REVIEW

Do platelet concentrates promote bone regeneration? literature review

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Platelet concentrates have been used in various applications within Oral and Maxillofacial Surgery and Implantology with the aim of promote tissue repair. The first generation of platelet concentrates is Platelet-Rich Plasma (PRP) and recent studies question its actual effectiveness on tissue healing because of the rapid release of growth factors. The second generation of platelet concentrates, the Platelet-Rich Fibrin (PRF), shows peculiar features in the release of growth factors, which occurs slowly and gradually and thus seems to promote a more promising effect over the tissues under repair in comparison with PRP, especially regarding to bone. However, the literature data are different and better results seem to be obtained when the PRF is mainly used in combination with other graft materials. Additional well-designed studies are needed to better clarify this matter.

Keywords: Bone Graft; Bone Regeneration; Platelet-Derived Growth Factor; Platelet-Rich Fibrin; Platelet-Rich Plasma

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Introduction

The use of blood products in order to promote tissue repair is relatively new. However, the Platelet-Rich Plasma (PRP) is already in use for some time by hematologists for transfusions and prevention of bleeding episodes in patients with severe thrombocytopenia [1]. Marx *et al.*[2], in 1998, introduced the first generation of platelet concentrates, which corresponds to the Platelet-Rich Plasma (PRP) and more recently in France, in 2001, Choukroun *et al.*[3] introduced Platelet-Rich Fibrin (PRF), known as a platelet concentrate of the second generation.

In the fields of Oral and Maxillofacial Surgery and Implantology several authors are using these blood products in order to promote the healing of soft and bone tissues [4, 5, 6, 7]. However, the actual effectiveness of this conduct is controversial in the literature, particularly with regard to the action of PRP. This is because some studies show that due to incorporation of activators of platelet degranulation in their prepration protocol, happens a rapid release of growth factors [4,8]. Therefore, the action on the tissues appears to be mild and immediate, particularly in the bone repair which is a complex process that takes about 2 to 3 times longer than healing of soft tissues [9, 10].

The use of PRF, in turn, has proven to be more promising, because in its preparation protocol it is not necessary to add external compounds and this promotes natural fibrin polymerization and consequently the slow and gradual release of growth factors that get trapped in their meshes [11,12]. Recent studies have shown good results using PRF in

order to promote bone regeneration, especially when combined with other graft materials [7, 13, 14]. Nevertheless, there are still few studies on this subject and more research is required to clarify the real action of these blood products on bone formation. The objective of this study is to review literature regarding the use of platelet concentrates in order to promote bone healing.

Platelet-Rich Plasma (PRP) X Platelet-Rich Fibrin (PRF)

Several methodologies have been employed to evaluate the effect of PRP and PRF on bone regeneration. Regarding *in vitro* studies, He *et al*. (2009) [15] showed increased proliferation of osteoblasts and superior ability to stimulate mineralization with PRF in comparison to PRP. Other *in vitro* studies also showed growth and proliferation of osteoblasts in contact with PRF [4, 8, 12]. In contrast, Garbiling *et al*. (2009) [16] observed that PRP showed increased release of growth factors when compared to PRF.

Another application of platelet concentrates occurs in reconstructive procedures for bone acquisition and installation of dental implants [17]. In the study by Cabbar *et al*. (2011) [18], the use of bovine bone alone or associated with PRP in maxillary sinus lifting procedures was compared and no advantage was observed for the association of such materials in bone formation and stability of the implants. In contrast, Poeschl *et al*. (2012) [19], reported higher resorption of the graft material and increased bone formation when PRP was associated with a hydroxyapatite derived from algae in maxillary sinus lifting surgery. In the systematic review of the literature by Roffi *et al*. (2013) [20], the authors observed that there is a growing important in the use of PRP in order to promote the integration of grafts or implants and many papers have been published in this area. However, the present knowledge in the literature on this subject is still scarse, since most studies are of poor quality [20]. On the other hand, several researchers have reported good results in the use of PRF in maxillary sinus lifting procedures [9, 13, 21]. Tajima *et al*. (2013) [22], for example, reported success in this type of approach using PRF as the only graft material together with the installation of the implants. The authors report a gain in height from 4.28 ± 1.00 mm preoperatively to 11.8 ± 1.67 mm postoperatively.

A number of animal studies have also been conducted with the aim of evaluating bone formation in critical-size defects with the use of platelet concentrates [4, 7, 23, 24]. Messora *et al*. (2008) [23] evaluated bone neoformation of critical defects in the skull of rats and observed more new bone in the defects filled with PRP in comparison with the control group after 4 and 12 weeks postoperatively. A similar study was conducted by Mariano *et al*. (2010) [24], in which the authors evaluated bone formation with the use of PRP in critical-size defects in the skull of diabetic rats. In this study, the authors also observed greater bone formation in the defects with PRP. Kang *et al*. (2011) [4] also showed promotion of bone formation with the use of PRF in bone defects in the skull of rats. However, in the current study by Oliveira *et al*. (2014) [7], after the histomorphometric evaluation of bone formation in defects in the rat skull, the authors concluded that the PRF alone had a positive, but mild effect on bone formation and that better results are obtained by the association of PRF with Bio-Oss. In contrast with the results of this study, other authors have also reported that the isolated action of PRF in periodontal [11, 25] and bone [26] regeneration is mild and more encouraging results can be achieved by the association of PRF with other graft materials [9, 27]. Tatullo *et al*. (2012) [13] found better results by the association of PRF with Bio-Oss in sinus lifting procedures when compared to the use of Bio-Oss alone. Pripatnanont *et al*. (2013) [14], observed greater promotion of bone regeneration when the PRF was associated with autogenous bone. Nevertheless, these authors did not observe good results when PRF was combined with other graft materials.

The filling of the alveoli following extraction with platelet concentrates has also been the subject of study by many authors. Gawai and Sobhana (2015)[28], extracted lower third molars of 10 patients bilaterally, and the alveolus was filled with PRP on one side. Patients were followed up clinically and radiographically after 1 week, 1, 2, 3 and 4 months. They found that PRP acted on the initial events of the healing process, thus promoting increased osteogenic stimulation in the first month. However, there was no improvement in bone healing after 4 months of follow-up [28]. In contrast, Mariano et. al. (2012)[29] used PRP to fill the lower third molar alveoli and observed greater bone formation after 1, 2 and 3 months of follow-up. However, there was no statistically significant differences in comparison with the control group after 6 months postoperatively [29]. Dorado *et al*. (2014)[30], in turn, carried out a systematic review of the literature on the use of PRP in order to promote alveolar repair and concluded that the scientific knowledge related to that conduct is poor, since only 3 studies met the inclusion criteria.

In relation to PRF studies also show divergent results. Baslarli *et al*. (2015) [5] studied the action of PRF in the lower third molar alveoli. The radiographic and scintigraphic assessments after 30 and 90 days showed no difference in bone formation between the alveoli with and without PRF [5]. Hatakeyama *et al*. (2014) [6] evaluated the repair of the alveoli of beagle dogs with loss of vestibular wall with filling of platelet-poor plasma (PPP), platelet-rich plasma (PRP) and Platelet-Rich Fibrin (PRF). In this study with more critical conditions for bone repair the authors observed worse results

with blood products having high concentration of platelets (PRP and PRF) and better results were found with PPP [6]. On the other hand, other authors found a lower rate of postoperative infectious complications after filling alveoli with PRF [31]. Rao *et al*. (2012) [8] and Singh *et al*. (2012) [32] observed improvements in healing, decreased pain and increased bone density in the third molar alveoli filled with PRF. This result can be explained by the activation of the defense system by interleukins and tumor necrosis factor present in PRF [16], which associated with migration of neutrophils play an important role in controlling immunity [32]. Sammartino *et al*. (2011) [33] also had good results with the filling of post-extraction alveoli with PRF for later implant placement. Similarly, Hauser *et al*. 2013 [34] observed higher maintenance of the crest of the alveolar ridge and better organization of bone tissue when premolar alveoli were filled with PRF.

Another application of platelet concentrates is the treatment of periodontal defects. PRP associated with hydroxyapatite (HA) was shown to be superior to the use of hydroxyapatite alone for the treatment of intra-osseous periodontal defects in patients with localized aggressive periodontitis in the study by Gupta (2014) [35]. In this study, the authors reported greater reduction in probing depth, increased clinical attachment gain and greater filling of the alveolus by bone in patients who received the association of those materials [35]. Mathur *et al*. (2015) [36] compared the use of autogenous graft and PRF in the treatment of 38 periodontal defects. In this study, a significant decrease of defects after 6 months was observed with both materials, but with no statistical differences between them [36]. Chang and Zhao (2011) [37] also observed decreased periodontal pocket depth with clinical attachment gain after the treatment of infra-osseous periodontal defects with PRF. Thorat, Pradeep and Palavi (2011) [11] observed greater bone gain in patients in whom the treatment of chronic periodontitis was associated with PRF in relation to isolated surgical treatment. In contrast, other authors such as Bajaj *et al*. (2013) [38] found no significant differences in the treatment of furcation defects in molars with PRF or PRP.

More recently, in 2014, Soydan and Uckan [39] described the technique of using PRF membranes for the treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Kim *et al*. (2014) [40] evaluated the action of PRF in the resolution of osteonecrosis in 34 patients; 26 patients (77%) had complete resolution in a period of 4 months of follow-up. This application of PRF is an exciting possibility, since osteonecrosis has no definitive treatment and is difficult to resolve [39]. The systematic review of the literature by Del Fabbro *et al*. (2015) [41] confirmed those findings and despite the few papers and small samples of the studies included the results suggest that the use of platelet concentrates with surgery bring good results in the treatment and/or prevention of bisphosphonate-related osteonecrosis of the jaw. In addition, platelet concentrates are also being used to fill bone cavities after enucleation of pathologies [42]. Patil *et al*. (2013) [42] reported the successful use of PRF for such purpose. However, in the study by Ramanathan and Cariappa (2014) [43], the authors observed no significant differences in bone repair of cavities filled with PRP in comparison with the control group after 6, 12, 18 and 24 weeks of radiographic follow-up.

Conclusions

According to the literature review performed, the action of PRP and PRF in bone regeneration still brings about differing opinions, with studies showing good results and others identifying no advantage in their use. In general, the most promising results are reported for the use of PRF, especially when combined with other graft materials. However, in order to clarify the matter additional well-designed studies are required, such as randomized controlled trials.

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Conflict of interest

The authors do hereby certify that there is no conflict of interest with any financial organization regarding the material discussed in this manuscript.

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