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Platelet concentrates effect on bone regeneration in dental surgery: A narrative review

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ABSTRACT

Platelet concentrates, which are enriched with growth factors are well-known to boost the healing process and have started to be in trend and utilized clinically in periodontal surgical procedures. Its autologous nature provides an advantage to the patients as it reduces treatment cost and minimizes the risk of cross-infection. Despite its exclusive application in promoting healing, there is data paucity on the role of platelet concentrates on bone regeneration. Therefore, this review aims to explore the potential bone regenerative effect of platelet concentrates that would be beneficial as one of the alternative options in periodontal regenerative procedures. Even though the application of platelet concentrates has shown promising outcomes, there is a need for further studies to discover the potential of platelet concentrates in bone regeneration.

Introduction

Growth factors secreted by activated platelets play pertinent roles in wound healing as they regulate the migration and proliferation of cells during healing. In addition to the natural growth factors released by cells, artificial growth factors can be supplemented to the injury or surgical site with the application of delivery vehicle. The common materials employed for the vehicular transport of growth factors include bone graft, collagen and polymers. These materials are processed into various forms such as micro-particles, sponge, film and sutures [1–3]. For instance, absorbable collagen sponge and particles are saturated with recombinant human bone morphogenetic protein (BMP)-2 used in surgical procedures [2]. Nevertheless, the delivery of recombinant human growth factors is expensive and tends to undergo rapid dilution after application, thus limiting the half-life for prolonged action [1,4].

In place of recombinant human growth factors, the usage of autologous platelet concentrates has gained attention as an alternative in delivering a high concentration of growth factors to indicated sites, and as a scaffolding for cells [5]. The process relies on the role of activated platelets as the natural source of growth factors through the invention of platelet concentrates. Hence, it provides a concentrated and rich suspension of growth factors in platelets such as platelet derived growth factor (PDGF), transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) [6]. These growth factors enhance wound healing. Nevertheless, the information on the potential aspect of bone regenerative capacity of platelet concentrates is still limited. Therefore, this review aims to explore and summarize the potential bone regenerative effect of platelet concentrates for clinical application.

Generation of platelet concentrates

First generation of platelet concentrates: platelet rich plasma (PRP)

The platelet-rich plasma (PRP) is regarded as the first generation of platelet concentrate. It is prepared by collecting a large volume of blood (*i.e.,* 20–60 ml) from a patient, followed by the addition of citrate dextrose anticoagulant [7–9]. Next, the preparation undergoes two steps of centrifugation. The first spin results in the separation of the low-platelet concentrated plasma from red blood cells and PRP. On the other hand, the second spin ends with the further separation of red blood cells and PRP, with the latter collected at the bottom of the tube [6,10–13]. Concerning the 5% platelets count observed in natural blood, PRP preparation yields a better result with 95% of quantified platelets [6,8].

PRP is stable and remains in a coagulated state for eight hours when kept at room temperature before activation [7,8]. This allows for blood to be collected beforehand prior to surgery and activated when needed [14]. In PRP preparation, bovine thrombin or calcium chloride is required to activate the polymerisation of fibrin clot before applying the

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PRP gel into the indicated area [6–9,12,13,15,16]. An immediate and rapid release of about 95% of growth factors was reported within the first one hour and almost completed within one day following the activation of PRP to facilitate healing [6,8,11,15,17].

However, there are contradicting views regarding the use of bovine thrombin as an activator. Several authors reported that bovine thrombin has the potential to induce coagulopathies and allergic reactions [6,10,13,18–22]. Furthermore, the addition of activator resulted in the formation of a tight, rigid, fragile, low-tensile strength, and non-condensed fibrin network that is unfavorable for cytokine release and cellular migration [11,23]. Notwithstanding the enhanced release of growth factors upon the addition of calcium chloride (*i.e.,* an activator) [24], the function of PRP promotes the release of growth factors for a short period [20].

Second generation of platelet concentrates: platelet rich fibrin (PRF)

An example of a second generation of platelet concentrate is the platelet-rich fibrin (PRF) introduced by Choukroun in 2001 [11,25]. As an autologous source of growth factors, it resulted in a product enriched with 97% of platelets and more than 50% of leukocytes [25]. The product possesses an anti-inflammatory effect which is attributed to the presence of leukocytes [18]. Based on the methods of preparation and comparative effects, PRF is considered to have more advantages relative to PRP. For instance, only five to ten millilitres of blood is collected from the patient and centrifuged into a sterile glass before surgery for centrifugation.

PRF is also cost-effective since anticoagulant or chemical activator is not needed during preparation [6,11,12,18–21,25–27]. These methods of preparation eliminate the risk of infection or allergic reaction. In contrast to PRP, single-step centrifugation is conducted at 3000 rpm for ten minutes [6,10,11,20,25,26]. This procedure resulted in the formation of three layers with PRF, acellular poor platelet plasma, and red blood cells fraction at the middle, upper, and bottom layer of the tube, respectively [6,18,19,25,26].

Another advantage of PRF over PRP is the formation of a three-dimensional flexible and dense fibrin clot with a strong network to support cellular migration. This is attributed to the natural polymerisation of the fibrin clot. Moreover, the PRF contributes to sustained and prolonged release of growth factors for more than seven days. A study by Kobayashi et al. [28] revealed a constant and greater concentration of growth factors such as PDGF, TGF-β1, VEGF, EGF and IGF in PRF compared to the PRP within 10 days of incubation. On the other hand, PRP exhibited greater release of growth factors only within 15 to 60 min of incubation.

During the process, growth factors are protected from rapid degradation due to the natural fibrin network in PRF [14,15]. PRF preparation also resulted in a clot characterised with homogenous structure, high stability, and ease of handling and placement compared to natural blood clot [6,26]. Furthermore, PRF can be compressed with a PRF box and used either as a membrane, solely or in combination with bone graft materials. Nevertheless, the physical integrity of PRF is compromised during long-time storage due to dehydration and increased likelihood of bacterial infection [19–21]. PRF requires the use of glass-coated tubes to facilitate clotting with a limited volume of the product [13,26].

Periodontal application and bone regenerative potential of PRP and PRF

Platelet concentrates, particularly PRP and PRF have been extensively used in various clinical applications including periodontal management of intrabony defect, furcation involvement, and root coverage procedure. Table 1 summarises the findings from several review papers on the application of platelet concentrates in periodontal management. Despite the high heterogeneity among studies in terms of study design, assessment of the outcomes and preparation techniques, the use of platelet concentrates either as a sole material or combined with other grafting materials yielded additional advantages on the clinical outcome [12,29–36].

Table 2 shows a summary of studies reporting the effects of PRP and PRF either used solely or in combination with grafting materials on bone regeneration. The review papers reinstated that the application of the platelets concentrates enhanced new bone deposition and healing. However, further research needs to be conducted to elucidate the role of platelets concentrates in bone regeneration. This is due to the heterogeneity of the studies, limited evidence, and inconclusive findings [37–39].

Third generation of platelet concentrates: concentrated growth factor (CGF)

Concentrated growth factor (CGF) is a recent generation of platelet concentrate that was firstly introduced in 2005 by Chen and Jiang [5]. The preparation of CGF and PRF is similar as the addition of an anticoagulant or chemical activator is unnecessary. Nevertheless, CGF is prepared using single centrifugation of alternate speed 2400 to 3000 rpm, whereas PRF employs a constant speed and single-step centrifugation. The procedure in CGF separates the whole blood into three layers consisting of platelet-poor plasma (PPP) at the top, CGF gel in the middle, and the red blood cells at the bottom of the tube [5,43]. In contrast, several papers have characterised CGF with four layers consisting of a serum layer at the top, followed by CGF buffy coat, growth factor liquid layer containing stem cells, and red blood cells at the bottom [11,44].

Since an alternate speed is employed in the preparation of CGF, there is an enhanced release of a growth factor which is facilitated by increased platelet rupture occurring during the centrifugation [5]. This centrifugation leads to the formation of a regular, cross-linked fibrin matrix with increased stability and strength. The platelet concentrate is also protected against plasmin degradation and enriched with growth factors more than PRP and comparable with PRF [5,11,45–47]. Several studies reported that CGF induces a constant and sustained release of growth factors longer than PRP and PRF, which may last up to 14 days [48–50]. Apart from the optimisation of growth factors, CGF and red blood cell layers were observed to contain CD34 positive cells, responsible for vascular maintenance and growth [51,52]. The differences between PRP, PRF, and CGF are summarised in Table 3.

Studies of CGF on its osteogenic potential

Alkaline phosphatase (ALP) is among the bone enzymes involved in the metabolism and differentiation of bone cells or osteocytes [53]. Although several studies focused on investigating the effect of CGF on cell proliferation, there are a few studies that considered osteogenic assays such as ALP analysis. For instance, Chen et al. [54] measured the activity of ALP and performed a mineralisation nodule assay to assess the proliferation and osteogenic differentiation of gingival-derived mesenchymal stem cells cultured with CGF and osteogenic medium. Masuki et al. [47] also reported increased proliferation of human periosteal cells upon culture with CGF. In a study by Zhang and Ai [52], rabbit periosteum-derived cells were cultured *in vitro* with CGF and the results were compared with the non-CGF culture. The authors observed a significant cell proliferation with greater ALP activity and angiogenic markers on day three, seven, 14, and 21 of the study. Similar findings were reported upon assessing the effect of CGF on osteogenic differentiation of osteoblast cells [53]. Accordingly, CGF resulted in a gradual increase in ALP activity until day 14 and a greater proliferation of osteoblast cells in the test group. Another study found that a 21-day culture of CGF induced proliferation of human bone marrow stromal cells and ALP activity [55]. The culture of rat bone marrow cells with CGF increased the activity of ALP with higher rates at day three to 14 [46]. Overall, the results from these studies revealed the potential of CGF in stimulating osteogenic cells and facilitating new bone deposition and formation.

Various animal studies have been conducted to evaluate the influence of CGF on bone regeneration. These studies involved an experimen-

Table 1
A summary on review papers evaluating the application of platelet concentrates in periodontal management.

Study	Types of periodontal defect	Treatment modality	Platelet concentrate	Results
Systematic review [40]	Intrabony defect Grade II furcation involvement	Open flap debridement (OFD) Guided tissue regeneration (GTR) Grafting materials Emdogain Or combined with PRF	PRF	Greater probing pocket depth reduction and radiographic bone fill with gain in clinical attachment level.
Systematic review and meta-analysis [15]	Intrabony defect	OFD GTR Grafting materials Or combined with PRP or PRF PRP alone PRF alone	PRP PRF	Positive adjunctive effect with PRF alone and PRP combined with bone graft.
Systematic review and meta-analysis [33]	Grade II mandibular furcation involvement	OFD Bone grafts GTR Or combined with PRF	PRF	Significant reduction in probing pocket depth, gain in vertical and horizontal clinical attachment level and reduction in vertical furcation depth when used as an adjunct with OFD. Significant gain in horizontal clinical attachment level and reduction of horizontal furcation depth when used as an adjunct with bone grafts.
Systematic review and meta-analysis [35]	Class I or II Miller gingival recession	Coronally advanced flap Or combined with either PRP, PRF or CGF	PRF PRP CGF	Significant outcome on root coverage parameters with the application of PRF and CGF.
Systematic review [12]	Intrabony defect Furcation involvement Gingival recession Extraction socket grafting Sinus floor elevation	Regeneration procedure Or combined with PRF	PRF	Favorable improvement in probing depth reduction, attachment level gain, root coverage, minimizes ridge resorption and post-extraction complications. Limited evidence on bone augmentation, peri-implantitis and sinus lifting.
Systematic review and meta-analysis [34]	Grade II mandibular furcation	OFD alone Or combined with PRP or PRF	PRP PRF	Significant differences in horizontal and vertical clinical attachment level gain and probing depth reduction with adjunct use of PRP or PRF.
Systematic review and meta-analysis [31]	Intrabony defect	Grafting materials GTR alone Or combined with PRP	PRP	Significant greater reduction of probing depth and clinical attachment level gain with adjunct use of PRP. No additive effect of PRP on GTR.
Systematic review and meta-analysis [32]	Intrabony defects	OFD Grafting materials GTR Or with adjunct use of PRP or PRF	PRP PRF	Significant probing pocket depth reduction as adjunct to OFD.
Systematic review and meta-analysis [36]	Gingival recession class I or II Miller	Connective tissue graft Coronally advanced flap Acellular dermal matrix Or combined with PRP or PRF	PRP PRF	Significant recession depth reduction of 0.34 mm. Significant gain in keratinised tissue width of 0.35 mm. Faster healing outcome.
Systematic review [30]	Intrabony defects	OFD Or combined with PRP or PRF	PRP PRF	Significant reduction in intrabony defect depth and greater radiographic bone fill with adjunct use of PRP or PRF. Clinical level attachment gain and radiographic bone fill with PRP and bone grafts.
Systematic review and meta-analysis [29]	Intrabony defect Grade II furcation involvement Gingival recession managed with soft tissue grafting or in combination with PRP	GTR Grafting materials Emdogain Connective tissue graft or allograft Or combined with PRP	PRP	Positive adjunctive effect with grafting materials but not significant when combined with a GTR procedure. No significant outcome on furcation defect and root coverage procedure.

tal induction of calvarial, femoral, and tibial bone defects. Thereafter, histological and radiographic examinations were performed to observe new bone formation. Durmuslar et al. [56] created peri-implant defects on the tibia of rabbits receiving CGF and compared them to a control group (*i.e.,* no CGF supplementation). The rabbits were sacrificed eight weeks later and the bone sample was observed histologically. A new bone was observed filling the peri-implant defect in the group that received CGF compared to the control group. In another study, histological examination at four weeks post-procedure revealed a small volume of new bone in peri-implant defect on the femur of male dogs that received CGF [57]. Both studies indicated that CGF could be considered as an alternative in facilitating bone regeneration.

In another study, calvarial bone defects of male Sprague-Dawley rats were filled with either CGF, PPP or left empty and the animals were sacrificed later at three-time points (*i.e.,* week two, four, and eight). Microscopic computed tomography (micro-CT) and histological examination showed that the CGF group had significant new bone formation compared to the other groups [46]. Using the same diagnostic techniques, parietal bone defect of New Zealand White rabbits was observed at six and 12 weeks between experimental groups that received PRP, PRF,

Table 2
Systematic review papers evaluating the effect of platelet concentrates on bone regeneration.

Study	Type of study reviewed	Treatment modality	Results
Andersen et al. [41]	Clinical	Non-union orthopaedic bone fracture treated with PRP PRP with bone graft PRP with mesenchymal stem cells Bone graft Recombinant human growth factor	Success of bone union with PRP when applied within 11 months of initial injury. PRP alone resulted in significantly lower bone union as compared to recombinant human growth factor and combination with other grafting materials.
Ortega-Mejia et al. [42]	Clinical	Sinus augmentation treated with PRF Bone grafts Combination of both PRF and bone grafts	Addition of PRF did not provide additional benefit on the augmented bone even though a minor increase of new bone formation is observed.
Marcazzan et al. [14]	Animal	Surgically created bone defect treated with PRP PRF Combination of PRP or PRF with bone graft	Potential better regeneration with the combined effect of PRP or PRF with grafting materials with limitations on large animal species studies included.
Bastami and Khojasteh [39]	Animal Clinical	Surgically created bone defect, extraction socket, sinus augmentation and cleft grafting treated with PRF Bone substitutes Combination of both PRF and bone substitutes Sinus augmentation, alveolar ridge preservation, intrabony defect, endodontal lesion, peri-implant bone regeneration treated with PRF Bone substitutes Combination of PRF with bone substitutes or with growth factor	Animal studies: Comparable amount of bone formation on the use of PRF alone. Clinical studies: Favorable outcome on the application of PRF alone during sinus augmentation, endodontal lesions and peri-implant bone defect. Non-significant influence of PRF on socket preservation. Significant role of PRF in intrabony defect.
Plachokova et al. [38]	Clinical	Intrabony defect, sinus augmentation, oral-maxillofacial reconstruction, socket preservation treated with PRP Combination of PRP with bone graft	Favorable outcome observed with the application of PRP in periodontal management with the unfavorable influence of PRP on sinus augmentation.
Sánchez et al. [22]	Clinical	Mandibular defect, socket preservation, ridge and sinus augmentation treated with PRP combined with bone graft	Potential of PRP in facilitating bone formation rate.

Table 3
Differences between platelet concentrates.

Type of platelet concentrate	Centrifugation process	Activator	Complete release of growth factors	Clot structure
Platelet rich plasma (PRP)	Two steps of centrifugation	Bovine thrombin or calcium chloride	24 h	Non-condensed fibrin network that is tight, rigid and fragile with a low tensile strength.
Platelet rich fibrin (PRF)	Single step of centrifugation at 3000 rpm for ten minutes	Does not requires an activator	One week	Flexible and dense fibrin clot with a strong fibrin network.
Concentrated growth factor (CGF)	Single step of centrifugation with alternate speed ranging from 2400 rpm to 3000 rpm	Does not requires an activator	14 days	Regular, cross-linked fibrin matrix with increased stability, strength, and protection against plasmin degradation and enriched with growth factors.

CGF, or left empty. A similar finding of greater bone formation was observed in the groups that received PRP, PRF and CGF compared to the control group [58]. Aside from studies focusing on bone formation, a study by Wang et al. [59] evaluated the effect of CGF on new cartilage formation in osteoarthritis-induced temporomandibular joint (TMJ) in goats. A condylar defect was created on both right (*i.e.,* test group) and left sides (*i.e.,* control group) of TMJ with the test group receiving CGF, whereas saline was administered to the control group. Upon sacrificing the goats one month after the procedure, the test group recorded a significantly higher amount of new bone and cartilage formation compared to the control group. The observations from these animal studies provide an evidence on the potential ability of CGF in facilitating new bone formation.

CGF in dental application

Several studies have evaluated the regenerative potential of CGF in endodontic management. Experimental studies revealed that CGF enhanced mineralisation, migration and proliferation of human stem cells of apical and dental papilla cells [60–63]. These findings were confirmed following a significantly higher expression of markers of mineralisation such as ALP, bone sialoprotein, dentin matrix protein-1 and dentin sialophosphoprotein in CGF treated dental papilla cells compared to controls. Jun et al. [64] also reported that a significant enhancement of dental pulp cell proliferation and differentiation in dental papilla cells retrieved from a premolar of a patient cultured with CGF. Meanwhile, *in vivo* potential of CGF as a root canal medication was investigated in beagle dogs by Xu et al. [62]. Upon filling CGF into the extirpated root canal of single-rooted anterior teeth, histological and radiographic examinations showed continuous root development of immature teeth with the regeneration of dentine-pulp complex at eight weeks after the procedure.

Concentrated growth factor (CGF) as a source of growth factors is well known for its role in facilitating healing. CGF has been applied in the extraction socket for the management of alveolar osteitis. Ac-

cordingly, two studies compared the treatment of alveolar osteitis using CGF to control groups that received either conventional intervention of socket curettage and irrigation or laser intervention [65,66]. In comparison to the control group, CGF treated group recorded earlier granulation tissue formation at day four and earlier reduction in pain score within day seven. Another recent study reported that the application of CGF in the extraction socket immediately after tooth extraction was associated with lesser occurrences of dry sockets [67]. These studies reinstate the role of CGF in promoting rapid healing following tooth extraction and minimising the occurrence of postoperative complications.

Although there was no significant difference between the CGF group and that composed of acellular dermal matrix, a better bone density and formation was observed with cone-beam computed tomography (CBCT) analysis in the CGF group at six months after the grafting of alveolar cleft patients [68]. Furthermore, a combination of CGF with Bio-Oss in treating jaw defect resulted in significantly greater bone density upon panoramic and CBCT radiographs at one year after the operation when compared with control groups that received only Bio-Oss [69].

CGF has also been widely used in clinical settings for periodontal procedure as seen in the management of class I and II Miller gingival recession during root coverage involving a coronally advanced flap. The application of CGF facilitated healing after the procedure and groups that received CGF had lesser postoperative pain [70,71]. CGF was also applied in sinus augmentation procedure to assist immediate implant placement, which led to new bone formation a few months later based on panoramic and CBCT radiographic analysis [72,73].

Isler et al. [74] reported no significant difference between the use of collagen and CGF for the management of peri-implantitis six months after the procedure based on the clinical improvement and reduction in defect depth. Therefore, these studies reinstate the potential of CGF as a substitute for bone graft materials in clinical application. Other applications of CGF also include the management of intrabony defect and grade II mandibular furcation. CGF and bone graft substitute performed better than the sole use of bone graft in terms of probing depth reduction and bone fill one year after the surgery [43,62,75]. Thus, CGF contributed significantly to clinical improvement in the long term.

Likewise, despite the high heterogeneity among studies in terms of blood collection process, blood volumes, concentrations of CGF, and fabrication process of CGF, a review paper also revealed that bone regeneration significantly improved with the combination of CGF and other materials [76]. This corroborates the findings of a systematic review that evaluate the influence of CGF during implant placement as CGF alone or in combination with other materials was found to enhance bone formation surrounding the implants [77].

Conclusions

Notwithstanding the positive attributes of platelet concentrates as revealed in the reviewed studies, certain limitations need to be considered. The application of platelet concentrates have shown promising outcomes in bone regeneration. However, most of the studies focused on the role of the platelet concentrates with a combination of other materials, which indicate that their specific role of platelet concentrates in bone regeneration requires further elucidation. Further studies are required to explore in depth on the bone regenerative effect of platelet concentrates as it can be beneficial for patient management during periodontal regenerative procedures.

Declaration of Competing Interest

The authors declared no conflict of interest related to this article.

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