

Educational Article

Platelet concentrates in periodontics: review of *in vitro* studies and systematic reviews

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Abstract – Clot formation is the first step of the healing process, and clinical procedures always find ways to stabilize this clot better. Platelets play a significant role in clot formation, and Platelet Concentrates (Pc) are an abundant reservoir of platelets. This article aims to review the *in vitro* research and systematic reviews on PCs that are currently available. Broadly, PCs mainly include Platelet-rich plasma and platelet-rich fibrin. PCs are an excellent source for growth factors such as PDGF-AA, TGF β 1, VEGF, EGF, and IGF. Numerous systematic reviews and meta-analyses have analyzed the clinical application of PCs in various periodontal procedures. In alveolar ridge preservation, PCs are known to reduce postoperative pain, edema, trismus, and inflammation. PRF had shown significant improvement in achieving root coverage and recession depth reduction. PCs exhibited a positive influence on CAL gain when used as an adjunct to OFD in treating infra-bony defects. PCs have a positive effect on bone maturation in the short term. Besides, PCs can be used in regenerative endodontics, treatment of medication-related osteoradionecrosis of Jaw (MRONJ), and accelerating tooth movement. In conclusion, PCs positively affect soft tissue healing, while their role in hard tissue healing is still unclear.

Introduction

The human body has an enormous, remarkable, and determinant ability for self-healing. The disease is usually caused by abusing our bodies or depriving them of fundamental needs that keep us healthy for long periods of time. Despite the body's astonishing healing capacities, sometimes it needs a little help. The most fundamental aspect of wound healing is clot formation, and platelets are the principal cells responsible for clot formation [1].

The four critical phases of wound healing include the hemostasis, inflammatory, reparative, and remodelling phases. Blood clot (hemostasis phase) serves as a scaffold that allows cell movement and proliferation. If any deviation occurs at this stage, the healing cascade is altered and leads to unwanted complications [2]. Platelet concentrates (PC) provide these platelets and act as a scaffold, thus playing a significant role in the first and crucial stage of wound healing. The growth factors released from the alpha (α)-granules of platelets in these concentrates have additional benefits in other stages of wound healing [3].

Platelet concentrates are blood-derived products obtained after the centrifugation of a patient's own blood containing activated platelets enmeshed within a fibrin matrix scaffold. Since this process enhances the soft and hard tissues healing, PCs are being successfully used in numerous medical and dental fields over the last few decades [4,5].

The use of autologous PC in the different fields of dentistry started in the early 1970s. Apart from acting as a reservoir for growth factors, they have advantages such as patients' acceptance, cost-effectiveness, and no ethical issues as they are autologous in origin. However, these concentrates cannot be prepared in patients with thrombocytopenia, platelet dysfunction, or patients on systemic anticoagulants [6].

Periodontal healing is an orchestra of cells and signalling molecules, *i.e.*, growth factors at an appropriate time in a suitable environment. There is substantial evidence regarding the application of growth factors in wound healing and the use of PC in Periodontology. However, with increasing research in this field, variations in the study characteristics, and results, there are speculations regarding their application in Periodontology. Hence, this article aims to comprehensively review the available *in vitro* studies and systematic reviews to understand

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Table I. Classification and preparation forms of various PCs.

Platelet concentration	Preparation forms
Pure Platelet-Rich Plasma (P-PRP)	Liquid or activated gel form
Leukocyte-and Platelet-Rich Plasma (L-PRP)	Liquid or activated gel form
Pure Platelet-Rich Fibrin (P-PRF) – or Leukocyte-Poor Platelet-Rich Fibrin	Activated gel form
Leukocyte- and Platelet-Rich Fibrin (L-PRF)	Activated gel or solid form (fibrin Matrix)

the role of PC in Periodontology. (Review Question: What is the Role of Platelet concentrates in Periodontics).

Biological journey of platelet concentrates – from PRP to I-PRF

PRP was the first PC prepared with anti-coagulants using a two-spin centrifugation procedure [7]. Numerous fields of medicine, including dentistry, have used this invention to produce a six to eight times increase in growth factors at the site of application. Despite the extensive application of PRP in various fields, controversy existed regarding anti-coagulants, which negatively affect wound healing by inhibiting the formation of a clot, which is vital for the physiologic wound healing process [8]. Later, Platelet rich fibrin matrix (PRFM) was formulated, which demonstrated enhanced endothelial cell proliferation and angiogenesis in chronic wounds.

Choukroun *et al.*, in the early 2000s, pioneered Platelet-rich fibrin, a unique formulation that employed collection and centrifugation of blood without anti-coagulants [9]. Two significant improvements reported were that the anti-coagulants did not inhibit the wound healing cascade and natural clot formation. Besides, PRF contains host immune cells (namely leukocytes), promoting local wound healing and fighting infection. PRF is a 3-dimensionally stable fibrin scaffold formed following 12 minutes of centrifugation [10]. Later, it was hypothesized that reduced centrifugation speeds and times would increase the leukocyte number and the growth factor release from PRF. When blood is centrifuged at low g-forces (700 g for 12 min (L-PRF) vs. 60 g for 3 min (i-PRF)), without anti-coagulants, a plasma-rich top liquid layer is formed, composed of fibrinogen and thrombin that have not yet converted to fibrin [11]. As a result, following centrifugation, i-PRF remains liquid for around 10–15 min before fibrin formation. Similar to PRP, i-PRF is now being used to provide angiogenic and regenerative growth factors. Unlike PRP, liquid PRF turns to fibrin quickly after being injected locally [8].

The PCs can be broadly classified into (Tab. I)

- (1) Second generation – Includes L-PRF.
- (2) Third generation – Includes A-PRF, i-PRF.
- (3) Fourth generation – Currently under research (Focusing on tissue engineering triad).

Table II. Methods and protocols for PC preparations.

Platelet concentrates	Preparation
PRP [7]	PRP Method: Blood collected in sterile tubes containing anti-coagulant. First Spin: 'Soft Spin', After separation of erythrocytes, Second Spin: 'Hard Spin', PRP should be separated from platelet poor plasma (PPP). Buffy Coat Method: Blood should be collected and stored at 20–24°C First Spin: High Speed PPP formed at the top should be removed and buffy coat layer (WBC and Platelets) should be transferred into another tube. Second Spin: Low speed to separate WBC's
L-PRF or S-PRF [12]	2700 rpm for 12 min
A-PRF [12]	1500 rpm for 14 min
A-PRF + [10]	1300 rpm for 8 min
i-PRF [13]	700 rpm for 3 min

Preparation of platelet concentrates

Numerous techniques are described in the literature for the preparation of platelet concentrates. Despite the heterogeneity in its preparation, one common finding is the use of anticoagulants in PRP preparation and centrifugation of whole blood without anticoagulants for PRF preparation. Heterogeneity for PRP still exists. However, the PRF preparation protocol is standardized with the introduction of the Choukroun PRF Duo Quattro System. PRF preparation needs a PRF box to compress the centrifuged PRF to form sheets or membranes. The methods and protocols are listed in Table II.

Growth factors in platelet concentrate

The growth factors in platelet concentrates include platelet derived growth factor (PDGF), transforming growth factor

Table III. Growth factors and platelet concentrates.

Author	Groups	Study design	Results
Kobayashi E <i>et al.</i> [14]	A-PRF vs. S-PRF vs. PRP	Six participants volunteered for 18 blood samples (three each for A-PRF, S-PRF and PRP). After preparation, samples were assessed for growth factor release at 15 min, 60 min, eight hours, one day, three days, and ten days. ELISA quantified the growth factor release of PDGF-AA, PDGF-AB, PDGF-BB, TGF β 1, VEGF, EGF, and IGF.	PDGF-AA was shown to be the most abundant growth factor produced from platelet concentrates, followed by PDGF-BB, TGF β 1, VEGF, and PDGF-AB. When compared to PRF and A-PRF, PRP produced substantially more growth factors after 15–60 minutes of incubation. For ten days, however, A-PRF (PDGF-AA, TGF β 1, VEGF, EGF) produced the most overall growth factors. Furthermore, as compared to PRP or PRF, A-PRF produced substantially more total protein after ten days. At all intervals, IGF was greater in the PRF group, while PDGF-BB was highest in the PRP group.
Miron RJ <i>et. al</i> [13]	PRP vs. i-PRF	PRP and i-PRF were compared for growth factor release prepared from 8 participants. Biocompatibility and migration of fibroblasts were measured after 24 hours, fibroblast proliferation after 1, 3, and 5 days, and PDGF, TGF- β 1, and collagen-1 release after 3 and 7 days.	After ten days, PRP had a significantly greater total short-term release of growth factors, especially TGF- β 1 and VEGF. However, i- PRF had significantly higher total long-term release of EGF, IGF-1, PDGF-AB, PDGF-AA. Besides, both concentrates showed good biocompatibility and increased fibroblast proliferation and migration, with i-PRF inducing substantially more migration and PRP inducing significantly more cellular proliferation. In addition, as compared to PRP, i-PRF had the highest collagen-1 expression at both three and seven days, TGF- β levels at seven days, and PDGF at three days.
Ghanaati <i>et al.</i> [12]	S-PRF vs. A-PRF	For histological cell detection and histomorphometrical cell distribution assessment, standard platelet-rich fibrin (S-PRF) and advanced platelet-rich fibrin (A-PRF) were compared. On clots from four separate human donors, immunohistochemistry was conducted for T and B lymphocytes, monocytes, neutrophilic granulocytes, platelets, and CD34 positive stem cells.	In both PRF groups, platelets were seen throughout the clot. On the other hand, the A-PRF group had more platelets at the distal portion, away from the buffy coat (BC). In both groups, T- and B-lymphocytes, monocytes and stem cells were found in the vicinity of the BC. In the A-PRF group, more neutrophilic granulocytes were present in the distal section of the clot. Neutrophils were mainly detected at the red blood cell –BC interface in the S-PRF group.

Table III. (continued).

Author	Groups	Study design	Results
Arora S <i>et al.</i> [15]	PRP vs. S-PRF (Supernatant of PRF)	A total of 16 individuals were recruited, eight for PRP and eight for PRF preparation. The levels of PDGF-AB, TGF- β 1, VEGF, and platelet counts in baseline whole blood, PRP, and PRF were measured and compared.	TGF- β 1 release was significantly higher in PRP than in PRF, but there was no statistical difference in PDGF-AB concentration or VEGF release between the two products. When activated PRP was used instead of PRF, VEGF and PDGF-AB significantly increased over baseline whole blood values.
Chatterjee A <i>et al.</i> [16]	PRF vs. PRF matrix gel (PRFM)	A total of 15 individuals participated in the study. After preparation of PRF and PRFM, the samples were quantified for PDGF, VEGF, EGF, FGF, TGF, and IGF levels for 23 days.	Compared to the PRF, PRFM had a better release of growth factors. PRFM had statistically significant difference compared to PRF in terms of PDGF, EGF, FGF, TGF and IGF release. However, PRF had a steady and consistent release of growth factors over the study period.

(TGF), vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF). The initial release of growth factors was better with PRP while prolonged release was observed with different PRF concentrates. PDGF was shown to be the most abundant growth factor produced from platelet concentrates (most with PRP), followed by PDGF-BB, TGF β 1, VEGF, and PDGF-AB. Future studies should study the timing and concentration of the growth factor release to the timeline of the wound healing to achieve desired clinical results. The *in vitro* studies are listed in [Table III](#).

Discussion

Application of platelet concentrates in periodontology Alveolar Ridge Preservation Procedures (ARP)

A systematic review involving five studies, evaluated the role of PCs in alveolar ridge preservation alone or in combination with bone grafts compared to controls. Of the 5 studies included, two studies had high risk of bias. The results have found that L- PRF minimized alveolar ridge resorption (vertical and horizontal dimensions) in ARP with or without bone grafts. PRP, on the other hand, might have no effects. Evidence shows that PC reduces postoperative pain, edema, trismus, and inflammation, enhancing patients' quality of life and comfort immediately after the ARP. The evidence on the effect on the proportion of new vital bone, however, is still inconclusive. Besides, scarce evidence shows that platelet concentrates positively affect new bone formation and bone density [17].

Another systematic review which included seven controlled trials (320 extractions in 190 patients) found similar results (improved soft tissue healing and reduced postoperative symptoms) but underlined the heterogeneity in the existing research in standardizing variables like type and location of the

socket, computed tomography (CT) assessment of baseline alveolar bone levels, reason for extraction, and minimally traumatic extraction techniques. Furthermore, the evidence for the use of PC in the maintenance of the alveolar ridge is limited, necessitating research with adequate control groups [18].

Treatment of furcation involvement

The role of PC, in grade II or III furcation defects, as an adjunct to open flap debridement (OFD), bone grafts with OFD alone was compared in a systematic review and meta-analysis of randomized controlled studies with at least six months follow-up. A total of 10 studies were included, with only 1 study with high risk of bias. The results suggested improved outcomes in terms of clinical attachment level (CAL), vertical and horizontal furcation depths when PC were used as an adjunct to OFD. As an adjunct to bone grafts, improvements were seen only in horizontal CAL. Both PRF and PRP yielded favourable results. However, the data about the use of PC in combination with bone grafts and guided tissue regeneration (GTR) is scanty [19].

Gingival recession

The effect of autologous platelet concentrations as an adjunct to coronally advanced flap in the treatment of Millers Class I or II recessions was assessed in systematic review and meta-analysis of randomized trials. The study included 8 RCT involving 328 sites in 170 patients. The results show better clinical outcomes in root coverage for PRF, while PRP did not affect much. PRF had favourable outcomes in terms of RC, RD, CAL and Gingival thickness. However, though platelet concentrates could achieve root coverage, their effect on keratinized tissue width is minimal. Besides, they did not have any

significant effect in combination with connective tissue grafts. The study results should be interpreted with caution as the included studies exhibited high risk of bias [20].

Surgical treatment of periodontal diseases and periodontal regeneration

PC showed a positive effect on CAL gain, irrespective of the treatment approach used as an adjunct to OFD in treating infra-bony defects. Besides, PC (PRP) had significant short-term effects when used as an adjunct to guided tissue regeneration. However, long-term data suggests the superiority of the GTR membrane. Nevertheless, considering the high cost, technique sensitivity, and patient acceptance for GTR membranes, the dense fibrin network in PRF membranes can act as a barrier membrane. They do, however, resorb as soon as 21 days, which is one of the drawbacks [21].

A Cochrane systematic review analysing 38 randomized controlled trials revealed a superiority of PC as an adjunct to OFD in terms of Pocket depth (PD) reduction, CAL gain, and radiographic bone fills compared to OFD alone. When used as an adjunct to OFD and bone grafts, a significant benefit in PD, CAL, Radiographic bone fill was reported with platelet concentrates compared to OFD + bone grafts. Besides, PC did not have any significance as an adjunct to enamel matrix derivate (EMD) in the treatment of furcation. However, the authors reported low-quality evidence regarding the analysed data [22].

Sinus augmentation procedures

Numerous studies evaluated the efficacy of PC on maxillary sinus augmentation. In a systematic review of clinical studies utilizing PRF in maxillary sinus lift procedures, PRF performed better as a sole filling material for sinus augmentation when implants are placed simultaneously, and PRF appeared to hasten the maturation of a demineralized freeze-dried bone (DFDB) allograft [23]. However, it did not affect deproteinized bovine maturation. Also, in a similar systematic review of randomized controlled trials, no changes were observed in implant survival, percentage of residual bone graft, new bone formation, contact between newly formed bone and bone substitute, and soft-tissue area compared to the non-PRF group [24]. However, in another systematic review and meta-analysis of PC evaluating their effect on maxillary sinus augmentation, PC may decrease the time needed for bone grafts to mature and allow for early implant placement. Nevertheless, they do not enhance long-term bone growth. Therefore, routine PCs are not recommended as osteoinductive material combined with bone grafts in sinus augmentation procedures [25]. Besides, a recent systematic review concluded that the current data is insufficient in using PC as an adjunct to bone graft in sinus augmentation [26].

PCs in comparison to other biomaterials

A recent systematic review has evaluated the effect of bioactive materials for the treatment of periodontal intra bony defects [27]. The study involved RCTs with a total of 259 patients

with a follow-up period of 6-12 months. The study compared the effects of DFDBA and DFDBA+ bioactive material. The study results revealed PRP and PRF (PRF>PRP) to be better materials in terms of pocket depth reduction. In terms of CAL gain, PRF had a significant difference compared to other materials. In terms of bone fill, PRP had a significant effect. The study results suggest the superiority of PRP and PRF compared to other materials for the treatment of intra bony defects. However, most of the studies included had a moderate risk of bias.

Other oral applications of PC

In regenerative endodontics, the peri-apical bone fill was assessed, and it was noticed that L-PRF had better bone fill than the controls, but evidence regarding other PC is sparse and inconclusive. Moreover, PC can be used to achieve complete bone closure and complete resolution of MRONJ [28]. Furthermore, PRP can accelerate tooth movement in the short term but has no long-term effects. However, research is still on going with PC in these fields [29].

Clinical applications of I-PRF and A-PRF

Less than a decade ago, these two new formulations were proposed (A-PRF, 2014, i-PRF, 2016), and currently their biological basis is being understood. The research regarding their clinical application is still in nascent stages, and only time will prove their application in various clinical scenarios. However, few clinical studies and case reports show their application in Gingival recession [30], treatment of deep periodontal pockets [31,32], periodontal regeneration, enhancing gingival phenotype [33], orthodontic tooth movement [34,35], and various oral regenerative procedures. However, the evidence is weak to conclude their application in areas as mentioned above.

Clinical significance

- The outcome of the current review substantiates:
- Platelet rich fibrin (Injectable > Advanced > Leucocyte) have better release of growth factors when compared with the other PC, *in vivo*.
 - PC can be used as a better adjunct to various procedures in periodontology and implantology, with Platelet-rich fibrin, in most instances, has better clinical outcomes than other PC. This can be attributed to their three-dimensional structure, which contributes to better wound stability.
 - In root coverage Procedures, CGF and PRF are superior PC; however, only CGFs help in increasing keratinized gingiva, unlike PRF.
 - PC have a significant role in soft tissue healing and patient-centered outcomes; however, their role in hard-tissue regeneration is still unclear.
 - Most of the systematic reviews performed had a high-moderate risk of bias and low-quality evidence due to variations in study designs.

- Heterogeneity in study designs in terms of preparation of PC is a frequent observation among the studies reporting PC outcomes.
- The newest concentrates, such as i-PRF and A-PRF, are still in the early phases of development, and only rigorous testing procedures will show their therapeutic utility.

Conclusion

Platelet concentrates are abundant reservoir of growth factors and their selection has to be based on the type of defect and desired outcomes. PCs are excellent biomaterials for soft tissue healing, while their role in hard tissue healing is still unclear. The clinical outcomes with PC are way inferior to the results exhibited *in vivo*. Besides, there is an abundance of heterogeneity in the literature regarding their clinical application. Hence, Future well-designed RCTs should aim to deliver and exploit the inherent capabilities of these concentrates according to the timeline of the healing cascade to attain the best clinical outcome.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

Informed consent

The authors declare that informed consent not required.

Ethical statement

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