Autologous platelet concentrate for post-extraction socket healing: A systematic review

Key words  platelet concentrates, socket healing, systematic review, tooth sockete

Background: Autologous platelet concentrates are claimed to enhance hard and soft tissue healing due to the considerable amount of growth factors that are released after application in the surgical site. However, their actual efficacy for improving tissue healing and regeneration in oral surgery applications is controversial. Tooth extraction socket healing represents a proper model to study the effect of autologous platelet-enriched preparations due to the concomitant occurrence of different processes of both hard and soft tissue healing.

Purpose: To evaluate the efficacy of platelet concentrates for alveolar socket healing after tooth extraction, by conducting a systematic review.

Materials and methods: Medline, Embase and Cochrane Central Register of Controlled Trials were searched using a combination of specific search terms. The last electronic search was performed on 15 June, 2014. Manual searching of the relevant journals and of the reference lists of reviews and all identified randomised controlled trials was also performed. Randomised controlled trials evaluating the effect of a platelet concentrate on fresh extraction sockets were included. Further inclusion criteria were that at least 10 patients were treated (at least 5 per group) and there was a minimum follow-up duration of 3 months. Primary outcomes were postoperative complications, patient satisfaction and postoperative discomfort. Secondary outcomes were any clinical, radiographic, histological and histomorphometric variables used to assess hard and soft tissue healing. Assessment of the methodological quality of the trials was made. Results were expressed as fixed-effects models using mean differences for continuous outcomes and risk ratios for dichotomous outcomes, with 95% confidence intervals (CI).

Results: The initial search yielded 476 articles. After the screening process, six articles met the inclusion criteria (199 teeth in 156 patients). Three studies were considered at high risk of bias, two at medium risk and one at low risk. A large heterogeneity in study characteristics and outcome variables used to assess hard tissue healing was observed. A meta-analyses of two studies reporting histomorphometric evaluation of bone biopsies at 3 months’ follow-up showed greater bone formation when platelet concentrates were used, as compared to control cases (P <0.001; mean difference 20.41%, 95% C.I. 13.29%, 27.52%). Beneficial effects of platelet concentrates were generally but not systematically reported in most studies, in particular when considering the effects on soft tissue healing and the patient’s reported postoperative symptoms like pain and swelling, although no meta-analysis could be done for such parameters.

Conclusions: Although the results of the meta-analysis of the present review are suggestive for a positive effect of platelet concentrates on bone formation in post-extraction sockets, due to the
limited amount and quality of the available evidence, they need to be cautiously interpreted. A standardisation of the experimental design is necessary for a better understanding of the true effects of the use of platelet concentrates for enhancing post-extraction socket healing.

Conflict of interest statement: The authors declare they have no conflicts of interest.

Introduction

Tooth extraction is performed for a wide variety of reasons, such as: tooth decay with extensive destruction of tooth structure, which makes the tooth non restorable; periodontal disease with loss of tooth support and mobility; trauma; root fracture; acute infection; impaction, or for orthodontic reasons. Post-extraction socket healing causes many important alterations in the volume and shape of the socket itself, which are the results of concomitant mechanisms of bone resorption and apposition. A succession of events leading to the healing of the alveolar socket after extraction was described by several histological studies. The greatest amount of bone loss occurs in the horizontal dimension, mainly on the facial aspect, causing narrowing of the ridge. A consistent vertical reduction also takes place, more pronounced at the buccal side. Bone volume decrease after tooth extraction can have an important effect on the possibility of an effective substitution with dental implants. Insufficient bone volume in the site can complicate implant insertion, creating the need for a bone grafting procedure before or immediately after implant placement.

Many socket preservation procedures with the use of different biomaterials have been proposed by scientific literature. Autologous platelet concentrates are a group of biomaterials derived from human blood. Several commercial systems for preparing autologous platelet concentrates are available today, which allow the preparation of products with different composition and biological activity, but all are characterised by a concentration of platelets higher than in the systemic blood. Platelet concentrates have been classified into four main categories, according to their fibrin matrix density and their content in leukocytes. The three types of platelet concentrates mostly used in the clinical setting are the following: (i) platelet-rich plasma (PRP, also defined as L-PRP), which is characterised by the presence of leukocytes, a high platelet concentration (up to 5 to 8 times the baseline value). It is prepared from anti-coagulated blood undergoing a double centrifugation step and requires an activator before use; (ii) plasma rich in growth factors (PRGF, also defined P-PRP) is characterised by the absence of leukocytes, a modest increase in platelet concentration (2 to 3 times the baseline value). It is prepared from anti-coagulated blood undergoing a single centrifugation step, and requires an activator before use; (iii) platelet-rich fibrin (PRF, also defined L-PRF) is characterised by the presence of most platelet and leukocytes in a dense fibrin matrix that does not require an activator before use. It is prepared from non-anti-coagulated blood undergoing a single centrifugation step.

Tooth extraction socket healing represents a proper model to study the effect of autologous platelet-enriched preparations in wound healing because it is the ending point of different simultaneous processes of both hard and soft tissue healing in a septic environment, like the oral cavity. Scientific literature however is rather controversial regarding the true effect of autologous platelet concentrates in the healing process. In fact, some studies have shown the positive effect of haemocomponents in enhancing tissue healing after bone grafting procedures, like maxillary sinus augmentation or the treatment of bony defects, while others reported no significant effects of platelet concentrates.

In oral surgery applications, though most studies report a beneficial effect on soft tissue healing, their actual effect in enhancing bone regeneration is still unproven. The aim of the present systematic review was to evaluate the efficacy of platelet concentrates for enhancing alveolar socket healing after tooth extraction. The PICO question leading the review was: “In patients undergoing tooth extraction, does
the local application of autologous platelet concentrate improve clinical, radiographic and histological outcomes related to socket healing as compared to control?”

**Materials and methods**

This study is reported by following the PRISMA statement (http://www.prisma-statement.org/).

**Eligibility criteria**

Only randomised controlled trials of both parallel and split-mouth design assessing the efficacy of platelet concentrates for healing and regeneration of hard tissues in patients undergoing tooth extraction were included. Studies were included only if a test group using platelet concentrates was compared with a control group in which platelet concentrates were not used. Platelet concentrates could be used alone or in combination with other materials, but for study inclusion they had to be the only difference between test and control. Any type of platelet concentrate was to be included. Randomised controlled trials (RCTs) treating at least 10 patients (at least 5 patients per group) were considered. Studies were included if the follow-up duration was at least 3 months.

**Search strategy**


The reference list of all identified RCTs and of relevant reviews was also scanned for possible additional studies. Online databases providing information about current clinical trials in progress were checked (http://clinicaltrials.gov/; http://www.centerwatch.com/clinicaltrials/; http://www.clinicalconnection.com/). No language restriction was placed.

**Data collection**

The titles and abstracts of the retrieved articles were screened independently by two reviewers (MDF, SC) to identify all eligible studies apparently meeting the inclusion criteria. When the abstract was not available or did not provide sufficient data to allow unequivocal evaluation, the full text was obtained and checked. Publications that did not meet the selection criteria were excluded. Disagreements were resolved by discussion. The full text of all the eligible articles was obtained and the characteristics of the studies were examined by the reviewers to either confirm study inclusion for data analysis or to exclude the study. Relevant data were extracted from the included studies and analysed.

Primary outcome measures were:

- any complication and adverse event (e.g. alveolar osteitis, acutely infected or inflamed alveolus)
- patient satisfaction (through a questionnaire)
- postoperative discomfort/quality of life (e.g. postoperative pain on a visual analogue scale [VAS], swelling).

Secondary outcome measures were:

- radiographic evaluation of bone healing (e.g. assessment of bone density or trabecular bone pattern at the extraction site)
Risk of bias assessment

The methodological quality of the included studies was evaluated independently and in duplicate by two reviewers (MDF, SC) as part of the data extraction process. The risk of bias of the included trials was assessed based on the following eight quality criteria: randomisation method; concealed allocation of treatment; sample size calculation; completeness of information on reasons for withdrawal by trial group; definition of exclusion/inclusion criteria; comparability of control and test groups at entry; calibration and blinding of outcome assessors; blinding of patients. All these criteria were judged as adequate/inadequate/unclear. The authors of the identified studies were contacted for clarification or to provide missing information.

In order to summarise the validity of the studies, they were grouped into the following categories: low risk of bias (plausible bias unlikely to seriously alter the results) if all quality criteria were judged adequate; moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were considered unclear; high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were judged inadequate. Criteria for assessing the risk of bias of RCTs in the present review were adapted from the guidelines reported in the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreement between the two reviewers was resolved by discussion. If agreement was not obtained, a third reviewer was consulted (ST).

Data analysis

Heterogeneity among studies for the estimates of treatment effects was assessed using Cochran’s test for heterogeneity, considering it significant if $P < 0.1$. The quantification of the heterogeneity was calculated with $I^2$ statistics, which describes the percentage total variation across studies that is due to heterogeneity rather than chance. If $I^2$ was over 50% it was considered significant (substantial heterogeneity).

For each trial, for dichotomous outcomes (e.g. postoperative alveolar osteitis, yes/no), the estimate of effect of an intervention was expressed as risk ratios together with 95% confidence intervals. For continuous outcomes (e.g. % of newly formed bone, alveolar bone height and width change), mean differences (change score) along with 95% confidence intervals (CIs) were used to summarise data for each treatment group. The statistical analysis unit was the patient and not the tooth.
It was planned that sensitivity analysis should be performed to evaluate the effect of the risk of bias on the overall estimates of effect. Meta-analyses were performed only with studies with similar comparisons reporting the same outcome measures. Risk ratios were to be combined for dichotomous data, and mean differences for continuous data using random-effects models if at least four studies could be included in the meta-analysis, while if there would be less than four studies then a fixed effects model was chosen. The software RevMan (Review Manager Version 5.3, 2014; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for meta-analysis computations. Data from split-mouth and parallel group studies were to be combined. The appropriate standard errors were to be estimated where these were not presented in the trial reports. The generic inverse variance procedure in RevMan 5.2 was to be used to combine these two subgroups in the analyses. Furthermore, for the effect of the follow-up duration (<4 months and ≥4 months) and of the type of platelet concentrate used (platelet-rich plasma (PRP), platelet-rich fibrin (PRF) or plasma rich in growth factors (PRGF)), evaluation was planned by means of subgroup analyses.

## Results

The article selection process is presented in Fig 1. The electronic search retrieved 474 articles while 11 studies were identified from the manual search. After the removal of duplicates, 476 articles resulted and were screened. Twenty-two full-text articles were assessed for eligibility. A total of 16 studies were excluded after full-text evaluation: 5 studies because the treatment was not allocated randomly; 2 studies because platelet concentrate was not the only difference between test and control group; 1 study because the full text was unretrievable; 1 study because it was not pertinent with the aims of the review; 1 study because some patients had multiple extracted teeth considered in the test and control group; and other 6 studies due to a too short follow-up. Finally, a total of 6 randomised controlled trials were included.

One article reported of a hybrid split-mouth/parallel study design in which 20 patients needing a single tooth extraction were randomly assigned to either the test or the control group, while in three additional patients multiple extractions were performed in different mouth regions so that plasma rich in growth factors (PRGF) was used in one area but not in any other. Therefore these three patients were excluded from the analysis and only the parallel branch of the study was considered.

The main characteristics of the included studies and the outcome measures are summarised in Table 1 and Table 2.

A total of 199 teeth in 156 patients were included in this review. One hundred teeth belonged to the test group and 99 to the control group. Four RCTs

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<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>Study design</th>
<th>Study setting</th>
<th>Sponsored study</th>
<th>Country</th>
<th>No. patients</th>
<th>Mean age (range), y</th>
<th>No. teeth</th>
<th>Intervention</th>
<th>FU, weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anitua, 1999</td>
<td>RCT (pa)</td>
<td>PrC NR</td>
<td>Spain</td>
<td>20</td>
<td>41.5 (35–55)</td>
<td>10</td>
<td>Test 10 Ctr 10</td>
<td>PRGF ± ABG none ± ABG</td>
<td>10 to 16</td>
</tr>
<tr>
<td>Alissa et al, 2010</td>
<td>RCT (pa)</td>
<td>Univ no</td>
<td>UK</td>
<td>23</td>
<td>30.5 (20–52)</td>
<td>15</td>
<td>Test 14 Ctr 14</td>
<td>PRP none</td>
<td>12</td>
</tr>
<tr>
<td>Ogundipe et al, 2011</td>
<td>RCT (pa)</td>
<td>Univ NR</td>
<td>Nigeria</td>
<td>60</td>
<td>24.7 (19–35)</td>
<td>30</td>
<td>Test 30 Ctr 30</td>
<td>PRP none</td>
<td>16</td>
</tr>
<tr>
<td>Célio-Mariano et al, 2012</td>
<td>RCT (sm)</td>
<td>Univ NR</td>
<td>Brazil</td>
<td>15</td>
<td>NR (18–22)</td>
<td>15</td>
<td>Test 15 Ctr 15</td>
<td>PRP none</td>
<td>6 mo</td>
</tr>
<tr>
<td>Kutuk et al, 2012</td>
<td>RCT (pa)</td>
<td>Univ pu</td>
<td>USA</td>
<td>16</td>
<td>52 (19–75)</td>
<td>8</td>
<td>Test 8 Ctr 8</td>
<td>PRP + MGCSH collagen</td>
<td>12</td>
</tr>
<tr>
<td>Girish Rao et al, 2013</td>
<td>RCT (sm)</td>
<td>Univ pu</td>
<td>India</td>
<td>22</td>
<td>NR</td>
<td>22</td>
<td>Test 22 Ctr 22</td>
<td>PRF none</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

Ctr = control; PRGF = plasma rich in growth factors; PRP = platelet-rich plasma; ABG = autogenous bone; MGCSH = medical-grade calcium sulfate hemihydrate; FU = follow-up; y = years; NR = not reported; PrC = Private Centre; Univ = University; pu = public sponsor
Table 2  Type of extraction and outcome variables of the included studies.

<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>Tooth type / reason for extraction</th>
<th>Outcome variables</th>
<th>Evaluation methods</th>
<th>Effect of platelet concentrate as reported in the study</th>
</tr>
</thead>
</table>
| Anitua, 1999<sup>43</sup> | Various tooth types / un treatable tooth with vertical fracture or severe periodontal disease | Soft tissue healing | – Clinical assessment  
– Histological analysis  
– Histomorphometric analysis | In PRGF group better epithelialisation, more mature bone and better organised trabeculae than control group (no quantitative evaluation provided) |
| Alissa et al, 2010<sup>44</sup> | Various tooth types / mostly caries (60.9%) and endodontic failure (21.7%) | Incidence of complications | – VAS for pain evaluation; 1–week questionnaire for swelling, bruising, bleeding, bad taste, food stagnation, satisfaction, analgesics taken  
– Socket complications: alveolar osteitis, infection, inflammation  
– Soft tissue healing index of Landry et al<sup>23</sup>  
– Radiographical analysis (periapical radiographs)  
– Histomorphometric analysis | In PRP group less pain & analgesic consumption in the first 2–3 days ($P = 0.02$ to $0.04$), borderline less complications ($P = 0.06$) and improved hard ($P = 0.01$) and soft tissue healing ($P = 0.03$) than control group |
| Ogundipe et al, 2011<sup>45</sup> | Mandibular third molars / impaction | Post–op quality of life | – VAS for pain evaluation, difference in facial swelling and mouth opening  
– Radiographical evaluation of bone healing (mod. method used by Kel ley et al<sup>49</sup>) | In PRP group less pain ($P < 0.05$), swelling and trismus (NSD); enhanced and faster bone healing (NSD) than control group |
| Célio–Mariano et al, 2012<sup>46</sup> | Mandibular third molars / impaction | Hard tissue healing | Radiographic bone density (periapical radiography) | In PRP group accelerated alveolar bone formation than control group ($P <0.01$) until 3rd month, NSD at 6th month |
| Kutkut et al, 2012<sup>47</sup> | Maxillary central and lateral incisors, maxillary canines, maxillary and mandibular premolars | Soft tissue healing | – Clinical assessment of mesial, distal, buccal, lingual changes  
– Radiographical assessment of bone density in the extraction site and mesial and distal bone resorption  
– Vertical and horizontal socket dimensions measured on casts made from alginate impression at baseline and at 3 months follow–up, using a 20 mm implant spacer probe  
– Histomorphometric analysis of trephined samples taken at 3 months | In PRP group limited bone resorption after tooth extraction (NSD); higher vital bone % ($P <0.05$); faster soft tissue closure (not quantified) than control group |
| Girish Rao et al, 2013<sup>48</sup> | Mandibular third molars / impaction | Hard tissue healing | Radiographical assessment of optical density within the socket (RVG, Radio Visio–Graphic Analysis) | In PRF group non significantly higher mean pixels at all time intervals than control group |

CT = computerised tomography; VAS = Visual Analogue Scale; NSD = not significantly different

had a parallel design and two RCTs a split-mouth design. In all studies there was a fairly balanced ratio between test and control cases.

Methods for the concentrate preparation adopted in the different studies are detailed in Table 3. There was a great heterogeneity in the protocol for preparing the platelet concentrates, in the type of platelet concentrate used, and there was a relative lack of information about the actual increase of platelet concentration after the centrifugation process.

#### Risk of bias assessment
Risk of bias assessment results are presented in Table 4. Only one study was classified at low risk of bias<sup>44</sup>, two at medium risk<sup>43,45</sup>, and three at high risk of bias<sup>46–48</sup>. 

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Table 3  Methods for platelet concentrates preparation.

<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>Centrifugation system, manufacturer</th>
<th>Volume of blood drawn, ml</th>
<th>Anticoagulant solution</th>
<th>Centrifugation parameters: No.; speed; time</th>
<th>Increase of platelet concentration from baseline</th>
<th>Activator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anitua, 199943</td>
<td>PRGF System, BTI Biotechnology Institute, Vitoria, Alava, Spain</td>
<td>10–20</td>
<td>10% trisodium citrate</td>
<td>1×; 160 g; 6 min</td>
<td>2–3 fold</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Alissa et al, 20144</td>
<td>– PCGSTM II, 3i Implant Innovations, Palm Beach Gardens, Florida, USA – Bench-top centrifuge (IEC Model i-703A, International Equipment Company, Needham Heights, MA, USA)</td>
<td>27</td>
<td>Citrate dextrose</td>
<td>1×; 3200 rpm; 12 min</td>
<td>NR</td>
<td>Autologous thrombin</td>
</tr>
<tr>
<td>Ogundipe et al, 201145</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td>NR; NR; NR</td>
<td>NR</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Célio-Mariano et al, 201246</td>
<td>NR</td>
<td>25</td>
<td>3.2% trisodium citrate</td>
<td>1×; 160 g; 20 min + 1×; 400 g; 15 min</td>
<td>3–5 fold</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Kutkut et al, 201247</td>
<td>NR</td>
<td>5</td>
<td>10% trisodium citrate</td>
<td>NR; NR; 10 min</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Girish Rao et al, 201348</td>
<td>NR</td>
<td>9</td>
<td>Acidulated citrate dextrose</td>
<td>1×; 360–400 rpm; 20 min</td>
<td>up to 4 fold</td>
<td>Calcium gluconate</td>
</tr>
</tbody>
</table>

min = minutes; NR = not reported; rpm = round per minute

Table 4  Quality assessment of the included studies.

<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>Study type</th>
<th>Randomisation method</th>
<th>Concealed allocation of treatment</th>
<th>Sample size calculation</th>
<th>Completeness of information on dropouts</th>
<th>Definition of inclusion / exclusion criteria</th>
<th>Comparability of groups at entry</th>
<th>Calibration / blinding of assessors</th>
<th>Blinding of patients</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anitua, 199943</td>
<td>parallel</td>
<td>a</td>
<td>u</td>
<td>i</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>NA</td>
<td>M</td>
</tr>
<tr>
<td>Alissa et al, 201044</td>
<td>parallel</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>NA</td>
<td>L</td>
</tr>
<tr>
<td>Ogundipe et al, 201145</td>
<td>parallel</td>
<td>a</td>
<td>a</td>
<td>i</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>NA</td>
<td>M</td>
</tr>
<tr>
<td>Célio-Mariano et al, 201246</td>
<td>split-mouth</td>
<td>u</td>
<td>u</td>
<td>i</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>i</td>
<td>H</td>
</tr>
<tr>
<td>Kutkut et al, 201247</td>
<td>parallel</td>
<td>a</td>
<td>i</td>
<td>i</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>u</td>
<td>i</td>
<td>NA</td>
</tr>
<tr>
<td>Girish Rao et al, 201348</td>
<td>split-mouth</td>
<td>u</td>
<td>u</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>u</td>
<td>H</td>
<td></td>
</tr>
</tbody>
</table>

a = adequate; i = inadequate; u = unclear; NA = not applicable; H = high; M = medium; L = low

Primary outcome measures

Complications/adverse events

Alissa et al44 evaluated socket complications on 21 out of 27 patients. Healing was uneventful in 18 patients with 24 extraction sites, while 3 patients with three extraction sites developed 2 alveolar osteitis and 1 acutely inflamed alveolus, all in the control group44. The difference between groups was borderline significant (P = 0.06). Ogundipe et al45 declared they recorded intraoperative complications but did not report them in the results. The authors were contacted to obtain such information but they provided no answer.

None of the other studies accounted for intrasurgical or postsurgical complications.
Quality of life

Postoperative quality of life was evaluated in one study using a modified health-related quality of life questionnaire that assessed patient perception of recovery in four areas: pain; oral function; general activity; and other postoperative symptoms. The study reported significant positive effects of platelet concentrate only for the presence of bad taste or bad smell in the mouth.

Pain

Pain levels in the first week after surgery were assessed using a Visual Analogue Scale (VAS) in two studies. These studies reported a significantly lower pain level in the test group in the first postoperative week, indicating a beneficial effect of platelet concentrates in reducing pain perception postoperatively. However, due to the non-homogeneity of data provided that prevented comparison among these two studies, no meta-analysis could be performed for pain assessment. In fact, one study presented VAS data using box-and-whiskers plots, while the other used mean values but standard deviations were not provided. We asked authors to provide missing information but received no answer. None of the other included studies evaluated postoperative pain or quality of life.

Secondary outcome measures

Hard tissue healing

Different techniques and methods were used to evaluate hard tissue healing. Histological analysis was performed in three studies, all of which reported a better bone quality in biopsies retrieved from sites treated with platelet concentrates, as compared to control sites. The study reported significant positive effects of platelet concentrate only for the presence of bad taste or bad smell in the mouth.

A meta-analysis of the studies presenting histomorphometric evaluation of bone formation. Outcome: percentage of bone tissue.

![Fig 2](image-url)
to control group” but did not quantify such a statement nor provide statistical evaluation47. In the same study, linear measurement of alveolar crest width and height was performed on casts made from alginate impression at baseline and at 3 months’ follow-up, using a 20 mm implant spacer probe, showing no significant difference between groups47.

Girish Rao et al48 radiographically evaluated optical density within the socket using a software-mediated Radio-Visio-Graphic (RVG) analysis that allowed measurement of the number of pixels in the residual cavity, which was considered proportional to the size of the defect48. The results did not reveal a statistically significant higher mean in the test group as compared to control group, at all time intervals.

Due to differences in assessment methodology, no meta-analysis could be done among these studies for radiographic outcomes.

**Soft tissue healing**

Three studies reported data about soft tissue healing43,44,47. Anitua et al43 evaluated epithelialisation clinically and histologically, and connective tissue formation histologically at the defect site.

Alissa et al44 used the healing index described by Landry and coworkers23, assessing healing trough parameters as tissue colour, epithelialisation of wound margins, bleeding on palpation, granulation and suppuration.

Kutkut et al47 assessed soft tissue appearance and the presence of infection and symptoms, reporting no significant effect of platelet concentrates on soft tissues47. Conversely, the other two articles found a significant positive effect of the use of platelet concentrate43,44.

Given the heterogeneity among parameters, no meta-analysis was done to evaluate the effect of platelet concentrates on soft tissue healing after tooth extraction.

**Discussion**

The present systematic review aimed at evaluating the efficacy of a platelet-rich preparation in enhancing the healing of an alveolar socket after tooth extraction.

With respect to a previous systematic review, the present study reports updated results confirming, in general, the uncertainty regarding the actual effect of platelet concentrates on socket healing50. In fact, though most of the included studies reported a positive effect of platelet concentrates, major limitations have to be considered; firstly, the heterogeneity of the outcome variables, of the method(s) chosen for socket healing assessment. No meta-analysis could be performed for most of the outcome measures, for which only a qualitative description was provided. Among the most important confounding factors, there is the indication for extraction, which can have a profound effect on the healing pattern of the alveolar socket5,14. Due to the heterogeneity of outcome variables among the included studies, the effect of such a factor could not be explored. None of the included studies reported data about socket healing for infected teeth. Only the study by Girish-Rao et al48 excluded “patients with dental infection of bone, active gingivitis or periodontitis”. Although this variable would have increased the heterogeneity of the studies, it would be interesting to investigate the effect of platelet concentrates in such a situation, which is rather common when performing tooth extraction. In a histomorphometric study in humans, Ahn and Shin reported that after tooth extraction, sites previously affected by advanced periodontal disease tend to regenerate more slowly than disease-free sockets51. The latter showed new bone formation exceeding 50% of the total tissue after 8 weeks, while the diseased sockets took about 16 weeks to achieve the same outcome51. While a previous study has shown positive outcomes when using platelet concentrates for post-extraction implants in infected sockets52, no evidence is still available regarding infected socket healing. Further comparative studies are needed to understand if platelet concentrates are able to accelerate the healing process in infected sockets.

Another factor that should be considered is the method of preparation of the platelet concentrates. In many included studies, the preparation methods were not described in detail (see Table 3). Moreover, such methods were rather heterogeneous, leading to platelet-rich preparations with different characteristics and possible biological activities. For exam-
ple, while PRGF contains a negligible amount of leukocytes53, with the specific aim of reducing the concentration of pro-inflammatory cytokines17,43,53, other preparations like PRP or PRF contain a medium to high concentration of these cells16,18. It still has to be made clear if the presence of leukocytes may represent a true benefit for the biological activity of platelet concentrates.

It also has to be considered that only one study was judged at low risk of bias44 while most of the studies presented a medium43,45 or high46-48 risk of bias due to flaws in the experimental design. This aspect should be considered in further research in order to standardise the study protocol, reducing the risk of confounding factors and biases.

With regard to the association between platelet concentrates and the use of graft materials for filling the socket, the present review could not prove any type of effect. In fact, only in one study, the post-extraction sockets were filled with autogenous bone in both groups43. This study found better hard and soft tissue healing in the test group, in which PRGF was mixed with autogenous bone. In another study in the test group, MGCSH (medical-grade calcium sulphate hemihydrate) was combined with PRP in the test group47. These few reports did not allow any conclusion to be drawn about the effect of platelet concentrates combined with autogenous bone or bone substitutes, nor to make comparisons with previous studies evaluating graft materials in socket healing14,54.

The effect of the use of platelet-rich preparations on bone healing appeared to be heterogeneous. In some studies with histologic and histomorphometric evaluation, it seemed that PRP could produce a wider and earlier organisation of bone trabeculae and greater bone volume percentage as compared to the control43,44,47. However, other authors using different techniques had not found any significant difference between control and test groups48. Results from different types of radiographic analysis provided generally better outcomes for the test groups although not always achieving significance44-46. Other authors investigated the role of platelet-derived growth factors in the bone healing process55. Even though most growth factors are involved in different steps of bone healing, representing signalling molecules that support the formation of a fibrin matrix, and promote proliferation of osteoblasts and osteoid formation, the evidence for a relevant clinical effect is still poor. For these reasons, the efficacy of platelet concentrate in enhancing bone healing should not be considered supported by sufficient literature as also stated in a previous review55. On the contrary, a positive effect on soft tissue healing has been observed in most of the included studies, even though it was not systematically assessed. Moreover, as found in other comparative studies dealing with various surgical procedures56-59, a beneficial effect of platelet concentrates on postoperative quality of life could be evidenced, as a consequence of the enhanced soft tissue healing42,44,45.

Finally, it was observed that the content of platelet alpha granules might have a bactericidal effect, mediated by molecules called thrombocidines60. This aspect was confirmed by recent in vitro studies on the microbicidal effects of PRP on various oral bacterial species61-63 as well as against C albicans63. Such properties of the platelets could represent an important tool in the fight against postoperative infections that would deserve further investigation.

**Conclusions**

Based on the results of the present systematic review, the following conclusions can be made:

- A positive effect of platelet concentrates in accelerating bone healing is only suggested but could not be clearly demonstrated by radiographic assessment.
- There is limited histological evidence of better bone quality as well as histomorphometric evidence of greater bone formation in the first 3 months after tooth extraction, when using platelet concentrates.
- There is suggestion (but not clear evidence) of the beneficial effect of platelet concentrates on soft tissue healing after tooth extraction.
- There is limited evidence that the use of platelet concentrates is associated with the reduction of patients’ pain perception in the first postoperative week.
References


