Effects of platelet-rich plasma in association with bone grafts in maxillary sinus augmentation: a systematic review and meta-analysis

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Abstract. This systematic review evaluated the effect on bone formation and implant survival of combining platelet-rich plasma (PRP) with bone grafts in maxillary augmentation. A comprehensive review of articles listed in the PubMed/MEDLINE, Embase, and Cochrane Library databases covering the period January 2000 to January 2015 was performed. The meta-analysis was based on bone formation for which the mean difference (MD, in millimetres) was calculated. Implant survival was assessed as a dichotomous outcome and evaluated using the risk ratio (RR) with 95% confidence interval (CI). The search identified 3303 references. After inclusion and exclusion criteria were applied, 17 studies were selected for qualitative analysis and 13 for quantitative analysis. A total of 369 patients (mean age 51.67 years) and 621 maxillary sinus augmentations were evaluated. After the data analysis, additional analyses were performed of the implant stability quotient, marginal bone loss, and alveolar bone height measured by MD. The results showed no significant difference in implant stability ($P = 0.32$, MD 1.00, 95% CI −0.98 to 2.98), marginal bone loss ($P = 0.31$, MD 0.06, 95% CI −0.05 to 0.16), alveolar bone height ($P = 0.10$, MD −0.72, 95% CI −1.59 to 0.14), implant survival ($P = 0.22$, RR 1.95, 95% CI 0.67–5.69), or bone formation ($P = 0.81$, MD −0.63, 95% CI −5.91 to 4.65). In conclusion, the meta-analysis indicates no influence of PRP with bone graft on bone formation and implant survival in maxillary sinus augmentation.

Key words: platelet-rich plasma; dental implants; sinus floor augmentation; meta-analysis.

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The amount and quality of bone tissue are considered crucial factors when planning implant-supported rehabilitations. The posterior maxilla is not considered the most favorable site for implant placement due to the low bone quality and the fact that pneumatization of the sinus limits the installation of implants or decreases their long-term survival rate, increasing the difficulty of rehabilitation. An alternative to counter these problems is the achievement of a sinus lift associated with a graft, thereby increasing the volume of bone to a level sufficient for implant placement, since longer implants show higher success rates, particularly in this area of poor bone density.

Regenerative treatment using platelet-rich plasma (PRP) may be indicated in association with grafting, since this combination may improve the healing process of bone tissue; this is due to the high quantity of blood-associated growth factors that are found in PRP. Furthermore, the use of PRP improves graft handling, stimulates soft tissue healing, and reduces patient discomfort. Some studies seeking to prove the efficacy of platelet concentrations in association with grafting have published favorable results. On the other hand, other studies have reported no benefit of PRP in relation to bone formation.

Thus, there is no consensus regarding the benefits of the use of PRP in association with grafting after a maxillary sinus lift. It is therefore necessary to perform a careful analysis of clinical studies through a systematic review and meta-analysis to assess bone formation in patients. The null hypotheses of this study were: (1) The use of PRP in association with grafting has no effect on bone formation; (2) The use of PRP in association with grafting has no effect on implant survival rates.

Materials and methods

Registry protocol

This systematic review was structured following the PRISMA checklist and was performed in accordance with models proposed in the literature. Moreover, the methods used in this systematic review were registered with PROPERO, an international prospective register of systematic reviews (CRD42014015648).

Research strategy and information sources

The article selection was performed by two independent reviewers (CAAL and CCM) according to the inclusion and exclusion criteria. Clinical studies that compared the use of PRP with grafting to bone grafting alone were sought. After performing searches in the selected databases, a careful analysis was done to identify any cases of disagreement between the authors. Studies were selected on the basis of their titles and abstracts and assessed according to the inclusion and exclusion criteria. The reviewers analyzed and discussed the articles until consensus was reached; remaining disagreements were resolved by discussion with a third reviewer (EPP).


Criteria for the selection of studies

Article selection in the database search was initially performed by means of an analysis of titles and abstracts. After the first selection step, the full content of the articles was analyzed against the inclusion and exclusion criteria. Thus, the PICO question recommended in the PRISMA statement was delimited: (1) population: patients selected for dental implant surgery; (2) intervention: patients treated with PRP and sinus augmentation with bone grafting; (3) comparison: patients treated with bone grafting alone; (4) outcomes: to analyze the influence of PRP in association with bone grafting when compared with bone grafting alone on bone formation and the implant survival rate. The PICO question was structured as follows: Does PRP improve the properties of the graft in terms of bone formation and the rates of implant survival after maxillary sinus lift?

Inclusion and exclusion criteria

The inclusion criteria used in this study were the following: randomized controlled trial (RCT) or prospective study; articles published in the English language. The exclusion criteria were the following: in vitro studies, animal studies, reviews, retrospective studies, and studies evaluating the association of PRP but without a comparison between graft only and graft with PRP.

Quality assessment

The quality of selected studies was evaluated using the PRISMA criteria by means of 27 questions established by Moher et al. Therefore, these studies were separated into categories of RCTs and prospective studies.

The methodological quality of all studies included was graded using the five-point Jadad scale (Table 1). This widely used scale evaluates the reporting of studies based on criteria related to the method of randomization, adequacy of blinding, and the completeness of follow-up. The minimum and maximum scores for the studies included were 1 and 5, respectively. Articles with a score of 3–5 were classified as high quality, and those with a score of 0–2 were classified as low quality.

An inter-examiner test (kappa) was performed to evaluate the selection of titles and abstracts, with the following final values of concordance for the databases: PubMed/MEDLINE, kappa = 0.81; Embase, kappa = 0.88; Cochrane, kappa = 1.

Data analysis

The software Reviewer Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to perform the meta-analysis; values were considered significant when P < 0.05. Bone formation, implant stability, marginal bone loss, and alveolar bone height were assessed as continuous outcome variables by inverse variance (IV) method and recorded as the mean difference (MD) with 95% confidence interval (CI). The implant survival rate was assessed as a dichotomous outcome by Mantel–Haenszel method and recorded as the risk ratio (RR) with 95% CI, with the weight contribution of each study.
Results

General outcomes and selection

Details of the search strategy are illustrated in Fig. 1. The searches performed in the databases retrieved a total of 3330 articles: 2836 from PubMed/MEDLINE, 460 from Embase, and seven from the Cochrane Library. After duplicate references had been removed, 1013 studies remained for the data synthesis. Following a detailed review of titles and abstracts, 30 studies were eligible for analysis, presenting a high level of agreement between reviewers according to the kappa value.20 Thirteen studies were excluded after full text analysis, for the following reasons: absence of a comparator group,23,24,26 comparison of another bone graft type,27 cases series or report,28,29 and insufficient data.30

Studies were evaluated regarding feasibility for data synthesis (qualitative and quantitative); not all studies were selected for the quantitative analysis due to some missing data. Thus, 17 studies3,6,8,15,33–44 were selected for the qualitative analysis (Table 2) and 13 studies3,6,8,15,33–35,37,38,40–43 for the quantitative analysis (Table 3). Of the 17 studies selected, 12 were RCTs and five were prospective studies. These included a total of 369 patients and 621 maxillary bilateral or unilateral sinus lifting procedures. The mean age of participants in the 12 studies reporting patient age was 51.67 years.

For this systematic review, only studies comparing graft in association with PRP and graft alone were included. Most studies reported the use of autogenous bone grafting from the iliac crest,7,8,15,36,38–40,42,43 but autogenous bone from intraoral sites, such as the symphysis and/or external oblique ridge2 and the mandibular ascending ramus27 was also used. Some studies used heterogeneous materials such as bovine-derived grafts,3,33,35 algae-derived hydroxyapatite,26 freeze-dried bone allograft,44 and b-tricalcium phosphate.44

Effect of PRP on bone formation

Through qualitative analysis of the 12 studies evaluating the influence of PRP in association with bone grafting by histomorphometry, no consensus was found regarding the use of PRP in bone formation in maxillary sinus lifting.3,6,7,15,34–36,38,40–42,44 Some studies reported that the use of PRP may increase or accelerate the process of bone formation,7,8,15,33–35,37,40,41,44 while others found no benefit in the use of PRP compared with bone grafting only.3,6,36,38,39,42,43

The quantitative analysis was performed with nine studies.6,15,34,35,38,40–42 No significant difference was observed for the use of PRP with bone graft compared to graft alone on bone formation (P = 0.81, MD = 0.63, 95% CI = −5.91 to 4.65) (Fig. 2).

Effect of PRP on implant survival

Six studies3,34,35,39,42,43 evaluated the difference in implant survival rates after sinus lift by analyzing the influence of PRP in association with grafting. In the qualitative analysis, only two studies showed higher survival rates with the use of PRP,35,43 while the other studies showed no significant difference3,34,39,42. Two studies34,39 were not included in the quantitative analysis because they did not report the number of implants for each group evaluated. In the statistical analysis with the remaining four studies,3,35,42,43 no significant difference for the use of PRP with bone graft compared to bone graft alone was observed for the survival rate of implants (P = 0.22, RR 1.95, 95% CI 0.67 to 5.69) (Fig. 3).

Effect of PRP on implant stability

The stability of implants was analyzed by studies comparing the implant stability quotient (ISQ)3,6 and bone-to-implant contact (BIC).15,37 In both cases, the analyses showed no differences for PRP in association with bone grafting compared to grafting alone, except in one study,37 which presented higher values for the group with PRP.

In the quantitative analysis, only the studies reporting the ISQ were used, and no statistical difference was found between the groups (P = 0.32, MD 1.00, 95% CI −0.98 to 2.98) (Fig. 4A).

Effect of PRP on bone properties

The marginal bone loss after 1 year of follow-up3,37,43 and the alveolar bone height3,35 were each compared in two studies; no statistically significant difference was found for marginal bone loss (P = 0.31, MD 0.06, 95% CI −0.05 to 0.16) (Fig. 4B) or alveolar bone height (P = 0.10, MD −0.72, 95% CI −1.59 to 0.14) (Fig. 4C).

Discussion

This systematic review included studies that assessed the influence of PRP in association with bone grafting after a sinus lift. Not all of the studies selected for the
A systematic review was used in the meta-analysis. Four studies selected for the qualitative analysis were not used in the quantitative analysis, as they reported insufficient data and this could have compromised the statistical analysis.

Regarding bone formation, the analyses compared the association of PRP independent of the type of bone graft used. Thus, the index referred to was bone formation, as used in previous studies. In this way, only the values for bone or vital bone were used for the bone substitutes, because the existence of bone grafts and newly generated bone were distinguished.

The results obtained from the meta-analysis verified that the first hypothesis of this study should be accepted: no significant impact on bone formation in the sinus lift was observed in response to PRP in association with bone grafting. These results are consistent with those of previous studies that have shown inconclusive results regarding the use of PRP.

The literature cites conflicting reports on the benefits of PRP used in sinus augmentation. PRP has been shown to be beneficial early in regeneration and to possess regenerative potential when used with autologous bone; it has also been shown to improve the osteoconductive properties, increasing the volume of new bone formed. However, this advantage of platelet concentrates in accelerating graft healing in maxillary sinus augmentation procedures could not be shown in one study, and in another, the recorded effects of PRP were no longer apparent after an interval longer than 6 months.

Bae et al. performed a meta-analysis to assess the influence of PRP in association with bone grafting and showed benefits to bone formation after a maxillary sinus lift, which conflicts with the results obtained in the present study. This difference is probably related to the fact that the former analysis included a smaller number of studies: only eight.

Furthermore, several factors may influence the role of PRP in bone grafting as a successful regenerative therapy, including variations in manufacturing methods and differences in concentration. Studies have indicated that a low concentration...
Table 2. Characteristics of the studies included.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Control group</th>
<th>Test group</th>
<th>Age, years, mean</th>
<th>Patients, n</th>
<th>Sinuses augmented, n</th>
<th>Implants, n</th>
<th>Follow-up, months</th>
<th>Effect of PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khairy et al.</td>
<td>RCT</td>
<td>Autogenous bone</td>
<td>Autogenous bone + PRP</td>
<td>38</td>
<td>15</td>
<td>15</td>
<td>NR</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>Yilmaz et al.</td>
<td>RCT</td>
<td>Bovine-derived xenograft</td>
<td>Bovine-derived xenograft + PRP</td>
<td>56.9</td>
<td>10 (SM)</td>
<td>20</td>
<td>NR</td>
<td>8</td>
<td>Positive</td>
</tr>
<tr>
<td>Poeschl et al.</td>
<td>Prospective</td>
<td>Algae-derived HA (AlgOss/C Graft/Algipore)</td>
<td>Graft/Algipore + PRP</td>
<td>55.7</td>
<td>25</td>
<td>31</td>
<td>28</td>
<td>7</td>
<td>Positive</td>
</tr>
<tr>
<td>Stenport et al.</td>
<td>Prospective</td>
<td>Autogenous bone</td>
<td>Autogenous bone + PRP</td>
<td>58</td>
<td>11</td>
<td>22</td>
<td>NR</td>
<td>3</td>
<td>Positive</td>
</tr>
<tr>
<td>Cabañes et al.</td>
<td>RCT</td>
<td>Autogenous bone</td>
<td>Autogenous bone + PRP</td>
<td>36</td>
<td>16</td>
<td>16</td>
<td>85</td>
<td>8</td>
<td>Positive</td>
</tr>
<tr>
<td>Torres et al.</td>
<td>RCT</td>
<td>Allogenic bovine bone</td>
<td>Allogenic bovine bone + PRP</td>
<td>NR</td>
<td>87</td>
<td>286</td>
<td>24</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Aimer et al.</td>
<td>RCT</td>
<td>Autogenous bone</td>
<td>Autogenous bone + PRP</td>
<td>58.5</td>
<td>4</td>
<td>8</td>
<td>NR</td>
<td>60</td>
<td>Positive</td>
</tr>
<tr>
<td>Schaaf et al.</td>
<td>Prospective</td>
<td>Autogenous bone</td>
<td>Autogenous bone + PRP</td>
<td>55</td>
<td>11</td>
<td>22</td>
<td>NR</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Kassolis and Reynolds</td>
<td>RCT</td>
<td>Freeze-dried bone allograft + membrane</td>
<td>Freeze-dried bone allograft + PRP</td>
<td>NR</td>
<td>10</td>
<td>20</td>
<td>NR</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Raghoobar et al.</td>
<td>RCT</td>
<td>Autogenous bone</td>
<td>Autogenous bone + PRP</td>
<td>58.4</td>
<td>5</td>
<td>10</td>
<td>30</td>
<td>20.2</td>
<td>None</td>
</tr>
<tr>
<td>Thor et al.</td>
<td>Prospective</td>
<td>Autogenous bone</td>
<td>Autogenous bone + PRP</td>
<td>58</td>
<td>19</td>
<td>38</td>
<td>152</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>Wiltfang et al.</td>
<td>RCT</td>
<td>β-TCP</td>
<td>β-TCP + PRP</td>
<td>46</td>
<td>39</td>
<td>45</td>
<td>NR</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

HA, hydroxyapatite; NR, not reported; PRP, platelet-rich plasma; RCT, randomized clinical trial; SM, split mouth design; β-TCP, β-tricalcium phosphate.

*Patients’ maxillary sinus grafted.
Table 3. Quantitative analysis of outcomes evaluated for selected studies (n = 13).

<table>
<thead>
<tr>
<th>Author</th>
<th>Outcomes evaluated</th>
<th>Control group (Only bone graft)</th>
<th>Test group (PRP + bone graft)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khairy et al. 6</td>
<td>% Bone formation</td>
<td>39.5% (± 7.4)</td>
<td>27.3% (± 6.3)</td>
</tr>
<tr>
<td>Yilmaz et al. 33</td>
<td>Alveolar bone height</td>
<td>11.33 mm (± 1.71)</td>
<td>11.34 mm (± 1.84)</td>
</tr>
<tr>
<td>Poeschl et al. 34</td>
<td>% Bone formation</td>
<td>22.3% (± 12.3)</td>
<td>29.0% (± 13.2)</td>
</tr>
<tr>
<td></td>
<td>Implant survival</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cabbar et al. 3</td>
<td>Height of residual crest</td>
<td>5.6 mm (± 1.4)</td>
<td>4.7 mm (± 1.3)</td>
</tr>
<tr>
<td></td>
<td>% Bone formation</td>
<td>15.8% (± 7.5)</td>
<td>16.1% (± 3.8)</td>
</tr>
<tr>
<td></td>
<td>ISQ</td>
<td>75.4 (± 6.4)</td>
<td>74.4 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>Implant survival</td>
<td>14 implants</td>
<td>1 implant lost</td>
</tr>
<tr>
<td>Badr et al. 8</td>
<td>ISQ</td>
<td>61 (± 2.6)</td>
<td>60 (± 2.4)</td>
</tr>
<tr>
<td>Torres et al. 35</td>
<td>Implant survival</td>
<td>129 implants</td>
<td>153 implants</td>
</tr>
<tr>
<td>Aimetti et al. 37</td>
<td>Bone-to-implant contact</td>
<td>20.5% (± 5.57)</td>
<td>46.75% (± 13.60)</td>
</tr>
<tr>
<td>Schaaef et al. 38</td>
<td>% Bone formation</td>
<td>35.3% (± 10.7)</td>
<td>33.3% (± 11.7)</td>
</tr>
<tr>
<td>Conso1 et al. 40</td>
<td>Bone density bone (HU)</td>
<td>451.38 (± 62.81)</td>
<td>709.23 (± 69.99)</td>
</tr>
<tr>
<td>Thor et al. 15</td>
<td>% Bone formation</td>
<td>29.2% (± 4)</td>
<td>39.3% (± 5.7)</td>
</tr>
<tr>
<td>Kassolis and Reynolds 41</td>
<td>% Bone formation</td>
<td>13% (± 6)</td>
<td>14% (± 7)</td>
</tr>
<tr>
<td>Raghoeb et al. 42</td>
<td>Marginal bone loss</td>
<td>1.03 mm (± 0.05)</td>
<td>0.98 mm (± 0.10)</td>
</tr>
<tr>
<td>Thor et al. 43</td>
<td>Marginal bone loss</td>
<td>3.9 mm (± 0.8)</td>
<td>3.7 mm (± 0.9)</td>
</tr>
<tr>
<td></td>
<td>Implant survival</td>
<td>152 implants</td>
<td>152 implants</td>
</tr>
</tbody>
</table>

HU, Hounsfield units; ISQ, implant stability quotient; NR, not reported.

could have contributed to the results obtained. Future studies assessing these parameters are required in order to obtain more conclusive results.

The most common bone graft used in the studies included in this review was autogenous bone. This may have influenced the results, since the autogenous bone graft has long been considered the gold standard in the sinus area. 17,21,18 It is considered the gold standard graft, 13 because of factors such as osteogenic capacity, biocompatibility, low immunogenicity, and accelerated healing. 39,60 All studies using PRP in association with biomaterials 8,33,35,41,44 observed positive effects of PRP, except one. 3 Despite the fact that these materials have higher porosity, delay healing, and even cause foreign body reactions, 3,16,62 these grafts present high success rates in maxillary sinus lift, regardless of the material used, 63 mainly when associated with PRP according to the studies selected.

Another factor, that can influence the results, is the donor site for the bone graft. The donor site that was most prevalent in these studies was the iliac crest. 7,8,15,36,38,40,42,43 However, this site has disadvantages in terms of postoperative donor site morbidity, a longer period of recovery, pain, discomfort, and possible injuries such as iliac wing fracture or paresthesias. 34 Only two studies 6,67 used intraoral donor sites, such as the mandibular symphysis and external oblique ridge. However, bone grafts from this intraoral donor site comprise corticocancellous bone and present less osteogenic potential and a lower rate of resorption, than cancellous bone. 71 Thus, the use of small chips is recommended to accelerate resorption and to increase the contact between the bone graft and receptor site. 37,59

Although an effect on bone formation of PRP in association with grafting was not...
observed, PRP can be used to facilitate the handling of bone grafts when they are particulate, thereby improving the stability of the graft in the site after the sinus lift and reducing the postoperative discomfort of patients due to accelerated healing.9

The use of PRP has been shown to be favourable for bone regeneration in other situations in dentistry.64,65 However, this positive effect was not found when PRP was used in association with grafting for sinus augmentation. Future comparison studies are needed that use the same type of graft, taken from the same site, and with standardization of PRP preparation.

Concerning the quality of the studies selected, 12 studies showed a high level of evidence, while five studies showed a low level according to the Jadad scale.19 This could be related to difficulties in blinding the surgeon, requiring the help of an assistant to prepare the graft with or without PRP.35 However, the blinding of investigators (histological or radiographic assessments) and patients could also be used to improve the level of evidence. Five studies reported double-blinding, but only two studies reported use of the CONSORT checklist; this could be considered a limitation of the present study.

In conclusion, the current meta-analysis indicates that there is no influence of PRP in association with bone graft on bone formation and implant survival in maxillary sinus lift.

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None.

Competing interests
The authors declare that there was no conflict of interest in the elaboration of this study.

Ethical approval
Not applicable.

Patient consent
Not applicable.

References

Fig. 3. Forest plot for the event ‘implant survival’.

Fig. 4. Forest plot for the events (A) ‘implant stability quotient’, (B) ‘marginal bone loss’, and (C) ‘alveolar bone height’.


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