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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.[1] The posterior maxilla is not considered the most favourable 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 success rate, increasing the difficulty of rehabilitation.[2,3] 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,[4] since longer implants show higher success rates, particularly in this area of poor bone density.[5]

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.[6–8] Furthermore, the use of PRP improves graft handling, stimulates soft tissue healing, and reduces patient discomfort.[9] Some studies seeking to prove the efficacy of platelet concentrations in association with grafting have published favourable results.[10–13] On the other hand, other studies have reported no benefit of PRP in relation to bone formation.[8,14,15]

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[16] and was performed in accordance with models proposed in the literature.[1,17,18] Moreover, the methods used in this systematic review were registered with PROSPERO, 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).

Searches were performed in the databases PubMed/MEDLINE, Embase, and Cochrane for research studies published in English between January 2000 and 20 January 2015, using the following Keywords: (dental implant) AND (platelet-rich plasma OR platelet concentrate OR PRP and sinus augmentation OR sinus floor augmentation OR maxillary sinus lift) AND [limit to OR clinical trial OR randomized controlled trial OR comparative study OR controlled trial AND humans]. In addition, manual searches of the following journals for articles published between January 2000 and 20 January 2015 were conducted by all three reviewers: *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Clinical Periodontology*, *Journal of Oral Rehabilitation*, *Journal of Periodontology*, and *Periodontology 2000*.

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 rehabilitated with implants after maxillary sinus lift with bone grafting; (3) comparison: patients rehabilitated with implants after maxillary sinus lift with bone grafting in association with PRP compared to 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, retrospectives 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.[16] 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[19] (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.

Table 1. Quality assessment of the studies selected; Jadad scale.

Quality criteria	Khairy et al.[6]	Yilmaz et al.[33]	Poeschl et al.[34]	Stenport et al.[7]	Cabbar et al.[3]	Badr et al.[8]	Torres et al.[35]	Bettega et al.[36]	Aimetti et al.[37]	Schaaf et al.[38]	Schaaf et al.[39]	Consolo et al.[40]	Thor et al.[15]	Kassolis and Reynolds[41]	Raghoebar et al.[42]	Thor et al.[43]	Wiltfang et al.[44]
1. Was the study described as random?	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
2. Was the randomization scheme described and appropriate?	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
3. Was the study described as double-blind?	Yes	No	No	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	No	No	No
4. Was the method of double-blinding appropriate?	Yes	No	No	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	No	No	No
5. Was there a description of dropouts and withdrawals?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jadad score	5	3	1	1	1	5	5	3	3	5	3	5	1	3	3	1	3
Quality of study	High	High	Low	Low	Low	High	High	High	High	High	High	High	Low	High	High	Low	High

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 3303 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,[2,21–26] comparison of another bone graft type,[27] cases series or report,[28–31] and insufficient data.[32]

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 studies[3,6–8,15,33–44] were selected for the qualitative analysis (Table 2) and 13 studies[3,6,8,15,33–35,37,38,40–43] 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 ridge[6] and the mandibular ascending ramus[37] was also used. Some studies used heterogeneous materials such as bovine-derived grafts,[3,33,35] algae-derived hydroxyapatite,[34] freeze-dried bone allograft,[41] and β-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.[3,6,15,34,35,38,40–42] 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 studies[3,34,35,39,42,43] 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 difference.[3,34,39,42] Two studies[34,39] 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)[3,8] 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-up[37,43] and the alveolar bone height[33,35] 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

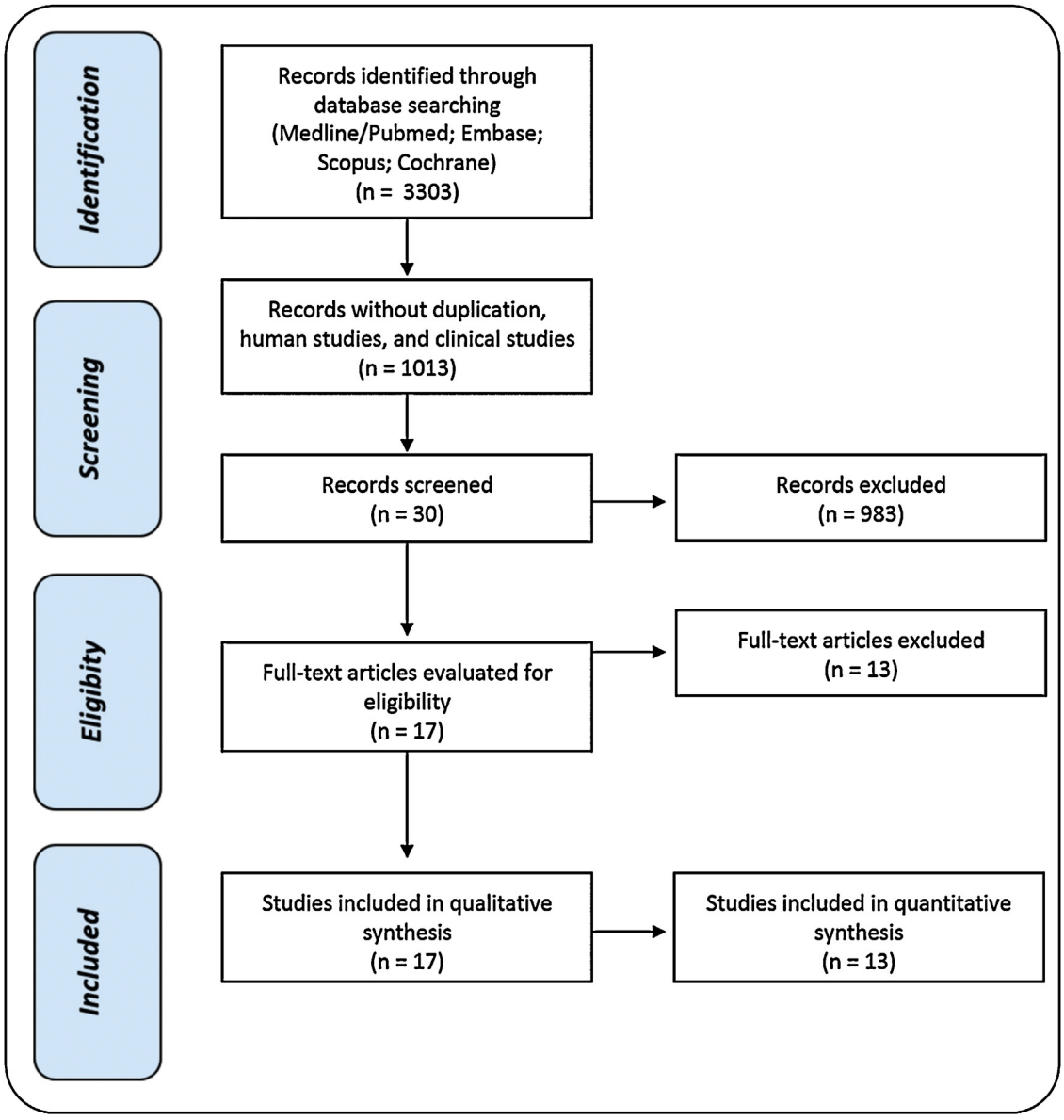

Fig. 1. Flow diagram of the literature search and results.

systematic review were used in the meta-analysis. Four studies[7,36,39,44] selected for the qualitative analysis were not used in the quantitative analysis, since 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.[45] 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.[4,46]

The literature cites conflicting reports on the benefits of PRP used in sinus augmentation. PRP has been shown to be beneficial early in regeneration[15] and to possess regenerative potential when used with autologous bone[40]; it has also been shown to improve the osteoconductive properties, increasing the volume of new bone formed.[35] However, this advantage of platelet concentrates in accelerating graft healing in maxillary sinus augmentation procedures could not be shown in one study,[9] and in another, the recorded effects of PRP were no longer apparent after an interval longer than 6 months.[40]

Bae et al.[45] 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.[43,47,48] Studies have indicated that a low concentration

Table 2. Characteristics of the studies included.

Author	Study design	Control group	Test group	Age, years, mean	Patients, *n*	Sinuses augmented, *n*	Implants, *n*	Follow-up, months	Effect of PRP
Khairy et al.[6]	RCT	Autogenous bone	Autogenous bone + PRP	38	15	15	NR	6	None
Yilmaz et al.[33]	RCT	Bovine-derived xenograft	Bovine-derived xenograft + PRP	56.9	10 (SM)	20	NR	8	Positive
Poeschl et al.[34]	Prospective	Algae-derived HA (AlgOss/C Graft/Algipore)	Algae-derived HA (AlgOss/C Graft/Algipore) + PRP	55.7	25	31	28	7	Positive
Stenport et al.[7]	Prospective	Autogenous bone	Autogenous bone + PRP	58	11	22	NR	3	Positive
Cabbar et al.[3]	Prospective	Bone xenograft bovine	Bone xenograft bovine + PRP	53.7	10	20	28	13.4	None
Badr et al.[8]	RCT	Autogenous bone	Autogenous bone + PRP	36	16[a]	16	85	NR	Positive
Torres et al.[35]	RCT	Anorganic bovine bone	Anorganic bovine bone + PRP	NR	87 5 (SM)	144 10 (SM)	286	24	Positive
Bettega et al.[36]	RCT	Autogenous bone	Autogenous bone + PRP	50.5	18	32	111	24	None
Aimetti et al.[37]	RCT	Autogenous bone	Autogenous bone + PRP	58.5	4	8	NR	60	Positive
Schaaf et al.[38]	RCT	Autogenous bone	Autogenous bone + PRP	NR	34	68	NR	NR	None
Schaaf et al.[39]	RCT	Autogenous bone	Autogenous bone + PRP	NR	34	68	245	NR	None
Consolo et al.[40]	RCT	Autogenous bone	Autogenous bone + PRP	47	16	32	NR	NR	Positive
Thor et al.[15]	Prospective	Autogenous bone	Autogenous bone + PRP	55	11	22	NR	NR	Positive
Kassolis and Reynolds[41]	RCT	Freeze-dried bone allograft + membrane	Freeze-dried bone allograft + PRP	NR	10	20	NR	NR	Positive
Raghoebar et al.[42]	RCT	Autogenous bone	Autogenous bone + PRP	58.4	5	10	30	20.2	None
Thor et al.[43]	Prospective	Autogenous bone	Autogenous bone + PRP	58	19	38	152	12	None
Wiltfang et al.[44]	RCT	β-TCP	β-TCP + PRP	46	39	45	NR	NR	Positive

HA, hydroxyapatite; NR, not reported; PRP, platelet-rich plasma; RCT, randomized clinical trial; SM, split mouth design; β-TCP, β-tricalcium phosphate.
[a] Patients' maxillary sinus grafted.

of platelets is not ideal, while high concentrations may exert inhibitory effects.[48–50] Thus, an intermediate concentration (approximately 1,000,000/ml) is recommended to promote the stimulation effect of platelets.[15,51,52]

The number of centrifugations is another important characteristic (one or two centrifugations).[35,52] One centrifugation generates a lower leucocyte count and lesser concentration of platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β),[35] and the absence of leukocytes causes proteases to be secreted that are destructive to growth factors.[53] Two centrifugations, on the other hand, causes significant differences in the method of cell separation, changing the amounts of cells (platelets and leukocytes) and the levels of growth factors in the PRP samples.[35,48–50,54,55] The variation in concentrations and numbers of centrifugations may be considered a limitation of this study, since these were not standardized for all studies.

The second study hypothesis is also accepted: no statistically significant impact was observed for the role of PRP in association with bone grafting in increasing implant survival rates. Although implant survival rates were assessed in six studies, two studies[34,39] were not used due to missing data for the number of implants for each group, and this could have contributed to the results. However, the results found are in agreement with those of previous studies.[45,56]

The implant survival rate is more related to possible complications in the sinus area than to the use of PRP.[3] Membrane integrity is an important factor for the longevity of both grafts and implants, and perforation of the membrane can lead to postoperative complications such as contamination of the maxillary sinus, which can compromise osseointegration.[57] However, studies reporting membrane perforation during the surgical phase[3,6,33,35,43] did not observe postoperative complications, except for one study in which the patient lost the implant after sinus contamination.[3] Of note, one potential means of preventing possible contamination is to cover the perforation with a collagen membrane or even PRP. Sealing the region avoids failure of the bone graft or implant.[33,35]

Furthermore, after the data tabulation, it was possible to perform additional quantitative analyses: marginal bone loss, the ISQ, and bone height after bone grafting also did not show a statistically significant effect of PRP. However, only two studies were selected for each parameter and this

Table 3. Quantitative analysis of outcomes evaluated for selected studies ($n = 13$).

Author	Outcomes evaluated	Control group (Only bone graft)	Test group (PRP + bone graft)
Khairy et al.[6]	% Bone formation	39.5% (± 7.4)	27.3% (± 6.3)
Yilmaz et al.[33]	Alveolar bone height	11.33 mm (± 1.71)	11.34 mm (± 1.84)
Poeschl et al.[34]	% Bone formation	22.3% (± 12.3)	29.0% (± 13.2)
	Implant survival	NR	NR
		0 implant lost	1 implant lost
Cabbar et al.[3]	Height of residual crest	5.6 mm (± 1.4)	4.7 mm (± 1.3)
	% Bone formation	15.8% (± 7.5)	16.1% (± 3.8)
	ISQ	75.4 (± 6.4)	74.4 ± 6.4
	Implant survival	14 implants	14 implants
		1 implant lost	1 implant lost
Badr et al.[8]	ISQ	61 (± 2.6)	60 (± 2.4)
Torres et al.[35]	Implant survival	129 implants	153 implants
		5 implants lost	2 implants lost
	Alveolar bone height	9.4 mm (± 0.7)	10.4 mm (± 0.7)
	% Bone formation	21.3% (± 4.5)	31% (± 5)
Aimetti et al.[37]	Bone-to-implant contact	20.5% (± 5.57)	46.75% (± 13.60)
	Marginal bone loss	1.03 mm (± 0.05)	0.98 mm (± 0.10)
Schaaf et al.[38]	% Bone formation	35.3% (± 10.7)	33.3% (± 11.7)
Consolo et al.[40]	Bone density bone (HU)	451.38 (± 62.81)	709.23 (± 69.99)
	% Bone formation	29.2% (± 4)	39.3% (± 5.7)
Thor et al.[15]	% Bone formation	13% (± 6)	14% (± 7)
	Bone-to-implant contact	20% (± 15)	17% (± 13)
Kassolis and Reynolds[41]	% Bone formation	33.3% (± 1.3)	26.5% (± 6.8)
Raghoebar et al.[42]	% Bone formation	41.1% (± 8.3)	38.4% ± (11.3)
	Implant survival	15 implants	15 implants
		0 implant lost	1 implant lost
Thor et al.[43]	Marginal bone loss	3.9 mm (± 0.8)	3.7 mm (± 0.9)
	Implant survival	152 implants	152 implants
		2 implants lost	0 implant lost

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.[37,51,58] It is considered the gold standard graft,[6] because of factors such as osteogenic capacity, biocompatibility, low immunogenicity, and accelerated healing.[59,60] All studies using PRP in association with biomaterials[3,8,33–35,41,44] 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,[61,62] 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[6,37] 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 revascularization than cancellous bone.[37] Thus, the use of small chips is recommended to accelerate revascularization 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

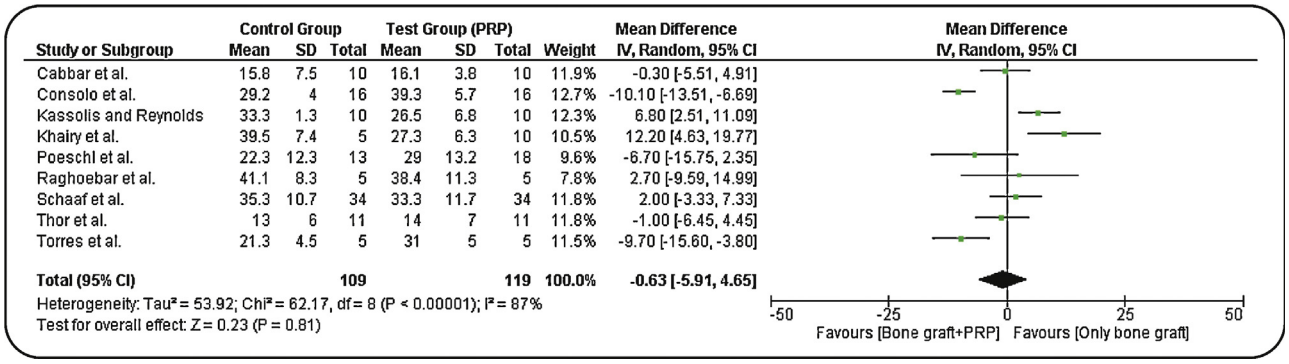

Fig. 2. Forest plot for the event 'bone formation'.

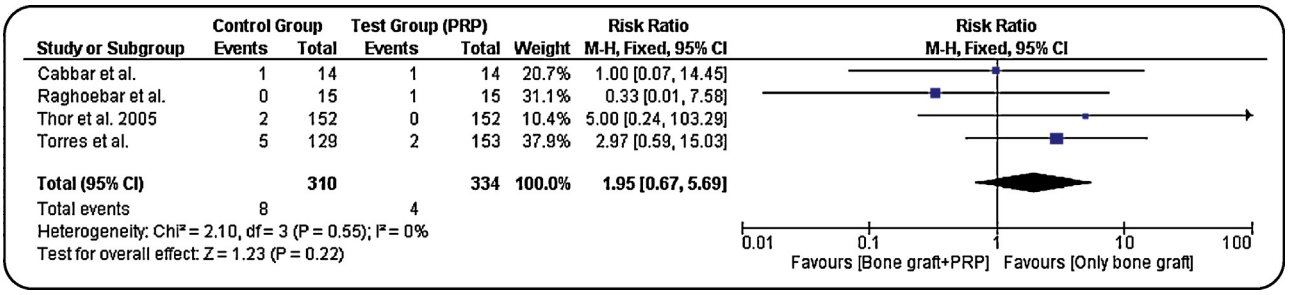

Fig. 3. Forest plot for the event 'implant survival'.

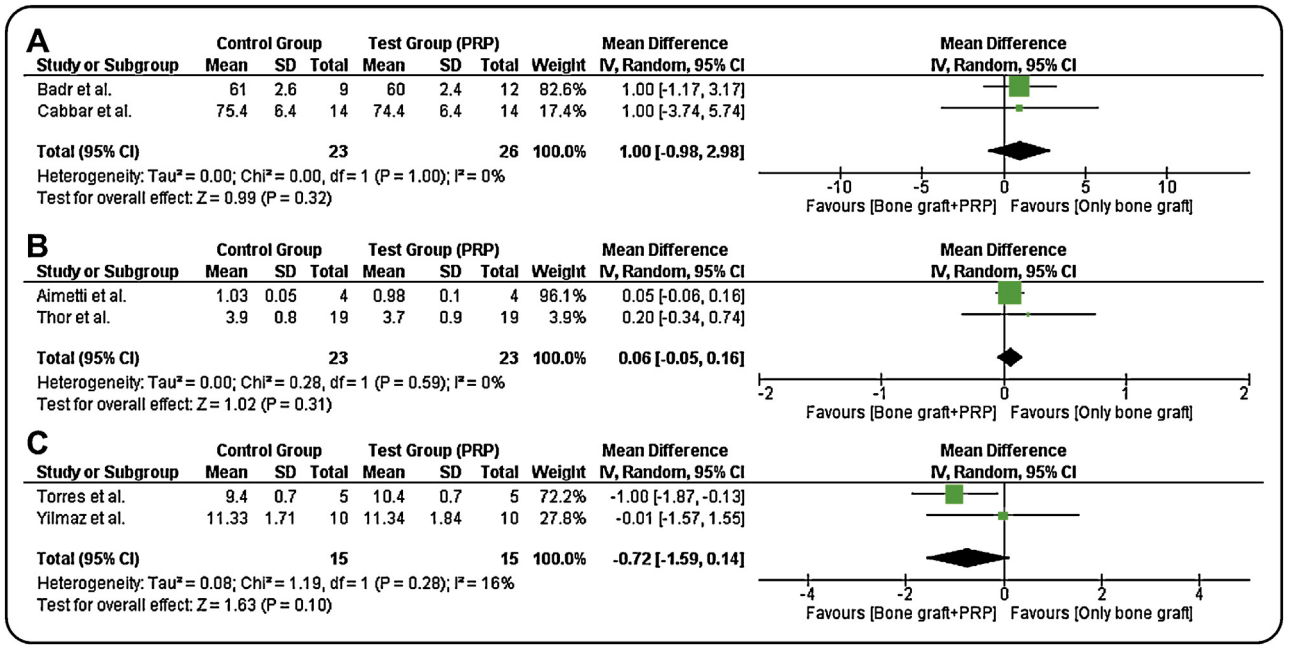

Fig. 4. Forest plot for the events (A) 'implant stability quotient', (B) 'marginal bone loss', and (C) 'alveolar bone height'.

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[3,6,35] 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[6,8,33,35–42,44] showed a high level of evidence, while five studies[3,7,15,34,43] 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 to the level of evidence. Five studies[6,8,35,38,40] reported double-blinding, but only two studies[8,35] reported use of the CONSORT checklist[66]; 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.

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