

The Use of Platelet Rich Plasma in Bone Regeneration: A Systematic Review

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1. Abstract

1.1. Background and Objective: The bony defects left behind after some dental surgical procedures could have implications on future prosthodontic treatment options. The objective of this review is to systematically investigate the effect of Platelet Rich Plasma (PRP) on bone regeneration and wound healing, on humans, following extractions, cyst and tumor removal, and mandibular fractures.

1.2. Materials and Methods: A literature search was carried out during February 2020 using an electronic search in two databases: Dentistry & Oral Sciences Source and MEDLINE. The key terms used were “platelet rich plasma” and “bone regeneration”. Studies were screened and were selected based upon the inclusion criteria.

1.3. Results: The search generated 827 articles and only 5 articles met the inclusion criteria and were used for data extraction. Two of the studies were case control studies and the other three were randomized clinical trials. Two studies demonstrated a significant improvement in bone densities for patients following mandibular third molar extractions. One study reported beneficial effects of PRP on bone regeneration following cyst/tumor removals, but another study did not find a significant difference. The study about mandibular fractures showed significant improvements in bone density for patients taking PRP, three and six months after surgery. In most studies, the use of PRP improved soft tissue healing. Due to the heterogeneity of the studies, a meta-analysis was not possible.

1.4. Conclusion: Some clinical evidence was found supporting the benefits of PRP in the treatment of bony defects following these surgical procedures. However, the evidence is inconsistent between some studies, requiring more extensive research to for-

mulate a clear conclusion.

2. Introduction

Bone is a specialized supportive connective tissue that has a relatively good healing capacity; however, it has limited regeneration potential in large defects such as those left behind after tooth extraction and cyst removal. In recent years, our increased understanding of the role of growth factors in the healing process has helped develop new ways of treating many types of wounds.

The primary function of platelets in the blood circulation is to initiate blood clots, however, activated platelets are considered an autologous source of growth factors that contribute to the healing process of the site of injury [1,2].

Platelet Rich Plasma (PRP) is the fraction of blood that is isolated when a patient's whole blood is centrifuged. This is done to increase the concentration of the platelets compared to whole blood. Growth factors reported to be present in PRP include Platelet-Derived Growth Factor (PDGF), Transforming Growth Factors-b (TGF-b), Vascular Endothelial Growth Factor (VEGF), Epithelial Growth Factor (EGF), Insulin Growth Factor-1 (IGF-1), Basic Fibroblast Growth Factor (bFGF) [3-7].

Theoretically speaking, injecting a high concentration of platelets in a bony wound will increase the amount of growth factors secreted at the site of injury. This will boost the initial bone healing process, and the natural bone healing mechanism will take over when the direct effects of PRP wear off.

This method was first used by Dr. Robert E. Marx [8] in 1998 in a study to test their ability to enhance bone grafts to repair mandibular defects. The grafts that were supplemented by PRP showed higher rates of maturation and greater bone density than standard bone grafts. Since then, the clinical use of PRP injections to en-

hance soft-tissue maturation has been used in many surgical fields such as otolaryngology, head and neck surgery, neurosurgery, general surgery and various musculoskeletal conditions.

However, controversy still exists regarding its added benefit in the enhancement of bone regeneration. The aim of this systematic review is to determine whether PRP is effective in dentistry as a means to enhance osteogenic healing following mandibular fractures, tooth extractions and removal of cysts.

3. Materials and Methods

3.1. Protocol Development

This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement, so before the start of the review, a protocol was set up to decide on search strategies and inclusion criteria.

The PICOS question for the review was: Is there any additional benefit when using PRP on the process of bone regeneration following tooth extractions and other procedures that require removal of bone structure?

- Population (P): Humans that require tooth extractions, cyst removals, or jaw fractures.

- Interventions (I): Use of PRP alone or in combination with other techniques.

- Comparison (C): Surgical procedures without PRP.

- Outcome (O): Bone regeneration and soft tissue healing in addition to post-operative quality.

- Study Design (S): Randomized Controlled Clinical Trials, split mouth or parallel arm.

3.2. Search Strategy

An electronic search was carried out on two databases (Dentistry & Oral Sciences Source, and MEDLINE). The literature was searched for articles published between the year 2000 and December 31, 2019, also a language restriction was placed to only include articles written in English. Two search terms “platelet rich plasma” and “bone regeneration” were used together, and their known synonyms. The resulting search combinations included: “platelet rich plasma” OR “PRP” OR “autologous platelet concentrate” OR “platelet concentrates” AND “bone regeneration” OR “bone healing”.

3.3. Inclusion Criteria

- Randomized Controlled Trials with at least 10 patients per study.

- Studies testing bone healing following mandibular fractures, tooth extractions and cyst removals combined with PRP.

3.4. Exclusion Criteria

- Animal trials and in vitro studies.

- Case reports and clinical trials with no controls.

- Studies relating to implant therapy.

- Unavailability of the full text version of the article.

4. Screening Process

The search generated a total of 827 results, of which there were 116 duplicates. 244 full text articles were available and were screened by two reviewers. After going through the abstracts and titles, 197 articles were excluded because their subjects were not completely relevant to our review. The remaining 47 articles were further examined, and only 5 met the inclusion criteria and were used for data extraction (Figure 1).

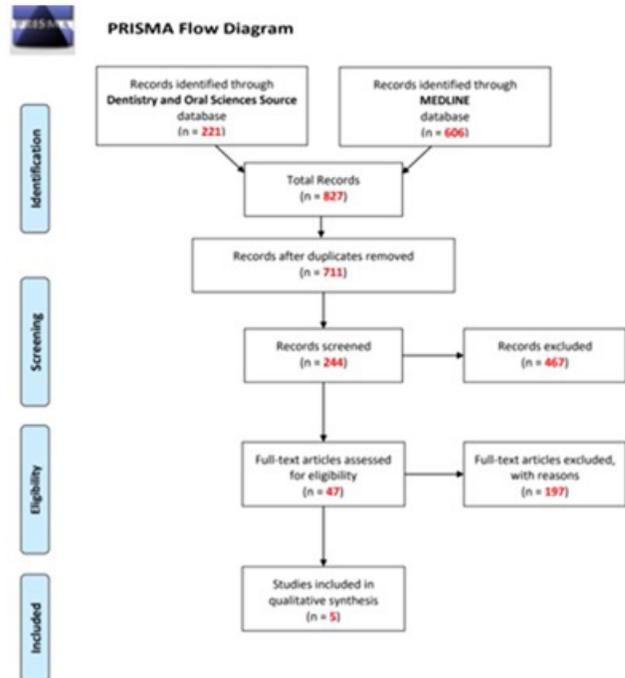


Figure 1: PRISMA Flow diagram of the study selection process

5. Results

The included studies were grouped on the basis of the procedure performed. The results of each study are summarized in (Table 1).

5.1. Quality assessment of the included studies

Quality and risk assessment were independently conducted by two authors and are represented in figures 2 and 3. Discrepancies were solved by discussion until reaching consensus. Included RCTs were rated following the Cochrane collaboration tool for assessing risk of bias. All studies failed to provide a detailed report about the random sequence generation increasing the risk of bias. Allocation concealment was achieved by only two studies that addressed the method of randomization. All studies showed low risk of bias in the Incomplete outcome data and Selective reporting criteria except for one. Two studies showed low risk for performance bias while the rest failed to provide enough details. Blinding of outcome assessment was achieved by two studies, two studies with insufficient data, and one study with high risk of bias.

Table 1: Included studies: Results

Study (Year)	Study Design, Duration	No. of patients	Mean Age±SD and/or Range	Surgical Procedure	Groups T: Test C: Control	PRP Preparation	Outcome
(Bhujbal et al., 2018)	case control study split mouth 6 months	20	25.2±7.19	Tooth extraction w/wo PRP	T: PRP C: w/o PRP	1200 rpm/10 min 2000 rpm/10 min PRP + 10% CaCl ₂	VAS: Less pain w/PRP , 1st day NS (T: 0.4±1.0 vs. C:0.3±0.9, p > 0.05) 3 rd NS(T:0.1±1.1 vs. C:0.1±1.4, p> 0.05) 7 th day NS (T: 2.0±0.9 vs. C: 2.3±1.0, p>0.05) Assessment of swelling: Less swelling w/PRP. 1st day SS (T:0.16±0.7 vs C:0.23±0.09, p<0.05) 3rd SS(T:0.19±0.07 vs.C:0.3±0.09, p<0.05) 7 th day NS(T:0.1±0.04 vs. C:0.1±0.04, p=1.0) Radiologic Assessment: 1st month SS(T:2.90±0.90 vs. C:1.86±1.30,p<0.05) 3rd month SS(T:5.19±1.33 vs. C:4.03±1.49,p<0.05) 6th month SS(T:9.61±1.45, vs C:6.62±2.34,p<0.05)
(Nathani et al., 2015)	RCT split mouth 16 weeks	10	22 18-28	Tooth extractionw/ wo PRP	T: PRP C: HA+BG Granules	2400 rpm/10 min 3600 rpm/15 min PRP +10% CaCl ₂	VAS: Less pain w/PRP, 1 st day SS(T:1.8 vs. C:2.7) 3rd day SS(T:1.1 vs.C:2) 7th day NS (T,C:0) Assesment of tissue healing: improved healing with PRP, 1st day SS(T:3.4 vs C:2.2.7) 3 rd day SS(T:3.8 vs.C:3.1) 7th day SS(T:4.9 vs. C:4) Radiographic Assessment: 8-,12-,16- weeks gray level value (T:144.29 vs C:138.04)

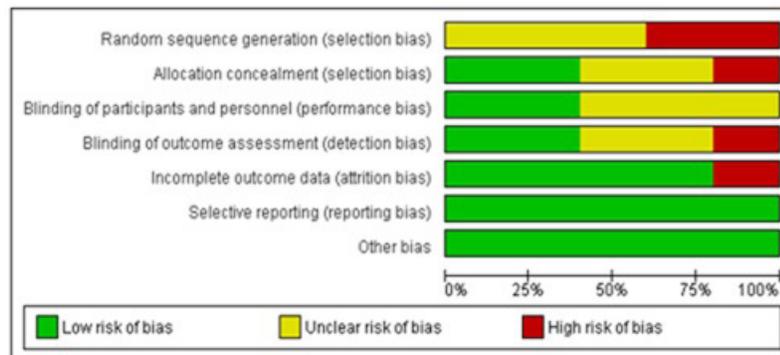


Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 2: Included studies: Results (continued)

Study (Year)	Study Design, Duration	No. of Patients	Mean Age \pm SD and/or Range	Surgical procedure	Groups T: Test C: Control	PRP preparation	Outcome
Nagaveni et al., 2010)	RCT 6 months	20	14-Jul	Cystectomy w/wo PRP	T: PRP+ Ortograft n:10 C: Ortograft n: 10	1300 rpm/10 min 2000 rpm /10 min PRP +10% CaCl ₂ + Thrombin	Defect bone fill: Improved bone consolidation w/PRP, 1st month SS (T:9.5 \pm 1.0; 58% vs C:15.6 \pm 0.9;31%,p=0.01) 2 nd month SS (T:8.9 \pm 0.8;60% vs, C:14.9 \pm 1.1;34%,p=0.01) 4th month SS (T:4.9 \pm 1.4;78% vs, C:13.3 \pm 1.6;41%, p=0.001) 6 th month SS (T:1.3 \pm 2.1; 94% vs, C:12.0 \pm 1.8; 47%, p=0.001)
Ramanathan et al., 2013)	Case-Control study 24 weeks	11	24-50	Cystectomy w/wo PRP	T: PRP n:6 C: w/o PRP n:5	1300 rpm/10 min 2000 rpm /10 min PRP +10% Calcium Gluconate + Gelfoam	<p>Assessment Of lesion margins: Enhanced bone regeneration w/PRP, 6th week NS(T: 50% partly reduced vs. C: 100% unchanged) 12th week NS (T:66.7% partly reduced and completely absent vs. C:40% partly reduced, 20% completely absent) 18 th week NS(T:50% completely absent vs. C:20% completely absent) 24th week NS (T,C:100% completely absent) (p>0.05)</p> <p>Assessment of interior bone fill: Enhanced bone fill w/PRP, 6th week NS (T:16.7% vs C:0%) 12 th week NS (T:60% vs. C:40%) 18 th week NS(T:33.3% complete closure vs. C: radiolucency present) 24th week NS(T: 80% complete closure vs, C:60% complete closure) (p>0.05)</p>
(Daif et al., 2013)	RCT 6 months	24	32 17-42	Vestibular incision + inter-maxillary Fixation w/wo PRP	T: PRP n: 12 C: w/o PRP n:12	1200 rpm/20 min 2000 rpm/15 min PRP +10% CaCl ₂ + Thrombin	Bone Density Measurement: Improved bone consolidation w/PRP, 1st week NS (T:542 \pm 93 vs,C:515 \pm 81,p=0.4) 3rd month SS(T:728 \pm 58 vs. C:600 \pm 78, p=0.0002) 6th month SS(T:1024 \pm 188 vs, C:756 \pm 53, p=0.0001)

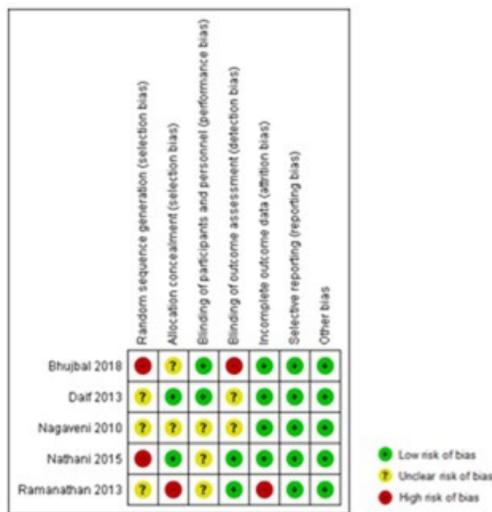


Figure 3: Cochrane risk of bias. Studies were judged for having risk of bias as high, low or unclear.

5.2. Mandibular 3rd molar Extraction

There were two studies, and both showed improved results with PRP. The first study [9] compared control sites to sites in which PRP was used. The second study [10] compared sites in which PRP was used, with sites in which synthetic graft material in the form of granules [combination of Hydroxyapatite (HA) and Bioactive glass (BG)] were placed. Both studies demonstrated a decrease in postoperative pain (measured using VAS scores) with PRP. The difference was significant on the 1st and 3rd days postoperatively. However, the first study [9] did not find the difference to be statistically significant by the 7th day. Soft tissue healing was assessed in terms of the healing index given by Laundry and Turn Bull [11], and both studies recorded improved soft tissue healing with PRP. The study [10] showed a mean score on the 1st day of 3.4 in PRP site, 2.7 in HA site, on 3rd day 3.8 in PRP site and 3.1 in HA site, on 7th day mean score of 4.9 in PRP site and 4 in HA site. By doing the Mann-Whitney U-test for comparison, it was found that the differences were significant. There was also a significant decrease in postoperative swelling during the 1st and 3rd days after surgery [9]. Most importantly, mean grey values obtained by digital radiographs, reflect that PRP helped increase bone density in extraction sites. Mean bone density scores after 3 months were 131.24 in case sites and 131.21 in control ($P < 0.01$); after 6 months these scores were 135.67 and 133.80 in the case and control sites respectively ($P < 0.00001$). Nathani et al. (2015) [10] recorded bone densities of 144.2905 (PRP) and 138,0425 (HA) ($P < 0.0033$).

5.3. Cysts and Benign Tumours of the Jaw

Two studies were reviewed, both of which showed better results with PRP. One study evaluated cases in which only PRP was used and compared to a control group [12]. The second study used PRP in combination with Orto graft, a BIO ceramic composite [90% hydroxyapatite and 10% B-Tri-calcium phosphate] in cases compared to controls in which only Orto graft was used [13]. In the

first study [12] healing changes at the margins of bony defects in the study group occurred rapidly in comparison to the control group (measured radiographically), contrarily to the study group, the control group upheld an unaffected state of healing at the 6th week, whereas half of the study group advanced to 'partly reduced' margin. Throughout the course of 12 weeks, 66.7% of the study group exhibited progression towards 'partly reduced' or 'completely absent' defective margins, while only 40% showed 'partly reduced' and 20% 'completely absent' in the control group. The differences are statistically insignificant ($p > 0.05$) as the lesion margins in both groups were completely absent by the 24th week. Another evaluation to assess the sites interior bone regeneration was done in the same study showing more rapid healing in the subjects compared to the control group, however, by the 24th week 80% of the study subjects and 60% of the control subjects showed complete consolidation of the bony defect, the differences were statistically insignificant ($p > 0.05$). The second study [13] measured the defective bone fill radiographically and found that following the first month, 58% of the defect was filled in the study group while 31% defect fill was recorded in the control group. Subsequently, post-operative radiographs show 94% defect bone fill in the study subjects at the 6th month, while the control group had only 47% defect bone fill. Unlike the first study, the second study was found to be statistically significant ($p < 0.001$).

5.4. Mandibular Fractures

Daif et al [14] found PRP effective during the healing process in mandibular fractures. Two groups were assigned equally, whereas group A was treated with titanium mini plates and screws, alongside to PRP injected along the fracture line. Group B was treated with titanium mini plates and screws only. The examination of both groups was obtained by using Cone-Beam Computed Tomography (CBCT) to measure the bone density in Hounsfield units (HU). Group A showed greater soft tissue wound healing in contrast to group B, in which sutures were removed from group A earlier than group B (8- and 15-days post-surgery). A CBCT scan was taken for every patient at the 1st week, 3rd, and 6th months after surgery to assess the bone density with respect to HU. Scans taken 1 week after surgery showed that differences in bone density measurements between the two groups, as outcomes ranging from (435-754 HU) in group A and (432-690 HU) in group B were statistically insignificant ($p = 0.4$). However, differences between both groups at the 3rd ($p = 0.0002$) and 6th ($p = 0.0001$) months after the surgery were statistically significant, whereas bone density measurements had outcomes ranging from (825-1490 HU) in group A and (710-890 HU) in group B 6 months' post-surgery.

6. Discussion

This systematic review was intended to assess the current studies that employed the use of PRP in bone regeneration as it pertains to tooth extractions, cyst enucleation, and mandibular fractures. The review is qualitative as a complete meta-analysis of the compiled

studies could not be done, due to the heterogeneity of the results and the slight variations in the PRP preparations.

Two studies [9,10] reported on the application of PRP in teeth sockets post-extraction of third molars. Both studies conducted split-mouth assessments on soft tissue healing and pain in addition to radiographic evaluation of bone density. All assessments showed improved results when using PRP, as they were in accordance with the findings of Anitua et al (2008), Sammartino et al (2005), and Alissa et al (2010) [9,15-17]. The first study [9] evaluated the application of PRP only and reported better epithelialization and a significant increase in bone density on the 3rd and 6th months post medical treatment. The second study [10] contrasted the efficacy of PRP with HA granules, each conducted separately in different sockets of a single individual at the same session. The study was done to eliminate such bias whereas different factors can affect bone regeneration and can vary in different patients. Both materials were significantly biocompatible and did not show any amplified tissue reactions. Nevertheless, it is safe to state that PRP is an autologous source rather than homologous as HA, making its use more precautionary and compliant with soft tissue healing along with bone consolidation. Both studies administered different techniques in PRP preparation, in addition to having different evaluation criteria. Although PRP showed better bone consolidation in both studies, a larger number of clinical cases and a long-term post-operative follow-up duration is essential to proper closure on the efficacy of PRP.

The application of PRP has shown various outcomes due to differences in technique preparations and limitations to a small sample size. Two studies [12,13] reported on bone regeneration following a cystectomy at the enucleation site using PRP. Nagaveni et al. illustrated that the study group had a trend towards more rapid healing in contrast to the control group. Okuda et al (2005) [18] noted that PRP in combination with hydroxyapatite led to significant clinical advancement. In this study, PRP was utilized in conjunction with bone graft. Though clinical improvement is evident, a histo-morphometric analysis is required to accurately conduct a qualitative assessment of bone regeneration. This is critically important to assess the competency of PRP since the results acquired are of various combinations, leading to conflicting conclusions on the ability of PRP to enhance healing. On the last follow-up week, differences between both groups were statistically significant. Contrarily, Ramanathan et al. [12] have stated that radiographic assessments indicate that PRP promotes faster bone growth in cystic cavities, however, evidence suggests the differences are not of significance between the study and the control groups. Unlike the first study, Ramanathan et al employed the use of Gelfoam rather than bovine thrombin to accelerate gel formation. More investigations are required to point out the effects of different preparation techniques to evaluate the long-term efficacy of PRP used on larger sample size.

Only one study assessed the impact of PRP on bone regeneration in mandibular fractures [14]. Clinical assessments have shown that oral mucosa healed more rapidly in the study group. Furthermore, the study used CBCT scans to assess bone density measurements. Although the study group demonstrated significantly improved bone density on the 3rd and 6th-month post-surgery, greater measurements were recorded by Cieslik-Bielecka et al (2008) [19]. The variation in the results can be justified on the premise that different protocols have been used for PRP preparation and different techniques were employed to measure bone density. According to Nomura et al (2010) [20], CBCT values might have a nonlinear correlation to bone mass density, requiring further investigations to elaborate on the accuracy of these values.

Postoperative pain is a significant measure for patients to determine their experience with surgery [21]. Two studies monitored pain following tooth extractions using VAS. In both studies the level of pain was significantly lower during the first day after surgery, with the differences equalizing until the seventh day when there is almost no pain in both the study and control groups. Similar findings were noted by studies conducted by Mancuso et al (2003), Vivek et al (2009), and Gawande et al (2009) [22]. This could be explained by the anti-inflammatory effect of PRP therapy and quicker soft tissue healing [23]. However, in most studies the patients knew they were receiving PRP injections, which could have influenced the patients' perception of pain in the follow up. To retrieve truly accurate data, blinding of the patients is required to eliminate the chance of placebo.

It is important to point out that the number of studies included in this review is low as we were limited to the full text articles openly available to us. The outcomes in the studies can only be expected when performing the same dental surgical procedures, and not procedures outside the ones described in the studies. Additionally, the lack of a standardized protocol for the preparation of platelet rich plasma solutions may result in some variance and needs to be taken into account. However, the clinical results are important enough to have some relevance to all dentists. The ultimate goal of this therapy would be to preserve as much periodontal structure as possible to permit implant based prosthodontic treatments in the future if the patients so wish. Still, more studies are required to establish PRP as an adjunct to dental procedures. Eventually, if enough substantial evidence is gathered to prove the efficacy of PRP therapy, guidelines for the use of PRP may be put in place for dentists to follow.

7. Conclusion

Based on the results of the studies, the present review demonstrated that PRP injections can in fact enhance various aspects of post-operative healing in varying capacities, including pain, swelling, soft tissue healing, and bone regeneration. Superior bone densities were achieved in patients taking PRP compared to HA granules following third molar extractions. Improved bone densities were

also observed inpatients 3 and 6 months following mandibular fracture surgery. However, evidence is weak in regard to its efficacy following cyst/tumor excisions.

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