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Review Article

Platelet Rich Plasma: Clinical Applications in Dentistry

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Abstract: Platelet rich plasma (PRP) is one of the new innovations of surgery today and is a new approach to tissue regeneration. It is helpful in both hard and soft tissue healing. PRP is derived from autologous blood and is a reservoir of various growth factors which are important for tissue repair. In the field of surgery, it tends to give an added advantage by both reducing bleeding and also helping in wound healing or tissue repair. Various studies have been carried out on humans to show the application and benefits of PRP in dentistry (especially enhancing healing of extraction sockets, implant surgery, periodontal surgery, bone regeneration etc). The use of PRP has also been proposed in the treatment of bisphosphonate- related osteoradionecrosis of the jaw (BRONJ), as a better treatment modality as compared to the conventional methods. The main aim of this short narrative review is to 1) create awareness about what is PRP, 2) its methods of preparation, 3) various clinical applications and its promising results. As PRP is an autologous preparation, it is free from the potential risks associated with any other grafts. It definitely holds a promise in near future. However, more RCTs are still required to support its evidence. In this review, articles were searched online in recent journals by using certain relevant keywords regarding the clinical applications of PRP.
Keywords: PRP, clinical applications, dental surgery, BRONJ.

Introduction

Platelet rich plasma (PRP) is a breakthrough in stimulation and acceleration in bone and soft tissue healing. It represents a relatively new biotechnology that is a part of growing interest in tissue engineering and cellular therapy. Because of its newness there is a potential for misunderstanding & misuse**.**

Platelet-rich plasma was first introduced in oral surgery by Whitman *et al.;* [1] in an article which stated that "through activation of the platelets and the resultant release of these growth factors, enhanced wound healing should be expected". PRP enjoyed a great increase in popularity after the publication of a landmark article by Marx et al[2] in 1998 that proved combining PRP with autogenous bone in mandibular defects resulted in significantly faster radiographic maturation & histo morpho metrically denser bone regenerate.

What is platelet rich plasma (PRP)?

It can be defined as "Volume of autologous plasma that has the platelet concentration above the baseline." [2] or "as a high concentration of autologous platelets in a small volume of autologous plasma" [3, 4]. Specifically, PRP is a platelet concentration with at least 1,000,000 per microliter in a 5 mL volume of plasma, when normal human platelet counts in the blood range from 150,000/1 L to 350,000/1 L.: the working definition of PRP today. Concentration lesser than this cannot be relied upon and the concentration more than this have not shown enhanced bone healing.

Biology of platelet rich plasma

Blood clot is the primary requisite for initiating all the soft tissue healing processes and bone regeneration activities of all the natural wounds.PRP is a simple strategy to concentrate platelets in the natural clot for accelerated complete healing. A natural blood clot contains 95% red blood cells (RBCs), 5% platelets and 1% white blood cells (WBCs) and many fibrin strands. A PRP blood clot is composed of 4% RBCs, 95% platelets and 1% WBCs. [5]

Biology of platelets

Platelets are the smallest corpuscular components of human blood which are formed as the end product of mitotic proliferation of mega karyocytes in the bone marrow. The important fact about platelets is their ability to secrete growth factors by the granules, which play an active role in wound healing. These growth factors, also called cytokines are small proteins each of 25,000 Daltons molecular weight. The various

granules of platelets and the growth factors secreted by them are:

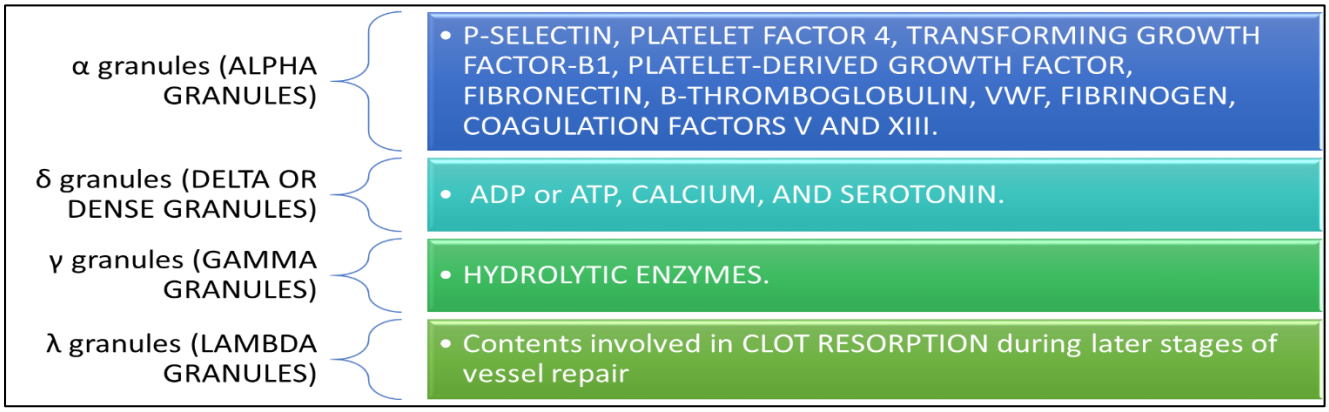

Fig-1: granules of platelets and various growth factors secreted

Components of platelet rich plasma

The growth factors and other cytokines present in PRP include **[**6]
Platelet-derived growth factor
Transforming growth factor beta
Fibroblast growth factor
Insulin-like growth factor 1
Insulin-like growth factor 2
Vascular endothelial growth factor
Epidermal growth factor
Interleukin 8
Keratinocyte growth factor
Connective tissue growth factor

Table 1: primary growth factors in PRP and their functions [6]

Growth Factor	Primary Functions
Epidermal growth factor	Regulation of cell proliferation, differentiation, and survival
Insulin-like growth factor	Key regulator of cell metabolism and growth Stimulates proliferation and differentiation functions in osteoblasts
Platelet-derived growth factor	Major mitogen for connective tissue cells and certain other cell types. Promotes the synthesis of collagen and structural proteins
Transforming growth factor (ie, alpha, beta)	Regulation of cell proliferation, differentiation, and apoptosis Induction of intimal thickening
Vascular endothelial growth factor	Regulation of angiogenesis

How many platelets are enough?

This question has been answered by the work of Haynes worth *et al.;* [8] who stated that there is a direct relationship between the platelet concentration and the proliferation of adult mesenchymal cells. Also the author provided with a graph shows that sufficient cellular response to platelet concentrations first began when a 4- to 5-fold increase over baseline platelet numbers was achieved. Lui *et al.;* [9] showed that the fibroblast proliferation is also enhanced by increasing the platelet concentration.

How to make platelet rich plasma?

8 ml patient's blood was taken from median cephalic vein & then added in test tube containing anticoagulant solution (3.8% of 0.5- 1ml Sodium citrate). These test tubes are then centrifuged at 1200rpm for 10 minutes. After the first centrifugation, plasma and RBC's are separated. Plasma, layer of buffy coat and some amount of RBC's were aspirated with the help of spinal needle and 10cc syringe and were emptied in plain test tube without any anti- coagulant. This test tube was again centrifuged at 2400rpm for 10 minutes. After second centrifugation platelet poor

plasma and platelet rich plasma got separated. Upper 2/3rd of the solution containing platelet poor plasma was aspirated out. Platelet rich plasma was made into gel form with the help of addition of 3-4 drops of Calcium chloride.

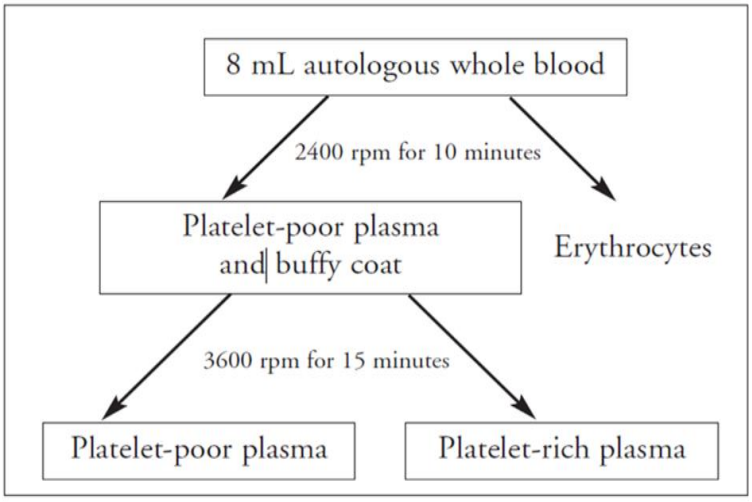

Fig-2: How to make PRP

How does platelet rich plasma work?

PRP works via the degranulation of the granules in platelets. Clotting activates the platelets which then start secreting the growth factors immediately. Within 10 minutes they secrete 70% of their stored growth factors and close to 100% within the first hour [4]. then they synthesize an additional amount of growth factors for 8 days till they are depleted and die. Therefore clinicians should activate it only when they are ready to use.

Advantages of platelet rich plasma

It is Safe as it is by-product of the patient's blood; therefore, disease transmission is not an issue. PRP can be generated in the dental office while the patients can undergo an outpatient surgical procedure. Hence it is convenient. It promotes faster healing because of the super saturation of the wound with PRP, and thus growth factors produce an increase of tissue synthesis and thus faster tissue regeneration. It is cost effective as expenses of the harvesting procedure are greatly reduced. It is Easy to use-PRP is easy to handle and actually improves the ease of application of bone substitute materials and bone grafting products by making them more gel-like. However, it cannot be used in patients with bleeding disorders. It does not reduce rapid venous hemorrhage and it is obviously not a substitute for good surgical techniques. Moreover, it cannot be used in patients on NSAIDS or anti-platelet drugs or in chronic liver diseases

The effects of PRP on healing the alveolar socket after tooth extraction

Tooth extractions a common dental procedure especially the 3rd molars are associated with pain, bleeding and discomfort. PRP tends to promote tissue repair, improving the quality of healing &healing time [11]. However, very few studies have been carried out on humans and contradictory results have been produced regarding the efficacy of PRP. Promising results were reported by Alissa et al.; [12], who conducted a pilot study on the effect of PRP on the healing of the hard and soft tissues of extraction sockets. Soft tissue healing was significantly improved in patients treated with PRP compared with patients of the control group (no treatment). Moreover, patients untreated with PRP experienced complications (dry sockets and acutely inflamed alveolus). Post-operative pain was also analyzed in the two groups (treated and untreated) and they reported significantly more pain in the control group, especially in the first three days post intervention. Ogundipe [13] in 2011 proved that when post 3rd molar extraction was treated with PRP they showed decrease pain and improvement in swelling and mouth opening. Ruktowski [14] showed that there was a significant increase in the radiographic density over the baseline level after extraction if PRP was used. However, a study conducted by Arenaz bua *et al.;* [15] showed no acceleration in bone formation at 6 months and no statistically significant difference in pain, swelling, trismus and infection when treated with PRP or not.

The above review of the literature suggests that the use of PRP in the alveolar socket after tooth extractions is certainly capable of improve soft tissue healing but there is insufficient evidence which supports the efficacy of PRP in improving bone regeneration.PRP in tooth extraction sites seems to influence the early phase of bone healing, thereby accelerating bone formation in the initial period after tooth extraction, its influence decreasing after a few days. Not univocal results were also obtained for post-operative pain but conclusive considerations in terms of efficacy and efficiency could not be formulated.

Table-2: Summary of RCTs on the use of PRP tooth extraction sockets [16]

Authors	Year of publication	Number of patients	Follow-up (wks)	Main results	Effect of PRP
Alissa et al.	2010	23	12	Statistical significant improvement in soft and bone tissuehealing; statistically significant reduced post-operative pain and complications	strong
Ogundipe et al.	2011	11	12	Statistical significantly reduced pain; improvement in swelling/interincisal mouth opening and bone density but not statistically significant	moderate
Ruktowski et al.	2010	12	25	Early and significant increased radiographic density over baseline measurements in PRP- treated sites; no significant improvement in post-operative pain and bleeding after PRP application.	moderate
Celio-Mariano et al.	2012	15	1-4-8-12-24	Significant improvement in bone healing in PRP- treated sites	strong
Arenaz-Bua et al.	2012	82	12-24	No acceleration of bone formation after PRP treatment. No improvement in pain, swelling, trismus and infection.	weak
Gurbuzer et al.	2008	12	1-4	No increased osteoblastic activity in PRP treated sites	weak

The use of Platelet Rich Plasma in periodontal surgery

The growth factors present in PRP are capable of forming a fibrin clot, promoting fibroblast proliferation and up regulating collagen synthesis in the extracellular matrix [17]. Thus, the use of PRP at injury sites might be able to promote wound healing and the regeneration of periodontal soft tissues. Moreover, the ability of these factors to accelerate bone repair by increasing the mitosis of osteoblasts & tissue vascularity might be useful in the treatment of infra-bony defects [18]. However, the therapeutic efficacy of PRP in periodontal therapy still remains controversial. Various studies have been reported the use of PRP in period ontology. Martinez *et al.;* [19] in 2009 showed that whereas it improves gingival recession, no significant change was seen in the clinical attachment level in periodontics. Moreover, Pradeep *et al.;* [20], who conducted a study on the treatment of mandibular furcation defects, have reported the lack of complete closure of furcation defects despite a significant improvement; this implies a limited role for autologous PRP as a regenerative material. The results of the systematic review by Del Fabbro *et al.;* [21] revealed that PRP may exert a positive adjunctive effect when used in combination with graft materials for the treatment of intrabony defects. However, no significant benefit of PRP was found for the treatment of gingival recession. Bhardwaj *et al.;* [22] found that the adjunct of PRP to bone graft appeared to be beneficial in the treatment of human periodontal intrabony defects.

Table- 3: Summary of RCTs of use of PRP in periodontal surgery [16]

Authors	Year of publication	Number of patients	Treatment	Follow-up (wks)	Main results	Effect of PRP
Pradeep et al.	2009	20	Treatment of furcation defects	24	No complete closure of furcation defects	weak
Menezes et al.	2012	60	Treatment of infrabony defects	48-192	Positive effect of PRP used with other graft materials in infrabony defects but not when used alone	weak
Saini et al.	2011	20	Treatment of infrabony defects	12-24-36	Positive effect of PRP used with other graft materials in infrabony defects	moderate
Bharadwaj et al.	2011	10	Treatment of infrabony defects	24	Significant improvement in PD, CAL and bone radio-density	strong
Ozdemir et al.	2012	14	Treatment of infrabony defects	24	Positive effect of PRP used with other graft materials in infrabony defects but not when used alone	weak
Harnack et al.	2009	22	Treatment of infrabony defects	24	No improvement in PPD and CAL derived from the adjunt of PRP to other graft material	weak
Rodrigues et al.	2011		Treatment of infrabony defects	12-24-36	Better clinical results for PRP used with other graft materials in infrabony defects than with PRP used on its own	weak
Dori et al.	2008	26	Treatment of infrabony defects	48	No adjunctive benefit with the use of PRP	weak
Dori et al.	2009	30	Treatment of infrabony defects	48	No adjunctive benefit with the use of PRP	weak
Piemontese et al.	2008	60	Treatment of infrabony defects	48	No adjunctive benefit with the use of PRP	weak
Keceli et al.	2008	40	Root coverage	6-36-48	No adjunctive benefit with the use of PRP	weak

The results of this analysis shows only one study which shows a strong effect of PRP while the others reflect the limited and heterogeneous data available and suggest that the specific selection of agents/procedures combined with PRP could be important in determining the final outcome of the treatment.

Use of Platelet Rich Plasma in soft tissues surgery & bone tissue surgery & implant surgery

In the field of bone tissue surgery, arecent study by Daif [23] investigated the effect of autologous PRP on bone regeneration in mandibular fractures. He concluded that direct application of the PRP along the fracture lines may enhance bone regeneration. Wojtowicz et al.; [24] compared the effects of stimulating the osteogenesis of the alveolar bone by transplants of autologous bone marrow and PRP. It was shown that newly formed bone increased under the influence of PRP.PRP has also been used in sinus lift procedures, where mixed results have come out. Esposito [25] showed that there was no significant improvement on using PRP along with bone substitutes in sinus lifts procedures, whereas Poeschl [26] showed successful results in maxillary sinus augmentation. The preparation of PRP, as applied to an implant surface, adheres to metal and might create a new dynamic surface which could potentially show biological activity. Anitua [27] in 2006 in which osseointergation was found to be improved by coating the implant surface. Similar results were found in a recent study by Anand *et al.;* [28] who concluded that coating the implant surface with PRP could improve the prognosis of immediate loading implants.

Table 4: Summary of RCTs, using PRP in soft/ bone tissue surgery & implant surgery [16]

Authors	Year of publication	Number of patients	Treatment	Follow-up (wks)	Main results	Effect of PRP
Anitua et al.	2006	295	Implantology	8	Improvement in implant prognosis	strong
Anand et al.	2012	11	Implantology	12-24-36-48	Improved early bone apposition around the implant	strong
Gentile et al.	2010	15	Reconstructive surgery of the jaw	2-4-12-24	Efficacy of PRP treatment in terms of patient satisfaction and low-morbidity	strong
Wojtowicz et al.	2007	16	Augmentation of mandibular bone	12	PRP is more effective than bone marrow, containing CD34+ cells	strong
Daif	2012	24	Bone regeneration of mandibular fractures	1-12-24	Direct application of the PRP along the fracture lines may enhance bone regeneration in mandibular fractures	strong
Khairy et al.	2012	15	Sinus lift	12-24	PRP- enriched bone grafts were associated with superior bone density at 6 months post grafting	strong
Poeschl et al.	2012	14	Sinus lift	28	Increased new bone formation when PRP was used	strong
Cabbar et al.	2011	10	Sinus lift	28	No statistically significant differences were observed	weak

The results of these studies demonstrate that PRP is effective in soft tissue healing and bone regeneration. PRP is used in bone regeneration after fractures; augmentation and even the reconstruction after jaw surgeries have shown strong effect of PRP on these treatment modalities. The combination of PRP application with other biomaterials seems to be promising as regards sinus lifting, but the results depend on the material used. Promising results have also been obtained in implant surgery, using PRP on its own as a coating material.

Endodontics

PRP can also be used in the field of endodontics. It has been used successfully in the treatment of peri apical lesions, infected necrotic pulp tissues, open apex.

The use of PRP in BRONJ surgery

BRONJ (Bisphosphonate-related osteonecrosis of the jaw) is currently recognized as a significant complication, which is related to the use of bisphosphonates , a widely-used class of drugs employed in the preventative treatment of various pathologies leading to the alteration of bone turn-over .BPs are capable of inhibiting osteoclast-mediated bone resorption, also displaying anti-angio genetic activity. The bones of patients treated with BPs are, therefore, poorly vascularized and poorly supplied with the substances necessary for wound healing .Although some of the cases reported were asymptomatic, most of them resulted in avascular area of necrotic bone in the maxillofacial area, with or without exposed bone [6]. BRONJ management is currently controversial, ranging from medical to surgical treatment, with no definitive standard of care. Aggressive surgical debridement is also controversial due to the risk of worsening bone

exposure. Occasionally, the bone is left exposed due to the difficulty of treating the lesion. PRP therapy has been proposed as a complement to conservative surgery in order to enhance bone healing. The rationale for the employment of PRP in patients' affected by BRONJ is based on the thesis that the presence of growth factors (usually repressed by BPs) constitutes a substitute stimulation to bone healing, which is similar to physiological healing. The growth factors in PRP might accelerate epithelial wound healing, decrease tissue inflammation after surgery, improve the regeneration of bone and soft tissues, and promote tissue vascularisation.

Table 5: Case reports of endodontic treatment applied to necrotic immature permanent teeth using PRP [30]

Authors	Sample size	Treatment procedure	Outcome
Johns, et al(2014)[12]	1	Bernald Solier syndrome, swelling in relation to right maxillary canine for 5 days.	There was substantial reduction in the periapical radiolucency after 1 year follow-up.
Hiremath, et al(2014)[13]	3	Large periraducular lesion	At 18th month the occlusal radiograph showed complete healing of the periapical lesion
I.B.Geeta(2013)[14]	1	established pulpitis in 46with cariouspulp exposure and sharp,intermittend pain	At 6 months, the tooth responded positively to pulp sensibility tests, and radiographic examination revealed a normal periodontal ligament space
Singh, et al.(2013)[15]	15	Periradicular lesion	At the end of six months, all patients showed complete bone regeneration.
Chen MY(2012)[16]	20	infected necrotic pulp tissue with abscesses	At the 6-7 months follow up,marked decreased in radiolucency.
Torabinejad(2011)[17]	1	Necrotic pulp & open apex	Tooth was asymptomatic half months later
Cehreli(2011)[18]	6	Immature necrotic permanent first molar	At the 10 months follow up,complete periapical healing.
Petrino(2010)[19]	6	Immature molar with apical periodontitis	Resolution of radiolucency after 6 months,and normal vitality

The use of platelet rich plasma in cosmetic surgery

There has been a recent widespread interest in use of PRP for anti-aging and regenerative purposes. It has been named as the vampire facial and can be used in face lifts, Reducing fine lines and wrinkles, Tightening and toning skin, Mild collagen and volume loss, Dark under eye circles &Acne scarring [31]. It is less invasive &less expensive than plastic surgery, takes about 20 minutes for each treatment, and offers improvements for up to 18 months. Within a few weeks of treatment, an overall improvement in skin hydration, texture and tone can be seen. New collagen and blood vessels begin to grow after three to six weeks, and reduction of fine lines and wrinkles and volume correction happens over the next three to six months. The effects of Cosmetic PRP can last 12 months to two years, depending on the individual.

Is the value of PRP limited to soft tissue?

Some have also implied that the value of PRP is mostly related to soft tissue healing enhancement because platelets do not contain BMP. Hence it is non-osteoinductive. [2]. However, bone graft healing and osteoconduction into bony defects and around the numerous bone substitutes used today arise from adult mesenchymal stem cells & their differentiation, leading to osteoblasts, all of which have already been proved to respond to PRP with accelerated bone formation[7].

Does platelet rich plasma promote infections?

Some have empirically suggested that PRP may promote infections due to the flawed logic that it is a blood clot and that blood agar is used in microbiology laboratories to culture bacteria. However, PRP is no different in substrate than the blood clot that forms in every wound and therefore could not support bacterial growth any more than any other blood clot [3]. In fact, PRP has a pH of 6.5 to 6.7 compared with a mature blood clot of 7.0 to 7.2. It has thus been counter-suggested that PRP actually inhibits bacterial growth. However, the clinician should know that preparation of PRP must use an aseptic technique.

Growth factors, platelet rich plasma & cancer?

Because growth factors stimulate cellular proliferations, there are concerns that BMPS and PRP might stimulate cancer. Although no growth factor can prove cancer. [4]. All growth factors act on cell membrane and not on cell nucleus & stimulate normal gene expression. Growth factors are not mutagens unlike true carcinogens like radiation, tobacco, UV lights etc. instead growth factors are normal body proteins. The security superficially related to PRP and cancer is that PRP is nothing more rather than the same blood clot that would be in any normal wound, except that it contains greater number of platelets.

Conclusion

PRP is new application of tissue engineering and can be used in the most varied areas of the dentistry, being applied in periodontal and maxillofacial surgeries. It is a storage vehicle for growth factors, especially PDGF and TGF-ß. Although growth factors and the mechanism involved are still poorly understood,

the ease of applying PRP in the dental clinic and its beneficial outcomes hold promise for further procedures. However, that is new area of the science and many clinical results still will be published, that will cover some unanswered queries about PRP. Certainly, the use of PRP is a step in the history evolution of the regenerative methods and the tissue engineering that will be used next years.

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