

# The Clinical Application of Platelet Concentrates: A Systematic Meta-analysis

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## ABSTRACT

**Background:** Autologous plasma rich in platelets is derived blood product whose uses in dentistry dates back to the 1990s and it has been gaining popularity ever since.

**Aim:** A systematic review of the available literature to determine the efficacy, safety and success of platelet concentrates in physiological systems as well as describing its vigilant use.

**Study design and methods:** A Medline search with keywords 'platelet rich plasma dental' further filtered using Boolean operators (AND, OR, NOT) and combination of specific keywords as follows: 'platelet rich fibrin', 'platelet rich plasma regenerative', 'platelet rich plasma periodontal', 'platelet rich plasma extraction' with a custom range of 10 years was performed, which yielded 88 results out of which 32 were selected based on the inclusion criteria.

**Results:** Significantly, successful outcomes have been witnessed in the field of osteoregeneration though it has been evidenced that adequate platelet rich plasma (PRP) additives are essential to bear a therapeutic potential. Favoring blood cell adhesion on the root surface optimizing periodontal healing, PRP has also shown positive effect on gingival repair; though controversial facts have also been reported. In the scope of implant dentistry, PRP has also reported greater implant-bone contact when used in both gel or liquid form. Emerging as a possible pulp capping agent along with properties of decreased chances root growth, PRP has successfully completed apexogenesis in cases of pulpotomy.

Research has shown that although clinical results from the comparison of PRP alone vs PRP and resorbable membrane or various graft materials has shown a varied results, additional research in the field is needed.

**Conclusion:** Platelet rich plasma has shown promising results in the field of regenerative dentistry, with high success rate in implantology, periodontology and oral surgery. Because of conflicting success rates reported in literature further research is warranted.

**Clinical implication:** Platelet rich fibrin has displayed various features of rapid clinical healing, excellent bone density, less surgical time, less resorption during healing and decreased postoperative pain, as compared to guided bone regeneration

procedures. Platelet rich plasma has also shown a myriad of applications ranging from hard tissue regeneration to soft tissue management, stretching across to the field of pediatric dentistry and endodontics.

**Keywords:** Platelet rich plasma, Platelet rich fibrin, Meta-analysis, Regenerative dentistry.

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## INTRODUCTION

Unveiling platelet rich plasma (PRP) into the field of dentistry dating back to the 1970s has been followed by an era of development. Platelets have held a history of simple hemostasis but scoping beyond its norm, it contains important growth factors which entitle it with the function of increasing cell mitosis, increasing collagen production, recruiting other cells to site of injury, initiating vascular ingrowth and inducing cell differentiation.<sup>1</sup>

Hence, logically increasing platelet concentration equates to increasing growth factors which pronounces rapid healing and regeneration. This concentrated form of platelets is in other words termed as platelet rich plasma, a volume of autologous plasma, labeled inherently safe and free from transmissible diseases that has platelet concentrate above baseline.<sup>1,2</sup>

On one thought were Whitmann et al in 1997 were extolled for introducing PRP into the field of oral surgery, on the other PRP was as not entirely greeted with approval; contradictory results too grasp a slice in literature.<sup>3</sup> The conflicting results in today's literature make it overwhelmingly evident that more research is needed before evidence-based surgeons can feel confident in recommending this procedure to their patients. Reliable and reproducible animal models have been developed to study this autologous material but well-designed, rigorous, standardized human trials need to be reviewed to prove its benefit.<sup>2,4</sup>

## AIM

A systematic review of the available literature on human trials was conducted to evaluate efficacy and safety

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of platelet concentrates in physiologic systems and to describe its vigilant use from studies which have shown comparative results.

## STUDY DESIGN AND METHODS

A systematic search of scientific papers published was performed in the electronic PubMed database of Medline and dental journals using specific keywords 'platelet rich plasma dental' further filtered using Boolean operators (AND, OR, NOT) and combination of specific keywords as follows: 'platelet rich fibrin' 'platelet rich plasma regenerative' 'platelet rich plasma periodontal' 'platelet rich plasma extraction' within the custom range of 10 years. The search was performed upto 1 September, 2014 (Flow Chart 1).

### Inclusion Criteria

Studies were selected if they met the following inclusion criteria: (1) Report written in English (2) human study population (3) all comparative studies which include case reports, case series, original research papers, review papers, *in vitro* studies and controlled clinical trials on PRP as well as PRF used in dentistry related studies with clinical or radiographic or histologic evidence. In the case of multiple publications of the same study, the one with the most detailed information was included.

### Exclusion Criteria

Studies were excluded if they did not meet the above inclusion criteria or were animal trials.

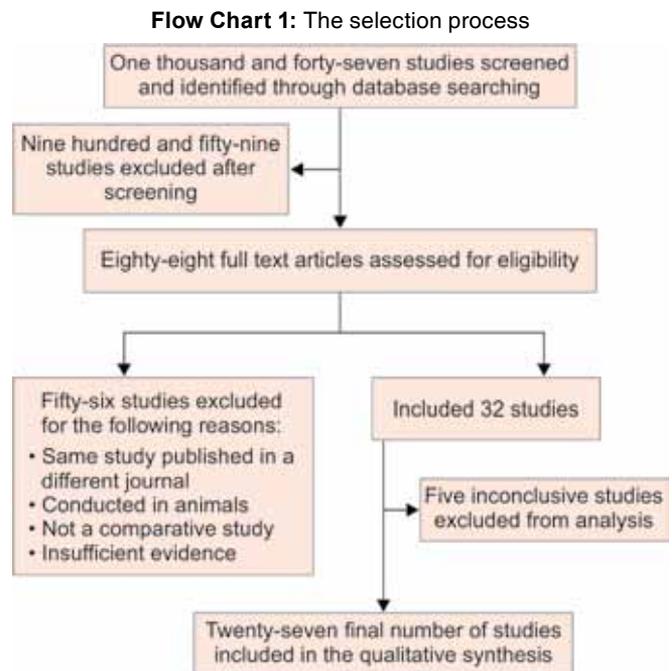
The electronic search yielded 88 papers; of which 32 papers were retrieved and a review was done that described the efficacious use of PRP and PRF.

### Data Collection

Once a study was included in the analysis, the authors used a predetermined data collection form to extract the following information: (1) The comparison exemplified in the studies with the results seen and (2) Year of publication. Data related to the supporting and contradictory evidences was reported separately. Any disagreements in the data collection reports was resolved by consensus.

## RESULTS

Eighty-eight papers gathered from the search results were further scanned on basis of the inclusion criteria. Thirty two comparative studies including case reports, case series, original research papers, review papers, *in vitro* studies and controlled clinical trials on PRP as well as PRF used in dentistry related studies with clinical or



radiographic or histologic evidence. The results of the studies were tabulated and assorted into two categories (Tables 1 and 2). Studies which failed to give conclusive results were excluded.

## DISCUSSION

Development of the bioactive surgical additives is one of the great challenges of clinical research which has been used to regulate inflammation and increase the speed of healing process.<sup>5</sup> Better understanding of physiologic properties of platelets in wound healing since last two decades led to increase in its therapeutic applications in the various forms showing varying results. As mentioned earlier, platelets isolated from the peripheral blood acts as an autologous source of growth factors in the form of PRP and PRF.<sup>1,6</sup>

Platelet rich plasma, an autologous platelet gel, is an amalgamation of seven known growth factors specifically, platelet derived growth factor as PDGF-AA, PDGF-BB, PDGF-AB, transforming growth factor beta 1 and 2, vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF). Platelet rich plasma is neither a fibrin glue nor osteoconductive, indeed it simply augments the tissue regeneration and healing.<sup>7</sup>

Approximately, 45 to 55 ml of patient's blood is withdrawn from venous puncture and centrifuged twice to separate red blood cells from plasma and form pure plasma concentrate subsequently. This platelet concentrate is then resuspended in the remaining platelet poor plasma, thereby creating a very concentrated PRP solution. The activator, topical bovine thrombin calcium chloride, is combined with PRP and PPP in a small quantity before use.

Table 1: Supporting evidences of the meta-analysis

Sl. no.	Supporting evidences reported	Authors	Year
1.	PRP and PRF with open flap debridement (OFD) vs OFD showed notable gain in relative vertical and horizontal clinical attachment level.	Bajaj et al, Pradeep and et al	2013 and 2012
2.	A combination of direct pulp capping agent and PRP increased vital tissue regeneration within the root canals of immature teeth associated with apical periodonitis.	Zhu W	2013
3.	Marked radiographic difference in periapical healing, apical closure and dentinal wall thickening revascularization carried out with PRP than without.	Jadhav et al	2012
4.	HA + PRP (experimental group) or HA + saline (control group): postoperative difference seen in the probing depth, attachment levels and bone measurements were statistically significant for the experimental group.	Menezes et al	2012
5.	PRP mixed with calcium sulfate hemihydrate showed greater vital bone volume at 3 months with rapid enhancement of bone healing compared to PRP free collagen resorbable graft.	Kutkut et al	2012
6.	PRP treated extraction sites reach comparable bone density in 1 week as compared to control sites in 6 weeks.	Rutkowski et al, Antonello et al	2010 and 2012
7.	Periapical healing with bone formation was more in relation to site grafted with PRP compared to control site without PRP.	Parikh et al	2011
8.	PRP with $\beta$ TCP revealed significant reduction in probing pocket depth and mean gain in clinical attachment level with linear bone fill as compared to TCP alone.	Saini et al	2011
9.	PRP with $\beta$ TCP + HA revealed significant reduction in probing pocket depth and better graft remodeling as compared to $\beta$ TCP + HA alone.	Kaushick et al	2011
10.	PRP vs control extraction socket showed notable reduction in probing depth and an improvement in the probing attachment level as well as new bone tissue in defect.	Sammartino et al, Oqundipe et al	2008 and 2011
11.	BPBM/GTR/PRP (experimental group) or with BPBM/GTR (control group): postoperative difference seen in the probing depth, attachment levels and bone measurements were statistically significant for the experimental group.	Camargo et al	2009
12.	PRF appears to be superior to collagen (Bio-Guides) as a scaffold for human periosteal cell proliferation.	Gassling	2002
13.	PRF in the sinus (BAOSFE) leads to endosinus bone gain.	Diss et al	2008
14.	Addition of PRP to connective tissue graft membrane resulted in increased width of keratinized tissue and advanced tissue healing.	Jankovic et al	2007
15.	Histologic sample from 4 months of healing time from group grafted with PRF and FDBA was identical to that of control group grafted with FDBA alone.	Choukroun et al	2006
16.	PRP comparable to MTA for incomplete apex formation.	Keswani et al	2005
17.	PRP with autogenous bone graft 88 patients with mandibular continuity defects were randomized to be reconstructed with autogenous cancellous bone grafts with or without addition for PRP, showing 1.6 to 2.2 times faster degree of maturation and significantly greater percentage of trabecular bone.	Marx et al supported by Garg et al	2004

Evolving further PRF is a second-generation platelet aggregation fibrin-rich gel produced from the venous blood by single centrifugation developed in France by Choukroun et al. A single centrifugation is performed, following which the middle layer obtained, contains the lowest level of red blood cells, and contains almost no platelets, while above there is a layer of plasma. Platelet rich fibrin contains clotting factors that form a fibrin network that traps various cytokines in the PRF.<sup>6</sup>

### Clinical Application

Significantly successful outcomes have been witnessed in the field of osteoregeneration by means of enhancing osteoprogenitor cells in the host bone and in bone grafts,<sup>8-10</sup> where PRP has shown promising results in combination with autogenous bone graft by Marx and Garg et al, DFBA by Choukran et al and TCP by Saini et al. Bone added osteotome sinus floor elevation supported

by Diss et al in conjunction with rapid clinical healing, excellent bone density, less surgical time, less resorption during healing and decreased post-operative pain, as compared to guided bone regeneration procedures<sup>8,11-31</sup> (Table 1). Acceleration of hard tissue maturation and block graft procedures also produces a quantity of immature hard osteoid tissue within lesser time than the conventional time, hence improves primary stability for implant along with 20% greater trabecular bone density and 85% greater proportion of mature haversian system in the initial months supported by no evidence of active resorption and remodeling, indicating a level of stable maturity.<sup>8,32</sup>

The main purpose of PRP is to reduce the use of autologous bone graft collected from the patients sites and reducing the mucosal incisions<sup>32</sup> Though Ozdemir, Raghoobar, Schaaf et al conveyed no beneficial effects of PRP with grafts in their literature<sup>33-43</sup> (Table 2).

**Table 2:** Contradictory evidences of the meta-analysis

Sl. no.	Contradictory evidence reported	Authors	Year
1.	The use of PRP did not improve the result obtained by enamel matrix derivative and natural bone mineral combined.	Döri et al	2013
2.	At 6 months, no statistical significant reduction of the gingival recession, clinical attachment level, probing pocket depth and bony defect depth were observed between group of $\beta$ -TCP and PRP/ $\beta$ -TCP combination.	Ozdemir et al and Döri et al	2012 and 2008
3.	No significant differences were seen between PRP and collagen membrane in GTR.	Goyal et al	2011
4.	BPBM/GTR/PRP (experimental group) or with BPBM/GTR (control group): no statistically significant postoperative difference seen in the probing depth, attachment levels and bone measurements.	Camargo et al	2009
5.	The use of PRP with anorganic bovine bone material (ABBM) failed to improve the result obtained with ABBM alone.	Döri et al	2009
6.	Topical use of PRP did not improve maxillary bone volume compared to conventionally treated patients.	Schaaf et al	2008
7.	No difference was seen in the treatment of recession with CTG or a CTG-PRP combination.	Keceli et al	2008
8.	Clinical performance across both sites showed no statistical significance. Enhanced bone activities in sites treated with PRP were seen 4 months after surgery, but a progressive extinguishment of the PRP effect is recorded after an interval longer than 6 to months.	Consolo et al	2007
9.	No significant difference was observed between sites, where PRP or fibrin has been used as a delivery system for rhBMP-2 (ANOVA). The application of fibrin gels or PRP gels to bone defects is not superior to leaving the defect untreated.	Jung et al	2005
10.	No beneficial effect of PRP when added to autologous bone grafts used for maxillary sinus.	Raghoobar et al	2005

But, the negative predisposition to the review on PRP could be attributed to the quality of PRP used, techniques to sequester the platelets, use of damaged platelets, not adequately activated platelets, or statistically insufficient data to draw a valid conclusions, distinctive response in animal models, isolation techniques equally holding odds minimal effects of PRP on bone healing.<sup>8</sup>

Wrapping up the literature appears to buttress that PRP may be effective in relatively small periodontal defects when they are grafted with autologous bone. When autologous bone is not present in the graft and there is large volume, PRP may not produce the desired stimulatory response because vital bone cells are needed for this stimulation to occur.<sup>44</sup>

In parallel, PRP placed in extraction sockets have reported early and improved bone formation.<sup>17,22</sup>

Tallying up to the various benefits, review has further articulated the impact of PRP over soft tissue grafts. Coherent property of PRP helps stabilize the graft over the root surface and on completion of suturing technique.<sup>45,46</sup>

Jankovic and Gassling et al appraised this platelet concentrate to show positive results in gingival and periodontal repair on account of significant reduction in probing pocket depth and mean gain in clinical attachment level with linear bone fill by favoring blood cell adhesion on the root surface.<sup>25,27</sup> This inference has been supported by Robert Marx who demonstrated with histologic evidence with the aim to explain how PRP enhanced the initial soft tissue migration and re-epithelialization

and a higher incidence of wound closure at days 3, 7 and 14 with records taken at 6th day showing no peripheral erythema with 95% epithelial covering opposed to only 5% or less epithelialization in controlled split thickness skin graft donor site with no epithelial budding or granulation tissue. Similar supporting data was reported by another study showing more advanced healing at the PRP site at 45 days.<sup>8</sup> Enhanced bone activities in sites treated with PRP were seen up to 4 months after surgery, but a progressive extinguishment of the PRP effect is recorded after an interval longer than 6 to 7 months.<sup>41</sup>

A combination of direct pulp capping agent and PRP increased vital tissue regeneration within the root canals of immature teeth associated with apical periodontitis. Flaunting its equity as direct pulp capping agent and aiding in the formation of incomplete apex formation, PRP has also step forth in the field of Endodontics.<sup>25,27</sup>

Moving a step further, the introduction of PRF brought in an added boon. Spelling out benefits of precluding use of anticoagulants, a 3D fibrin matrix aiding in cytokine retention for extended periods, formulation of a PRF membrane possessing elasticity and flexibility along with its lucrative simplicity, PRF has demonstrated improved implant bone contact as compared to PRP, though review in literature is yet a small number. Concentration of fibrinogen and growth factors is 12 and eight times more respectively in PRF as compared to PRP.<sup>48</sup>

However, at this stage of investigation, the results are yet far from absolutely conclusive. Much is still unknown



about PRP, and an adequate body of research should precede a widespread use of this adjunctive material, as would occur with any other biologic agent.

Research has proven various benefits of PRP which rope in decreased incidence of intra and postoperative bleeding and pain amalgamated with diminished potential for rejection bolstering graft acceptance.<sup>46</sup> But case selection also plays a very important role as its use is refrained in cases where calcification is not a desired outcome, combined with the region of grafting plays a very important role to promote beneficial effects.<sup>39</sup>

Hence undoubtedly, all clinicians involved with bone grafting have high hopes that PRP will eventually prove to be of great benefit in bone graft healing.

## CONCLUSION

Platelet rich plasma has shown a promising outcome in the field of regenerative dentistry. Extensive research has been done in the field of implant, periodontal and oral surgery. But, further evidence is needed in the field of endodontic regenerative science with definition of the specific therapeutic potential.

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