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RESEARCH ARTICLE

APPLICATIONS OF PLATELET CONCENTRATES IN THE FIELD OF ORAL AND MAXILLOFACIAL SURGERY

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ABSTRACT

Platelet concentrates (PC), also known as platelet gel or plasma rich in growth factors is supra-physiological concentrate of platelet in plasma, derived from autologous blood after its centrifugation. It has dynamic use in regenerative and repair therapy. It gained popularity in late 1970s in Europe, wherein fibrin sealants were used for haemostasis and tissue closure. Subsequently it evolved into platelet rich plasma (1st generation PC) and platelet rich fibrin (2nd generation PC).Common to both the generations are presence of multiple growth factors which has potential to catalyse soft and hard tissue healing. It has been used in field of medicine and dentistry in varied forms. This paper aims to review various applications of PC, specifically in field of Oral and Maxillofacial Surgery.

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INTRODUCTION

Platelet are known source of growth factors. Injury of tissue and rupture of vessels leads to initiation of coagulation cascade. The end stage in process of haemostasis results in formation of fibrin meshwork containing blood cells, including platelets. These platelets on activation release numerous growth factors which play a vital role in healing and repair. This beneficial action of platelets can be multiplied by generating a platelet concentrate which refers to supra-saturated concentrate of platelet above the baseline. It is derived by the process of centrifugation of autologous blood of the patient.[1] PC has gained popularity in past few decades as they are easily retrieved, and has shown its efficiency in field of regeneration and repair therapy. Being an autogenous preparation it shows minimal immune reaction and minimises the risk of disease transmission. Use of PC in field the of Oral and Maxillofacial Surgery aid in treatment outcome of procedures which range from healing of extraction sockets (including impacted tooth), implantology, cleft lip and palate repair, ulcer management, healing of cyst defect, as an adjunct to fat grafts and in aesthetic procedures such as skin rejuvenation, correction of alopecia, scar attenuation, and acne treatment. This paper is a sincere effort to provide a comprehensive literature on these varied applications and benefits of PC in Oral and Maxillofacial Surgery.

Evolution and Biology of PC

Fibrin glue (FG) also called as fibrin sealant or fibrin tissue adhesive are the precursor for PC and was introduced in late 1970's. It is plasma derivative containing fibrinogen, thrombin and calcium. Polymerisation of these components mimics the end stage of coagulation, resulting in fibrin clot formation. Fibrin glue aids in haemostasis and wound closure (tissue sealing). It also serves as melting agent or a framework to carry particulate bone grafts. Commercially available fibrin sealants are available as two components preparation, one containing fibrinogen concentrate dissolved in antifibrinolytic solution and other containing thrombin dissolved in diluted calcium chloride. Mixing the two components results in formation of fibrin matrix which attainshaemostasis and seals wound. The fibrin glue originally described was of allogenicorigin and carried risk of cross infection and immune reaction. Gibble and Ness[2] in 1990 introduced autogenous fibrin gel. However it didn't gain popularitydue to poor rheological properties (low resistance to stress), costly processing and lack of reproducibility

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Fibrin glue lack presence of concentrated platelet in its formulation and thereby does not release growth factors, limiting its role in wound healing and repair. This gave rise to the first generation platelet concentrate i.e. Platelet Rich Plasma (PRP). PRP is an autologous supersaturated platelet concentrate. By definition, platelet concentration in PRP is almost 5 times of that present in normal blood (the mean platelet count of whole blood is about 2,00,000 cells per µl, as compared to 14,0000 cells per µl in PRP). Platelets are known source of growth factors. They are the smallest blood cells which lack nucleus but contain mitochondria, microtubules and granules in its cytoplasm. The alpha granules of platelets are membrane bound structure containing numerous bioactive proteins. The bioactive proteins (the growth factors) released upon activation of these granules performs multiple role in regenerative processes including cell proliferation, matrix formation, osteoid production and collagen synthesis [Table 1]. T he possibility of its application in wound healing, surgery and to promote repair process in various diseases has driven many research and clinical trials. Use of autologous plasma having high concentration of platelet has been reported as early as 1970. However the necessary instruments were large, expensive and required large volume of blood. The availability of improved portable and affordable centrifuge machine in past few decades has tremendously increased the use of PRP in clinical practise. Starting in early 1990's use of PRP in maxillofacial surgery, dentistry, periodontal therapy and cosmetic surgery was reported widely. Subsequently use of PRP expanded to the field of Orthopaedics, regenerative medicine and tissue engineering. The preparation of PRP has been discussed in the following section.

One of major drawback of PRP is use of external additive including anticoagulant and bovine thrombin to prevent coagulation of the blood and for activation of PRP respectively. To eliminate this blood handling and the legal restrictions associated with it a new family of PC was developed by Choukran *et al* in France.[3] This 2nd generation of PC was called Platelet rich fibrin (PRF). The benefits of PRF included its complete autologous nature and simplified procedure of preparation. The comparison and benefits between 1st and 2nd generation of PC is discussed in Table 2.

Preparation of PC

Preparation of platelet rich plasma

PRP can be prepared by three methods, namely; gravitational platelet sequestration (GPS) technique, autologous selective filtration and standard cell separators. The most commonly used method of PRP preparation is gravitational platelet sequestration technique. Ituses the table top centrifugation machine and can be prepared just prior to surgery in clinics or in operating room. About 10-15ml of autologous blood is collected by venepuncture (volume of blood can be varied depending on amount of PRP to be prepared). The volume of PRP yield is about 10% of the total blood volume used (i.e. 10 ml of autologous blood will provide about 1 ml of PRP).[4] Tothis autologous blood an anticoagulant is added to prevent blood from clotting. To isolate the plasma the collected blood is centrifuged. The first spin also called as *soft spin* is given at speed of around 2500rpm for 10 minutes. First spin separates blood into three basic fractions (from least dense to most),platelet poor plasma on the top of the preparation which contains few platelets, middle layer comprising of plasma containing platelets and white blood cells (buffy coat) and the bottom most fraction comprising of red blood corpuscles. The operator then aspirates the upper layer of platelet poor plasma and middle layer of buffy coat along with the uppermost part of R.B.C, which is again centrifuged at speed of 3500rpm for 10 minutes *(hard spin),* leading to formation of two separate layers i.e. platelet rich plasma and bottom layer of red blood cells. The desired platelet rich plasma is retrieved and activated

Table 1. Growth factors in platelet concentrates and its functions

Growth Factors	Function
Platelet-Derived Growth Factor(PDGF)	Stimulates chemotaxis of monocytes and collagen synthesis, macrophages and neutrophils; proliferationof fibroblasts, smooth muscle cells, MSC and osteoblasts,
Transforming Growth Factor-Beta 1(TGF-b1)	Helps in formation of Matrix; regulates keratinocytesproliferation and stimulates biosynthesis of fibronectina and collagen production, promotes osteoclastic activity
Insulin like growth factor (IGF 1)	Protein synthesis and chemotaxis of fibroblasts. Stimulates bone formation by enhancing osteoblasticacticity.
Platelet derived endothelial growth factor (PDEGF)	Proliferation of keratinocytes and dermal fibroblast
Vascular Endothelial Growth Factor(VEGF)	Helps in mitosis of endothelial cells,Stimulates blood vessel permeability, stimulation of angiogenesis & Lymphangiogenesis
Epidermal Growth Factor (EGF)	Stimulates mitosis in epithelial-,mesenchymal- and fibroblasts; chemotaxsis of keratinocytes;stimulation of angiogenesis; regulation of the secretion of colAlagenase.
Platelet derived angiogenesis factor (PDAF)	Stimulates vascular endothelial cells aids in angioneogenisis
Platelet factor 4 PF 4	Chemotaxis of neutrophils, fibroblast and is a potent antiheparin agent.

Table 2. Comparison between Platelet rich plasma and platelet rich fibrin

Platelet rich plasma	Platelet rich fibrin
First generation platelet concentrate developed in the year 1970 and used 1st in the year 1987	Second generation platelet concentrates developed in france by choukran *et al* 2006
Derived from autologous blood	Derived from autologous blood
Method of obtain is comparatively complex and lengthy	Method to obtain PRF is simpler and faster
-	More cost efficient.
Addition of anticoagulant is must.	No anticoagulant needed
Biochemical additives like calcium chloride and bovine thrombin are added	No biochemical modification
Bilateral junction structure with strong thrombin structure	Unilateral junction with weak thrombin structure.
Rigid fibrin network, less entrapment of cytokines	Elastic fibrin network favouring entrapment of cytokines Better healing and hemostasis

by addition of bovine thrombin and 10 % calcium chloride.[5] The quality of PRP attend is highly variable and depends on various parameters. Different commercial centrifuge devices used to prepare PRP probably explains the non-standardized nature of PRP attend in different reports leading to variability of its clinical efficacy. The centrifugation process must be sterile and precise to separate platelets from rest of the blood in adequate concentration. Variability in factors governing centrifugation such as the time and force affects the nature of prepared PRP. High force of centrifugation can damage the platelets, and its granular content reducing the load of growth factors.[6] The efficacy of PRP also depends upon the number of platelets and its viability in the prepared concentrate. The concentration of platelet in PRP is directly proportional with the platelet count of the autologous blood from which it is derived. Patients with low platelet count or qualitative platelet disorders are not ideal for PRP preparation.

Various anticoagulant used in PRP preparation includes; anticoagulant citrate dextrose-A (ACD-A), ethylene diaminetetra-acetic acid (EDTA), and trisodiumcitrtrate solution. ACD is the more preferred anticoagulant. The citrate in ACD binds to calcium and prevents coagulation of blood, while dextrose supports platelet metabolism and viability.[7] Large number of platelet damage is observed with use of EDTA and is thus considered more harmful. Trisodium citrate solution although show no negative effects, with more beneficial effects of ACD, it is the most commonly used.[8] Addition of bovine thrombin during activation of PRP has been previously reported with possible risk to produce bleeding episode in patients. Certain commercial preparation of bovine thrombin has bovine factor Va, as contaminant. Antibodies produced against it may cross react with human factor Va producing coagulopathies.[4]

Preparation of platelet rich fibrin

PRF was introduced byChoukranet.al.in France. It is purely autologous and is derived without any biochemical handling (no addition of anticoagulant, bovine thrombin or calcium). Its simpler technique of preparation made it more popular and preferred over PRP. The protocol to obtain PRF is as follows; about 5-10 ml of venous blood is obtained (volume of blood can be varied depending on amount of PRF to be prepared)from the patient and is collected (no anticoagulant is used) in a vacutainer. The vacutainer is then placed in centrifugal machine and centrifuged at 3000 rpm for 10 minutes. This leads to formation of three layers; red lower fraction composed of red blood cells, middle layer containing fibrin clot, and upper straw coloured cellular plasma. PRF is obtained by discarding the upper straw colour fluid. The fibrin clot along with one millimetre of RBC layer is separated to be used as PRF.[9,10] Quick handling of blood is critical in preparation of PRF. Delay in collection of blood, transfer to vacutainer and centrifugation can lead to failure to prepare PRF of desired characteristic. As there is no anticoagulant added to the blood in preparation of PRF, platelets gets activated within few minutes (as soon as it comes in contact with tube walls), thus initiating the coagulation cascade, resulting in formation of diffuse non-uniform fibrin meshwork. In contrast to FG and PRP the process of polymerisation in PRF preparation is physiologic and slow wherein, thrombin acts on collected autologous fibrinogen thus forming unilateral junction structureof weak thrombin and flexible fibrin. This elastic Fibrin forms a mesh for platelets thus concentrating most of the platelets and growth factors.[11] Simple and faster procedure of preparation, minimal expense and no biochemical handling (no external additives used), are some of the advantages of PRF over first generation platelet concentrates. Further it also adds on to tissue adhesion and matrix for tissue forming cells as fibroblasts, endocytes aiding in tissue repair and regeneration. Comparison between biological structure, function and properties is given in [table 2]

Applications in oral and maxillofacial surgery:

Although use of Platelet concentrates dates back to 1970's, in history of regenerative medicineit is still an emerging toolwith varied applications. Use of Platelet derived growth factors is found to be a boon for many surgical procedures. It gained popularity as it an autologous source of multiple growth factors readily available using simple instrumentation and is cost efficient. Subsequently over a period of time the procedure to prepare these concentrates became simpler.Introduction of this dynamic agent in the field of Oral and Maxillofacial surgery was done by Whitman *et al* in the year 1997.[12]The following section reviews the literature for its varied applications.

1.***Post-extraction socket healing***

Extraction or exodontia refers to painless removal of tooth/teeth from alveolus with uneventful healing and minimal trauma to adjacent investing tissue. This is one of the most routinely performed oral surgical procedures in dental office. Pain at the extraction site, bleeding, delayed or eventful healing are few commonly known complications related to this surgical procedure. Use of concentrates of growth factors from PC at the extraction site leads to stimulation of collagen synthesis, matrix formation, angiogenesis, thus promoting healing of soft and hard tissue (table 1). Efficacy of use of PC in its varied form for healing of extraction socket has been reported in literature with both animal and human trials by the means of histologic, radiographic and scintigraphic evidence. A scintigraphic evaluation of uptake of radionucleotide at the extraction site among rats was studied by Lurie A *et al*.[13] Results of the scan depicted subsequent increase in the uptake of radionucleotide with time, achieving maximum uptake by16 days after extraction. Socket closurecan be attained by primary closure or with help of bone allograft, use of PC in both the situations have shown favourable results. Rutkowskiet. al emphasized on using a cost efficient and simpler method for correction extraction socket i.e. buffy coat platelet rich plasma (BC-PRP). He reported that use of BC-PRP in the experimental group showed maximum bone density during initial 2 weeks (suggesting diminishing action of BC-PRP after 1.5 to 2 weeks). No significant results regarding post-operative pain or bleeding was seen nevertheless, decrease in inflammation was promising.[14]Radiographic evaluation of postoperative socket at time interval of 1 week, 1 month, 2, 3 and 6 months was also reported by Celio m *et al*. Significant and faster healing was observed in 1st, 2nd and 3rd month after extraction while not much difference was noticed at the end of 7 days or in 6th month. Celio m *et al*. reported better healing prevalence in males as compared to females.[15] In contrast to results obtained by Rutkwoski, Alisa *et al* reported more pain in control group while a better life style in experimental (PRP treated) group.[16] Moreover they also mentioned lesser complications associated with control group in the study. Similar results on evaluation of pain in extraction socket has

been reported by Ogeundepi *et al* wherein significant reduction of pain was noticed by patients receiving PRP postoperatively as compared to control group. Besides the study focussed on other parameters related to post extraction complications, such as inadequate mouth opening, postoperative inflammation, bone density and trabecular pattern concluding a better use of PRP in each one of them.[17] Gruberer *et al* through his scintigraphic evaluation revealed that use of PRP alone at the socket site does not show osteoblastic activity, when evaluated at first and fourth week.[18] Another study by Arenazbua *et al* revealed no significant acceleration of rate of bone healing or diminishing post-operative complications.[19] Use of PC in post extraction socket is an inexpensive, easily available alternative to complex closure procedures. Role of PC in repair, healing and correction of post-operative complications is worth taking a note. However literature regarding its inefficacy and controversies cannot be neglected, thus suggesting need for more research and clinical trials to be done.

2. Implantology

Use of platelet concentrates in implant placement procedure has varied applications,ranging from ridge augmentation, sinus lift procedure, enhance peri-implant soft tissue healing time, protection of schiderian membrane and improving of bone quality. Ridge augmentation alone or preceded by sinus lift procedure pose a significant clinical challenge, especially in the cases where immediate implant placement is indicated. PC helps in regulating osteoblastic and osteoclastic activity thus helping in bone regeneration.[20] A retrospective study by Anitua *et al* used PC in implant placement after transcrestal sinus lift procedure, which resulted in stable augmented height after 3 years follow-up. Another similar study revealed use of PRP along with autogenous graft in atrophic maxilla to promote healing and handling of the grafts. Significant positive results regarding use of PRGF (Platelet rich growth factors), mesenchymal cells and fluro-hydroxyapatite in sinus lift augmentation was seen as compared with control group of fluoro-hydroxyapatite [21,22]. However Bae J. H. *et al* reported no significant effect of PRP on bone graft healing in maxillary sinus augmentation.[23] PRGF adsorbed over acid etched titanium implant surface helps in consolidation of bone by facilitating adhesion and proliferation of osteoblasts. Pilot study by Anitua *et al* stated that use of PRGF over implant surface promote osseointegration.[24]Acceleration of healing time before placement of implant using PRF was reported by Choukran *et al*.[25]Perforation of schiderian membrane. is one of the most common complication encountered during implant placement in posterior maxilla and can lead to infection of sinus and graft, subsequently leading to failure of implants. A pilot study by Silvio *et al* reported use of PRGF in schiderian membrane repair. Elasticity and tight adhesion of clot enriched with growth factors help in prevention of detachment of the membrane. Further lateral compression from clot; due to its hydraulic pressure nullify the force of detachment of membrane.[26] Although release of growth factors and their actions play a vital role in prevention of implant failure, literature concluding no reliable evidence of use of PRP in implant treatment cannot be excluded[27] thus demanding for much more exploration in this field.

3. Cleft palate and cleft alveolus surgery

Facial clefts are common congenital deformity associated with incomplete fusion of two or more facial processes. Although not life threatening they have huge impact on patients life, and leads to psychological, aesthetic, dental, speech and hearing problems. The treatment modality for cleft palate and alveolus has evolved over a period of time ranging from use of bone grafts (autogenous, allogenic, alloplast or combination) to using of mesenchymal stem cells for regeneration. Bone regeneration and differentiation of osteoblast can be accelerated by using various osteogenic growth factors, like those present in PC (chin et 2005; Kang *et al*., 2011). [28,29] Le monnier was 1st to report the application of PC for treatment of cleft palate and alveolus.[30] Animal trial by Farhad et.al. suggested that use of stem cells along with PRP in cleft palate reconstruction was feasible in rat models and further investigation towards tissue engineering may eliminate the need of bone harvesting such patients.[31] Tajimina *et al* suggested that use of PRP with bone marrow stromal cells promote proliferation of osteoblast.[32] Similar in vitro study by Arpornmaeklong *et al*. stated that TGF and PDGF from PC stimulate proliferation of osteoblast, but caused inhibition ofosteoblastic differentiation.[33]However dilution of body fluid circulation can nullify this inhibitory action of PRP on osteoblastic differentiation. [34] Use of PR in cleft patients has also shown to enhance soft tissue healing process. The fibrin network of PRP acts as osteoconductive scaffold enhancing three dimensional intercellular interactions which provide a favourable environment for maturation of osteoblast. This enhances immunomodulatary action and thus stimulates the healing process. A study reported by Marukawa suggests acceleration of this healing process through the growth factors concentrate decreases the incidence of bone resorption.[35] PRP fail to promote bone substitutes such as HA (hydroxyapatite) and beta-tricalcium phosphate, thus lacks osteoinductive property when used solely. It is necessary to combine PRP with living bone cells to be effective. The environment in which PRP is applied is important. PRP may be either effective or inhibitory according to the concentrations of growth factors and the stage of bone formation. Topical application of PRP also decrease incidence of oro-antral fistula, which is one of the most common complication of cleft palate repair.[36]Various studies related to use of PC in the treatment of cleft and their outcomes is enumerated in [Table 3]

4. Scars:

Interrupted or delayed healing is commonly seen in the form of scars**.** Arrested scars after trauma, surgery, burnor sports injury often results in undesirable aesthetics, limited function and adverse psychological impact on the patients. Freguson MW. *et al*.[37] mentioned the role of growth factors in wound healing by comparing the adult and embryonic scar healing mechanism. He suggested that by altering the ratio of growth factors present during adult wound healing; we can induce the wounds to heal perfectly with no scars, accelerated healing and minimum adverse effects. One of the recent study by Shin *et al* showed effective and promising significance of the fat grafts mixed with PRP, followed by skin resurfacing with nonablative laser for treatment of scar attenuation. [38]Whereas, Gentile *et al* reported combination of adipose cell derived stromal vascular fraction cells and PRP for scar on the face. Study showed favourable results with the comparative better healing and attenuation of scarin the patients receiving autologous fat combined with PRP when compared to control group. [39]Nita AC *et al* proved a synergetic effect of combining Co_2 laser, PRP and fat for contraction of scar tissue with excellent satisfaction rate for over 50% of the patients. Use of

Table 3. Previously reported studies with use of PC in patient with cleft alveolus

Study by	Combination used	Outcome / results
Giudice *et al*	Autogenous bone with PRP	Enhances osteointegration and also stimulates bone healing and favours earlier orthodontic movement.
Ouyang *et al*	Bovine porous bone mineral(BPBM) with PRP in periodontal infrabony defect.	Significant favorable clinical improvement in periodontal infrabonydefct than using BPBM alone.
Hibi *et al*	Autogenous mesenchymal stem cells and PRP	Promising results in osteoplasty by bone regeneration and bridging of cleft after 6 months.
Lee at al	Secondary autogenous bone graft with PRP in alveolar cleft	PRP showed improved bone remodeling in early phase but no long term results were satisfactory.
Rullo *et al*	Alveolar bone correction with bone graft added with PRP	Satisfactory results in healing of both hard and soft tissue.
Luacesrey *et al*	Alveolar reconstruction in secondary alveoloplasty with and without PRP	No significant difference was seen in bone regeneration amount in two groups.

PRP has also shown promising effects in improving the viscoelastic property and scars of deep burns[40] Similar results were reported by Kozarev *et al* in a comparative evaluation of combination of Er YAG laser and PRP and ErYAG alone on the control side of the atropic post traumatic scar and stated that the combination of fractional ablative laser and PRP is more effective than fractional laser alone in improving post traumatic scars.[41].

5. Peripheral neuropathies

There is emerging literature regarding beneficial effects of PRP for nerve regeneration. Although PC do not have neurotropic action, it helps in adhesion and recovery of injured CNS by its neuroprotective effect.[42]Giannessi *et al*. stated that PRP is not only asource of bioactive proteins, but also serves as a nerve guide to hold the scar reaction and thus induce axonal regeneration.[43] Role of PC for correction of neuropathies in facial region was reported by Scala *et al*.[44] They performed a clinical randomized trial in patients who underwent superficial parotidectomy. Application of PRP gel at the surgical site of parotidectomylead to positive effects, and showed a protective role against neurological deficit of facial nerve. A similar significant result of injecting PRP was recorded by Anjayani, *et al*.[45] in patients with Hansen's disease. This double-blind, randomized, clinical trial showed result promotinguse of PRP in nerve regeneration. Although there are many studies showing significant use of PRP in nerve generation, further investigation on this area is desirable.

6. Haemostasis

The most common complication seen after any minor or major surgical procedure includes post-operative bleeding, especially in medically compromised patients including haemophiliac, hypertensive patients and patients on antiplatelet & anticoagulant therapy. Haemostasis involves coagulation at bleeding site and usually takes place in 3 steps involving vasoconstriction, formation of platelet plug and formation of fibrin clot. Use of external concentrate of platelet by the means of PRF or PRP can result in multiplication of amount of platelet available naturally thus enhancing the haemostasis process. Platelet dense granule components including Adenosine Di Phosphate and polyphosphates, contribute to haemostasis and coagulation.[46]A study reported by ValleD. et.al. showed that useof PRP to prevent bleeding after dental extraction can be significant haemostatic agent in patients treated with anticoagulant therapy.[47] Patients receiving Platelet gel are reported to have less postoperative bleeding, pain and show accelerated tissue repair.[48] PRF regulates coagulation cascade by releasing thrombospondin-1 (TSP-1). TSP along with Von willebrand factor and fibrinogen helps in platelet aggregation. TSP also prevents proteolysis of Von willebrands factor thus maintaining the integrity of clot.[49]

7. Facial aesthetics

Use of PC although has great history dating back to 1970s they are dynamically and continuously evolving each day in the branch of dermatology. The regenerative and repair property of platelet concentrates and its growth factors are ideal to be used in dermatology and aesthetic medicine in head and neck region.

7a. Skin rejuvenation

Platelet concentrates are known source of growth factors and cytokines. Activation of these platelets promoteextracellular matrix formation, angiogenesis, cell proliferation and cell differentiation. Use of concentration of these platelets topically can lead to activation of dermal fibroblast cells by remodelling of extracellular matrix thus contributing to rejuvenation of skin. A comparative evaluation of use of readymade synthetic growth factors and use of autologous PRP was done by Gawdat *et al*. [50] It was a split face therapy where each side was assigned either autologous PRP(area A) or readymade growth factor (area B). Results revealed significant role of using PRP in skin rejuvenation with higher longetivity as compared with control area. Synergistic action of combining PRP with hyaluronic acid in skin rejuvenation was reported by Ulsal BG *et al*.[51] Various beneficial effects of aPRP on collagen production, stimulation of dermal fibroblast cells, MMP-1, Protein and mRNA in human dermal fibroblast was reported by Kim *et al*. In their study, they evaluated the effect of activated platelet-rich plasma and activated platelet-poor plasma for rejuvenation of aged skin. They concluded that aPRP and aPPP promotes tissue remodelling in aged skin.[52] PC also serves as adjuvant to laser treatment for skin rejuvenation in cosmetic dermatology. Promising effect using PC in face and neck revitalization was reported by Redaelli A *et al* in a series of 23 consecutive treated patients.[53] A more reliable and objective method of evaluation of efficacy of PRP in skin rejuvenation was given by Ozlem *et al*, in a non randomized clinical trial which focussed on histologic evidence. Results revealed significant increase in number of collagen fibre bundle in dermis, post treatment.[54]Recently use of derma roller and intradermal injection for skin rejuvenation, removal of wrinkles and sagging has been reported. Yuksel *et al* reported a clinical trial wherein they injected PRP with 27 gauge dermal roller. Derma rollers act by using micro needling technique that punctures the skin leading to micro bruising in dermis. The author concluded PRP as an effective and safe tool for

skin rejuvenation.[55] Few side effects like mild erythema, ecchymosis, hematoma, erythema, burning sensation and rarely infection are reported.[51]Use of PC in skin rejuvenation is an emerging tool and can be considered as promising, safe and effective alternative over expensive cosmetic procedures or surgery but more literature regarding the same is required.

7b. Acne scar

Various treatment options for reducing acne scars include dermabrasion, microdermabrasion, chemical peeling, and laser resurfacing. However use of these options are not cost efficient for everyone and their efficiency is found to be limited due to the fact that they are either marginally effective or have greater risk of morbidity. In contrast to these options, micro needling a recent advance has shown to have more beneficial effect over diminishing acne scars. A study by Chawla *et al*. suggested use of PRP and vitamin C along with microneedling to enhance its efficacy [56]. The significance of autologous platelet-rich plasma combined with erbium fractional laser therapy in facial acne scars was reported in a study by Zhu *et al* [57] that showed PRP combined with erbium fractional laser therapy is an effective and safe approach for treating acne scars with minimal side-effects, PC also simultaneously enhanced the recovery of laser-damaged skin

7c.Use in hair loss

Hair follicle growth and development require interaction of epithelial cells with dermal papilla cells for their differentiation. Reconstitution of hair follicles requires a three dimensional scaffold which act as a signal for regeneration[58] Platelet-rich plasma gel forms a three-dimensional scaffold that can release endogenous growth factors;it is mitogenic for a variety of cell types and is used in model tissue repair and regeneration systems. Treatment of alopecia including minoxidil and finasteride is limited due to its side effects. Patients consuming minoxidil mainly complain of headache and increase in other body hair. While loss of libido and teratogenic effects are associated with finasteride. PC derived growth factors can help to activate proliferation phase and differentiation of hair and stem cells to produce new follicular units. Beta FGF is reported to promote in vitro proliferation of papilla cells and thereby play a key role in elongation of hair shaft. Xiao SE, Miao *et al*. found that 5% activated PRP, significantly enhances cell proliferation and hair-inductive capability of mouse and human dermal papilla cells in vitro and promoted mouse hair follicle formation in vivo.[58]A study reported by Cervelli *et al*. aimed at investigation of safety and efficacy of AA- PRP (Activated Autogenous PRP) injection for pattern of hair loss. At the end of 3 cycles of the treatment, patients showed increase in mean no. of hair, increased hair density as compared with baseline values. Histologically, significant increase in epidermal thickness, no. of hair follicles, Ki 67 keratinocyte and small blood vessels was reported.[59] Similar positive results suggesting use of PRP in growth of hair follicle is reported by various studies. Navarro MR, *et al*. studied role of PC on female androgenic alopecia, results four months after the treatment, revealed a significant increase in the number of anagen hairs (growing hair follicle) while significant decrease among telogen (resting hair follicle).[60] Although PRP for treatment is found to be safe and effective method, a study by Khatu *et al*. revealed negative pull test, moderate significance in hair volume, density and calls for more evidence to prove the efficacy of PRP in hair growth.[61]

8. Maxillofacial trauma and reconstruction

Any defect after trauma/surgery can limit the function. Application of PC for hard and soft tissue maturation has shown stimulated and accelerated tissue healing. Platelet concentrate combined with leukocyte was reported by Bielecka *et al*. They used LPRP (leukocyte PRP) and L PRF (leukocyte PRF)for correction of mandibular odontogenic cystectomy and in patients with double mandibular fracture. Decreased bleeding during operation and lesser operating time was observed. While post-operatively minimal pain, hematoma and other post-operative complications were noticed. Other advantages mentioned were enhancement of flap, graft survival, faster epitheliazation, and decreased need of pressure dressings.[62] Addition of PRP to highly purified bovine allograft in bony cystectomy defect show promising effects of using PRP with defect filling upto 56% by 1st month while 92% by 6th month.[63]A study by Daif *et al*. reported, PC enhanced bone regeneration along the fracture lines in mandibular fractures.[64]According to Marx *et al* based on radiographic evaluation of mandibular continuity defect, the maturation rate for autogenous bone graft when combined with PC was moderately enhanced to the rate of 1.62 to 2.16.[65]In contrast to positive significance, Mustafa *et al*. who combined PRP and hyaluronic acid (HA) for correction of intrabony defect did not find any significant probing depth at the end of 1st and 6th month whereas increased radiographic bone density on experimental side was seen in 3rd month. [66]According to Cieslik-Bielecka *et al*. although promising results were found in correction of mandibular odontogenic cyst with considerable enhanced bone regeneration and increased bone mineral density (BMD) the author mentioned that L-PRP lacks its stimulatory action in the absence of autogenous bone graft as vital bone cells are needed for this stimulation.[62] Yet autogenous graft can show better results in simpler defects as odontogenic cyst. Wojtowicz *et al*. compared the effects of stimulating the osteogenesis of the alveolar bone by transplants of autologous bone marrow and PRP. It was shown that the rate of newly formed bone was increased under the influence of PRP.[67]

9. TMJ osteoarthritis

TMJ osteoarthritis commonly presented clinically as pain, stiffness or minimal mouth opening. It isusually caused due bruxism, unilateral grinding of teeth, over loading and genetic factors. Repeated trauma to the joint often results in resorption of the bone, sclerosis, flattening and osteophyte degeneration at the site. Cartilagearticulation or regeneration is indicated in osteoarthritis of various joints including tempero-mandibular joints. The lesser blood supply to the cartilage as compared to bone usually results to delay in healing of cartilage. Platelet concentrates can help in correction of this osteoarthritis by inducing angiogenesis, promotingosteo conduction and soft tissue healing. An animal trial by Shin *et al*. evaluated effect of leukocyte rich and platelet rich plasma on healing of horizontal medial meniscus tear in rabbit model and failed to show positive effect of single injection of PRP on enhancing healing of horizontal medial meniscus tears in rabbit model.[68] Anitua *et al* showed therapeutic effect of PRP in osteoarthritis by modulating synovial cell biology. They reported increased HA (hyaluronic acid) concentration and stabilized angiogenesis

after platelet concentrate exposure.[69] Injection of PRP in reducible anterior disc dislocation was reported by Hanceet. al. with significant results in recovery in terms of post-operative pain, Maximal incisal opening.[70] Hegab *et al* compared PRP and HA injection in patients with osteoarthritis and superior results were found with combination of PRP and HA when compared with HA used alone.[71] Pihut *et al* found significant reduction in pain by intra articular injection of PRP into TMJ in patients with TMJ dysfunction.[72]Negative significance was reported by Comert *et al* with no significant benefit of using PRP in TMJ osteoarthritis.[73]Use of PRP in TMJ osteoarthritis, arthrocentosis and TMJ dysfunction remains to be controversial with need for more studies regarding the same.

10. Bisphosphonate related osteonecrosis of jaw

Bisphosphanate are stable analogue of inorganic pyrophosphate and are anti-bone resorption drugs usually indicated in conditions as hypercalcemia, pagets disease, postmenopausal osteoporosis, bone metastasis and multiple myeloma etc. Bisphosphonate related osteonecrosis of jaw (BRONJ) refers to necrotic area of avascular bone with or without exposure in maxillofacial region. Treatment for BRONJ varies from using 0.12 % chlorhexidinegluconate mouthwash and systemic antibiotics to local surgical debridment. Bocanegraperez *et al* and Yokota *et al* observed accelerated angiogenesis in rabbits by combining vascular and single PRP injection.[74] A clinical study by Longo F et.al. evaluated therapeutic effect of PRP in wound healing of surgical and non-surgical therapy of BRONJ showing significant effects in wound healing.[75]According to a study reported by Sarkarat *et al*. which aimed to evaluate effect of PRP on drug induced BRONJ, no significant difference was found between experimental and control group in terms of degree of epithelisation, angiogenesis and sequestrum formation. However, significant difference was found in relation to amount of existing vital bone.[76] Significant results with complete wound healing and shorter BRONJ treatment period was reported by curie *et al* by using combination of necrotic bone resection and PRP in patients with BRONJ and history of I.V bisphosphonate therapy for metastatic bone diseases.[77]Debridement and removal of necrotic bone followed by application of autologous platelet concentrate enriched with growth factors along with significant healing also caused resolution of the oral lesion.[78] Use of PRP in patients with BRONJ can prevent progression of further necrosis enhance healing and reduce need for analgesic. Thus the use of PRP in patients with BRONJ should be promoted.

11. Dressing material for oral mucosal defect

The ability of Platelet concentrates to repair and regenerate the hard and soft tissue is not only limited to extraction sockets, bone or implant augmentation, but growth factors derived from these platelet concentrates can be used for dressing of oral mucosal defects too. Oral mucosal defect like leukoplakia, lichen planus are often encountered in our day to day practice. Excision is one of the most preferred options for treatment of these defects. Recent study done by Pathak *et al*. revealed that use of PRF membrane which is obtained with the help of compression machine (compressor derived platelet rich membrane) aids in healing of these lesions.[79] The significance of dressing these mucosal defects with PRF was given by a study conducted by Mohanty *et al*. wherein they concluded that addition of such a membrane over these mucosal lesions adds up to faster haemostasis, better workability, tear strength manipulation and healing.[80]

12. Oroantral communication

Oroantral communication is a non physiologic communication between oral and nasal cavity often lined by epithelium. The most common cause of such pathologic communication istrauma to the face, perforation from malignant diseases as malignant melanoma and injudicious use of instruments which can also lead to breakage of schiderian membrane. Treatment of such communication may vary from conservative approach of primary closure and antibiotics to surgical closure with the help of buccal or lingual flaps. A study done by Elshourbagy *et al* used bone substitute and PRF in closure of oroantral communication using revealed satisfactory healing of communication with minimal chances of infection and other complications as ulceration, allergic reaction, exposure of material. Densitometric measurements and radiographic evaluation showed significant results 3 months later post operatively.[81] Kapustecki *et al*. reportedbenefical effects of single stage primary closure of oroantral communication using PRP overresorable or non resorable collagen membrane. The author stated satisfactory results in closure of oroantral communication with no complications and encourages more clinical trial for introducing this technique commonly .[82]

13. Fat grafts

Use of fat grafts remains popular treatment modality for correction of minimal to moderate soft tissue defects, and commonly indicated in defects as tumour ablation, congenital deformity, and traumatic / surgical injury. They are more popular and most commonly preferred soft tissue fillers as these are comparatively cheaper, easy to obtain, can be retrieved under local anaesthesia and show minimum immune reaction as they are autogenous. Yet associated complications as fat necrosis due to insufficient vascular supply, variable resorbtionrate, microcalcifaction and cyst formation limit their use. Recently PRP has emerged to provide matrix to enhance this fat graft survival. PC upon degranulation release growth factors that can enhance angiogenesis and survival rate of fat grafts. Animal trial by Por *et al*. who used PRP without activation failed to show significant results using PRP with grafts when compared to control group treated with saline.[83] While in contrast to this, Piers Fraga *et al* used activated PRP implanted in subcutaneous ear of rabbit model and showed promising results with increase in viable adipocytes and angioneogensis.[84]Similarly results by Oh *et al*. revealed lesser fibrosis, chances of cyst formation, increased angiogenesis on addition of PRP with calcium chloride and bovine thrombin combined with fat grafts in a nude mice.[85] Histological evidence for these positive results was provided by Nakamura *et al* with increase in number of adipocytes, granulation tissue and capillary formation for atleast 120 days. They also showed lesser association of cyst and fibrosis formation in experimental group than in control.[86] Cervelli *et al* mentions the ratio of 40 % of PC to be ideal for combination with bone graft maintained for 50 weeks while more promising results were reported on combination of PRP with insulin.[87]Effective useof autologous platelet adhesives on dermal fat graft for reconstruction of a superficial parotidectomy was reported by Chandarana *et al*. with improved viability if the graft.[88] A study by Cervelli *et al*. for correction of hemifacialatropy

reveals positive outcomes of using PRP with fat in orofacial region.[89]

Conclusion

Applications of PRP in the field of oral and maxillofacial surgery are extensive ranging from healing of simple extraction socket to being adjunct to complex surgical reconstruction. This review paper is an effort to comprehend all the varied applications focussing on recent applications in this field of dentistry.

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