant, no mobility of implant)in test and control groups.; **Negative Studies** = Statistical no significant difference between clinical parameters in test and control groups.

Platelet rich fibrin (PRF): It is a second generation platelet concentrate [26].It was developed by Choukroun. It is devoid of bovine thrombin which is seen in PRP preparation. [26,27]The interaction between leukocytic cytokines and fibrin complex play a vital role in the regeneration.

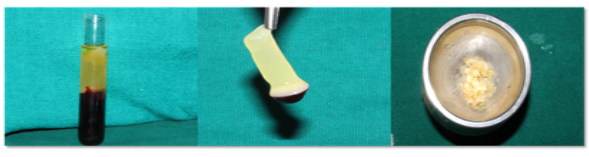
A physiological enriched fibrin complex matrix (PRF) releases growth factors in a controlled manner for longtime when compared to fibrin glue enriched with cytokines.

The preparation of PRF is simple. A blood sample is taken in 10 ml tube without anticoagulant and centrifuged at 3,000 rpm for 10 mins. The coagulation process is natural in test tube as it is devoid of thrombin [27]. It consists of 3 layers, upper layer-platelet poor plasma, middle layer- Fibrin clot with platelet, bottom layer-RBC **(Fig.5a).**

It contains cytokines such as IL-1, -4, -6, and growth factors such as Transforming Growth Factor beta 1 (TGF-β1), Platelet Derived Growth Factor (PDGF), and Vascular Endothelial Growth Factor (VEGF) [28,29]. PRF acts as a powerful scaffold with an integrated reservoir of growth factors for tissue regeneration. The fibrin matrix in PRF acts as natural guide for angiogenesis, natural support to immunity and guides the coverage of wounds **(Fig.5b).** [27]

Clinical implications, advantages, limitations and contraindications of PRF (Fig.6) [26-28]

Clinical implications	Advantages	Limitations
1. In sinus lift procedures 2. Socket preservations 3. Intrabony defects with or without bone grafts **(Fig. 5c).** 4. PRF membrane has been used for gingival recession coverage with coronally advanced or lateral pedicle flap for multiple and single recession respectively 5. Endo perio lesions 6. Furcation defects	1. It is completely safe. 2. Standard protocol for preparation.	1. As it is produced in limited quantities, which limits the utilization in general surgery or extensive surgical procedures. 2. PRF membranes are totally specific to the donor and cannot constitute an allogenic graft tissue. So PRF tissue banks are un feasible



A. B. C.

(Fig.5a):Platelet –rich fibrin in test tube (Fig.5b): Platelet-rich fibrin (Fig.5c):PRF mixed with bone graft

Difference between first and second generation platelet concentrate (Fig.7)[27]:

Platelet rich plasma(PRP)	Platelet rich Fibrin(PRF)
First generation platelet concentrate	Second generation platelet concentrate
Use of anticoagulants	No anticoagulants used
Fibrin polymerization is depends on the thrombin and calcium chloride and polymerization process is rapid.	Polymerization starts on contact with glass particles of the test tube which results in physiologic thrombin formation polymerization process is slow.
3-D organization of a fibrin network-condensed to tetra molecular structure which leads to a rigid network, not very favorable to cytokine enmeshment and cellular migration	3-D network-connected tri molecular allows the establishment of a fine and flexible fibrin network and able to support cytokines enmeshment and cellular migration
It can firmly seal biologic tissues because of gel in consistency	It can act as membrane because of it's elasticity and flexibility

Studies regard PRF application in different periodontal and implant surgical procedures (Fig.8):

Treatment of	Positive Studies	Negative Studies
Infrabony defects(RCT)	M Thorat et al. 2011[30] V. Rosamma Joseph et al.2012[31] A.R .Pradeep et al.2012[13] Chhya Bansal et al.2013 [32] Ajwani H et al.2015 [35],Agarwal .A et al. 2015 [36], A.R .Pradeep et al.2015 [37] Gupta SJ et al.2015 [38]	Mathur A et al.2015 [33] ,Shah M et al.2015 [34]
Gingival recession(RCT)	Del corso M et al.2009 [39] Sofia Aroca et al.2009[40] Padma R et al.2013[41] , Tunali M et al.2015[43]	Jankovic et al.2012[41], Eren G et al.2014[43], Thamaraiselvin et al.2015[45]
Sinus augmentation	Toffler M et al.20109(Early report of 110 pts) [46]	Zhang et al.2012(CS) [47]
Grade II furcation defects(RCT)	Sharma et al.2011[48] Bajaj P et al. 2013[49]	-
Post extraction socket filling(RCT)	Hauser F et al.2013[50]	-
Ridge preservation(RCT)	Barone A et al.2014[51]	-
Peri implant bone defects(RCT)	Hamzacebi.B et al.2015 [52]	-

RCT= Randomized clinical trial, CS= Case series

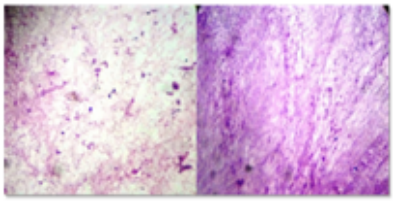
Positive results = Statistical significant difference between clinical parameters (PPD, CAL, Bone fill, Increase in keratinized width, root coverage, gingival thickness, bone formation around implant, no mobility of implant)in test and control groups.; **Negative results**= Statistical no significant difference between clinical parameters in test and control groups.

Titanium-prepared platelet-rich fibrin (T-PRF):

Some authors are worried about glass-evacuated blood collection tubes with silica particles as these particles may cause health hazards [53]. Only small fraction of these silica particles are sediment ting with red blood cells. Majority of silica particles suspends in a buffy coat so that these particles reach to patient when these product is used for treatment [54]. Although this is not practically concluded (the architecture of L-PRF change with type of material used for its preparation), some of the authors used more biocompatible material titanium for PRF preparation **(Fig.9).** [55]. Although basic histological structure similar between T-PRF and L-

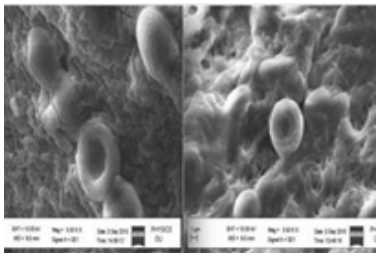
PRF, there is some difference in fibrin structure in T-PRF. The fibrin of T-PRF is more woven and thicker when compare with L-PRF. The difference may be due to the biocompatibility and hemocompatibility of titanium, which led to the formation of a more polymerized fibrin **(Fig.10, 11).** [55]. More research is required on T-PRF in terms of absorption time in body and clinical advantage over L-PRF.

(Fig.9): Titanium test tubes for T-PRF preparation



L-PRF **T-PRF**

(Fig.10): Histological analysis shows more number of fibroblasts and thicker fibrin structure in T-PRF when compares to L-PRF



L-PRF **T-PRF**

(Fig.11): SEM analysis shows more woven and thicker fibrin structure in T-PRF when compares to L-PRF

Advanced Platelet rich fibrin (A- PRF):

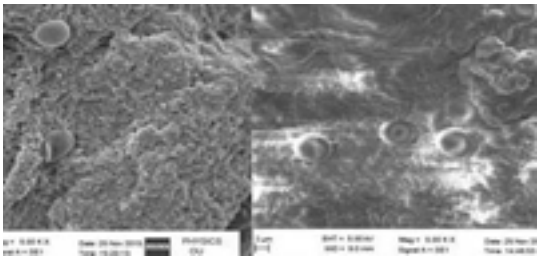
The centrifugation protocol is 1500 rpm 14 mins. Later it was modified to 1300 rpm 14 mins. It is based on the lower centrifugation protocol. Besides Platelets, Macrophages also produce growth factors. With the lower centrifugation protocol, it was proved that presence of macrophages in Advanced platelet rich fibrin. PRF clots formed with A-PRF centrifugation protocol showed a loose structure with more interfibrous space, and more cells in distal part of fibrin clot **(Fig-12).**More research is needed to find the effect of APRF on Periodontal Regeneration.[56]

Advanced Platelet rich fibrin (A- PRF) +:

The centrifugation protocol is 1300 rpm 8 mins. It is also based on lower centrifugation protocol. More research is needed to find the effect of APRF+ on Periodontal Regeneration.57

Injectable-PRF:

The centrifugation protocol is 700 rpm 3 mins. . This liquid PRF mix with bone grafts results steaky bone which uses for augmentation procedures. I PRF provides longer release of growth factors. I PRF releases growth factors even after 10 days. I-PRF demonstrated the ability to release higher concentrations of various growth factors and induced higher fibroblast migration and expression of PDGF, TGF-β, and collagen1 molecules which helps in regeneration.[57]



L-PRF **A-PRF**

Fig.12: SEM analysis shows more a loose structure with more interfibrous space in A-PRF when compares to L-PRF

CONCENTRATED GROWTH FACTORS (CGF): PRF uses constant centrifugation (2700 rpm 12 mins) speed, while CGF (Concentrated growth factors) utilizes altered centrifugation speed (2400-2700 rpm 12 mins) which leads to production of much larger, denser and richer fibrin matrix containing higher amount of growth factors [58]

STICKY BONE: The centrifugation protocol of autologous fibrin glue (AFG) is 2400-2700 rpm 2 mins. Less centrifugation time leads to availability of more growth factors. Sohn et al. 2010 fabricated-growth factors en riched bone graft matrix and called it as Sticky bone. Mixing of AFG (Autologous fibrin glue) to allo graft or to mixture of allo graft and xenograft produce Yellow sticky bone**.** Addition of exudates from CGF (Concentrated growth factors) is added to the above mixture leads to red color sticky bone formation. Uncoated tube uses for preparation of AFG [58]

BRIEF SUMMARY ON CENTRIFUGATION PROTOCOL OF VARIOUS PRF:

Various PRF	Centrifuge protocols
L-PRF	2700 rpm 12 mins
T-PRF	2700 rpm 12 mins
A-PRF	1500 rpm 14 mins
A-PRF(Modified)	1300 rpm 14 mins
A-PRF+	1300 rpm 8 mins
I-PRF	700 rpm 3-4 mins
CGF	2400 -2700rpm 12 mins
AFG	2400-2700 rpm 2 mins

Conclusion:

The preparation of platelet concentrates and clinical usage is simple and cost effective when compares to other regenerative materials i.e. GTR (guided tissue regeneration) membranes, EMD (enamel matrix derivatives) , bone grafts and substitutes. Most of the studies are showed that platelet concentrates are positive edge (either additive or alone) over other regenerative treatments i.e. GTR (guided tissue regeneration) membranes, EMD(enamel matrix derivatives), bone grafts and substitutes in periodontal regeneration .Despite the evidence of clinical advantage of these preparations, evidence of their beneficial effects is still lacking. Hence large and long term follow up randomized clinical trials are required for the determining the full effect of these preparations. They have been used for surgical procedures as they provide consistent benefits for the patient

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