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Platelet-Rich Plasma in Orthodontics

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Abstract

Platelet rich fibrin (PRF) is an improved version of Platelet Rich Plasma (PRP), a fibrin matrix which consists of growth factors and cytokine, can serve as a resorbable membrane facilitating wound healing. It is a second-generation platelet concentrate which is prepared from the patient's own blood free of any anticoagulant. This article discusses the use and application of platelet rich plasma in orthodontic treatment modalities.

Keywords:- Platelet Rich Plasma (PRP); Tooth Movement; Orthodontics.

1. INTRODUCTION ;

Form the beginning of the practice of Orthodontics, tooth movement and associated biological reaction has been one of the domain in research. Many researchers have studied all possible approaches to achieve tooth movement with maximum pace in most physiological manner **.[1]** As the demand for orthodontic treatment in the adult patients has increased, it has given impetus to discover the methods to achieve accelerated orthodontic tooth movement which has led to research in different modalities including chemical, surgical and mechano-surgical methods.

In 1983, Frost gave the concept of Regional acceleratory phenomenon(RAP), denoting the principle that when bone is surgically irritated, a cascade of inflammatory process is started which results in increased osteoclastogenesis causing faster tooth movement**.[3]** Majority of the procedures involve a direct insult to the bony tissue which alternatively promoted the need for non-invasive to less invasive procedures, leading to increased research in field of acceleration of orthodontic tooth**.[1-5]**

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From last few years several techniques for platelet concentrates are been invented. However, their applications have been confusing because each method leads to a different product with different biology and potential uses. The platelet concentrates are procured by the process of centrifugation. The final product is formed of mainly of biological regenerative material i.e. platelets and fibrin. On the basis of leukocyte and fibrin content, a classification was given in which platelet concentrates was placed into four categories**.[1-6]**

-Pure platelet rich plasma (PRP), such as cell separator PRP

-Vivostat PRF (Vivolution, Alleroed, Denmark)

-Leukocyte and platelet rich plasma (L-PRP)

- Pure platelet rich fibrin (P-PRF)

-L-PRF, such as Choukroun's PRF.

Advantages and disadvantages of its uses

Some studies have demonstrated that PRF is a healing biomaterial with a great potential for bone and soft tissue regeneration, without inflammatory reactions and may be used alone or in combination with bone grafts, promoting hemostasis, bone growth, and maturation [**1-10**]. This autologous matrix demonstrated in the in vitro studies a great potential to increase cell attachment **.[1-9]** Simonpieri., et al. reviewed advantages of the use of PRF as it acts as a stabilizing sheath and offers mechanical sustenance, such as the regeneration through PRF membranes both the bone volume and gingival tissue. They also reported satisfactory clinical results related to reshaping the whole alveolar bone and the restoration of gingival volume and peri-implant bone, achieving adequate mechanical and aesthetic properties **.[11]**

Advantages and disadvantages of its uses

Comparing to PRP it has several advantages over it: it's a minimized autologous blood manipulation [12] including easier preparation. This entire process is natural, without any external manipulation leading to the absence of any immunological reaction [8]. So, it's not required a chemical manipulation of the blood, which makes it strictly an autologous leukocyte-platelet-rich fibrin matrix [6- 11]. which acts as a biodegradable scaffold [20] that favors the development of microvascularization and is able to guide epithelial cell proliferation and migration to its surface [8-13]. It has a natural fibrin mesh with growth factors within that may keep their activity for a relatively longer period and stimulate tissue regeneration [7-18]. Used as a membrane, it avoids a donor site surgical procedure and results in a reduction in patient discomfort during the early wound-healing period [12]. It is an economical and quick option compared with recombinant growth factors when used in conjunction with bone grafts [11-19] It can be used in combination with bone grafts or as one layer, depending on the manipulation [21]. Comparing to PRP, it's more efficient and shows

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better clinical results [13-21]. While talking about disadvantages: The success of the PRF protocol depends on blood collection time and its way on to the centrifuge [8]. The final amount available is low because it is an autologous blood [10] and for the process is needed a glass-coated tube to achieve clot polymerization [1,3,4].

Growth Factor	Origin Cells	Recipient	Action
PDGF	Platelets, endothelial cells, macrophages, monocytes, Smooth muscle cells.	Fibroblasts, glial cells, macrophages/neutrophils smooth muscle cells	Collagenase Secretion Collagen Synthesis Stimulates macrophage and neutrophils
TGF-b	Platelets, Macrophages/monocytes, T-lymphocytes, neutrophils.	Fibroblasts, endothelial cells, epithelial cells, preosteoblasts, stem cells (marrow)	Stimulates osteoblasts, fibroblasts Collagen synthesis Collagenase secretion
PDEFG	Platelets, monocytes macrophages	Fibroblasts, Endothelial cells, epithelial cells.	Collagen secretion Mitogenesis of epithelial cells Chemotaxis
PDAF	Platelets, Endothelial cells.	Endothelial cells	Increases permeability of vessels Increases angiogenesis
IGF-1	Osteoblasts, macrophages, monocytes, chondrocytes	Fibroblasts, osteoblasts, chondrocytes.	Cartilage growth, Replication of preosteoblasts and osteoblasts, Bone matrix formation,
PF-4	Platelets	Fibroblasts, neutrophils	Attracts neutrophils and fibroblasts

Table 1: Summary of Growth Factors Released From Platelets

The invasive techniques such as conventional corticotomy have been significantly more effective than the non-surgical procedures or the less invasive procedure like micro-osteoperforations or peizopuncture.The reason for this is that the mechanical stimulation of higher osteoclastic activity leads to the alveolar bone resorption causing decrease thickness and weight of the alveolar bone, and loss of alveolar bone of the target teeth .[15-**17**] This phenomenon is absent in non-invasive procedures and thus, are not long lasting. So, in order to achieve effective biological response from minimally invasive procedures, biochemical adjuncts may be used which involves cytokines like prostaglandin and hormones like relaxin. But these supplementary hormones may cause unwanted systematic effects. .[16-**23**]

The process of healing wound initiates through formation of clot, further of proliferative stage which comprises of new epithelial formation, blood vessel formation, granulation tissue formation, deposition of collagen and finally maturation and contraction of collagen. .[**2-12**] This involves aggregation and adherence of platelets which favours the formation of thrombin and fibrin. Platelet-rich plasma (PRP) which is considered to be a rich source of autologous growth factors, is defined as an autologous concentration of platelets in a small volume of plasma. GFs are natural biologic mediators which are responsible for the regulation of key cellular events which are part of the tissue repair and regeneration process.4 Platelets contain biologically active proteins. Binding of these proteins within a developing

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fibrin mesh or to the extracellular matrix creates chemotactic gradients leading to aggregation of stem cells resulting in cell migration, differentiation, and promoting repair. Thus, use of autologous platelet concentrates is a promising application in clinical situations requiring rapid healing. .[**13-26**]

2. PRP: DEFINITION AND BIOLOGICAL COMPOSITION

Platelet-rich plasma (PRP) is an autologous concentration of human platelets in a small volume of plasma. Basically, it comprises of the concentrated platelets and the seven-fundamental growth factor which are actively secreted by platelets for commencement of wound healing.5 In 1998, Robert Marx introduced PRP in dental literature as an adjunct in mandibular reconstructive procedure, enhancing the radiographic maturation rate of the graft alone**. [25,26]**

3. MECHANISM OF ACTION

The action of PRP is initiated with the degranulation of cellular alfa-granules which consists of growth factors and cytokines which are generated during the clotting process while the coagulation occurs. Its initiation starts with the secretion of growth factors within the 1st 4 hours of clotting process with majority messengers derived in 1-2 hours. For next 5-7 days, the synthesis of additional GFs by the platelets continue after the initial burst of PRP-GFs following the stimulation of healing process by secretion of similar growth factors through inflammatory macrophages. Thus, the wound healing rate is dependent on the quantity of platelets present in the blood clot. PRP being a rich source of platelets provides an increased concentration of GF thus promoting the cellular activity and enhancement of healing procedure.

Further studies are required for the investigation of the use of PRP for tooth movement.[**23-26**]

4.1. PRP and Tooth Movement

Orthodontic tooth movement is because of gradual remodeling supporting alveolar bone which involves the process of osteoclastic resorption of established bone and

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Advantages of Platelet-rich fibrin over Platelet-rich plasma	Disadvantages of Platelet-rich fibrin
No biochemical handling of blood	Amount available is low, because of autologous blood
Simplified and cost effective process and use of bovine thrombin and anticoagulants not required	Quick handling of blood is needed, immediately after collection
Favorable healing due to slow polymerization	
More efficient cell migration and proliferation	
PRF has supportive effect on immune system	
PRF helps in haemostasis	

PRF = Platelet-rich fibrin

Table 2: The advantages of Platelet-rich fibrin over Platelet-rich plasma and disadvantages of Platelet

osteoblastic formation of new bone. The quality and quantity of orthodontic tooth movement is dependent on the turnover rate of alveolar bone. To shorten orthodontic treatment and to move the teeth faster, alteration of the balance between resorption and deposition is required. .[6-**23**]

For accelerating tooth movement, several non-invasive as well as invasive techniques have been proposed both clinically and experimentally which includes direct electric current stimulation13, low dose laser therapy and vibrational stimulation , injection of prostaglandin and relaxin and corticotomy -facilitated tooth movement. .[1-**3**]

Use of PRP has shown to improve orthodontic tooth movement as it is based on Rapid Accelerated Phenomenon. Mangal et al.[22] found that localized acceleration of tooth movement the effect of PRP is dependent on the concentration used and advised the method of synthesis for the success of accelerating tooth movement. Rashid.A et al.[19] investigated the effect of PRP on the orthodontic tooth movement rate in 6 skeletally mature males. The maxillary first premolar in each was bilaterally extracted. PRP was prepared and injected around the canine in one maxillary quadrant while the other served as the control. Closed Coil springs (150 g) were used to distalise the canine for 68 days using temporary anchorage devices. The results showed total maxillary tooth movement on the experimental side was significantly faster compared to the control side (mean movement of 15.60mm versus 9.46mm). Thus, with no obvious clinical or microscopic side effects, local injection of PRP in this study resulted in accelerated orthodontic tooth movement.

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Güleç A et al. [18]have studied the effects of PRP with different concentrations on orthodontic tooth movement and alveolar bone density. Seventeen individuals were grouped into two: A PRP injection with moderate concentration group and a PRP injection with high concentration group. In each group, 5-time points were studied: Third, Seventh, Fourteenth, Twenty-first, and Sixtieth day. Before orthodontic mesialization of the maxillary 1st molar, on the right sides of the molar buccal sulcus moderate and high concentrations of PRP were infused with injection, and the left

Various fields	Clinical application
Periodontal regeneration	Root coverage procedures
	Clinical conditions requiring good bone fill along with gain in clinical attachment
Oral surgery	In extraction sockets
	Preprosthetic surgery
	Periapical surgery
Implants	To enhance osseointegration of implants
Endodontics	For regeneration of the pulp tissue,

Table 3: Clinical applications of PRF

sides served as the controls. 3-dimensional digital models were used for tooth movements measurement. Histomorphometric analysis was done for the evaluation of osteoclastic activity and alveolar bone volume density in the 1st molar intraradicular region.[17-**23**] The results suggested reduction in the density of alveolar bone in the experimental groups compared with the control groups at Third, Seventh, Fourteenth, Twenty-first, and Sixtieth day. On third day, osteoclastic activity was higher with the experimental groups as compared to controls. On twenty-first day, the tooth movement rate with the high-concentration experimental group was 1.7 times greater than in the high-concentration control group and 1.4 times greater than in the moderate-concentration experimental group. On sixtieth day, in all groups alveolar bone density increased to original levels. The study found accelerated orthodontic tooth movement by reduction in density of alveolar bone on para-dental tissues by osteoclastic activity enhancement in a unique way by injecting both moderate and high concentrations of PRP. Faster tooth movement is often not without risk, primarily related to increased caution for root resorption. The rate of root resorption with and without the use of PRP is likely to need investigation with well-conducted clinical trials. Marx mentioned that the growth factors in PRP include platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF) .[18-27]

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4.2.PRP in Cleft Patients: Alveolar Bone Grafting

Cleft lip and/or palate are one of the most common congenital anomalies which affects the orofacial region. The use of PRP in the management of these conditions is based on the tremendous quantities of growth factors released by the platelets aid in bone graft maturation. In a preliminary study, to evaluate the PRP's efficacy for secondary alveolar bone graft procedures, 20 patients with unilateral or bilateral CLCP were studied. Twenty patients between the ages of 8 and 30 were randomly allocated to receive cancellous bone grafts from the anterior iliac crest mixed with PRP whilst the same without PRP was received by control group. Bone grafts with the use of PRP showed significantly more bone density up to 6-months post-surgery (1028.00 +/- 11.30 HU versus 859.50 +/- 27.73 HU).

Giudice G et al. [6] studied bone regeneration and soft tissue healing in sixteen patients aging between 9 and 11 years of age with alveolar clefts unilaterally. The patients were equally split between those treated with autologous bone grafts alone and autologous bone grafts with PRP and then followed up for 36 months. The authors found that the autologous bone graft group with PRP, underwent earlier and shorter duration of orthodontic treatment with mean time to orthodontics 155.0 days compared to 298.4 days and mean duration of orthodontics 294.5 days compared to 356.0 day.

The preceding study evaluated bone changes using plain film radiography, however, Sakio R et al.[20] used computed tomography. The authors acknowledge the low numbers in their study, with 23 patients receiving autologous iliac bone and marrow grafts with PRP and 6 patients the same intervention without PRP. All patients were aged between 7 and 8 and were not randomly allocated. Results of the analysis of the graft sites showed the remaining bone was not significantly different between those treated with PRP and those without at 1year post-surgery. This is consistent with earlier work that suggested bone changing through remodeling in the early phase may be enhanced by PRP. .[**23-30**]

4.3. PRF and Periodontally Accelerated Osteogenic Orthodontics

Periodontally Accelerated Osteogenic Orthodontics (PAOO) is procedure that is thought to accelerate movement of teeth by orthodontic forces combined with corticotomies and alveolar bone grafting. Such corticotomy/osteotomy procedures are not new and were described over half a century ago . Muñoz F et[9] al have studied pain post-operatively, infection, inflammation and stability post-orthodonticly by using Leukocyte and Platelet-Rich Fibrin (L-PRF) in PAOO. Eleven patients in need of orthodontic treatment whom were considered periodontally suitable were monitored immediately post-operatively and then 2 years post-treatment.32 Accelerated wounding healing with absence of any infection or toxicreactions was observed with mild or moderate post-surgical pain. Complete resolution was achieved in all patients by day 8 and active orthodontic treatment time was reported to be

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9.3 months. All cases were seemed stable for 2 years. While these results are promising, the few number of patients enrolled in the study and the absence of a control group will warrant further studies in this area. A case report has also been presented in the literature of a patient with a high buccal canine and bimaxillary protrusion where PRF was used alongside other treatment modalities. This was thought to enhance the healing of a segmental osteotomy and a localized single tooth corticotomy around the canine, all of which were performed under local anesthesia. The authors conclude that this resulted in a decrease in canine retraction time33.

4.4. PRF and Alveolar Ridge Preservation in Orthodontics

Che Y et al.[8] have proposed the use of PRF to minimize resorption of hard tissues immediately post-extraction. The authors put forward that by preserving the alveolar ridge at this time in orthodontic cases, the problems of orthodontic tooth movement, root resorption, alveolar bone cleft and gingival invagination could be minimized. This would be achieved by ensuring there is sufficient alveolar bone during space closure. Similarly, where extractions are followed by pre-prosthetic orthodontics, PRF use may contribute to preservation of hard tissue morphology improving the condition of implant sites and making for more aesthetic restorations.[34-38]

4. 5.Safety of PRP and Possibility of Infection

-The safety of PRP largely depends on the source of the blood used to synthesize the concentrate. With autologous source, the chances of adverse reaction and are negligible. In a sterile protocol, the chance of transmissibility of the blood-borne infections is also avoided. [34-38]

-As the PRP concentrate of the platelets is essentially like the natural clotting, the concentrate does not promote bacterial proliferation. .[31-38]

-Also, the PRP derived GF are only trans-membranous, they are not mutagenic and hence only stimulate natural healing process and have no role in tumor formation.[34

5.**Discussion;**

the treatment of patients in several dental specialties has been improved with the discovery of PCs. With this goal, PCs have also been introduced recently in orthodontics. It has been hypothesized that the anti-inflammatory properties of PCs may reduce the rate of OTM because OTM relies on inflammation [19]. In addition, PCs contain growth factors such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), epidermal growth factor, insulin-like growth factor (IGF), platelet-derived endothelial cell growth factor, and vascular endothelial growth factor. Their presence may influence the balance between osteoblasts and osteoclasts, decreasing turnover and inducing bone formation [19].

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TGF-β stimulates the proliferation of osteoblasts and osteoprotegerin and collagen synthesis in favor of bone formation [22,23]. Meanwhile, TGF-β decreases the action of osteoclasts and thus bone resorption, which is necessary for OTM to occur. This may explain why in some studies mentioned above, the rate of tooth movement decreased on the side where alveolar treatment with PCs was used [19]. Despite these data, the present systematic review suggests that PCs accelerate overall treatment time in canine retractions. It is not possible to assume that this result is also applicable to corticotomy, given that this has not been studied yet. Reinforcing these findings, some authors have stated that PCs increase OTM velocity [24-26]. As mentioned in PRP studies, PRF can also promote inflammatory and anti-inflammatory responses, and their precise effect could be closely related to the timing of growth factor release and the concentration and content of the growth factors [27]. Many growth factors, cytokines, and enzymes contained in PCs might demonstrate anti-inflammatory effects responsible for improved tissue healing capacity, while at the same time, many cytokines, such as tissue necrosis factors, might aggravate the inflammatory response and lead to accelerated OTM [28]. Liou [24] reported that injections of submucosal PRP accelerated OTM by stimulating the bone damage mechanism without surgical intervention and alveolar bone loss, while Güleç et al. [25] reported that the PRP injection technique might accelerate OTM by decreasing alveolar bone density.

PRP and PRGF are defined as substances containing a high concentration of autologous platelets in a small volume of plasma. They contain large amounts of platelets, growth factors, and coagulation factors [29]. In contrast, PRF has been defined as a second generation PC that does not require the addition of any platelet-activating substances (e.g., bovine thrombin or calcium chloride), unlike PRP or PRGF [13]. In other words, glass tubes can be used without any additives. In all included studies, PRF was preferred over PRP or

Gonen et al. [21] reported a significant increase in BBT in the PRF group and the BG group versus the control group, as well as between test groups, favoring BG alone. Furthermore, it has been reported that PCs and BG can be used together with optimal results [16]. The presence of a transitory matrix of PCs around particulate BG facilitates cellular migration throughout the fibrin network into the regenerative sites, as well as the development of neoangiogenesis and vascularization, promoting the healing of the site [35]. The sponge-like architecture of the PC membranes provides an ideal scaffold for free cell migration into the surgical site, while the release of growth factors for up to 28 days post-surgery provides the continuous long-term stimuli required for chemotaxis and the osteogenic differentiation of osteoblasts, periodontal ligament cells, and bone marrow mesenchymal stem cells [36]. An added advantage is that not using BG simplifies and reduces the cost of the technique. In canine distalization, filling a post-extraction socket with PCs causes neovascularization to occur through the PC clot, leading to the development of an epithelial covering. Despite the infectious and inflammatory potential of extraction sockets, rapid healing of the wound

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occurs without pain, swelling, and other attending signs of inflammation and infectious processes. In addition, this technique seems to reduce alveolar ridge resorption following tooth extractions [18]. A reason for this may be that TGF-β, which is present in PCs, stimulates the proliferation of osteoblasts and osteoprotegerin and collagen synthesis, favoring bone neoformation [22,23]. This systematic review presents several strengths, such as previous registration of the protocol, an unrestricted search of the literature (including the gray literature), a clear process of searching for studies, and the fact that data extraction and risk analysis bias were performed in duplicate. The overall quality of the included studies was deemed to be high. However, a limitation may be the availability of few studies in the literature and the heterogeneity of those studies, which makes it difficult to compare them. Further studies should specifically investigate the overall treatment time, comparing the use of PCs alone and in combination with BG in corticotomy, compared with BG + corticotomy and a control group. It may also be interesting to investigate whether PCs reduce the need for post-surgical non-steroidal anti-inflammatory drugs, the effect of combining PC injections and PC membranes in fresh extraction sockets, and the effect of repeated injections of PCs throughout the course of canine retraction to maintain a steady rate of accelerated OTM. In conclusion, the studies included in this review were very diverse, making it difficult to draw convincing conclusions. However, a tendency was observed for OTM to be accelerated by using PCs as an adjuvant in canine distalization after premolar extraction when distalization was started in the same session. Likewise, studies seem to indicate an association between the amount of canine retraction and PC injections. However, it is not possible to affirm that the use of PCs in corticotomy shortens the overall treatment time, as this question has not been studied adequately.

6. CONCLUSION

The application of PRP and PRF is becoming well established in many fields of both medicine and dentistry. While use in areas such as implant dentistry and oral surgery may seem obvious, in orthodontics, we are only just starting to see the publication of a handful of studies. The PRP's effect with localized acceleration of tooth movement is dependent on the concentration used. However, the method of synthesis is critical to the success of PRP based acceleration of tooth movement. The use of injectable PRP at a different stage of orthodontic treatment can improve the quality of the treatment outcome by influencing the bone quality and enhancing the rate of tooth movement. It is anticipated the use of PRP and PRF is likely to extend beyond just tooth movement however, the clinical efficacy of this rapidly evolving area will need to be carefully watched as laboratory based studies are undertaken in clinical practice. Further studies should involve well-planned randomized controlled trials investigating not only the potential benefits of PRP and PRF but also any potential risks or complications.

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