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**Platelet preparations in dentistry: How? Why? Where? When?**

Rodella LF *et al.* Platelet concentrates in dental practice

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**Abstract**

The aim of this article is to review the outcomes of platelet preparations in dentistry. A structured electronic search discovered 348 articles, which described the use of autologous platelet concentrates with a relevance to clinical dentistry. Among these articles, 220 articles investigated platelet rich plasma, 99 investigated platelet rich fibrin, 22 investigated plasma rich in growth factors and 7 investigated the use of concentrated growth factors. The majority of the platelet rich plasma, fibrin, and growth factor articles, reported beneficial treatment outcomes in terms of enhanced bone and soft tissue regeneration.

**Key words:** Platelet concentrates; Platelet rich plasma; Platelet rich fibrin; Plasma rich in growth factors; Concentrated growth factors; Growth factors; Dentistry

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**Core tip**: Autologous platelet rich plasma concentrates are rich in plasma, fibrin, and growth factors, which can be used as scaffolds and growth factors to promote guided tissue regeneration in dentistry and oral surgery.

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**INTRODUCTION**

Bone and soft tissue regeneration is frequently required in dentistry, mainly but not exclusively for implantology and periodontology. Tissue regeneration is a complex process of healing and tissue growth, which involves different biological elements and strategies. These include the use of bone grafts[1,2],biomaterials and growth factors[3], natural or synthetic scaffolds and more recently the use of stem cells[4,5]. Nowadays, a whole range of modern surgical procedures and a variety of dental materials are available. These are performed to reconstruct bony defects of the upper and lower jaw and for augmentation of lost structures of the residual alveolar ridge. Autologous platelet concentrates are a promising and innovative therapeutic approach in various medical fields, including dentistry[6-10]. Platelets play a crucial role not only in hemostasis, but also in the wound healing process, as they are reservoirs of growth factors and cytokines, which in turn are key promoters for bone regeneration and soft tissues maturation. After platelets are activated, they become trapped within a fibrin matrix and release growth factors. Together the fibrin can form a scaffold and the growth factors can stimulate tissue healing and regeneration repair responses. An improved understanding of the physiologic properties of platelets in wound healing over the last two decades, has led to more successful therapeutic applications, especially in oral surgery.

***Platelet concentrates***

Platelet concentrates are blood derivatives[11,12], prepared from the patient’s own blood and containing [autologous](http://en.wikipedia.org/wiki/Autotransplantation#Autologous_blood_donation) platelets, growth factors and cytokines involved in the key processes of tissue regeneration, including cell proliferation and differentiation, extracellular matrix synthesis, chemotaxis and angiogenesis. Platelets are packed with secretory granules, which are necessary to fulfill their functions. There are three types of secretory granules,  granules are the most abundant and have a high protein content. The granules contain cytokines and growth factors, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and the insulin*-*like growth factor (IGF) as well as several others. The release of these growth factors from activated platelets can promote healing in both soft and hard tissues.

Most platelet concentrations used as scaffolds used in guided tissue regeneration surgery, are termed Platelet-Rich Plasma (PRP), even if they differ slightly according to their preparation from a patients peripheral blood. These variations include differences in centrifugation speeds and times, differences in adding chemicals, and differences in the selection of supernatants and precipitates. These variations can cause differences in fibrin network structures, differences in leucocyte content and differences in growth factors. Therefore the term PRP alone can be non-specific, because it does not define the actual preparation protocol. Depending on the leukocyte content and fibrin architecture, there five main categories of PRPs that can be defined: (1) Pure Platelet-Rich Plasma (PPRP), such as cell separator PRP, Vivostat PRF[13] or Anitua's PRGF[14,15]; (2) Leukocyte and Platelet-Rich Plasma (LPRP); (3) Pure Plaletet-Rich Fibrin (PPRF), such as Fibrinet; (4) Leukocyte- and Platelet-Rich Fibrin (LPRF), such as Choukroun’s PRF; (5) and CGF. In the following paragraphs, the uses of PRP, PRF, PRGF and CGF in dentistry and oral surgery will be reviewed:

***Platelet rich plasma***

Platelet rich plasma (PRP) is [blood plasma](http://en.wikipedia.org/wiki/Blood_plasma) that has been enriched with [platelets](http://en.wikipedia.org/wiki/Platelet), and it was the first generation of platelet concentrates to be used in clinical practice by Marx in 1998[16]. PRP has a platelet concentration of 1000 × 109/L in 5ml of plasma, which is 5 times higher compared to the normal whole blood platelet count (200 × 109/L). PRP contains (and releases through [degranulation](http://en.wikipedia.org/wiki/Degranulation)) several different [growth factors](http://en.wikipedia.org/wiki/Growth_factor) and [cytokines](http://en.wikipedia.org/wiki/Cytokine) that can stimulate bone and [soft tissue](http://en.wikipedia.org/wiki/Soft_tissue) healing[17-19]. PRP is prepared by drawing peripheral venous blood from a patient’s arm. The fresh blood is immediately mixed with an anti-coagulant to prevent clotting and then the platelets are concentrated using a two-step gradient centrifugation method[20]. In this method, the first spin (called the hard spin) separates the red blood cells (RBCs) from the plasma containing platelets, leukocytes and clotting factors, the second spin (called the soft spin) is used to delicately separate the platelets and leukocytes, from the plasma. The soft spin produces PRP and separates it from the platelet-poor plasma (PPP), free from the interference associated with large number of red blood cells. Commonly, with commercially available systems, a one-step method is used to separate the RBCs, buffy coat and plasma into three distinct layers. The buffy coat contains platelets and leukocytes and is often collected as PRP. The top plasma layer is often called PPP, which is discarded, leaving the PRP to be injected into surgical sites to accomplish guided tissue regeneration.

***Platelet rich fibrin***

Platelet rich fibrin (PRF) consists of an intimate assembly of cytokines, glycanic chains, structural glycoproteins enmeshed within a fibrin scaffold, and is considered to be the second generation of platelet concentrates[21-23]. The cytokines, glycanic chains, structural glycoproteins can have synergetic effects on tissue healing processes. The PRF pioneers were Choukroun *et al*[24,25], who used it to promote the osseointegration of dental implants. Several studies have demonstrated the clinical effectiveness of autologous PRF to regenerate defects in hard and soft tissues. The preparation of PRF is similar to PRP, it consists of collecting peripheral venous blood from the patients arm. Except that no anti-coagulant is used during blood harvesting. After the blood is collected it is immediately centrifuged for 10 min to activate the platelets, leading to the initiation of a coagulation cascade. After centrifugation, the blood is sepatated into three different layers: acellular PPP (platelet poor plasma) on top, a PRF clot in the middle and red blood cells (RBCs) at the bottom of the test tube. The PRF clot obtained after centrifugation is collected, 2 mm below the lower dividing line, and the other layers are discarded. The clinical success of the PRF protocol is dependent on a quick collection of blood and its transfer to the centrifuge. Because no anticoagulant is used, the blood sample begins to coagulate almost immediately, and a failure to accomplish the quick preparation of PRF could cause a diffuse polymerization of fibrin, which is not ideal for tissue healing.

***Plasma rich in growth factors***

Plasma rich in growth factors (PRGF) are parepared from peripheral venous blood drawn from a patient’s arm. PRGF is prepared using a modified PRP protocol developed by Anitua[26-28]. The difference between PRGF and PRP s that PRGF is but it is optimized to deliver a more sustained release of growth factors. PRGF can create a three-dimensional fibrin scaffold which can be injected into a tissue defect, to maintain the regenerative space and be used as a scaffold for cells to accomplish tissue regeneration. The Leukocyte content of PRGF is eliminated to prevent the pro-inflammatory effects of the proteases and acid hydrolases contained whithin these cells. PRGF is prepared from a small volume of patient’s peripheral venous blood and is collected by a one-step centrifugation with sodium citrate added as the anti-coagulant (Endoret System). After activation, PRGF progressively releases a pool of proteins and growth factors, which accelerate soft tissue healing as well as osseous regeneration. For these reasons, PRGF is considered to be more potent for tissue regeneration in comparison to PRP. Four different formulations of PRGF with therapeutic potential can be obtained from a patient's blood depending on the degree of coagulation and activation of the samples. There are various formulations, which include the following: PRGF supernatant can be used as conventional eye-drop solution and cell culture media solution. Liquid PRGF can be used to coat dental implant surfaces to promote osseointegration. The fibrular and cellular scaffold-like PRGF can be to fill tissue defects as part of ulcer treatment, sealing tooth sockets after tooth extraction, and promoting the epithelialization of soft tissues.

***Concentrated growth factors***

Concentrated growth factors(CGFs), first developed by Sacco, in 2006, is an autologous fibrin network, rich in leukocytes and platelets[29,30]. CGF also contains autologous osteo-inductive growth factors derived from platelets and an osteo-inductive fibrin matrix. Similar to PRF, CGF is created using a one-step centrifugation method, but it requires a special programmed centrifuge (Medifuge MF200, Silfradent srl, Forli, Italy), which uses plastic tubes, coated with silica particles, and without the addition of exogenous substances. The final blood product is separated into three layers, two are discarded, and the CGF is collected from the buffy coat layer, which consists of a dense fibrin matrix that is rich in growth factors.

**STUDY STRATEGY**

A structured electronic search of scientific papers up to January 2015, was conducted using two medical databases (PubMed and the Cochrane Library) and specific keywords: “platelet concentrates in dentistry”, “PRF” “Platelet rich fibrin Choukroun”, “platelets in dentistry and maxillofacial surgery”, “PRP”, “CGF”, “PRGF”, “periodontal regeneration”. For each of these platelet concentrate categories, their therapeutic potential in dentistry was evaluated according to the following inclusion criteria: (1) clinical trials; (2) animal studies; (3) *in vitro* studies; (4) case reports; and (5) technical reports. Subsequently, the articles for each type of platelet concentrate (PRP, PRF, PRGF and CGF) were classified according to these inclusion criteria and study type.

**RESULTS**

A total of 563 articles were identified as meeting the inclusion criteria of investigating the clinical use of autologous platelet concentrates in dentistry. However, after all the studies not relevant to dentistry, or containing no data were excluded, there were 348 articles that were included in this review. Of the 348 articles, there were 220 articles (63.2%) were about PRP, 99 articles (28.4%) investigating PRF, 22 articles (6.4%) investigated PRGF and 7 articles (2%) investigated CGF (Figure 1).

The articles were classified according to the type of platelet preparations in dentistry and the type of research performed in the article, which are briefly described below and summarized in Table 1: (1) PRP: from 220 articles, 116 were human clinical trials, 46 regarded animal studies, 20 were about *in vitro* investigations, 3 were technical reports and 35 were case reports; (2) PRF, from 99 articles, 50 were human clinical trials, 13 regarded animal studies, 17 were about *in vitro* experiments, 1 was a technical report about PRF general properties and 18 were case reports; (3) PRGF, from 22 articles, 13 were human clinical trials, 5 regarded animal studies, 2 were about *in vitro* experiments and 2 were case reports; and (4) CGF: from 7 articles, 1 was a human clinical study, 1 regarded an animal study, 1 was about an *in vitro* study, 2 were technical reports about CGF properties and its application in dental implantology and 2 were case reports;

***PRP studies in dentistry***

PRP was used to treat periodontal intrabony defects in fifteen studies[31-45]. Nine studies described the use of PRP in cyst enucleations/periapical surgeries[46-54]. Forty-eight studies investigated PRP forin sinus floor elevation treatments[55-101]. Twenty-two studies reported using PRP for the treatment of periodontal and periimplant defects[102-123]. Four studies used PRP for covering the roots of teeth[124-127]. Six studies investigated the efficacy of PRP for the treatment of gingival recession[128-133]. Four studies evaluated the benefits of using PRP to repair furcation defects[134-137]. Twenty-five studies investigated PRP for the repair of mandible/maxilla fractures[138-160]. Thirty-one studies investigated the use of PRP use in endodontic surgery[161-188]. Eighteen studies investgated the use of PRP for dental extraction socket preservation before implant placement[189-206]. Twenty-two studies investigated the stimulating effect of PRP on alveolar bone regeneration and reconstruction[207-224]. Eight studies investigated the use of PRP to improve the healing and regeneration of soft tissues[225-231], mostly for periodontal ligament repair, and reducing the incidence of complications. Eight studies investigated PRP using *in vitro* protocols to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts[232-237].

***PRF studies in dentistry***

PRF was used in six studies to treat periodontal intrabony defects[238-243]. Four studies used PRF to regenerate tissue following cyst enucleations, and periapical surgeries[244-246]. Eleven studies investigated the ability of PRF to regenerate tissues following sinus floor elevation[247-256]. Eight studies investigated the use of PRF to treat periodontal and periimplant defects[257-263]. One study tested PRF as a potential root coverage repair treatment[264]. Two studies investigated the efficacy of PRF for gingival recession treatment[265-266]. Four studies investigated PRF to treat furcation defects[267-269]. Eight studies applied PRF to heal mandible or maxilla fractures[270-276]. Twenty one studies investigated the usefulness of PRF as part of endodontic surgery to repair periapical tissues [277-293] . Eleven studies investigated the ability to preserve tooth sockets after tooth exptraction in preparation for dental implant placement[294-302]. Nine studies investigated the ability of PRF to stimulate alveolar bone regeneration and reconstruction[303-309]. Ten studies investigated the ability of PRF to improve the healing and regeneration of soft tissues, especially periodontal ligament, reducing complications[310-319]. Four studies investigated the *in vitro* effects of PRF to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts[320-323].

***Platelet rich growth factor studies in dentistry***

Platelet rich growth factor (PRGF) was investigated in two studies to treat periodontal bone defects[324,325]. PRGF was investigated in two studies to regenerate tissues following cyst enucleations and periapical surgeries[326,327]. The potential of PRGF to heal tissues following sinus floor elevation treatment[328,329]. Two studies reported that PRGF had a positive effect on the healing of periodontal and periimplant defects[330,331]. One study investigated the use of PRF to cover the roots of teeth [332]. One study investigated the efficacy of PRGF to heal tissues following gingival recession treatment[333]. Two studies investigated the benefits of PRGF for the treatment of furcation defects[334,335]. One study investigated the effecrtiveness of PRGF to heal mandible/maxilla fractures[336]. One study investigated the effectiveness of PRGF to heal periapical soft tissues following endodontic surgery[337]. Four studies investigated the clinical potential of PRGF to preserve tissue in tooth extracton sockets prior to dental implant placement[338-340]. One study investigated the stimulating effect of PRGF on alveolar bone regeneration and reconstruction[341]. One study investigated the ability of PRGF to improve the healing and regeneration of soft tissues, especially the periodontal ligament [342]. Two studies investigated the *in vitro* effect of PRGF to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts[343,344].

***CGF studies in dentistry***

Compared to the other platelet articles, only a few had investigated the use of CGFs as part of dental treatment. A reason for the lack of CGF articles may be because it is newest of the platelet protocols and there has not been enough time for many articles to be published. Three studies were found which investigated CGF for tissue regeneration following sinus floor elevation[345-347]. One study investigated the *in vitro* CGF effectiveness of CGF to enhance the migration and proliferation of human dental stem cells and gingival fibroblasts[348]. One study investigated the healing effects of CGF for tissue repair following endodontic surgery[349]. Two studies investigated soft tissue and periodontal ligament healing after using to accomplish guided tissue regeneration[350,351].

**DISCUSSION**

Dentists have membranes, scaffolds, freeze-dried bone and many types of biomimetic biomaterials to help guide bone and soft tissue regeneration following surgery. All these biomaterials have advantages and limitations, and no single type of biomaterial has all the properties needed to be the universal dental regeneration biomaterial. The body’s natural scaffold regeneration material is the blood clot, and several protocols have been developed to improve the scaffold and growth factor properties of the blood clot by fractionating the blood into various fractions; PRP, PRF, PRGF and CGF as this review has demonstrated. These platelet rich fractions of blood have been shown to improve healing, quicken tissue regeneration, improve the quality of tissues that are regenerated, and to reduce the incidence of complications. Alternatively, there are also many studies, which have shown that platelet rich fractions of blood has had little or no effect on tissue healing and can give no advantages in comparison to biomimetic scaffolds. This explains the need to objectively investigate the uses of platelet rich fractions of blood as part of dental treatments.

After the careful analysis of the literature, the follow questions could be asked: (1) How is platelet rich fractions of blood prepared? (2) Why use platelet concentrates in dentistry? (3) Where to use platelet concentrates in dentistry? and (4) When to use platelet concentrates in dentistry?

The answer to the first question about how platelet rich fractions of blood are prepared; was answered in the previous paragraphs: All the techniques involvolve the centrifugation of the patient’s peripheral venous blood and the use of fractions containing fibrin and growth factors with the other components of blood; its red blood cells and leukocytes being discarded.

The answer to the second question about why platelet concentrates are used in dentistry is because they are an inexpensive natural scaffold and source of growth factors to stimulate tissue regeneration. Platelet concentrates are biocompatible and can sometimes offer potential benefits including rapid wound healing and bone regeneration. A controversial advantage is a reduction of postoperative pain, and an unequivocal advantage is the lack of risk of infectious disease transmission. Sometimes platelet concentrates cannot be used where a patient does not want to donate their own blood, or when a special-needs patient or child refuses to cooperate with the collection of their blood.

The answer to the third question about why autologous platelet concentrates is used in oral and maxillofacial surgery and periodontal regenerative therapy is because of some promising results for tissue regeneration following sinus floor elevation (especially with PRP and CGF)[55-101,345-347], bone filling of periodontal intrabony defects[102-123,238-243,324,325], regeneration of alveolar ridges[207-224,303-311,343], dental extraction socket preservation[189-206,294-302,338-340], gingival recession treatment[128-133,265,266], mandibular and maxilla fractures[138-160,270-276,333]. Platelet concentrates have been used to manage bisphosphonate-related osteonecrosis of the jaw (BRONJ) to enhance wound healing and bone maturation[271,272,352].

The answer to the fourth question about when to use platelet concentrates is the most difficult to reach for most dentists. A general rule of guidance is to use platelet concentrates, scaffolds, or biomaterials, in surgical situations where the prognosis for tissue repair is poor in the absence of a tissue regeneration scaffold and addition of growth factors[225-231,310-319]. Mostly platelet concentrates are used for periodontal regeneration and bone regeneration, although the scientific literature suggests the leading bioactive materials for periodontal and bone regeneration are Emdogain and GEM21S. Platelet concentrations can also be used for bone regeneration, although the use of bone substitute materials has become common for repairing bone defects.

**CONCLUSION**

Platelet concentrates serve useful purposes for situations where a patient is missing tissues and requires a scaffold and growth factors to accomplish tissue regeneration. Platelet concentrates can sometimes improve the healing of hard and soft tissues, however there are often competitor products; Emdogain, GEM21S, and freeze-dried bone which are equally effective, or even more effective for the same purposes as PRP, PRF and CGF. Some recent studies have mixed PRP with freeze-dried bone, added bone morphogenic proteins to platelet concentrates, or even added hydroxyapatite (for example Bio-Oss-*Geistlich-Switzerland*)[94,95]. Most platelet concentrates add thirty minutes to the time needed to treat patients. The additional time is needed to draw blood, centrifuge it, and islolate fractions and to add chemicals. For these reasons and to increase patient comfort, most dentists do not regularly use platelet concentrates as part of dental treatments. In some countries the dentist needs additional training and qualifications to perform phlebotomy, which means not all dentists are qualified to deliver platelet concentrates to patients. The widespread use of platelet products will increase among dentists if this treatment can prove to provide superior advantages to patients in terms of healing and regeneration. Few platelet contrates have proven to be more successful twhen compared to existing dental biomaterials, for this reason the use of platelet concentrates is likely to remain a small niche type of treatment.

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**Figure 1 Number of studies with platelet rich plasma, platelet rich fibrin, plasma rich in growth factors and concentrated growth factors in dentistry up to January 2015.** PRP: Platelet rich plasma; PRF: Platelet rich fibrin; PRGF: Plasma rich in growth factors; CGF: Concentrated growth factors.



**Figure 2 Platelet rich plasma, platelet rich fibrin, plasma rich in growth factors and concentrated growth factors application in dentistry up to January 2015.** PRP: Platelet rich plasma; PRF: Platelet rich fibrin; PRGF: Plasma rich in growth factors; CGF: Concentrated growth factors.

**Table 1 Number of different studies published in the literature using platelet rich plasma, platelet rich fibrin, plasma rich in growth factors and concentrated growth factors in dentistry**

|  |  |
| --- | --- |
|   | **Platelets concentrates** |
| Study type |  **PRP** | **PRF** | **PRGF** | **CGF** |
| Clinical trials | 116 | 50 | 13 | 1 |
| Animal studies | 46 | 13 | 5 | 1 |
| In vitro studies | 20 | 17 | 2 | 1 |
| Technical report | 3 | 1 | 0 | 2 |
| Case report | 35 | 18 | 2 | 2 |

PRP: Platelet rich plasma; PRF: Platelet rich fibrin; PRGF: Plasma rich in growth factors; CGF: Concentrated growth factors.