FEATURE ARTICLE

ADJUNCTIVE USE OF PLASMA RICH IN GROWTH FACTORS FOR IMPROVING ALVEOLAR SOCKET HEALING: A SYSTEMATIC REVIEW

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ABSTRACT

Purpose

The purpose of this study was to determine whether the adjunctive use of plasma rich in growth factors in postextraction sites could be beneficial in terms of hard-/ Q2 soft-tissue healing and patients' comfort.

Materials and Methods

An electronic search was performed on MEDLINE, EMBASE, Scopus, and CENTRAL. Only controlled clinical trials or randomized clinical trials that used plasma rich in growth factors in the test group were included. The primary outcomes were pain assessment, complications, and adverse events. Secondary outcomes were hard-tissue healing, bone remodeling, and soft-tissue healing.

Results

Eight comparative studies (5 randomized clinical trials) were included. Four studies had a split-mouth design. Six hundred fourteen teeth were extracted in 338 patients. Only qualitative analysis could be performed. Postoperative pain and the incidence of complications such as alveolar osteitis were consistently lower in the test group. Hard-tissue healing, evaluated by clinical, radiographic, histologic, and histomorphometric techniques, showed significantly better results for the test group in almost all studies. Better epithelialization, keratinized tissue thickness, and healing score were also reported.

Conclusion

Plasma rich in growth factors may bring advantages in some relevant clinical and radiographic outcomes, such as bone density and soft-tissue healing, after tooth extraction. It could also represent a useful tool for reducing adverse events, complications, and patients' discomfort, although it is still not quantifiable.

INTRODUCTION

Tooth extraction, in routine dental practice, is carried out for the tooth with hopeless prognosis affected by deep dental caries, periodontitis, or trauma or sometimes as a treatment protocol for orthodontic space creation.[1] The physiological process of postextraction alveolar socket healing involves a complex and intricate play of bone cell migration and maturation along

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with selective bone resorption and apposition.[2] These healing events are rather complicated and delayed, in various situations, leading to vertical and/or horizontal decrease of alveolar process dimension. During the healing period, some complications, such as alveolar osteitis (AO), bleeding, intense pain, infection, and trismus or swelling, associated with postextraction sites may arise.[3] Nonetheless, inadequate bone apposition or progressive bone resorption may occur, compromising the placement of implant-supported prosthetic rehabilitation. Bone loss and changes in the soft-tissue profile resulting from tooth loss and an unpleasant esthetic aspect can also hinder rehabilitation of the edentulous ridge using removable or fixed prostheses.[4]

The concept of "socket preservation" with various biomaterials is used in postextraction sites to hinder the alveolar process dimensional reduction and lessen the healing complications. Various systematic reviews indicate the use of biomaterials, such as bone substitutes, collagen sponges, barrier membranes, and growth factors, in the postextraction sites and have proven their efficacy on the basis of some clinical evidence.[5-9] Moreover, these preservation techniques may avoid additional bone augmentation at the time of implant rehabilitation. However, the efficacy of these alveolar socket-preservation treatments is still unclear. In a recent systematic review, it was concluded that the alveolar ridge resorption cannot be totally avoided; rather, it can be prevented with the use of such preservation techniques, although no specific technique is proved to be superior than the others.[10]

Previous clinical research on the use of different biomaterials, such as particulate hydroxyl-apatite,[11] bio-active glass,[12] polylactide/polyglycolic sponges,[13] barrier membranes,[14] and others, for socket preservation has been documented.[15] The origin of these biological materials is rather heterogeneous, and the cost of manufacturing processes to make them compatible for use in human applications often translates into an economic burden for patients. In addition, some patients reject the use of xenografts or allografts, arguing that they are afraid of the possibility of disease transmission from the donor, while others refuse autologous bone grafts because of the fear of pain and discomfort due to the harvesting procedure.[16] It has also been demonstrated that some graft materials are not completely degraded many years after implantation and only slightly promote osteogenic induction,[17] which also directly affects the formation of new bone and soft-tissue healing in the tooth-extraction sockets.

The use of biologic agents such as recombinant human bone morphogenetic protein-2, basic fibroblast growth factors, recombinant human platelet–derived growth factor, and transforming growth factor beta had proven to promote osteogenic induction in cases of alveolar socket preservation in recent studies.[18,19] In addition, the use of autologous platelet concentrates (APCs) is gaining popularity as a source of a number of growth factors in high concentrations, for regenerative treatments in many clinical applications. The contribution of blood-derived platelets to the bone-healing process is thought to be based on the growth factors stored in their granules and released on activation. APCs are advantageously used as a cost-effective adjunct to surgical regenerative therapy, even in combination with bone grafts.[20] Several systematic reviews have reported on the efficacy of the use of these APCs in postextraction sites, suggesting improvement of postoperative soft-tissue healing, control of postoperative symptoms, and adequate socket preservation.[21-24]

Plasma rich in growth factors (PRGF) is a biological concept developed and introduced at the end of the 1990s.[25] Among the various types of APCs, PRGF is characterized by a relatively modest increase of the concentration of platelets (2-3 times the serum platelet concentration), with respect to platelet-rich plasma (5-8 times), and by the absence of leukocytes.[26] The increased concentration of platelets delivers a wide array of platelet growth factors, which may promote osteogenic induction and may simultaneously facilitate soft-tissue healing in the postextraction sites. Various clinical trials have reported the use of PRGF in wound healing and preservation of postextraction sites.[25,27-30] However, no systematic review has been published to date that evaluates the scientific quality of these trials and the consistency among studies regarding the effect of using PRGF in postextraction sites. The aim of this systematic review is to investigate whether PRGF is effective in the preservation of the postextraction alveolus.

MATERIALS AND METHODS

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[31] The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO, no.: CRD42018091547).

Research Question

The research question was "Is the adjunctive use of PRGF in postextraction sites beneficial in terms of hard-/soft-tissue healing and patients' comfort?"

Search Strategy

An electronic search was carried out in the following databases: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), SCOPUS, and EMBASE, using a series of search terms combined with the Boolean operators "AND," "OR," and "NOT." The search string was designed using the following keywords: (plasma OR plasma rich in growth factors OR PRGF OR pure platelet rich plasma OR P-PRP OR

endoret) AND (post extraction sites OR extraction socket healing OR socket preservation OR tooth extraction OR third molar extraction OR third molar surgery). The last electronic search was carried out on March 2018. In addition, a hand search was performed in the following dental journals: *British Dental Journal*, *British Journal of Oral and Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *Clinical Oral Investigations*, *European Journal of Oral Implantology*, *European Journal of Oral Sciences*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Dentistry*, *Journal of Implantology*, *Journal of Maxillofacial and Oral Surgery*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Periodontal Research*, *Journal of Periodontology*, and *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*. The bibliographies of the included studies and of the reviews were also searched for possible additional eligible studies. Finally, we searched the following trial registries for ongoing studies: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched on February 20, 2017) and World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched on February 20, 2018).

Inclusion Criteria

The inclusion criteria for the eligible studies were as follows:

- The study had to be a comparative prospective clinical trial (randomized or controlled) with parallel or split-mouth design involving postextraction sites in human subjects. Both single and multiple extraction sites were considered.
- The study had to use PRGF alone or in adjunct to any grafting material (eg, bone substitutes) in the experimental group, and the only difference to the control group had to be the use of PRGF.
- Studies with patients with systemic illness, with smoking habits, or who underwent radiotherapy were included in this review.
- No restriction on the language, sample size, follow-up duration, or year of publication was applied.

Study Selection and Data Collection

Two independent reviewers (S.P. and M.D.F.) screened the title and abstract of the articles retrieved from the electronic search, based on the set of inclusion criteria. The full text of the relevant eligible studies was further assessed independently by the same 2 reviewers to ensure that the studies met the inclusion criteria. The disagreements between the reviewers were resolved by discussion, and the reasons for exclusion were recorded for each excluded study.

Relevant data of the included studies were extracted using an Excel spreadsheet (Microsoft, Redmond, WA).

The primary outcomes evaluated were

- Postoperative pain (measured with a visual analog scale)
- Any adverse effects/complications such as infection, swelling, alveolitis, AO, or any type of symptoms in the postoperative period.

The secondary outcomes evaluated were

- Assessment of hard-tissue healing (by radiographic or histomorphometric analysis)
- Clinical or radiographic evaluation of marginal bone remodeling (eg, bone height at the vestibular and lingual or palatal aspect and bone width at the extraction region)
- Assessment of soft-tissue healing (using the healing index proposed by Landry or other standard indexes)

Risk of Bias Assessment

Risk of bias (RoB) was assessed by two independent reviewers (S.P. and M.D.F.) for all the included clinical trials, and the discrepancies were resolved by discussion and in consent with a third reviewer (S.T.). The assessment was carried out using parameters such as random sequence generation, allocation concealment, blinding of outcome assessment, comparability of control and treatment groups at entry, clear definition of inclusion and exclusion criteria, clear definition of outcome assessment, completeness of outcome data reporting, recall rate, sample size calculation, and the number of surgeons involved. The criteria of RoB assessment were modified from the guidelines reported in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0.

The summary of the RoB assessment of the studies was validated by grading them into high, medium, or low risk. A study was considered to be at high risk if it was found to have two or more of the assessed parameters classified at high risk or one parameter at high risk and three or more at uncertain risk; it was considered to be at medium risk if one of the parameters was classified at high risk and no more than two at uncertain risk; and it was considered to be at low risk if none of the parameters was classified at high risk and no more than three at uncertain risk.

Data Analysis

The data from different studies were combined by meta-analysis only when at least two studies with similar

comparisons were found, reporting the same outcome measurements at comparable observation times after tooth extraction. For each trial, for dichotomous outcomes (such as postoperative AO recorded as yes or no), the estimation of the effect of an intervention is expressed as risk ratios with 95% confidence intervals (CIs). For continuous outcomes (such as percentage of newly formed bone and alveolar bone height and width changes), mean differences with 95% CIs were used to synthesize data for each treatment group. The statistical analysis unit was, if possible, the patient, unless all compared studies expressed the results using the tooth as the unit of analysis. If a meta-analysis could not be performed for a given outcome, then a qualitative report of the results is provided. Risk ratios for dichotomous data and mean differences for continuous data were combined using random-effects models if at least 4 studies could be included in the meta-analysis; otherwise, a fixed-effects model was adopted. Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for meta-analysis calculations and graphs.

RESULTS

The electronic search retrieved a total of 694 articles. After discarding the duplicates, unrelated records, and articles excluded for specific reasons, 8 studies were included for qualitative analysis in this review (Figure 1).[25,27-30,32-34]

The main features of the included studies are summarized in Tables 1 and 2. The excluded studies are listed in Table 3, with reasons for their exclusion.[35-41]

Primary Outcomes

Postoperative Pain

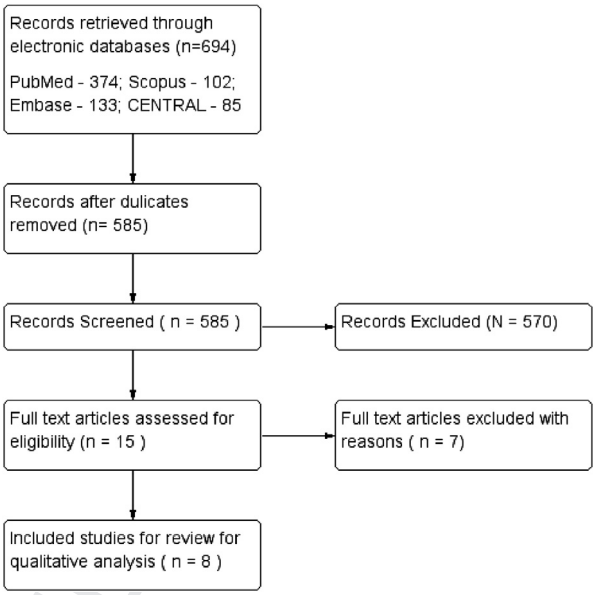
Five out of 8 studies evaluated postoperative pain for a follow-up duration of 7 days.[27-29,33,34] The studies reveal that postoperative pain was comparatively lesser in the postextraction sites treated with PRGF than the control sites. Postoperative pain was almost absent in the PRGF-treated sites in one of the studies,[27] having the scores of 0.17 and 0.00 at day 3 ($P < .001$) and day 7 ($P < .03$), respectively (Table 4).

Adverse Events/Complications

In one of the included trials that had the occurrence of AO as the primary outcome, lower incidence of AO and acute inflammation was documented in the PRGF-treated sites than in control sites.[29] In the split-mouth study, 18 of 40 patients presented with AO in the control sites, whereas only 4 cases of AO occurred in the sites treated with PRGF in patients who also developed AO on the control site.[29]

In another study, PRGF was as effective as fibrin glue for prevention of severe bleeding in patients with blood coagulopathies and thrombocytopenia.[32]

Figure 1. Flow diagram of the study selection process.



Secondary Outcomes

Hard-tissue Healing

The included trials have evaluated hard-tissue healing under a variety of assessments such as clinical, radiological, histologic, and histomorphometric analyses.

Residual socket volume (RSV) was the parameter used to clinically assess hard-tissue healing in two studies[28,33] and was found to be better in the sites treated with PRGF. RSV was calculated as the ratio of the socket dimensions at each follow-up to the socket dimensions at baseline. Both the studies[28,33] used RSV evaluation at 7th, 14th, and 21st day of postextraction follow-up. Comparisons between values relative to the experimental and control sides showed better healing and faster socket closure for the side treated with PRGF, with differences statistically significant at day 7 and borderline at day 14. Because no other included study used this parameter, its relevance is limited.

One study carried out radiological assessment using cone-beam computerized tomographical analysis.[27] The study claimed to have higher ($P < .001$) percentage of regenerated sockets (96.7%), higher ($P < .001$) regenerated socket volume (96.5 ± 8.0%), higher ($P < .001$) radiodensity (Hounsfield unit) of bone formed (450.0 ± 106.7), and faster bone formation at the postextraction sites treated with PRGF than at the control sites. The study also reported higher new bone formation ($P < .049$) under histomorphometric analysis in the sites

Table 1. Main characteristics of the included studies.

Study	Study design	Patients (N)	Age, mean (range)	Teeth (n)		Intervention		Follow-up
				Test	Control	Test	Control	
Anitua et al., 2015[27]	RCT	60	T: NR (29 – 74); C: NR (18 – 67)	36	24	PRGF	None	10-12 wks
Cocero et al., 2015[32]	RCT	120	NR (6 - 78)	98	106	PRGF	Fibrin glue	1 wk
Mozzati et al., 2014[28]	RCT (sm)	34	62.7 ± 12.2 (NR)	34	34	PRGF	None	3 wks
Mozzati et al., 2014[33]	CCT (sm)	20	63 ± 8 (NR)	57	57	PRGF in irradiated area	None in nonirradiated area	3 wks
Farina et al., 2013[30]	CCT	28	55.2 (34 – 74)	18	18	PRGF	None	4-6 wks (*T1* = 1 m), 7-10 wk (*T2* = 2 m)
Haraji et al., 2012[29]	CCT (sm)	40	22.1 ± 1.7 (18 - 45)	40	40	PRGF	None	Up to 7 d
Mozzati et al., 2010[34]	RCT (sm)	16	22.5 (18 - 35)	16	16	PRGF	No PRGF	Up to 1 wk
Anitua, 1999[25]	RCT	20	T- 41 (35 - 55) C- 42 (38 - 54)	10	10	PRGF ± ABG	ABG	10 to 16 wks

ABG, autogenous bone graft; C, control group; CCT, controlled clinical trial; NR, not reported; PRGF, plasma rich in growth factors; RCT, randomized clinical trial; sm, split-mouth; T, test group.

with PRGF (63.1 ± 13.8%) than that in control sites (35.6 ± 35.3%).[27] Histologic analysis showed better bone quality in biopsies from sites treated with PRGF than in those from control sites.[25]

On the contrary, one study reported that the PRGF-treated group did not show any enhancement in early (4 and 8 weeks) bone deposition in comparison with the control group.[30]

Soft-tissue Healing

Better epithelialization was seen in the sites treated with PRGF. Epithelialization was rather rapid and excellent compared with that in control sites.[25] The measurement of the thickness of the epithelial layer indicated a thicker layer in the sockets treated with PRGF. The thickness of keratinized gingiva (140.6 µm; 95% CI: 70.41–210.81; $P < .038$) was higher in the PRGF group than that in the control group.[27]

In diabetic subjects, soft-tissue healing was significantly faster and better with the use of PRGF at test sites.[28] The difference between the healing index scores was found to be highly significant at 3, 7, and 14 days ($P < .05$). However, at the end of 21 days, the healing index scores were pretty similar and not significant ($P = .33$) in both PRGF (4.0 ± 0.2) and control groups (4.1 ± 0.4).[28]

Risk of Bias

The RoB summary is presented in Figure 2. Four studies were classified as having a low RoB,[25,27,29,32] two as having a medium risk,[28,33] and two as having a high RoB.[30,34]

DISCUSSION

The aim of this systematic review was to assess the clinical studies that evaluated the effect of adjunctive use of PRGF in postextraction sites and critically appraise the same in terms of the listed primary and secondary outcomes. A total

Table 2. Methods and results of the included studies.

Study	Teeth treated	Postsurgical complications	Study outcomes	Effect of PRGF
Anitua et al., 2015[27]	Mandibular molar (1st, 2nd, and 3rd)	1 PRGF/1 CTRL (tumefaction); 0 PRGF/0 CTRL (infection)	1. Percentage of regenerated sockets. 2. Percentage regenerated volume, bone density; pain; soft-tissue healing score; inflammation score; histomorphometric analysis—percentage of new bone formation; keratinized gingival thickness	PRGF-treated sites enhanced hard- and soft-tissue healing of sockets with better epithelialization and increased thickness of keratinized epithelium with the absence of inflammation. The sites also presented with almost negligible postoperative pain.
Cocero et al., 2015[32]	Molar, premolar, canine, incisor	2 PRFG/3 CTRL (severe secondary bleeding)	Number of complications; bleeding rate after 7-day follow-up period	PRGF works as well as fibrin glue as a local hemostatic agent to control for bleeding after extraction.
Mozzati et al., 2014[28]	NR	NR	1. Residual socket volume; pain; healing index, and postsurgical complications. 2. Patient satisfaction; effects of smoking habits, HA1C, EODS, and glycemia on socket reduction.	PRGF application after extraction improved the healing process in diabetic patients by accelerating socket closure (epithelialization) and tissue maturation, proving the association between PRGF use and improved wound healing in diabetic patients.
Mozzati et al., 2014[33]	Bilateral similar teeth (all types)	0 PRGF/2 CTRL (bone exposure with soft-tissue necrosis)	Residual socket volume; pain; healing index, and postsurgical complications	PRGF proved to be effective in the management of patients with a history of head and neck radiotherapy, accelerating and fostering mucosal healing and avoiding postextraction bone exposures.
Farina et al., 2013[30]	Single-rooted tooth or single roots of hemisected mandibular molars.	NR	Micro-CT analysis, histologic and histomorphometric evaluation for bone deposition.	PRGF-treated group did not show any enhancement in early (4 and 8 weeks) bone deposition compared with the control group.
Haraji et al., 2012[29]	Maxillary and mandibular third molars	AO (outcome); 4 PRGF/18 CTRL	Alveolar osteitis, pain, healing score	The application of PRGF may significantly reduce the incidence of AO or its associated pain and may accelerate healing. The prophylactic use of PRGF after third-molar extraction may be suggested especially in the patients at risk of AO.

(*continued*)

Table 2. Continued

Study	Teeth treated	Postsurgical complications	Study outcomes	Effect of PRGF
Mozzati et al., 2010[34]	Impacted mandibular third molars	NR	Inflammatory cytokines (real-time PCR): IL-1b, IL-6, IL-10, TGF-β2, BMP-2, BMP-4; clinical parameters and pain; facial swelling	Postoperative pain and the swelling, measured at all experimental times, were reduced in the presence of PRGF. The cytokine profile in the PRGF was favorable for enhanced and unprecedented healing
Anitua, 1999[25]	All types	1 PRGF/1 CTRL	Biopsy and histological analysis	No negative effect has been found in the use of PRGF. Better epithelialization and osseous regeneration of mature bone has been found in a larger quantity and quality than in control areas.

AO, alveolar osteitis; CTRL, control; NR, not reported; PRGF, plasma rich in growth factors; TGF-β, transforming growth factor beta.

Table 3. List of excluded studies with reasons for exclusion.

Excluded study	Reason for exclusion
King et al., 2018[35]	PRGF used in postextraction sites with alveolar osteitis
Ntounis et al., 2015[36]	Use of PRP as the experimental group
Geurs et al., 2014[37]	Use of PRP as the experimental group
Mozzati et al., 2011[38]	Case-control study in patients on intravenous bisphosphonate therapy; the occurrence of bisphosphonate-related osteonecrosis of the jaw was the only outcome reported.
Anitua et al., 2015[39]	Case series
Nazaroglou et al., 2009[40]	Case report
Anitua, 2001[41]	Report of two cases

PRGF, plasma rich in growth factors.

of 8 clinical trials were included and analyzed in this review. Most of the studies were judged as having a medium to high quality based on the criteria set for the RoB assessment. The lack of at least 2 studies with similar data set for any outcome variables prevented us from carrying out a standard meta-analysis and presenting the results through a forest plot. However, the qualitative analysis was rigorously performed to get the best conclusion about the efficacy of the adjunctive use of PRGF in postextraction sites.

One study[29] used AO as the primary outcome and reported that there was significantly lower incidence of AO in the sites treated with PRGF than in control sites. Indeed, very few studies reported adverse events or postsurgical complications, such as tumefaction, infection, and bleeding, in the postextraction sites treated with PRGF at the end of follow-up (Table 2). Although it was not possible to perform a quantitative evaluation regarding the various complications, the qualitative synthesis proved to be in favor of using PRGF in postextraction sites to lower the incidence of postsurgical complications. One controversial question is regarding the feasibility of using autologous hemocomponents when the subjects are affected by hematological diseases. The study that recruited the subjects with blood disorders, for example, coagulopathies and thrombocytopenia, in need of extraction suggested that PRGF can represent an effective

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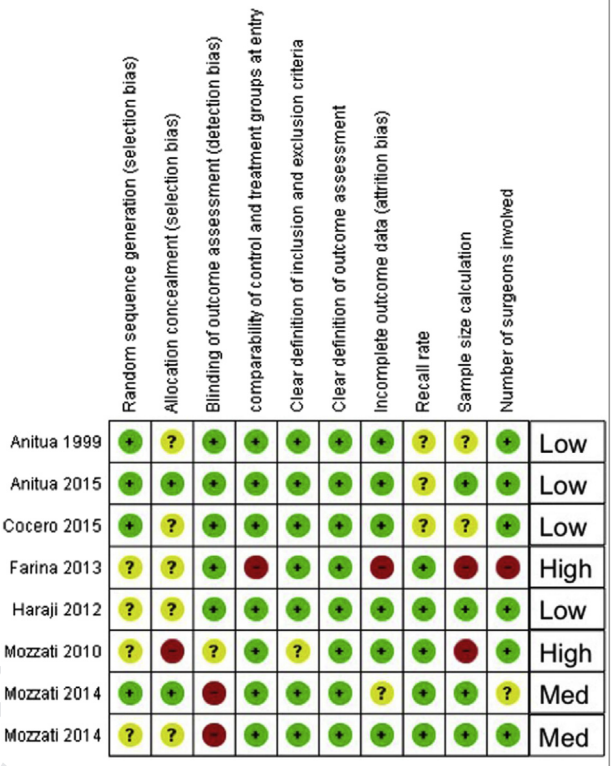
Table 4. Postoperative pain outcomes.

Study	Study design	Postoperative pain outcomes
Anitua et al., 2015[27]	RCT (P)	The postoperative pain was almost absent in the PRGF-treated sites, having the scores of 0.17 and 0.00 at day 3 ($P < .001$) and day 7 ($P < .03$), respectively, compared with that in control sites. There was a highly statistical difference between the two.
Mozzati et al., 2014[28]	RCT (SM)	VAS score for postoperative pain was similar in both sides, dropping to zero after 4 days.
Mozzati et al., 2014[33]	CCT (SM)	VAS score for postoperative pain dropped to zero at day 4 in PRGF-treated sites compared with control sites (at day 6).
Haraji et al., 2012[29]	CCT (SM)	The VAS score for postoperative pain intensity was constantly lower in the PRGF group than that in control sites at all observation times but achieved significance at the end of the 4th day (1.69 vs 2.19).
Mozzati et al., 2010[34]	RCT (SM)	VAS score for postoperative pain for PRGF-treated sites (0.19 cm) was significantly lower than that for control sites (0.49 cm), suggesting 61.22% reduction at the end of 7 days.

CCT, controlled clinical trial; PRGF, plasma rich in growth factors; RCT, randomized clinical trial; VAS, visual analog scale.

Figure 2. Risk of bias summary.



local hemostatic agent similar to fibrin glue, controlling the incidence of severe secondary bleeding.[32]

Proper hard- and soft-tissue healing are the predictable outcomes to evaluate the success of alveolar socket preservation. In this review, six studies assessed the pattern of hard-tissue healing at different time points and with different outcomes: socket depth/dimension reduction, percentage of sockets with regenerated bone, bone density, and histologic and histomorphometric parameters.[25,27-30,33] The variability of assessment methods for evaluating hard-tissue healing in the different studies did not allow for quantitative evaluation of the effect of PRGF on such outcomes. Nevertheless, the trend of the studies suggested a positive effect of PRGF because most of them concluded that there is evidence of potential of PRGF in effective hard-tissue regeneration, in terms of newly formed bone quality and quantity.

On the other hand, one of the included studies[30] reported that the effect of PRGF on new bone formation/deposition was rather nonbeneficial. That study concluded that the PRGF-treated group did not show any enhancement in early (4 and 8 weeks) bone deposition in comparison with the control group. However, the study was found to have strong biases and was critically questioned on its experimental design.[42] In fact, in that study, all the subjects who had smoking habits and all those with teeth extracted due to periodontal disease were included in the PRGF group (representing more than 50% of cases: 6 out of 11), whereas no patient with a history of periodontitis or smoking habits was allocated to the control group.[30] A question was also raised regarding the protocol of allowing the sites with PRGF to heal by secondary intention as in this article; it was unclear if sutures were systematically applied or not.[30] In fact, even though adhesive properties of PRGF should keep it in place, there exists a chance of dislodgement or

escaping of the PRGF gel into the oral cavity if not secured by sutures, leading to noneffectiveness of PRGF.[42] Moreover, the study did not mention the sites of extraction, if not bilateral or one tooth/arch that could result in crossover effect. The high number of biases made the results of this study unreliable and might be a reason for its findings being not in line with the other studies.

Indeed, also in other included studies, there was no explicit mention of the application of sutures to secure PRGF in situ at the end of the surgical procedure, which may be considered a sort of bias for these studies.[25,28,29,33]

Better epithelialization and enhanced socket healing were reported in 4 studies.[25,27,28,33] Keratinized gingiva formed on the sites of healing sockets was significantly thicker in the PRGF group. The inflammation was found to lesser in the sites treated with PRGF and resolved faster. This finding is in concordance with findings of other studies using different platelet concentrates such as PRP, which may limit inflammation, interacting with macrophages to improve tissue healing and regeneration,[43] promote new capillary growth,[44] and accelerate epithelialization[45] in chronic wounds. It was also found that the PRGF had an advantage in enhancing soft-tissue healing and reducing the extent of inflammation in subjects with delayed healing in case of diabetes mellitus.[28] The dissolution time of PRGF in vivo has never been evaluated, but the kinetics of growth factor delivery by PRGF has been studied in vitro.[46] After a rapid initial release of platelet granules' content in the first hour, the gel-like PRGF kept on releasing growth factors up to 8 days of incubation.[46] After that time, almost 30% of the growth factor amount was retained in the fibrin matrix. Another in vitro study, performed under different experimental conditions, reported that the PRGF membrane, after a slow but continuous release of growth factors, dissolves within 5 days of incubation.[47] Of course, the in vivo kinetics release and matrix dissolution might be different. Nevertheless, the sustained release of growth factors could explain the reported beneficial effects of PRGF on soft tissues in the first week after extraction. On the other hand, it is still controversial if PRGF may have a stimulating effect on bone tissue because of the slow healing of the latter. However, it may be hypothesized that the fast and predictable soft-tissue closure at postextraction sites observed with PRGF may also have a positive protective effect for the healing of underlying hard tissues, triggering the bone-healing process and controlling the incidence of postoperative contamination of the site and of postoperative discomfort.

Regarding the effect of the adjunct of PRGF on postoperative quality of life, no quantitative evaluation through meta-analysis could be performed because of differences in methods of assessing the outcome and in reporting the results. In fact, regarding pain evaluation using a visual analog scale, a few studies[27,29,34] assessed the mean of scores achieved on a 10-point scale and others[28,33] assessed the follow-up day at which the score drops to zero. One study reported mean values and standard deviations,[27] another study only reported the values on a graph,[34] and another one did not report the standard deviation.[29] Two studies reported pain daily,[27,34] and others reported the mean values only on selected days.[29] Nevertheless, the trend of the studies evaluating quality of life was in favor of a reduction of the intensity of postoperative pain and symptoms in patients treated with the adjunct of PRGF, suggesting that the use of PRGF may be beneficial for postoperative pain control. This is in agreement with what was reported for other clinical applications such as maxillary sinus floor elevation[48] and endodontic surgery.[49]

Finally, some limitations of this review should be acknowledged. For example, no distinction was made between studies dealing with single extraction sites and studies in which multiple extraction sites were treated, and no correlation was attempted between the effect of the treatment and other potential confounding factors, such as the socket location, the reason for extraction, and the presence and condition of the adjacent teeth and alveolar bone. Indeed, because almost no study provided individual patients' data, such correlations were unfeasible in this systematic review. It is recommended that in future studies, the individual patients' data are reported in detail to determine the weight of the aforementioned factors on the treatment outcomes.

CONCLUSION

Qualitative analysis of the studies suggested that PRGFs could represent a useful tool for improving postextraction hard- and soft-tissue healing and reducing adverse events, complications, and patients' discomfort. However, because a quantitative analysis could not be performed, the actual benefits of PRGF on healing and pain control in extraction sockets are still not quantifiable. More studies, with standardized protocols, are needed to confirm and strengthen the results of this review.

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