REVIEW ARTICLE

PLATELET RICH CONCENTRATES & ADVANCEMENTS IN REGENERATION: A REVIEW

Vipin Agarwal, Vivek Vijay, Megha Phogat Rana, Arvinder Pal Singh, Prabhjeet Singh

Department Of Periodontology, Seema Dental College And Hospital, Rishikesh

ABSTRACT:
Platelet- rich fibrin is a second generation platelet concentrate and is defined as an autologous leukocyte and platelet-rich fibrin biomaterial. It was first developed by Choukroun for the first time in France. It has been used extensively in various disciplines in dentistry. In periodontal therapy it is used in combination with bone graft materials for periodontal regeneration, ridge augmentation, sinus lift procedures for implant placement and for coverage of recession defects in the form of a membrane. This membrane consists of a fibrin 3-D polymerized matrix in a specific structure, with the incorporation of platelets, leukocytes, growth factors and presence of circulating stem cells.
Key words: Platelet rich fibrin, regeneration, growth factors.

Corresponding author: Post Graduate Student, Department Of Periodontology, Seema Dental College And Hospital ,Rishikesh, Email Id: dr.prab22@gmail.com

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INTRODUCTION

One of the great challenges of clinical research has beenthe development of bioactive surgical additives, which helpto regulate inflammation and increase the speed of healingprocess[1].The healing of hard and soft tissues both, is mediated by a wide range of intra and extraarticular events, which in turn are regulated by various signaling proteins. Understanding of this entire process is still not complete[2,3]; however, it is known that platelets play a crucial role not only in hemostasis, but also in the wound healing process.

Although use of fibrin adhesives in many field related protocols is well documented, it has remained controversial owing to complexity of the production protocols, risk of cross infections, etc. The development of platelet concentrates technologies leads to development of a new kind of fibrin adhesive, concentrated Platelet Rich Plasma (cPRP), but because of the legal restrictions on blood handling, another new family of platelet concentrate appeared in France. This new biomaterial has widespread application in several branches of dentistry such as periodontology, oral and maxillofacial surgery, oral Implantology, Endodontolgy[4].

Platelet rich fibrin (PRF) is a fibrin matrixin which platelet cytokines, growth factors and cells are trapped and may be released after a certain time and that can serve as a resorbable membrane.[5] It can be obtained from blood with the help of a simple process. PRF is basically a concentrate of growth factors that promote wound healing and regeneration which is used in various disciplines of dentistry to repair various lesions and regenerate dental and oral tissues.

DEVELOPMENT OF PLATELET CONCENTRATES

Platelets isolated from the peripheral blood are an autologous source of growth factors. In medical practice, platelet concentrateis derived from blood, and is used for the prevention and treatment of hemorrhages due to conditions like severe thrombocytopeniaof central origin, such as due to medullary aplasia, acute leukemia, etc[4]. The development of platelet concentrate as a bioactive

surgical additive, stems from the use of fibrin adhesives[6].Since 1990, medical science has recognized several components in blood, which are a part of the natural healing process, and when added to wounded tissues or surgical sites, have the potential to accelerate wound healing. Fibrin glue was first described in 1970 and is formed by polymerizing fibrinogen with thrombin and calcium. It was originally prepared using donor plasma; however, because of the low concentration of fibrinogenin plasma, the stability and quality of fibrin glue was low. These adhesives can be obtained from the patient or canbe obtained commercially, the latter carrying a small risk of disease transmission. PRP is an autologous modification of fibrin glue, derived by methods that concentrate autologous platelets, and has been described and used in various applications with apparent clinical- success. It is an easily available source of growth factors to support bone and soft tissue healing. PRP is a simple strategy to concentrate platelets or enrich natural blood clot. A natural blood clot contains 94% red blood corpuscles (RBCs), 5% platelets and1% white blood corpuscles (WBCs), while PRP contains 95% ofplatelets[4].PRP obtained from autologous blood is used to delivergrowth factors in higher concentration to the site of bone defect ora region requiring augmentation. The drawbacks of PRP includebiochemical blood handling with addition of anticoagulants.

The PRF is a second generation platelet concentrate which is animprovement over tradionally prepared PRP.

CLASSIFICATION OF PLATELET CONCENTRATES

Platelet concentrates can be classified into four categories.

1) P-PRP - Pure Platelet Rich Plasma,
2) L-PRP - Leucocyte and Platelet Rich Plasma,
3) P-PRF - Pure Platelet Rich Fibrin,
4) L-PRF - Leucocyte and Platelet RichFibrin[7].

PREPERATION OF PRF

This preparation protocol is very simple: a blood sample iscollected without an anticoagulant in 10-mL tubes and is immediatelycentrifuged at 3,000 rpm (800 g) for 10 min. Even whenthrombin or calcium is not added to the blood sample, mostplatelets can be activated in a few minutes through contact withthe tube walls to trigger the intrinsic coagulation cascades.Therefore, another characteristic of Choukroun's PRF is that the resulting fibrin gel is less stiff than that prepared by the addition of thrombin.[1,8]

ADVANTAGES OF PRF OVER PRP:

1. Simple and cost effective method of preparation of PRF
2. Eliminates the use of bovine thrombin and there by reduces the chances of cross infection. It has been discovered that the use of bovine thrombin may be associated with the development of antibodies to the factors V, XI and thrombin, resulting in the risk of life threatening coagulopathies[5].
3. Slow natural polymerization of PRF on contact with glass particles of the test tube results in physiologic thrombin concentration, while in PRP, there is sudden fibrin polymerization depending on the amount of surgical additives (thrombin and calcium chloride)[9].
4. Fine and flexible 3-D structure of PRF more favourable to cytokine enmeshment and cellular migration.3-D network-connected tri-molecular or equilateral junctions in PRF allows the establishment of a fine and flexible fibrin network able to support cytokines enmeshment and cellular migration while3-D organization of PRP consists of a fibrin network condensed tetra molecular or bilateral junctions constituted with strong thrombin concentrations which allows the thickening of fibrin polymers leading to a rigid network, not very favourable to cytokine enmeshment and cellular migration[9].
5. PRF has supportive effect on immune system[10].
6. PRF helps in hemostasis[10].
7. An in-vitro study showed that PRF is superior to PRP, considering the expression of alkaline phosphatase and induction of mineralization, caused markedly by release of TGF-β1and PDGF-AB[11]

ROLE OF PRF IN WOUND HEALING:

Wound healing consists of three phases:

1. Inflammatory phase (1-4 days) (substrate-preparation phase)

2. The proliferation phase (2-22 days) (collagen-building phase)

- Epithelisation
- Angiogenesis
- Granulation tissue formation
- Collagen deposition

3. Maturation (remodeling phase) (6-12 months)

- Collagen maturation and contraction

PRF consists of a fibrin matrix polymerized in a tetra molecular structure with the incorporation of platelets, leukocyte and cytokines, and the presence of circulating stem cells[12]. PRF stimulates osteoblasts, gingival fibroblasts, and periodontal ligament cells proliferation as a mitogen. Its molecular structure with low thrombin concentration is an optimal matrix for migration of endothelial cells and fibroblasts[13]. It permits a rapid angiogenesis and an easier remodelling of fibrin. The Leukocytes and key immune cytokines like IL 1β, IL 6,IL 4 and TNF α trapped in PRF give it the anti-infectious effect and lets PRF act as an immune regulation mode[14].It features all the necessary parameters permitting optimal healing.

PRF matrix can release various growth factors and cytokines locally at the wound site for a prolonged periodof time which play important role in various stages of wound healing promoting periapical tissue generation. Growth factors are released from the alpha-granules in the platelets when they are activated, secreted, or aggregated by collagen or epinephrine[13]. TGF-beta and PDGFare the typical two growth factors which promote healing of soft tissue and bone through stimulation of collagen production to improve wound strength and initiation of callus formation[15].

Platelet-derived growth factor (PDGF) is a potent activator for cells of mesenchymal origin. It is among the first cells to reach at the wound site. Strayhorn[16] et al suggested that PDGF might act mostly on osteoblastic cell proliferation, exerting most of its effects during the early phases of woundhealing[16]. It also stimulates chemotaxis, proliferation, and new gene expression in monocytes-macrophages and fibroblasts in vitro, cell types considered essential for tissue repair.

Vascular endothelial growth factor (VEGF) is a major angiogenic growth factor. It acts on endothelial cells, being produced by numerous cell types, including vascular smooth muscle cells (VSMC), fibroblasts etc. initiating blood vessel formation.

Transforming growth factor Beta-1 (TGF beta-1), anti-Inflammatory regulator, is the most powerful fibrosis agent amongst all cytokines and can induce a massive synthesis of collagen and fibronectin either by fibroblasts or osteoblasts[5].

The physiologic fibrin matrix of PRF, obtained as the resultof slow polymerization, has the ability to hold various growth factors and cytokines and release them at the wound site for a prolonged time period. Moreover, the fibrin matrix itself shows mechanical adhesive properties and biologic functions like fibrin glues: it maintains the flap in a highand stable position, enhances neoangiogenesis, reduces necrosis and shrinkage of the flap, and guarantees maximal root coverage. It plays an important role in angiogenesi sand wound coverage[17].

Angiogenesis requires an extracellular matrix to allow migration, proliferation and phenotype differentiation of endothelial cells. The angiogenesis property of the fibrin matrix is explained by the 3-dimensional structure of the fibrin gel and the simultaneous action of the cytokines trapped in fibrin meshes[18]. Furthermore, main angiogenesis soluble factors such fibroblast growth factor basic (FGFb), vascular endothelial growth factor (VEGF),angiopectin and platelet derived growth factor (PDGF) are included in fibrin gel which can bind to fibrin with high affinity.

Fibrin matrix guides the wound coverage affecting the metabolism of fibroblasts and epithelial cells. The epithelial cells around the wound margins lose their basal and apical polarity and produce basal and lateral extensions towards the wound site. These cells then migrate onto the transitory matrix made by fibrinogen, fibronectin, tenascin and vitronectin[18]. Fibrin, fibronectin, PDGF and TGF-Bare essential to modulate integrin expression, fibroblast proliferation and their migration inside the wound. After migration and degradation of fibrin, fibroblasts start the collagen synthesis.PRF also aids in trapping circulating stem cells brought to the wound site due to initial neovascularization during hemostasis and healing[18]. Set in the fibrin matrix, these cells converge on a secretory phenotype, allowing the vascular and tissue restoration. This aspect of PRF serving as a net to the stem cells can be beneficial in cases of wided effects

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PLATELET RICH FIBRIN IN PERIODONTAL SURGERY

PRF can be considered as a natural fibrin based biomaterial favourable to the development of a microvascularisation and able to guide epithelial cell migration to its surface. The interest of such a membrane is evident, namely to protect open wounds and accelerate healing[19].Its utilisation seems to be of high interest in cases of infected wounds as this matrix also contains leucocytes and promote their migration. Fibrin and its degeneration products helps in providing natural support to immunity by

modulating CD11/CD18 receptors etc[20], in vivo release of growth factors was a proposal to optimize the clinical application. So keeping this in mind PRF is routinely used in various surgical procedures like root coverage, stabilisation of graft in various procedures, placements of implants in borderline cases, ridge augmentation and pre-prosthetic surgeries.

STUDIES ON PLATELET RICH FIBRIN IN ROOT COVERAGE

s. no.	Author /year	Methodology	Result
1	Aroca S[21] et al/ 2009	Modified coronally advanced flap + PRF (Test) Vs Modified coronally advanced flap.(Control) 20 subjects with Miller class I or II recession. Mean recession value at baseline = 2.9 ± 1.1 mm for test and 2.5 ± 0.9 mm for control sites. At baseline gingival thickness was 1.1 ± 0.3mm for test and 1.1 ± 0.3mm for control sites.	• At 6 months complete root coverage at 74.6% control sites & 52.2% of test sites. • Mean root coverage of 80.7% at test sites and 91.5% at control sites. • Increase in gingival thickness to 1.4 ± 0.5 mm for test and 1.1 ± 0.3mm for control sites
2	Aleksic Z[22] et al /(2010)	Coronally advanced flap + PRF membrane (PRF group) Vs Coronally advanced flap + CTG (CTG group) Parameters recorded were vertical recession depth (VRD), probing depth(PD), clinical attachment level (CAL), keratinized tissue width (KTW), healing index(HI) at 1st, 2nd& 3rd week post- surgically. Follow up of 12 months	• Mean root coverage of 79.94% in PRF group & 88.56% in CTG group. • KTW increases in both the groups. • HI enhanced in PRF group.
3	Jankovic S[23] et al /(2012)	6 month randomized controlled clinical study including 15 patients with class I and class II Millers defect. Coronally advanced flap + PRF Vs Coronally advanced flap + CTG	• Enhanced wound healing and less patient discomfort in PRF group • Mean root coverage of 88.68% in test group and 91.96% in control group. • Complete root coverage was achieved in 75.85% of cases in PRF group and 79.56% in control group. • More gain in keratinized tissue width in CTG group
4	Padma R [24] et al /(2013)	15 subjects with bilateral isolated Miller's class I and class II recession were taken. Coronally advanced flap + PRF (test) Vs Coronally advanced flap (control) Clinical parameters compared are recession depth , clinical attachment level and width of keratinized gingiva.	• Mean root coverage in test group at 1, 3 and 6 month is 34.58, 70.73, 100% respectively. • Increase in width of keratinized gingiva from 2.94 ± 0.77mm at baseline to 5.83 ± 1.67 at 6 months .
5	Erren G , Atilla	22 subjects with 44 defects miller class I & II	• Percentage of root coverage

	G[25] /(2014)	included in split mouth trial. Coronally advanced flap + PRF (test) Vs Coronally advanced flap + SCTG (control) Clinical parameters considered Gingival recession depth (RD), gingivalrecession width (RW), keratinized tissue width (KTW), recessionarea (RA), probing depth (PD), clinical attachment level(CAL) and gingival thickness (GT) were evaluated at baselineand 6 months.	in test group was 92.7 % and in control group was 94.2 %. • KTW and GT were increased in both groups. • Complete root coverage was achieved in 72.7% cases in test group and 77.3% cases in control group.
6	Thamaraiselvan M[26] et al /(2015)	20 subjects each with singleMiller's class I or II buccal recession defect were included. Coronally advanced flap + PRF (test) Vs Coronally advanced flap (control) Clinical outcome was determined by measuring the following clinical parameters such as recession depth (RD),recession width (RW), probing depth (PD), clinical attachment level (CAL), width of keratinized tissue (WKT),gingival thickness (GTH), plaque index (PI), and gingival index (GI).	• The root coverage was 65.00 ± 44.47% in the control group and 74.16 ± 28.98% in the test group at 6th month. • Increase in GTH in the test group was observed.
7	Tunalı M[27], et al/(2015)	A total of 44 Miller ClassI/II gingival recessions that were bilateral, adjacent, and greater than 3 mm insize were selected. Test group(L-PRF) Vs Control group (CTG).	• After 12 months, root coverage was 76.63% and 77.36% in the L-PRF and CTG groups, respectively.
8	Gupta S[28]et al /(2015)	Thirtyisolated Miller class I or II sites in 26 subjects were selected. Coronally advanced flap + PRF (test) Vs Coronally advanced flap (control) Parameters:- probing pocket depth (PPD), Recession depth (RD), Clinical attachment loss (CAL), Keratinised tissue width(KTW) and Gingival tissue thickness (GTH) were evaluated at baseline, 3 months and 6 months postoperatively.	• Mean percentage root coverage was 91.00±19.98% and 86.60±23.83% for test and control group respectively. Complete root coverage was obtained in 12 (80%) and 11 (73.3%) subjects in test and control group respectively.

DISCUSSION

Aroca S[21] et al in 2009 concluded that MCAF is a predictable treatment for multiple adjacent Miller Class I or II recession-type defects. The addition of a PRF membrane positioned under the MCAF provided inferior root coverage but an additional gain in GTH at 6 months compared to conventional therapy which is consistent with the results concluded by Jancovic et al[23] which also stated that no difference could be found between PRF and CTG procedures in gingival recession therapy, except for a gain in keratinized tissue width obtained in the CTG group and enhanced wound healing associated with the PRF group. Another study by Padma R[24] et al to study the additional benefits of PRF when used along with coronally advanced flap (CAF). It was concluded that CAF is a predictable treatment for

isolated Miller's class I and II recession defects. The addition of PRF membrane with CAF provides superior root coverage with additional benefits of gain in CAL and WKG at 6 months postoperatively which is not in accordance with previous studies by Aroca et al[21] and Jancovic et al[23]. Aleksic Z[22], et al in 2010 also stated that utilization of the PRF resulted in a decreased postoperative discomfort and advanced tissue healing but root coverage achieved in CTG group was superior as compared to PRF group. These results are in accordance with that achieved by Jankovic et al[23] in which percentage root coverage achieved by CTG group was better as compared to PRF group.Eren G, Atilla G[25] in 2014 conducted a study to evaluate the clinical efficacy of platelet-rich fibrin (PRF) in combination with coronally advanced flap (CAF) in the treatment of localized gingival recessions. It was concluded that that localized gingival recessions could be successfully treated with CAF+PRF as well as CAF+SCTG. Results achieved by both the techniques were comparable and no significant difference was there, as in other studies.[22, 23]Thamaraiselvan M[26] et al conducted a study to determine whether the addition of an autologous platelet rich fibrin (PRF) membrane to a coronally advanced flap (CAF) would improve the clinical outcome in terms of root coverage, in the treatment of isolated gingival recession. Previous studies by Aroca et al[21], Jancovic et al[23] and Aleksic et al[22] stated similar results as by this study that CAF is a predictable treatment for isolated Miller's class I and II recession defects. The addition of PRF to CAF provided no added advantage in terms of root coverage except for an increase in GTH.

Tunalı M[27], et al in 2015 conducted a study that evaluated the safety and effectiveness of using L-PRF membranes as a substitute for free connective tissue grafts (CTGs) as a treatment method for gingival recession defects. It is suggested that L-PRF membrane may be an alternative graft material for treating multiple adjacent recessions greater than 3 mm in size without a requirement for additional surgery and creating a second surgical site and unnecessary discomfort to the patient can be avoided. Gupta S[28]et al in 2015 conducted a study to compare the clinical efficacy of coronally advanced flap (CAF) alone and in combination with autologous platelet rich fibrin membrane (PRF) in Miller's class I and II gingival recessions. The difference was found to be non‑significant for root coverage. Both groups showed significant differences in all parameters at 3 and 6 months respectively except difference in gingival tissue thickness. It was concluded that Combination of PRF to CAF procedure did not provide any added advantage in term of recession coverage in Miller class I and II recessions. These results are in accordance with the previous studies.[21, 22, and 23]

Conclusion

The use of PRF as an adjunct in wound healing and periodontal regeneration has shown promising results. It has been successfully used for correction of osseous defects, for correction of mucogingival problems. However, most studies with PRF have shown short term results only. More controlled clinical trials with long term results are needed to conclude the efficacy of this biomaterial on a long term basis and to optimize its use in daily procedures. In addition to clinical trials, histopathological studies are also required to learn about the nature of the newly formed tissue in the defect and to understand the biology, efficacy and its mode of action of PRF more effectively.

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