Review Article

Platelet-rich growth factor in oral and maxillofacial surgery

Uma Shanker Pal, Shadab Mohammad, Rakesh K. Singh, Somdipto Das, Nimisha Singh, Mayank Singh[1]

Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, [1]Department of Prosthodontics, King George's Medical University, Lucknow, Uttar Pradesh, India

Address for correspondence:
Dr. U. S. Pal,
Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, Shah Mina Road, King George's Medical University, Lucknow 226003, Uttar Pradesh, India.
E-mail: uspalkgmc@yahoo.co.in

ABSTRACT

Platelet-rich growth factor is an innovative regenerative therapy used to promote hard and soft tissue healing. It involves the application of autologous platelet-leukocyte-rich plasma containing growth factors and thrombin directly to the site of treatment. It is the intrinsic growth factors released by activated platelets which are concentrated in a topical gel formula. Clinically, it is an affordable treatment with potentially broad spectrum of applications in maxillofacial surgery especially in the treatment of complex or refractory wounds. The present article reviews its various applications not only in the specialization of oral and maxillofacial surgery but also in regenerative medicine.

Key words: Alveolar clefts, bisphosphonate related osteonecrosis of the jaw, bone healing, nerve regeneration, platelet rich growth factors

Introduction

Platelet-rich growth factor (PRGF) is a boon in recent years in the field of regenerative medicine and also gaining attention of various scientists in the field of regenerative medicine. The inherent property of PRGF mainly to promote soft and hard tissues has its application in the various fields of medicine and surgery including oral and maxillofacial surgery.

Human body's relatively poor capability to auto regenerate increases the demands for tissues and organs. Neither is there an abundance of organ donors in our society nor the actual replication of lost tissues possible by transplantation, which prompted the field of regenerative medicine as the subject of interest among the various research workers.

PRGF is also a less invasive procedure and reduces donor-site morbidity. In the presence of body's proteins and polypeptides responsible for cellular communication and naturally available scaffold in the form of three dimensional fibrin network, PRGF is a promising way of utilization of body's natural reservoir in the field of regenerative medicine.

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This review is a sincere effort to accumulate the literature of the various applications of PRGF in oral and maxillofacial surgery into a comprehensive one.

Platelet-rich growth factor

PRGF contains platelets in the pool of plasma. The optimal platelet count in PRGF is a poorly defined subject in the literature. Whitman *et al*.[1] stated that the platelet count in PRGF should oscillate between 500,000 and 1,000,000 cells/L. In the initial work of Marx *et al*.[2] the mean platelet count achieved was 785,000 cells/L using the same protocol as Whitman *et al*. Landesberg *et al*.,[3] evaluating different centrifugation speeds, determined the best protocol to be the one that provided a platelet count of 935,000 cells/L. At this stage of knowledge about this autogenous growth factor concentration, several studies have shown that a platelet count between 500,000 and 1,000,000 cells/L is considered optimal.[4-6]

The first attempt to standardize a platelet concentration

for platelet rich growth factor (PRGF) was proposed by Marx. The author argued that the best biological response occurs when a 4-5 fold increase over the baseline platelet number is achieved. Hence, the ideal PRP should present a platelet count of over 1 million cells/L.[2]

Platelets are considered living depots of enormous growth factors which once activated after centrifugation by calcium chloride or autologous thrombin, release biologically active proteins which help in tissue mitogenesis, differentiation, and morphogenesis.

The proteins derived from platelets include platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF). Plasma contains certain natural growth factors in the name of insulin-like growth factor (IGF) and hepatocyte growth factor (HGF).

Some of the main roles of these enumerated growth factors are given below:
PDGF: A glycoprotein, PDGF has a molecular weight of approximately 30 kd. PDGF is a family of five homo- and heterodimers (αα, αβ, ββ, γγ, and δδ isomers) of disulfide-bonded polypeptides encoded by four genes (α, β, γ, δ), which bind to two different receptor tyrosine kinases (PDGF receptors α and β) at the cell surface.[7] PDGF-C (2000)[8] and PDGF-D (2001)[9] were recently discovered in comparison to PDGF-α and PDGF-β.

PDGF-αβ and PDGF-ββ are seen to have strong mitogenic effects on stem cells and osteoblasts and promote angiogenesis and collagen synthesis, thus enhancing the process of wound healing. PDGF αβ and ββ are secreted by platelets at the injury site, whereas αα isoform is secreted by unstimulated osteoblasts cell lineages.[10,11]

During early wound repair (proliferative phase), PDGF leads to proliferation of fibroblasts which synthesize provisional matrix composed of glycosaminoglycans and fibronectin.[12] PDGF-αβ and PDGF-ββ, but not PDGF-αα, promote contraction of collagen matrices[13] and mediate the fibroblast-dependent secretion of collagenases, which is important in the late stage of wound healing (remodeling phase).[14]

TGF: TGFs are proteins of molecular weight of approximately 25 kd. TGF-β exists in three isoforms, namely TGF-β1, TGF-β2, and TGF-β3. TGF-β family belongs to a superfamily of proteins that includes inhibin, activin, antimullerian hormone, bone morphogenetic protein, decapentaplegic, and Vg1.[15]

TGF-β1 is a multifunctional peptide that controls proliferation, differentiation, and other functions in many cell types. The TGF-β receptor is a serine/threonine kinase which controls the production of the extracellular matrix. Its topical application leads to an enhanced production of collagen and fibronectin.[16] It has also been shown that TGF-β stimulates mesenchymal precursor cells in the periosteum to proliferate and differentiate.[17]

VEGF: It induces both chemotaxis and endothelial differentiation thus leading to angiogenesis.[18] It is mitogenic and promotes the chemotaxis and differentiation of epithelial, renal, and glial cells as well as fibroblasts.

EGF: It has both chemotactic and mitogenic effects on epithelial cells and fibroblasts. It is a potent stimulator for granulation tissue formation. Fibroblasts, preosteoblasts and prechondrocytes have a high number of receptor for EGF.[19]

IGF: The IGFs are polypeptides which have a large sequence homology to insulin.[20] This group of proteins, also called the IGF-axis, consists of two types of membrane receptors: IGF receptors I and II (IGFR-I and II), two ligands (IGF-I and II), a group of six IGF-binding proteins (IGF BP-1 to 6), and a few IGFBP-associated proteases.[21] IGF-II seems to play an important role in early cell development,[22] whereas IGF-I is relevant at a later point of time in maximizing growth. Although IGF-II is the most abundant growth hormone in bone, IGF-I was found to be more potent[23] Furthermore, IGFs stimulate efficient reepithelization of wounds.[24]

Studies have revealed the anti-inflammatory effect of plasma rich in growth factors which could be mediated by the inhibition of transactivation of transcription factor kappa B (NF-κB) and the expression of CO × 2 and CXCR 4 due to the high content of plasmatic HGF, IL-4 and tumor necrosis factor-alpha (TNF-α).[25]

Clinical applications in oral and maxillofacial surgery
The ability of PRGF in accelerating soft and hard tissue healing has stimulated the research of its clinical applications in various areas of oral and maxillofacial surgery, which includes healing of extraction sockets including impacted tooth, implantology, cleft lip and palate, ulcer management, and bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Platelet-rich growth factor and bone healing
One of the initial studies of regenerative medicine in healing sockets was done by Anitua *et al*. in 1999.[26]

The study consisted of 20 patients divided into both the study and the control groups. It was found that the bony and soft tissue healing was extensive with well-organized bony trabeculae in the study group. On the contrary, the control group showed only presence of connective tissue with little matured bone. This study also correlates well with the study by Célio -Marino *et al*.[27] Fifteen patients with bilateral impacted molar were taken for study, and following extraction, one of the socket was treated with PRGF and the other by secondary healing. It was shown with the help of radiographic bone density measurements that bone formation was significantly faster compared with normal healing ($P < 0.01$). Although the difference is insignificant on the seventh day and sixth month, but bone formation was faster and better on first, second, and third months.

But Gürbüzer *et al*.[28] found no significant differences between sockets healed with and without PRGF ($P > 0.05$) using bone scintigraphy. The author gave the reasoning that both the platelet counts and level of growth factors in PRP are dependent on preparation methods.[26,27,29] Similarly, the effect of PRGF in wound healing is dose dependent. Gürbüzer stressed that highly concentrated platelet preparations (6-11 folds above normal range) could have an inhibitory effect on bone healing by stimulating osteoclastogenesis.

PRGF and implants including sinus lift

Another field where PRGF is used with excellent results is in the augmentation of maxillary sinus floor for implant placement. It is found that PRGF along with bone grafts not only facilitates manipulation and administration of the graft but the fibrin scaffold can also be used as an autologous sealant biomaterial in cases of Schneiderian membrane. Anitua *et al*.,[30] carried out a prospective study of 5 patients and concluded that not only PRGF facilitates bone augmentation but also reduces inflammation in the study group as compared with the control group. In this series, new vital bone in the study areas compared with the control was 21.4-8.4%. The number of blood vessels per mm^2 was also high in the study area (116-7).[31] Similar positive results were also shown by Riaz *et al*.[32] Pieri *et al*.[33] conducted a study of mesenchymal stem cells, PRGF, and fluorohydroxyapatite with fluorohydroxyapatite alone. He concluded that after 12 weeks, there is a significant rise in sinus lift augmentation in the test site rather than the control site (42.51% vs. 18.98%; $P = 0.001$).

But Schaaf *et al*.[34] radiographically compared the difference in sinus lift due to autogenous bone grafts and PRGF. The author conducted the study on 34 patients and the bone density was evaluated both histomorphometrically and with help of computed tomography (CT) scan. Spearman correlation coefficient suggested no difference in bone density histomorphometrically and CT in therapy with PRP ($P = 0.55$; without PRP: $P = 0.80$). Similar results were also supported by the studies of Zhang *et al*.[35] and Andreas Schlegel *et al*.[36] on sinus floor elevation with bone substitutes and bone substitutes mixed with PRGF. Casati *et al*.[37] conducted a study on mongrel dogs to study the effect of PRGF on bony dehiscences around peri-implant surfaces and found no significant differences in healing ($P > 0.05$). Hence, following review about PRGF application in bone healing, no significant results were found of its applications in sinus lift or bony dehiscence healing in terms of bone density or bone to implant contact.

PRGF and BRONJ

Patients who are on intravenous therapy of bisphosphonates are found to have higher incidence of aggressive and extensive BRONJ than patients with oral bisphosphonates.[38] Conservative management of BRONJ especially grades II and III are found to be partly successful[39] with resolution rate of 50% as compared with 80% with surgical management. The surgical management usually consists of wide resection of the bone till healthy bone is reached. Healthy bone is judged mainly by the color, fresh bleeding from the bone, though Pautke *et al*.[40] developed a fluorescence-guided technique which consists of tetracycline uptake of healthy bone which delineates it from necrosed bone. Due to the paracrine effects on stimulated cells by the PRF,[41] bone remodelling following surgical resection of BRONJ is mainly affected by bone remodelling associated with osteoclastic resorption and bone formation involving osteoblasts, osteoclasts, blood vessels, and perivascular stromal tissue.

In the study conducted by Curi *et al*. in 2011,[38] 25 patients with BRONJ who failed to get treated conservatively were managed surgically with wide resection and application of PRGF. Twenty patients were found to have complete healing in a median follow-up period of 36 months. It was concluded from the study that treatment of refractory BRONJ with a combination of bone resection and PRP was found to be an effective therapy in most patients and should be considered an alternative treatment modality for management of advanced cases. Similar results of the efficacy of PRGF in bone regeneration and wound healing were also shown by Lee *et al*.[42]

PRGF and alveolar clefts

Alveolar bone grafting has become an essential procedure in the treatment of cleft lip and palate. Both

autologous and xenografts are used for the regeneration of bone in the region of clefts. Among autografts, iliac crest is one of the good treatment options, as it is osteoconductive and the chances of rejection due to graft-versus-host response are not present. But in spite of these advantages none of the studies reported significant differences in bone density when either autografts or xenografts were used.

Oyama *et al*.[43] conducted one of the initial studies of bone grafting with iliac crest cancellous bone with PRGF in 7 patients. The samples were divided into study and control groups, where PRP was mixed with bone grafts and only bone grafts used. Quantitative evaluation of the regenerated bone was made with three dimensional CT scans. The results were analysed as a ratio of volume of regenerated bone (VRB) to volume of alveolar cleft (VAC). It was found that in the study group, the minimum percentage of VRB/VAC was 71.27% (6 patients) and the maximum was 87.32% (2 patients) (average, 80.19% + 6.77% [SD]). In controls, the minimum percentage of VRB/VAC was 47.47% (9 patients) and the maximum was 77.97% (10 patients) (average, 63.67% + 13.94% [SD]).

Similar results were also concluded by Marukawa *et al*.[44] and Behnia *et al*.[45]

But Lee *et al*.[46] conducted a longitudinal study to evaluate the outcomes of secondary autogenous bone grafts with PRP in alveolar clefts. It was found that no significant differences were observed in the bone resorption rate between the study group where PRP was added and the control group where it was not. Regarding prognostic factors, continuous mechanical stress affected bone resorption with or without PRP. The authors suggest that PRP may enhance bone remodeling in the early phase; however, PRP seems to be insufficient as a countermeasure against bone resorption following secondary bone graft in the long term.

PRGF and nerve regeneration

PRGF does not have its affect only in bony healing but also in soft tissue healing. It is also used in various applications in sports medicine such as tendonitis, Achilles tendon repair, tennis elbow, muscle injuries.[47] It also found its applications in nerve regeneration, which can be both peripheral and central nervous system (CNS).

It is seen that most CNS diseases have a series of common pathological changes in the later period of diseases which induce apoptosis of neurons and glial cells. This aggravates neurological dysfunction in later life. Hence, its applications can be used as a novel therapeutic approach for CNS diseases, especially for traumatic brain or spinal cord injury, autoimmune diseases and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

Although PRGF is not a neurotrophic factor, it does have a neuroprotective effect to promote adhesion and recovery of injured CNS. The various roles of PRGF suggested are as follows:

1. The cytokines in PRGF have protective actions on neurons from excitatory amino acid toxicityor nitric oxide toxicity of free radicals.[48,49]
2. The trophic factors of PRGF have the potential in promoting axonal outgrowths and remyelination.[50-52]
3. PRGF has been found to consist of certain proteins which even regulate neurotransmitter secretion.[53]
4. The various growth factors in PRGF, such as PDGF, VEGF, TGF-β, facilitate angiogenesis and collagen formation.[54]
5. The cytokines in PRGF have a role in activation of endogenous neural progenitor cells, and thus causing proliferation, migration, and differentiation to replace injured nerve cells.[55]

Although there has been reported evidences in literature regarding the applications of PRGF in nerve regeneration and repair, but its role in humans is yet to be warranted.

PRGF and hair transplantation

PRGF is basically a protein molecule which has a role in angiogenesis after it interacts with cell-specific receptors, which stimulates healing and growth of new organic structures. Uebel, *et al*.[56] conducted a study for the first time on the effects of PRGF in hair micrograft implant surgery. PRGF acts as a mediator to bring about togetherness among stem cells which are primitive ectodermal cells and dermal papilla derived from mesenchymal cells. Finally, this gives rise to the future follicular unit, which consists of the hair shaft, sebaceous glands, erectus pilus muscle, and the perifolliculum.

The author found a statistically significant difference observed in the yield of follicular units when comparing two groups: One in which PRGF added to the other where it was not ($P < 0.001$). The experimental group with the platelet plasma growth factor showed a density of 18.7 follicular units/cm^2, whereas the control group showed 16.7 follicular units/cm^2. The difference of 2.4 follicular units/cm^2 (95% confidence interval, 1.6-3.2 follicular units/cm^2) represented a 15.1% increase in the yield of follicular unit density between the two

groups. Hence, the study proved the role of PRGF in treating baldness surgery.

Conclusion

Maxillofacial pathology where PRP is used includes fracture non-union, osteomyelitis, osteoradionecrosis, healing of extraction socket following removal of impacted molars, nerve regeneration, alveolar clefts, and also in cosmetic surgery including hair transplantation surgery. Our early experience in the use of PRP has found it to be a potentially effective clinical adjunct in the management of complex wounds and defects of both hard and soft tissues in the maxillofacial region with minimum morbidity of the donor.

This review is an effort to accumulate, among the innumerable data, certain applications of PRGF as reported in the literature. But none the less, we still recommend that extensive work in the field of regenerative medicine is still required to search for its other hidden effects.

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