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Research Article

CLINICAL APPLICATIONS OF PLATELET DERIVATIVES IN DENTISTRY: A NOVEL APPROACH

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A B S T R A C T

The platelets play a vital role in the process of healing and are known to release several growth factors. The growth factors present in platelets guide the regenerating cells to stimulate regeneration of bone and maturation of soft tissue. Various platelet aggregates such as PRGF, PRP, and PRF can be used as an adjunct in wound healing, correction of osseous defects, apexification, revascularization, etc. This review article focuses on the different types of platelet concentrates and their clinical application in various fields of Dentistry in a wide range of treatment modalities.

INTRODUCTION

The main goal of the modern surgery is low invasiveness and a high rate of clinical healing which is known as "regenerative surgery".[1] Use of platelet is becoming more popular in various fields of dentistry.

Various platelet aggregates have been used for the improvement of reparation and regeneration of the soft and hard tissues after various dental surgical procedures. Using platelet concentrates is a way to accelerate and enhance the body's natural wound healing mechanisms.[2]

Platelet-derived products or platelet concentrates acts as biological mediators aiding the healing response. The growth factors present in platelets are important to guide the regenerating cells to the area of healing. Various growth factors released from the platelets include platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-ß), platelet derived epidermal growth factor (PDGF), platelet-derived angiogenesis factor, insulin-like growth factor 1 (IGF-1), and platelet factor 4. These factors signal the local mesenchymal and epithelial cells to migrate, divide, and increase collagen and matrix synthesis[3, 4, 5]. Thus, use of platelet concentrates is a promising method in the field of dentistry and can be used in various clinical situations requiring rapid healing.

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Classification

Platelet derived products or platelet concentrates are classified into:-

First Generation Platelet Concentrates

The first generation platelet concentrates include **Platelet rich plasma (PRP) and platelet rich growth factors (PRGF).**

PRP was introduced by Marx.[6] and is defined as high concentration of autologous platelets in a small volume of autologous plasma.[7] It is clinically used to deliver growth factors in high concentrations to the site of bone defect or a region requiring augmentation.[8]

However, the method of preparation of PRP is technique sensitive as well time consuming. It also requires the use of bovine thrombin for the activation of PRP to release growth factors at the site of placement.[9-11]. Studies suggest that use of bovine thrombin has been associated with development of antibodies to clotting factors V, XI and thrombin, which had occasionally lead to life threatening coagulopathies.

PRGF (platelet rich growth factors) were developed by Anitua[3] to overcome these disadvantages. He simplified the method of preparation of PRP and also replaced the use of bovine thrombin with calcium chloride. PRGF releases growth factors as well as bioactive proteins at localized injected sites which stimulates tissue regeneration.

Second Generation Platelet Concentrates

PRF (Platelet rich fibrin) was first developed by Choukroun in France in 2001. PRF is a second generation platelet

concentrate, prepared without the addition of any anticoagulants.[8]

PRF consists of an autologous leukocyte-platelet-rich fibrin matrix[12,2], composed of a tetra molecular structure, with cytokines, platelets, and stem cells within it [13, 14], which acts as a biodegradable scaffold [17] that favors the development of microvascularization and is able to guide epithelial cell migration to its surface [14, 16]. PRF may serve as a vehicle in carrying cells involved in tissue regeneration [17] and seems to have a sustained release of growth factors [18] in a period between 1 and 4 weeks, stimulating the environment for wound healing in a significant amount of time [19]. It has a complex architecture of strong fibrin matrix with favorable mechanical properties and is slowly remodeled, similar to blood clot [19].

PRF is advantageous as it is a simplified and efficient method of preparation technique, obtained by autologous blood sample[20], no use of bovine thrombin reducing the chances of cross infection, slow natural polymerization which results in physiologic thrombin concentration and flexible 3-D structure of PRF which is more favorable to cytokine enmeshment and cellular migration.[8]

CLINICAL APPLICATIONS IN DENTISTRY

Oral and Maxillofacial Surgery

PRGF (Platelet rich growth factors)

The use of PRGF as regenerative surgery is a promising concept in advanced dental surgery.

Anitua *et al* conducted the study to analyze the use of PRGF as filling material in extraction socket. It was reported that patients treated with PRGF had superior soft tissue healing and radiological findings.[21] Pain and inflammation were also observed to be lower in the PRGF group after one week.[21]

Another study conducted by Anitua *et al* described the successful use of PRGF in implant placement using sinus elevation technique.[22] Pilot study of Taschieri *et al*. showed that PRGF may be helpful in reducing complications following sinus lift surgery.

Other studies have also shown that when the surface of the dental implant is soaked in PRGF, there is formation of fibrin membrane around the implant and there is release of growth factors. These growth factors were thought to improve the process of osseointegration.[23-25]. Studies have shown that PRGF can be safely used in immediate loading implants .[24]

PRGF in combination with block-graft can be used in the treatment of atrophic jaw. It improves the healing process, post-operative appearance of the patient as well as minimizes graft exposure and post operative complications.[26]

Cocero *et al*. studied the role of PRGF and compared it with fibrin glue in patients who underwent dental extraction procedures. The results demonstrated that PRGF as a local haemostatic agent works equally well as the fibrin glue.[27] PRGF is beneficial because it is autologous origin and also causes early neo-angiogenesis. [27]

PRGF can be effective in the management of patients with a history of head and neck radiotherapy as it accelerates mucosal healing and prevents post extraction bone exposure.[28]

Anitua *et al*. reported that when a symptomatic Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) patient was managed by resection of necrotic bone and the application of PRGF, the patient became asymptomatic (no mandibular sensitivity or pain) after one year and the bone was partially regenerated.[29] PRGF demonstrated positive results by enhancing the regeneration of osseous tissues, epithelial tissues and neo-vascularization. The treatment with PRGF can also reduce the risk of developing BRONJ in high-risk patients undergoing the treatment with bisphosphonates, after tooth extraction.

In cases of advanced internal derangement of the temporomandibular joint (TMJ), studies have shown that pain was reduced in patients who was given injection of PRGF following arthroscopy than the injection of hyaluronic acid (HA).[30]

PRF (Platelet rich fibrin)

Use of PRF in oral and maxillofacial surgery has been implicated in different procedures such as socket preservation, sinus lift and bone augmentation, and healing in donor site with good results.[31, 2]

According to studies it was observed that PRF plugs can be used as filling material in residual extraction sockets. It will act as a stable blood clot for neovascularization and accelerated tissue regeneration and can also be used to improve wound healing in immunocompromised and diabetic patients. In cases of wide sockets and lesions where primary closure is difficult, PRF can also be used in membrane form as it promotes re-epithelialization of the site and accelerates the wound healing process by protecting the surgical site[32, 33]resulting in reduction of patient discomfort during the early wound-healing period.[34]

PRF can also be used as an adjuvant in patients on anticoagulant therapy as it stimulates coagulation pathway along with thrombospondin and helps in wound closure.[32]

In sinus lift procedures and implantation, Choukroun *et al*[35] evaluated the use of autologous PRF in combination with freeze-dried bone allograft (FDBA). The results showed improved bone healing, enhancement of bone regeneration and decreased healing time prior to implant placement.PRF is a simple and inexpensive biomaterial in systematic use during a sinus lift. [36]

Simonpieri *et al*.[37] suggested using a mix of PRF with a bone graft in cases of bone defects or in immediate implants. Good clinical results were noted. He also observed that when PRF membranes were used along with FDBA and 0.5% metronidazole, there was no implant or graft loss. [38,39] PRF membranes protects the surgical site and it may act as a "biological connector" attracting stem cell, promoting neo-angiogenesis and favors the migration of osteoprogenitor cells to the center of the graft.

The role of PRF was studied by Mazor *et al*[36] in a maxillary sinus lift procedure. The results stated that it can be used as the sole filling material during a simultaneous sinus lift and implantation procedure or in combination with other bone graft materials in various direct and indirect sinus lift techniques.The addition of PRF to the bone graft can lead to a reduction of the volume of bone substitute used and seems to improve revascularization of the graft by supporting

angiogenesis. Good amount of regenerated bone in the subsinus cavity up to the tip of implants was reported. PRF can also be used along with beta Tricalcium phosphate (β-TCP) in sinus lift procedures.

Tofler *et al*.[33] also recommended the use of PRF membrane to seal an undetected sinus membrane perforation during a lateral window osteotomy in a maxillary sinus lift procedure.

Endodontics

The use of Platelet Rich Plasma (PRP) as a potentially ideal scaffold for regenerative endodontic therapy has been documented in the literature.[40] However, there is controversy regarding activation of PRP, using bovine thrombin. Thus, it led to the development of the second generation Platelet concentrate known as Platelet Rich Fibrin (PRF).

PRF is advantageous over PRP as it is autologous in nature. It has a simple method of preparation and significantly releases key growth factors like PDGF, TGF, VEGF and TGF-β that enhances healing. Studies have shown that PRF can be used in regenerative endodontics as it could release growth factors with its own biological scaffold. This could be attributed to study conducted by Huang *et al*., who reported that PRF promotes dentinogenesis by stimulating proliferation of human dental pulp cells. It also enhances odontoblasts differentiation by increasing the protein expression of Osteoprotegerin (OPG) and Alkaline Phosphatase (ALP) activity.[41]

Shivashankar *et al* [42] and Geeta *et al* [43]successfully used PRF as a scaffolding material in an infected necrotic immature tooth for pulpal regeneration and tooth revitalization. PRF might serve as potential scaffold material as it is rich in growth factors, enhances cellular proliferation and differentiation, and acts as a matrix for tissues ingrowth.[44]

Bakhtiar *et al*. also demonstrated that PRGF can be used in apical closure with continued increase of dentinal wall thickness.[45]

PRF has also been utilized for regenerative pulpotomy procedures where coronal pulp is removed and the pulp wound is covered by PRF followed by thick layer of MTA and interim GIC restoration.[43]

Use of Platelet rich fibrin is a novel therapeutic option in regenerative periapical endodontic surgery. PRF acts as matrix which maintains the integrity of the bone graft material and also enhances revascularization between the bone graft particles through neo-angiogenesis.[39, 12] The fibrin matrix of PRF gets slowly resorbed and releases various growth factors. Platelet rich fibrin matrix can be used to restore apical lesions after periapical surgeries like root end resection etc as it has benefits for organizing the osteoblasts and causes bone formation with its mineralization process.[46]

Geeta *et al* [43] also studied a case where PRF membrane was used successfully to create artificial root-end barriers for apexification of nonvital immature tooth as it induces faster periapical healing. Literature have also documented the use of PRF membrane with GTR technique in periapical surgeries performed in the esthetic zone.[47-49]

Periodontics

The bioactive platelet aggregates have been used as a technique to improve repair and regeneration of the soft and hard tissues after various periodontal surgical procedures.[2]

Studies have shown that the aggregation of platelets occurs in a small volume of plasma.[51] This results in high concentrations of growth factors such as PDGF, TGF-β etc in PRP. These growth factors are released in damaged periodontal sites causing regeneration of lost structures by stimulation of periodontal ligament cells and osteoblasts.[50]

Several studies have also well documented the use of PRGF in guided bone regeneration (GBR). In–vitro-studies on PRGF have shown an increased human gingival fibroblast proliferation, migration and cell adhesion on collagen matrix, stimulated release of growth factors and hyaluronic acid.

PRF has been used in membrane form to treat gingival recession in single and multiple teeth. Soft tissue procedures also utilize PRF membrane in procedures like gingival grafts, sub epithelial grafts, because of its property of accelerated soft tissue healing. PRF membrane releases most of growth factors after at least 1 week.[51]

In guided bone regeneration (GBR), PRF membrane allows the migration of osteoblasts and angiogenic cells to the osseous defect.This causes blood clot to mineralize and there is new bone formation.[52]

Simonpieri *et al*. [38] used PRF membranes for regeneration of both the bone volume and gingival tissue using the concept of "natural bone Regeneration" (NBR). Anil kumar *et al*.[53] also reported the use of Platelet rich fibrin membrane for root coverage in localised gingival recession in mandibular anterior teeth using combined laterally positioned flap technique.

Studies have shown that PRF is a healing biomaterial which could serve as bone filling material in intrabony or 3-walled osseous defects, furcation defects, treatment of combined periodontic endodontic lesion and periodontal plastic surgery. PRF can be used alone or in combination with bone grafts. In combination with a bone graft PRF membrane and PRF gel can be used for treatment of combined periodontic- endodontic lesion [54]. In Vitro studies have demonstrated that it increases cell attachment [55] and causes stimulation and differentiation of osteoblasts.[56]

According to study done by Chang *et al*[57] it was found that PRF increases the expression of phosphorylated extracellular signal-regulated protein kinase (p-ERK) and stimulates the production of osteoprotegerin (OPG) which in turn causes proliferation of osteoblasts.[58, 50]

Studies have also reported the antibacterial effect [59] and regeneration potential of PRF in periodontal surgery.

Prosthodontics

PRGF can be used in patients of denture-induced fibrous hyperplasia as it causes accelerated wound re-epithelialization, reduction of bleeding and other signs of inflammation.[63]

Studies have investigated that bone implants when coated with Platelet rich growth factors before insertion into the host tissues, facilitates the anchorage of the dental prosthesis. The osseointegration as well as longevity of the implant is improved due to the presence of various growth factors in platelet concentrate.[11]

Platelet aggregate biomolecules are also considered in bone remodeling process due to presence of many growth factors and osteogenic proteins and may be used for the ridge augmentation procedures.

Pedodontics

Studies upon the use of Platelet aggregate molecules in Pedodontics are scarce. Study conducted by Keswani D *et al* [60] evaluated and compared the effects of platelet-rich fibrin (PRF) and mineral trioxide aggregate (MTA) both clinically and radiographically as pulpotomy agents in permanent teeth with incomplete root development. Patidar S. *et al* [61] also compared the effect of PRF with MTA as pulpotomy agent in primary molars.

These studies reported that there were no significant differences between the two. Thus, it was concluded that PRF could be used as an alternative to MTA in pulpotomy procedures of primary molars as well as permanent teeth with incomplete root development.

Mishra *et al* [62] assessed the role of PRF in immature necrotic permanent tooth as revitalizing agent. This study successfully observed that PRF clot may serve as a scaffold for regeneration of vital tissue in necrotic immature teeth. In Pedodontics, the use of Platelet concentrates hold a promising future but still further studies are needed.

CONCLUSION

Various studies have demonstrated satisfactory clinical results regarding the use of platelet concentrates. Their use is minimally invasive with low risks and various advantages both in fields of Dentistry and Medicine including Orthopedic and Plastic Surgery.

Platelet aggregates such as PRGF, PRP, and PRF can be used as an adjunct in wound healing, correction of osseous defects, apexification, revascularization, etc in various fields of dentistry. The results obtained from its vast therapeutic applications are quite encouraging but long‑term clinical trials and studies are needed to understand about the effectiveness and credibility of these bioactive platelet aggregates. More histopathological evaluations are also required to understand their biology, efficacy, mode of action as well as to establish a scientific evidence-based rationale for the success of these platelet aggregates molecules.

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