Review Article

Platelet-rich Fibrin: A Paradigm in Periodontal Therapy – A Systematic Review

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Abstract

Periodontal tissue regeneration has always been a challenge for the periodontists owing to its structural complexity. Although with tissue engineering as a growing multidisciplinary field, this aim has partially been fulfilled. In recent years, platelet-rich fibrin (PRF) has gained wide attention for its utilization as a biocompatible regenerative material not only in dental but also in medical fields. The following systematic review has gathered all the currently available *in vitro*, animal, and clinical studies utilizing PubMed electronic database from January 2006 to August 2016 highlighting PRF for soft and hard tissue regeneration and/or wound healing. Although results are encouraging but require further validation from clinical studies to justify the potential role of PRF in periodontal regeneration so that this relatively inexpensive autologous biomaterial can be utilized at a wider scale.

Keywords: *Intrabony defect, platelet concentrates, platelet-rich fibrin, regeneration, wound healing*

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Introduction

Primary objective of day-to-day ongoing researches is to optimize healing and the biggest challenges that the researchers are facing is the development of a regenerative biomaterial to regulate inflammation and accelerate wound healing.[1]

Healing is a complex process that involves organization of cells, biochemical triggers, and extracellular matrix synthesis for repair of the tissue.[2] Role of platelets in hemostasis and wound healing is well established, but the exact mechanism of healing in depth is still unclear.[3]

Role of platelets in regeneration was proven way back in the 1970s,[4] owing to the fact that it is a reservoir of growth factors that are responsible for neovascularization, collagen synthesis, cell division, cell differentiation, induction, and migration of other cells to the injured site.[5]

Postperiodontal surgery, wound healing occurs through a complex interaction between gingival fibroblasts, periodontal ligament cells, osteoblasts, and epithelial cell. Damage of blood vessels results in fibrin formation followed by platelet aggregation and elaboration of growth factors in the tissues.[6] This cellular interaction is under molecular control of biochemical mediators, i.e., cytokines and growth factors.

The crucial role of platelets in inflammation and wound healing is due to the presence of several growth factors and cytokines.[7] Furthermore, they contain fibrin, fibronectin, and vitronectin that provide connective tissue, a matrix and create an efficient network for cell migration.[1] This has led to the idea of using platelets as therapeutic tools to improve tissue repair, particularly in wound healing.

Search Strategy for the Identification of Studies

The PubMed database of the US National Library of Medicine was utilized as the electronic databases, and a literature search was accomplished on articles using

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combination of various MeSH and free text words "Platelet rich fibrin or PRF and Periodontal therapy," "Platelet rich fibrin or PRF and clinical applications," "Platelet rich fibrin or PRF and Periodontology" from January 2006 to August 2016. A total of 49 scientific papers (14 *in vitro*, 2 animal, and 33 clinical studies) meeting the criteria were scrutinized. There was no restriction on the language and publication status imposed on the articles. Further additional studies were sought by searching the reference lists of identified trials and reviews.

Classification of Platelet-rich Concentrates

Following the debates about the various components of these platelet-rich concentrate preparations, a first classification was proposed by Dohan Ehrenfest *et al*., 2009,[8] which is now widely accepted. The classification is simple and is based on the presence or absence of leukocytes and the density of fibrin architecture in platelet concentrates. Depending on the difference in these parameters, it can be divided into the following four main types, i.e., pure platelet-rich plasma, pure platelet-rich fibrin (PRF), leukocyte and platelet-rich plasma, and leukocyte and PRF which are described here forth in Figure 1.

Proposed Mechanism of Action

Properties of platelet concentrates depends on the techniques used as Choukroun's PRF is based on mechanical concentration process.[9,10] PRF is a condensation of suspended growth factors within platelets [Figure 2].[11-14] These growth factors are considered as tissue regenerative boosters and are ramified in wound healing. Based on elaborated growth factors from PRF, optimization of clinical usage of PRF can be done.[15,16]

Application of Platelet-rich Fibrin in Clinical Periodontology

A convincing healing bioregenerative material, PRF, shows compelling data in various *in vitro* and clinical studies. It can be utilized in various procedures such as management of intrabony defects, gingival recession, furcation defects, extraction socket preservation, and accelerated healing of wound. The following are some of the important studies highlighting its regenerative potential in the field of Periodontology [Table 1].

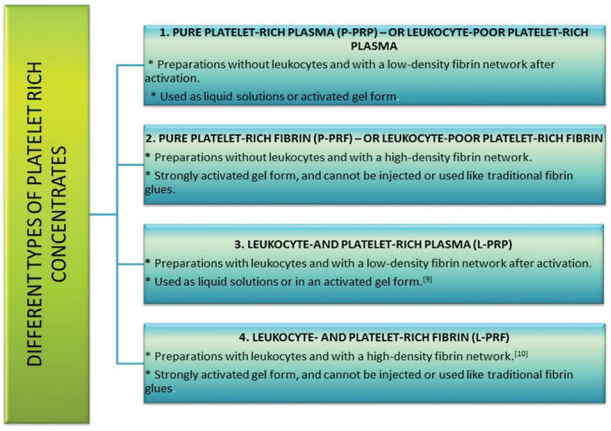

Figure 1: Description of different types of platelet rich concentrates

Discussion

The regeneration of the lost periodontal structures is the ultimate aim of the periodontal therapy to restore the health, function, and esthetics of periodontium. From periodontal point of view, the experimental and *in vitro* studies emphasizing the role of PRF on periodontal regeneration and periodontal wound healing are important and hereby discussed.

The breakthrough *in vitro* study that introduced PRF in medical field was conducted by Choukroun *et al*. It highlighted improved neovascularization, wound closing with accelerated tissue remodeling in the absence of infectious events.[16]

PRF used either in combination with bone grafts (bovine porous bone mineral, nanocrystalline hydroxyapatite, and demineralized freeze-dried bone allograft [DFDBA]) or pharmacologic agents such as metformin gel was found to be more effective in terms of improvements in clinical parameters and radiographic defect depth reduction compared to when bone grafts or metformin used alone.[17-20,24] Furthermore, the clinical and radiographic results of PRF used alone were comparable to DFDBA for periodontal regeneration.[19]

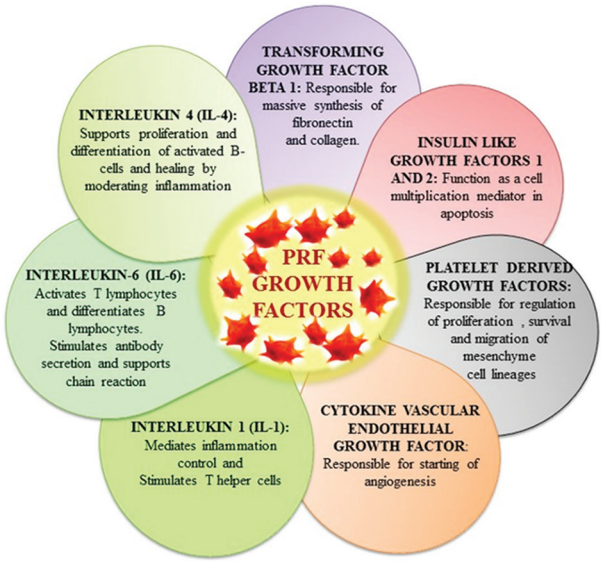

Figure 2: Role of platelet-rich fibrin growth factors and cytokines in tissue regeneration and wound healing. Transforming growth factor β1, insulin-like growth factor 1 and 2, platelet-derived growth factor, cytokine vascular endothelial growth factor, and interleukin 1, 4, and 6

Table 1: The studies implicating the role of platelet-rich fibrin in clinical periodontology

Serial number	Author's name	Year	Type of study	Conclusion
		PRF in regeneration of intrabony defects		
1	Agarwal *et al*.[17]	January 2016	RCT	PRF + DFDBA more effective than DFDBA with saline
2	Pradeep *et al*.[18]	June 2015	RCT	PRF + 1% MF group showed better results in clinical parameters and radiographic defect depth reduction compared to MF, PRF, or OFD alone
3	Shah *et al*.[19]	January 2015	RCT	PRF showed comparable results to DFDBA in terms of clinical parameters
4	Elgendy and Abo Shady[20]	January 2015	RCT	PRF + NcHA more effective clinically and radiographically compared to NcHA
5	Gupta *et al*.[21]	July 2014	RCT	Emdogain superior to PRF in terms of percentage defect resolution
6	Panda *et al*.[22]	July 2016	SRM	Together with OFD, PRF can be utilized as a sole regenerative material
7	Pradeep *et al*.[23]	December 2012	RCT	Either PRF or PRP with OFD demonstrated similar probing depth reduction, clinical attachment gain, and radiographic bone fill. PRF is less time consuming and relatively less technique sensitive
8	Lekovic *et al*.[24]	August 2012	RCT	PRF group resulted in improvement in clinical parameters while PRF + BPBM group augmented the PRF effects in pocket depth reduction, clinical attachment gain, and defect fill
9	Sharma and Pradeep[25]	December 2011	RCT	PRF + OFD group demonstrated greater probing depth reduction, clinical attachment gain, and bone fill in comparison to OFD alone group
		PRF in recession defects		
1	Eren *et al*.[26]	August 2016	RCT	Root coverage with CAF+PRF resulted in significant increase in GCF TIMP-1 (levels and decrease in GCF MMP-8 and IL-1β levels as compared to CAF + CTG group
2	Femminella *et al*.[27]	February 2016	RCT	PRF enriched palatal bandage not only accelerated wound healing at the site of graft harvestation but also reduced the patients's morbidity
3	Moraschini and Barboza Edos[28]	November 2016	SRM	PRF showed no improvement in terms of root coverage, keratinized mucosa width, or clinical attachment level of Miller Class I and II gingival recessions compared to the other treatment modalities such as CTG group
4	Keceli *et al*.[29]	November 2015	RCT	Addition of PRF to CAF + CTG group added no further additive value except increasing tissue thickness
5	Doğan *et al*.[30]	September 2015	RCT	Gingival recession defects treated with concentrated growth factor enhanced the keratinized gingival width and gingival thickness
6	Aras *et al*.[31]	August 2015	*In vivo*	Denuded root surfaces after orthodontic treatment when treated with CAF + PRF showed satisfactory occlusal and periodontal results
7	Gupta *et al*.[32]	April 2015	RCT	In case of Miller Class I and II recessions combing CAF to PRF provided no added advantage in terms of recession coverage
8	Thamaraiselvan *et al*.[33]	January 2015	RCT	In case of Miller Class I and II recessions combing CAF to PRF provided no added advantage in terms of recession coverage except for increase in gingival tissue thickness
9	Tunalı *et al*.[34]	January 2015	RCT	In comparison to CTG group, leukocyte-PRF group showed better results in terms of root coverage indicating that it can be an alternative graft material for management of multiple adjacent recessions greater than 3 mm in size
10	Shetty *et al*.[35]	January 2014	RCT	Amniotic membrane can be successfully used as an autologous alternative to PRF in reducing the need for a second surgical site

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Table 1: Contd...

Serial number	Author's name	Year	Type of study	Conclusion
11	Agarwal *et al*.[36]	January 2013	RCT	Double lateral sliding bridge flap+PRF showed an advantage of a single step procedure that resulted in complete root coverage and increased zone of keratinized gingiva
12	Padma *et al*.[37]	September 2013	RCT	For Miller Class I and II recessions, addition of PRF with CAF provides superior root coverage and added benefits of gain in clinical attachment levels and width of keratinized gingiva
13	Jankovic *et al*.[38]	April 2012	RCT	Laterally, positioned pedicle flap revised technique along with autologous suspension of growth factors and PRF for managing Miller Class II recessions showed stable 80% root coverage after 6 months
14	Jankovic *et al*.[39]	August 2010	Comparative study	PRF and CTG showed no difference except for greater gain in keratinized tissue width in CTG group whereas enhanced wound healing in PRF group
15	Aleksić *et al*.[40]	January 2010	RCT	No clinical advantage of PRF compared to enamel matrix derivative in covering gingival recession with CAF procedure
16	Del Corso *et al*.[41]	November 2009	*In vivo*	Reduced postoperative discomfort and enhanced tissue healing were the advantage of using PRF
17	Aroca *et al*.[42]	February 2009	Controlled clinical trial	Modified CAF+PRF resulted in inferior root coverage results but an added gain in gingival tissue thickness compared to conventional therapy
		PRF in furcation defects		
1	Pradeep *et al*.[43]	October 2016	RCT	Combining rosuvastatin, PRF, and porous hydroxyapatite shows synergistic effects as a regenerative material
2	Bajaj *et al*.[44]	October 2013	RCT	PRF or PRP both were effective with uneventful healing of sites
3	Sharma and Pradeep[45]	October 2011	RCT	The use of autologous PRF showed significant improvement implying its regenerative role
		PRF and *In Vitro* studies		
1	Kawase *et al*.[46]	May 2015	*In vivo*	Advocated the use of heat compression technique in preparing PRF for guided tissue regeneration procedures since it reduces the rate of biodegradation of PRF membrane without affecting its biocompatibility
2	Fan *et al*.[47]	February 2013	*In vivo*	PRF has positive biological effect on human gingival fibroblasts and hence can be utilized in tissue engineering when combined with seed cell human gingival fibroblast
3	Clipet *et al*.[48]	February 2012	*In vivo*	Showed that soluble growth factors can potentially stimulate tissue healing and bone regeneration
4	Gassling *et al*.[49]	May 2010	*In vivo*	PRF was found to be superior to collagen membrane (bioguide) as a scaffold for human periosteal cell proliferation
5	Dohan Ehrenfest *et al*.[50]	September 2009	*In vivo*	PRF cocultured with leukocytes (called chaperone leukocyte) shows double contradictory effect of proliferation/differentiation observed on osteoblasts
6	Choukroun *et al*.[16]	March 2006	*In vivo*	Highlighted accelerated tissue cicatrization because of development of neovascularization, fast wound closing, and tissue remodeling and absence of infectious events
		PRF in soft tissue healing		
1	Del Fabbro *et al*.[51]	Winter, 2014	SRM	Suggests positive role of platelet concentrates on bone formation in postextraction sockets
2	Jeong *et al*.[52]	September 2014	Animal study	Sinus lift done simultaneously with dental implants are neither predictable nor reproducible when PRF is used as the sole grafting material
3	Hatakeyama *et al*.[53]	February 2014	RCT	Both PRF and PRP promote maturation of bone in the presence of abundant osteogenic cells

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Table 1: Contd...

Serial number	Author's name	Year	Type of study	Conclusion
4	Hauser *et al*.[54]	June 2013	RCT	Socket preservation by PRF results in predictable results
5	Gürbüzer *et al*.[55]	May 2010	RCT	PRF might not lead to enhanced bone healing in impacted mandibular third molar extraction sockets 4 weeks after surgery

RCT=Randomized control trial, SRM=Systematic review and meta-analysis, DFDBA=Demineralized freeze dried bone graft, MF=Metformin, OFD=Open flap debridement, NcHA=Nanocrytalline hydroxyapatite, BPBM=Bovine porous bone mineral, CAF=Coronally advanced flap, CTG=Connective tissue graft group, TIMP-1=Tissue inhibitor of matrix metalloproteinases-1, MMP-8=Matrix metalloproteinase-8, IL-1β=Interlukin 1β, PRF=Platelet rich fibrin, PRP=Platelet-rich plasma, GCF=Gingival crevicular fluid

Although the efficacy of PRF as compared to Emdogain was found to be inferior in terms of defect resolution.[21]

Studies have shown similar probing depth reduction, clinical attachment level gain, bone fill at sites treated with PRF, or PRF with open flap debridement. However, due to the fact that PRF is less technique sensitive, it may be considered as a better treatment option than PRF.[23]

PRF being a reservoir of soluble growth factors and cytokines (transforming growth factor beta-1, insulin-like growth factor 1 and 2, platelet-derived growth factor, cytokine vascular endothelial growth factor, and interleukin 1, 4, and 6) that not only help in tissue regeneration but also accelerate wound healing. Studies have shown that PRF, when used with coronally advanced flap for recession coverage, has shown to decrease matrix metalloproteinase-8 (MMP-8) and interleukin beta levels but increase in tissue inhibitor of MMP-1 levels at 10 days, thereby promoting periodontal wound healing in the earlier phase of the process.[26,27]

A systematic meta-analysis by Moraschini and Barboza Edos[28] and clinical studies by Keceli *et al*.[29] and Gupta *et al*.[32] have highlighted the inconsistent results of PRF in covering Miller Class I and Class II gingival recessions with no improvement in terms of root coverage, keratinized mucosa width, or clinical attachment level, but it was shown to have increased the gingival thickness.

Further, Padma *et al*.[37] in a randomized controlled trial proved predictable treatment for isolated Miller class I and II recession defects when used with coronally advanced flap. It provided superior root coverage with added benefit in gain in clinical attachment level and width of keratinized gingiva after 6 months postoperatively.

On comparing with PRF and connective tissue graft (CTG) in gingival recession procedures, it was found that there was a greater gain in keratinized tissue width in CTG group but better wound healing in PRF group.[39]

Similar to the management of infrabony defects, the use of PRF in furcation defects when combined with bone grafts (hydroxyapatite) and rosuvastatin has shown better results emphasizing its role in periodontal regeneration.

Various *in vitro* studies have shown a positive biological effect in human gingival fibroblast which can have a potential role in the management of gingival recession and periodontal tissue engineering.[47]

It is well established that PRF contains soluble growth factors that not only stimulate tissue healing but also bone regeneration.[48] For guided tissue regeneration procedures, PRF has proved to be superior scaffold as compared to collagen membrane when used for *in vitro* cultivation of periosteal cells.[49]

PRF has also shown remarkable positive healing effects when used for the preservation of extraction socket and in sinus lift procedures during simultaneous dental implantation (Jeong *et al*., 2014).[52]

The studies show outstanding results with PRF in regenerating periodontal osseous defects and preserving extraction healing socket. Although there were conflicting data when PRF was used for managing gingival recession defects for root coverage.

Conclusion

Studies have confirmed that PRF is a therapeutic regenerative biomaterial with immense potentiality that has widespread clinical applications in medical as well as dental perspectives. The use of PRF alone or in combination with other biomaterials (such as bone grafts, soft tissue grafts, and pharmacologic agents) provided safe and promising results in the form of improvements in clinical and radiographic parameters in the management of periodontal osseous defects and hard tissue preservation of extraction socket. Although in denuded root coverage procedures in cases of gingival recessions, PRF showed some contradictory findings, and the results were not that favorable, but still, it provided an added advantage in terms of increment in gingival tissue width and thickness (gingival biotype). Tissue biotype is an important factor because it narrates the way a tissue will respond to inflammation, trauma, and surgical insult. Hence PRF does result in thick gingival

biotype which shows greater dimensional stability during remodeling and enhancing collateral blood supply to the underlying osseous structure as compared to thin biotype which may compromise it.

Although the potentiality of this nonexpensive, autologous biomaterial is encouraging, preparation and storage after preparation form the loop holes that need attention. The time interval between the speed of handling and ultimately its usage is highly crucial for its structural integrity and leukocyte viability. Hence, these limitations should be focused and worked upon by the researchers. Further validation is needed in the form of long-term randomized control studies with larger sample sizes to affirm the benefits and identifying the hidden potential of PRF as a biomaterial in the field of clinical periodontology.

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Conflicts of interest

There are no conflicts of interest.

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