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Does the use of platelet-rich plasma in sinus augmentation improve the survival of dental implants? A systematic review and meta-analysis

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ABSTRACT

Background: Platelet-rich plasma is considered an effective modality to promote bone regeneration, improve hard and soft tissue healing in surgical procedures including sinus augmentation. However, the survival of dental implants in sinus augmented sites with platelet-rich plasma has shown equivocal results in recent studies.
Purpose: In this systematic review, data on dental implants' survival in sinus augmentation sites with platelet-rich plasma were examined.
Materials and methods: Randomized controlled trials on the topic with a minimum mean follow-up of 6 months with no language restriction were considered. Other study designs on the topic were excluded. Accordingly, relevant articles were searched in Clinicaltrials.gov, Cochrane databases, PubMed/Medline, and Scopus up to April 2021. Using the Cochrane risk of bias assessment tool, the listed studies' risk of bias was evaluated. From the included studies, the pertinent information was taken and pooled for qualitative and quantitative analysis using R software 4.1.1.
Results: Six randomized controlled trials involving 188 patients who underwent sinus augmentation with and without platelet-rich plasma, and 781 implants were included for qualitative and quantitative analysis. Four hundred and eleven implants were placed in the intervention group (with platelet-rich plasma) and 370 implants were placed in the control group (without platelet-rich plasma). The pooled estimate (OR 0.84, 95% CI 0.37 to 1.91; $I^2 = 0\%$) indicated that there was no statistically significant difference observed between the groups. The test for subgroup differences showed no statistically significant differences between the subgroups ($p = 0.45$) with no heterogeneity ($I^2 = 0\%$).
Conclusion: The bias associated with selective reporting of outcome data was considered as some concern for bias. This systematic review revealed that the effect of platelet-rich plasma is uncertain on the survival of dental implants.

1. Introduction

Maxillary sinus augmentation is a surgical procedure to improve the bone quantity and quality in the maxillary posterior edentulous region.[1] An increase in the bone quality and quantity in the atrophic maxilla, allows for placement of implant with optimal size.[2,3] Maxillary sinus augmentation with autograft is considered as gold standard owing to osteoconductive, osteoinductive, and osteogenic properties.[4,5] However, other bone grafts such as allograft, xenograft, synthetic graft, alloplastic graft, polymer-based graft, and growth factors have been reported to be beneficial.[4–8] Nevertheless, the addition of platelet-rich plasma (PRP) to bone grafts has shown improved vascularization, an increase in new bone formation, and better hard and soft tissue healing.[9–12]

PRP is a platelet concentrate obtained from an individual's own blood after centrifugation.[13] PRP contains 5 to 10 times higher

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concentrations of platelets than the whole blood, proteins, protein-based bioactive factors, and leukocytes in varying amounts.[13,14] Most surgical procedures use PRP in gel concentration, which is obtained by mixing thrombin and calcium chloride with liquid PRP.[14,15] The addition of thrombin and calcium activates the platelets to release proteins, cytokines, chemokines, and growth factors that are important for regulating the cellular processes.[13] Release of platelet-derived growth factor (PDGF), is known to accelerate hard and soft tissue wound healing, while transforming growth factor β (TGF- β) promotes connective tissue repair and bone regeneration.[13,14] Since it is autologous in nature, any risk of immune reaction, disease transmission, or cross-contamination is non-existent.[14–16] PRP has been broadly used in various dental surgical procedures, as an adjunct to promote wound healing and bone regeneration.[17,18] Application of PRP has shown to be beneficial in the reconstruction of mandibular fractures, healing of extraction sockets, treatment of periodontal infra-bony defects, treatment of bisphosphonate-associated osteonecrosis, distraction osteogenesis for restoration of the atrophic mandible, and as an implant coating material in immediate loading protocol.[19-24]

Preliminary investigations have reported that PRP increased bone graft survival during maxillary sinus augmentation and subsequently increased implant survival in long term.[25,26] Additionally, it reduced the patient discomfort and the consolidation time of the graft, thereby reducing the overall healing time.[9–11] Lee et al. in year 2008 conducted a histologic and histomorphometric study and analyzed the survival rate of 97 implants placed in 52 grafted maxillary sinuses using 50% autogenous bone graft combined with 3 substitute graft materials (mineralized allogenic bone, natural FHA, Bio-Oss), and PRP. The results showed 77%–100% formation of new vital bone with a 100% implant survival rate.[27] Khairy NM et al. in a randomized clinical trial evaluated the bone quality of 15 augmented sinus with autologous bone grafts mixed with and without PRP and followed by implant placement. The group with autologous bone grafts enriched with PRP showed a statistically significant mean bone density value ($p = 0.041$) at 6 months post grafting and 6 months post implantation.[28] Karaca EO et al. studied the survival and success of 43 implants at 1 and 5 years after sinus augmentation with bone grafts and PRP. The results demonstrated a survival rate of 100% and 83% success rate at 5 years follow-up.[29]

On contrary, there are studies that report that there is no beneficial effect of PRP on bone formation, bone graft healing, and implant survival.[30–33] Researchers believe that PRP shows beneficial effects on bone healing in critical sized defects and defects with reduced vascularization and has no adjunct role in augmentation surgeries involving smaller defects like maxillary sinus.[11,33] Some studies highlighted that PRP is beneficial when immediate loading protocol for implants is opted where PRP may promote faster healing,[34–36] and that PRP effects on delayed healing protocol seem to be nugatory. Given the reported benefits of PRP, the complexity of the augmentation procedure, and the conflicting reports on the effects of PRP on implant survival, further investigation is needed to validate the evidence. Thus, this systematic review was aimed to analyse the effect of sinus augmentation with PRP on dental implant survival.

2. Material and methods

The exploration adopted the guidelines following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[37] The research protocol was registered in PROSPERO-International Prospective Register of Systematic Reviews (CRD42020184501). To begin with, a research question was devised applying the conventions namely Population, Intervention, Comparison, and Outcome (PICO) framework (Table 1). Randomized controlled trials involving patients who had undergone sinus augmentation with bone graft and PRP and who had received dental implants with a minimum mean follow-up of 6 months were considered. The publication's language was not restricted in any way. Non-randomized controlled trials, retrospective studies, case series, case reports, animal studies, as well as review papers, conference abstracts, and numerous publications of the same pool of patients, were all excluded. The following databases namely PubMed, CENTRAL, clinicaltrials.gov, Cochrane registry, journal databases, and Scopus were searched using keywords up to April 2021 to find relevant papers (Table 2). Additionally, from each of the chosen full-text publications and review articles, the reference source was manually searched.

Table 1
PICO framework. PICO, Participant, Intervention, Comparison, and Outcome.

Focus question	Does the PRP used in sinus augmentation improve the survival of dental implants?
Participants	Patients with edentulous atrophic maxilla who required sinus augmentation and dental implants
Intervention	Sinus augmentation with PRP and dental implants
Comparison	Patients who underwent sinus augmentation with bone graft only and received dental implants
Outcomes	1. Cumulative survival and success of dental implants
Study design	Randomized controlled trials

Two reviewers looked through the titles and abstracts of the papers that would have qualified for inclusion, followed by full-text assessment for relevance. A third reviewer (M.M.B) was consulted to resolve any disagreement between the reviewers in the selection process. From each included study, the reviewers independently extracted the pertinent data, which they then entered into a spreadsheet. The data sheet included: name of the author, year of publication, study design, and setting, sample size, and age, number of patients with smoking history, the total number of implants, implant brand, PRP preparation, type of intervention, graft healing time, implant healing time, implant success criteria, number of failed implants, reasons for implant failure, mean follow-up duration, loss to follow-up, complications, implant survival rate, and success rate. The authors clarified any unclear data in the included studies with the corresponding authors.

Risk of bias assessment of the selected studies was done independently by 2 reviewers (I.S., S.A.) using the Cochrane risk of bias tool for randomized controlled trials.[38] This tool contains 5 domains, each domain has signalling questions which are used to rate the studies as 'high risk', 'some concern' or 'low risk'.

Statistical analysis was done in accordance with the Cochrane handbook of systematic review. Kappa (k) coefficient was used to assess the data extraction agreement between the reviewers. Data were analyzed using R software 4.1.1 using Meta for package.[39] The odds ratio and 95% confidence interval were used to present the dichotomous data. Mantel Hansel method of pooling the data with a fixed effect model was employed to perform a meta-analysis. The studies with split mouth design were adjusted for design effect (within-patient correlation) assuming a correlation coefficient of 0.07 and re-estimated the results for including in the meta-analysis. The confidence interval was estimated using the Hartung and Knapp estimator to adjust test statistics and confidence intervals. Heterogeneity was assessed with the Cochran Q test along with I^2 statistics. I^2 statistics range from 0% to 100%. I^2 index less than 25% is indicative of low heterogeneity, between 25% and 75% represents average heterogeneity, and more than 75% means that considerable heterogeneity is present.[40]

3. Results

One thousand nine hundred and fourteen studies were found using electronic searches. Hand searching found 5 records. After removing the duplicates, 1100 records remained. One thousand and seventy six records were excluded after titles and abstracts were scrutinised. Twenty-four records were chosen for full-text evaluation. Following a full-text evaluation, 18 records were eliminated because they contained several publications using the same patient pool, systematic reviews, and non-randomized clinical research. Thus, for qualitative and quantitative analysis, 6 randomized controlled studies[29–31,33,41,42] fulfilled the

Table 2
Search strategy.

Population	Patients with edentulous atrophic maxilla	#1 ("mouth, edentulous" [MeSH Terms] OR ("mouth" [All Fields] AND "edentulous" [All Fields]) OR "edentulous mouth" [All Fields] OR "edentulous" [All Fields]) AND ("atrophy" [MeSH Terms] OR "atrophy" [All Fields] OR "atrophic" [All Fields]) AND ("maxilla" [MeSH Terms] OR "maxilla" [All Fields])
Intervention	Maxillary sinus augmentation Platelet rich plasma Dental implants	# 2 ("maxillary sinus" [MeSH Terms] OR ("maxillary" [All Fields] AND "sinus" [All Fields]) OR "maxillary sinus" [All Fields]) AND augmentation [All Fields] AND ("platelet-rich plasma" [MeSH Terms] OR ("platelet-rich" [All Fields] AND "plasma" [All Fields]) OR "platelet-rich plasma" [All Fields] OR ("platelet" [All Fields] AND "rich" [All Fields] AND "plasma" [All Fields]) OR "platelet rich plasma" [All Fields]) AND ("dental implants" [MeSH Terms] OR ("dental" [All Fields] AND "implants" [All Fields]) OR "dental implants" [All Fields])
Comparison	Maxillary sinus augmentation with bone grafts only	# 3 ("maxillary sinus" [MeSH Terms] OR ("maxillary" [All Fields] AND "sinus" [All Fields]) OR "maxillary sinus" [All Fields]) AND augmentation [All Fields] AND ("bone transplantation" [MeSH Terms] OR ("bone" [All Fields] AND "transplantation" [All Fields]) OR "bone transplantation" [All Fields] OR ("bone" [All Fields] AND "graft" [All Fields]) OR "bone graft" [All Fields])
Outcome	Dental implant Survival rate	#4 ("survival rate" [MeSH Terms] OR ("survival" [All Fields] AND "rate" [All Fields]) OR "survival rate" [All Fields]) AND ("dental implants" [MeSH Terms] OR ("dental" [All Fields] AND "implants" [All Fields]) OR "dental implants" [All Fields])
Databases	–	1. PubMed 2. Cochrane registry, CENTRAL 3. Journal databases (Elsevier, Wiley, Quintessence Publishing) Clinical trials.gov 4. Scopus
Search strategy	–	Data base 1: #1 AND #2 AND #3 AND# AND4 Data base 2,3 &4: "platelet rich plasma AND sinus augmentation AND dental implants"
Filters	–	Medicine and dentistry (Elsevier) Dentistry, Journal (Wiley)
Journals searched through database	–	Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research, International Journal of Oral and Maxillofacial Implants, Journal of Oral Implantology, Journal of Prosthetic Dentistry, Journal of Prosthodontics, International Journal of Prosthodontics and Journal of Periodontology.

criteria (Fig. 1). A good to excellent inter-examiner reliability was reported (k = 0.94, 95% confidence interval [CI]: 0.92 to 0.96).

Tables 3 and 4 present detailed descriptive information as well as the results of the included research, respectively. The featured research was published during the years of 2008 and 2017. The typical follow-up time was between 6 and 24 months. One hundred and eighty-eight patients underwent bone augmentation procedures with bone grafts and received 781 implants. Four hundred and eleven implants were placed in the intervention group and 370 implants were placed in the control group. One study reported 31 patients with a history of smoking,[41] while 2 studies excluded smokers,[30,42] and 3 studies did not report the smoking history.[29,31,33] Three included studies had adopted the bilateral split-mouth design for sinus augmentation procedure.[29,31,33] Three studies used autografts[30,31,33] while 3 studies employed xenografts[29,41,42] as bone grafting material. All included studies described the PRP preparation procedure, but there were differences regarding the amount of whole blood collected, and platelet concentration level. Two studies used autologous thrombin,[29,30] 3 studies used calcium chloride (at 10% or 30% concentration) to activate PRP,[33,41,42] and 1 study failed to mention the activating agent.[31] The healing time for bone graft ranged 3–8 months and healing time after implant placement ranged 3–6 months.

One study adopted Buser's criteria to assess implant success,[29] 2 studies defined their own criteria,[32,41] and 3 studies did not report any criteria for measuring the outcome.[31,33,42] Of the 781 implants, 12 implants failed in the intervention group and 14 implants failed in the control group. Most of the studies did not mention the reason for failure except one study which reported compromised residual bone height (less than 4 mm) levels as a reason for failure.[42] However, the most common complication observed among the studies was sinus membrane perforation or dehiscence, followed by sinusitis and peri-implant infection. The follow-up period ranged from 6 months to 5 years, and only 2 studies reported the loss to follow-up.[30,42] The implant survival rate for the intervention group ranged from 93.3% to 100% and 96.2%–100% for the control group. The weighted mean values for implant survival, based on the implant number, were 98.05% for the intervention group and 97.25%. for the control group.

The risk of bias assessment revealed 'low risk' for 3 studies,[29,41,42] and 'some concern' for 3 studies[30,31,33] (Figs. 2 and 3). The aim of this bias assessment is to assess the effect of assignment to intervention. The pre-specified analysis plan for the included studies was unavailable for analysis. So, the bias associated with selective reporting of outcome data was considered as some concern for bias.

Data from 6 studies were included for meta-analysis. One study did not report any implant failure in both the arm.[30] The pooled estimate (OR 0.80, 95% CI 0.37 to 1.91; $I^2 = 0\%$) indicated that there was no statistically significant difference observed between the groups (Fig. 4). Among the 6 included studies, 3 studies had split-mouth design[29,31,33] and 3 studies had a parallel-group design.[30,41,42] The data for split-mouth studies and parallel-group studies were pooled separately as 2 subgroups for further subgroup meta-analysis to analyse systematic differences. In the subgroup meta-analysis, the pooled estimate at 95% CI for split-mouth and parallel-group studies was 1.40 (0.52–3.76) and 0.28 (0.06–1.19) respectively (Fig. 4).

4. Discussion

Five systematic reviews have been published on the topic related to PRP, bone formation, and implant survival.[43–47] Out of these, four focused specifically on the effect of PRP on sinus augmentation as the primary outcome.[43–46] However, from a clinical care point of view, a successful rehabilitation with implants is the ultimate treatment goal of all maxillary sinus augmentation procedures. Only one systematic review qualitatively analyzed the interaction between PRP and implant survival.[47] This review included 4 RCTs which studied the implant failure based on the patient number. There was no clear identification of the total number of implant failures per se. Also, the data was pooled irrespective of the split-mouth or parallel-group study designs. Further, the systematic review missed 2 RCTs in their analysis. Another review noted adequate corroboration to support PRP for sinus augmentation

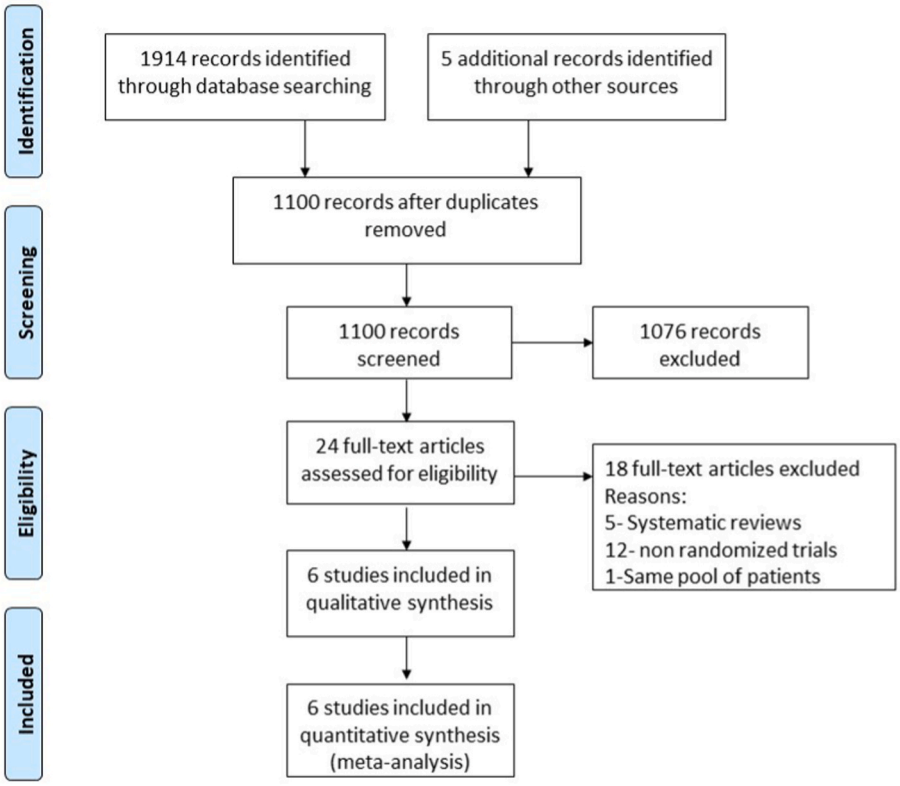

Fig. 1. PRISMA flow diagram for study selection.

but lacked evidence for implant survival.[46] Other reviews indicated no significant difference in the implant survival and bone formation between the PRP treated group and control group,[44–46] while another review concluded that PRP might have a positive effect on bone regeneration and implant survival.[43] In the present review, we have included the relevant RCTs conducted in the topic so far and performed subgroup analysis with respect to split-mouth and parallel-group designs. Implant survival was analyzed based on the failure of implants by number in PRP reinforced sinus augmented areas. Further, equivocal results were demonstrated amongst the reviews.

The included studies in the present review were either split-mouth design or parallel-group design. The decision to pool the data for both study designs separately were opted to analyse the systematic differences.[48–50] Lesaffre et al. recommended that split-mouth design and parallel-group design be pooled separately for analysis to avoid inaccurate confidence interval and incorrect conclusion on clinical significance.[51–53] Though no heterogeneity was observed, there was no significant difference ($p = 0.45$) between the subgroups during the analysis of implant survival rate. Split mouth studies presented the effect of treatment that favored the control group whereas parallel-group studies favored the intervention group.

Various PRP preparation methods have been demonstrated in the scientific literature.[13–18] There is no consensus in the amount of blood volume, type of anticoagulant used, single spin or double spin centrifugation, centrifugation time, centrifugation force, and the type of activating agent used to activate the platelets.[16,17] The PRP preparation techniques used in the included studies of the current review also differed indicating that the clinical efficacy and viability of the PRP formulation could be inconsistent. Activation of PRP using thrombin or calcium chloride are considered a crucial step in PRP preparation protocol as it initiates degranulation of platelets to release growth factors from alpha granules and helps to form a matrix or platelet gel.[13–17] However, some researchers believe in spontaneous platelet activation that occurs after exposure to collagen in the connective tissue of the patient or thawing the frozen platelets is adequate for platelet activation.[54,55] Despite the prevailing differences, all the published protocol aims to achieve an optimal PRP formulation with a concentration of platelets at least 3–5 times higher than the baseline levels of the whole blood.

Al -Moraisai et al., Corbella et al., and Danesh-Sani et al. analyzed the bone regeneration capabilities for different bone grafts used in maxillary sinus augmentation and reported that autografts showed higher new bone formation than the xenografts at 6 months of healing time.[56–58] However, when the healing time is greater than 6 months, both the grafting materials showed similar bone regeneration. This implies that though autologous bone grafts heal faster than xenografts, with time both materials showed similar clinical efficacies.[56–58] Additionally, Danesh-Sani et al. have indicated that when growth factors like PRP or platelet-rich fibrin are combined with different bone grafts, a higher bone regeneration potential (88.3%) at 6 months of healing time was noted.[58] The included studies in the present systematic review employed PRP combined with either autograft or xenograft. The healing time of the studies using autografts was less than 6 months and the studies using xenografts had healing time ranging 6–8 months before implant placement. Since the studies using xenografts had longer healing time, bone regeneration potential of both type of grafts could be similar across the studies.

The implant success referring to osteointegration and survival was assessed using well established criteria.[59,60] Buser's criterion was adopted by one included study,[29] and 3 studies did not report any criteria to evaluate implant success.[31,33,42] The method for measuring the study outcome is an important domain for assessing the risk of bias of an individual study. If appropriate methods are not described by the studies, it could undermine the quality of the study. In addition to surgical-related factors, prosthetic-related factors such as implant overload, poor prosthetic design can result in implant failure. None of the included studies reported the prosthetic complications or failure encountered during treatment. Kim J and Jang H reported perforation of

Table 3
Descriptive data of the included studies.

Study (year)	Design	Setting	Study sample	Age range (Years) Mean (M)	Dropouts	Number of implants	Intervention	Healing time before implant placement	Healing time after implant placement	Implant Success/ survival criteria	Implant brand name	Is the statistical analysis, corrected for clustering?	P=ICC
Schaaf et al. (2008)	prospective, controlled, randomized study Split-mouth design	Giessen and Erlangen, Germany	34	NR	NR	244 (245)	Sinus augmentation I-Autogenous bone graft + PRP C- Autogenous bone graft without PRP	4 months	6 months	NR	NR	No	0.07
Kacara et al. (2017)	prospective controlled randomized study Split-mouth design	Yeditepe University's Faculty of Dentistry	(10)25 M-6 F-4	53–72 M-65	5	43	Sinus augmentation I- DBBM + PRP C- DBBM/ collagen membrane	8 months	4 months	Buser's criteria	Osseospeed TM, Astra Tech AB, Sweden	No	0.07
Raghoebar et al. (2005)	prospective controlled randomized study Split-mouth design	Department of Oral and Maxillofacial Surgery of the University Hospital, Groningen	M-2 F-3	57–62 M-58.4 + 1.9	–	30	Sinus augmentation Implant-retained overdentures I-autologous bone + PRP gel C- autologous bone only.	3 months	3 months	NR	Branemarks, Nobel Biocare, Sweden	No	0.07
Torres et al. (2009)	RCT Parallel group design	Clinic Dental Alcala, Madrid, Spain	87 (Smokers included) M-40 F-47	52–78	–	282 (286)	144 sinus floor augmentations I- Anorganic bovine bone + PRP C- Anorganic bovine bone without PRP	6 months	6 months	Own criteria	Osseotite, Biomet 3i Inc., USA	Yes	NAD
Badr et al. (2010)	randomized, controlled, parallel-group clinical trial Parallel group design	Oral an Maxillofacial Surgery Unit, University Dental Hospital of Manchester	22 M-14 F-8 I –13 C-9	17–73 M-36	–	85	onlay block grafts I- autogenous bone grafts + PRP C- autogenous bone grafts without PRP	3–4 months	5–6months	Own criteria	OsseoSpeed, Astra Tech, Sweden	Yes	NAD
Torres et al. (2010)	RCT Parallel group design	Dental Clinic Alcala, Madrid, Spain	30 M-13 F-17 I –15 C-15 diabetes,	48–76	–	97	43 alveolar bone augmentation I- anorganic bovine bone + PRP C- anorganic bovine bone	6 months	6 months	NR	Osseotite, Biomet 3i Inc., USA	Yes	NAD

(*continued on next page*)

Table 3 (*continued*)

Study (year)	Design	Setting	Study sample	Age range (Years) Mean (M)	Dropouts	Number of implants	Intervention	Healing time before implant placement	Healing time after implant placement	Implant Success/ survival criteria	Implant brand name	Is the statistical analysis, corrected for clustering?	P=ICC
			heart failure, and osteoporosis										
Total			188			781							

Design effect Deff = 1 + p (n – 1)	cluster adjusted effect size	cluster adjusted standard error	PRP activation agent	Amount of blood collected	Platelet concentration
1.4	0.2311	0.6836	NR	450 mL citrate phosphate dextrose anticoagulated blood	11-12 times above the baseline level of whole blood.
1.02	0.2852	0.8328	autologous thrombin	20 ml blood was withdrawn from the patient through a venipuncture in the antecubital vein. The drawn blood was mixed with 2 ml of anticoagulant solution	NR
0.99	1.1663	1.6768	10% calcium chloride solution patient's serum, as source of autologous thrombin,	6 ml of anticoagulant citrate dextrose-A was collected in a 60 ml syringe. From the venipuncture the syringe was filled with whole blood up to 60 ml.	NR
NAD	NAD	NAD	30% calcium chloride solution	10 and 20 cm^3 of blood was withdrawn via venous aspiration into 4.5 cm^3 test tubes and mixed with a 3.8% sodium citrate solution	2.97 ± 0.7-fold over peripheral blood
NAD	no events	no events	autologous thrombin	54 ml of blood was drawn using a green aphaeresis needle into a 60 ml syringe pre-filled with 6 ml of anticoagulant citrate dextrose solution.	4- to 7-fold (5.4 ± 0.9) increase in platelet concentration above the baseline level with up to 78% platelet recovery rate.
NAD	NAD	NAD	30% calcium chloride solution	10–20 ml of blood was withdrawn via venous aspiration into 4.5 ml test tubes and mixed with a 3.8% sodium citrate solution at a ratio of 5/1	NR

RCT- Randomized controlled trial, I- intervention group, C- control group, M − Male, F- Female, DBBM-deproteinized bovine bone mineral, PRP- Platelet-rich plasma, NR-Not reported, NAD- No adjustment done, ICC-Intraclass correlation coefficient.

Table 4
Outcomes of the induced studies.

Study (year)	Number of implants /group	No. of implants failed	Reason for failure	Complication	Loss to follow-up	Follow-up	Survival rate of implants	Success rate of implants	Other outcome measures	Other outcomes
Schaaf et al. (2008)	I-122	9 (3.67%)	NR	Sinusitis-2	NR	6 months	96.33%		Radiographic imaging (CT)	Resorption
	C-122	I- 5 C- 4		(5.88%)			I −96% C-96.7%		Panoramic radiography	Median I -0mm C- 2 mm
Kacara et al. (2017)	I −22	7	NR	peri-implant infection	NR	5 Years	I - 100%	PRP-82%	Radiographic measurements	Marginal bone loss 1.57 ± 0.49 (1.5)
	C-21	I −4 C-3					C- 100%	C-85%	Periapical radiographs	1.54 ± 0.41 (1.50)
Raghoebar et al. (2005)	I −15 C-15	I −1 C-0	NR	Sinus membrane perforation-1	NR	20.2 # 4.3 months	I −93.3% C-100%		Microradiography Light microscopy	The average density (arbitrary gray values) at the 1^{ST} PM& 1^{ST} M I - 91 ± 23.1, 71.8 ± 23.8, C- 84.6 ± 19.6, 90.7 ± 13.5 bone in augmented (pre)molar region I - 38.4 ± 11.3% C- 41.1 ± 8.3%
Torres et al. (2009)	I-153 C-129	7 I −2 C-5	6- When residual bone height 4 mm, 1- residual bone height between 4 and 7 mm.	Sinus membrane dehiscence was observed in five cases (5.74%)	NR	24 months	I −98.9% C-96.2%	92.8%	Histological and histomorphometric	Height of AB I - 10.4 ± 0.7 C-9.4 ± 0.7 mm
Badr et al. (2010)	I −48 C-37	0	None	1 PRP-antral communication 1 C- soft tissue wound dehiscence occurred	0	6 months	I −100% C-100%		ISQ -RFA device Ridge mapping	I −61.6 ± 2.6 C- 60 ± 2.4 Graft resorption I −1.4 ± 0.5 C- 1.6 ± 0.5, *P* = 0.5
Torres et al. (2010)	I −51 C-46	2 I −0 C-2	NR	Ti mesh exposure	0	24 months	97.5% I −100% C-97.3%		Radiographs (orthopantomography) computed tomography (CT) Histological analysis	ABH I −3.5 ± 0.7 C-3.1 ± 0.8 (p < 0.05) ABW I −4.1 ± 0.6 C-3.7 ± 0.6 (P < 0.05)
Total	I- 411 C-370	I-12 C-14					I- 98.02% C- 97.25%			

ABH- average bone height gained; ABW- average bone width gained, Ti – titanium, I- intervention group, C- control group, PM- Premolar, M-Molar, PRP- Platelet-rich plasma, NR- Not reported.

the maxillary sinus membrane as the most common complication to occur after maxillary sinus augmentation (10%–34% of patients).[61] This result is consistent with the present review, the common complication reported by the included studies was maxillary sinus membrane perforation. Additionally, Kan JY et al. reported that smokers are more susceptible to sinus membrane perforation as cigarette smoke causes thinning of the sinus membrane.[62] Only one study in the present review included 31 patients with a history of smoking and reported that smoking coupled with reduced residual bone height had a negative effect on implant survival.[41] Though smoking is believed to cause a deleterious effect on implant osteointegration in the augmented maxillary sinus, few studies have reported no statistically significant difference in implant failure between patients with or without a smoking history.[63,64]

Dettori JR indicated that the follow-up period is an important attribute in the assessment of implant survival and efficacy of PRP.[65] Though a 5 year mean minimum follow-up period is considered as an ideal duration for evaluating the outcome of implant, studies included in the

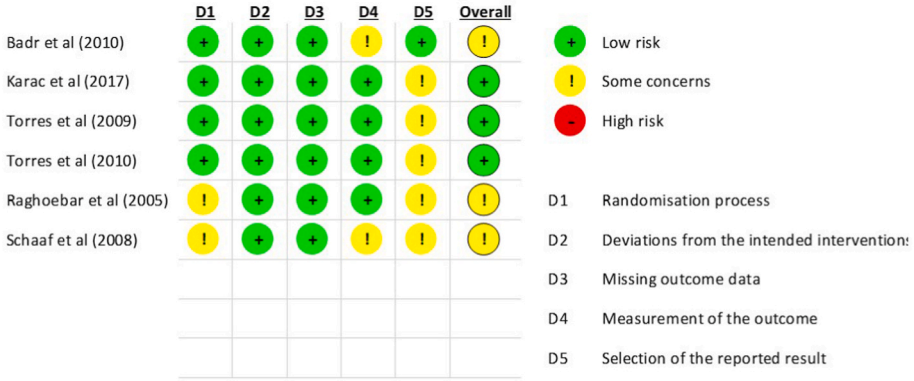

Fig. 2. Cochrane risk of bias assessment for the included studies.

Fig. 3. Summary of Risk of bias assessment of the included studies.

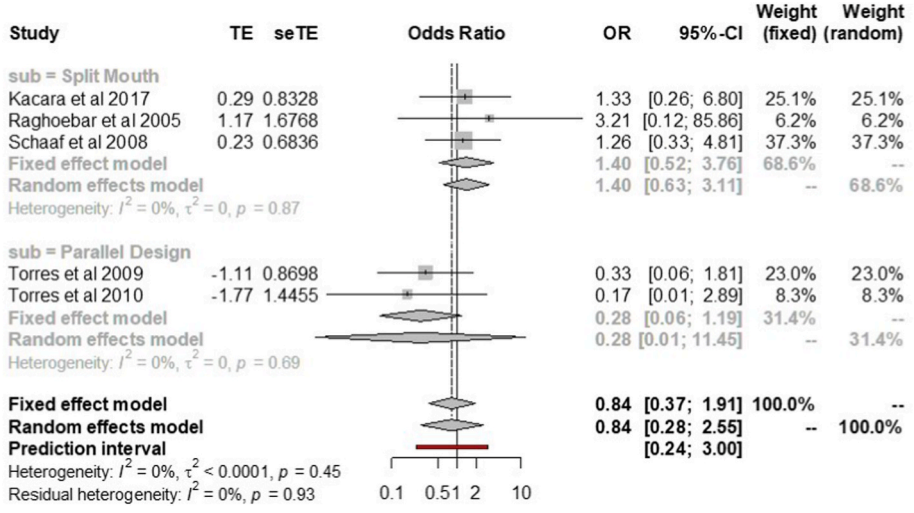

Fig. 4. Meta-analysis of the included studies.

present review had follow up ranging from 6 months to 5 years. Few included studies did not report loss to follow up or dropouts as loss to follow-up in RCTs has the potential to seriously impair the study's validity and reliability. Differences in the drop-out rates between the control group and treatment group undermine the sample size calculation and randomization process.[65] Additionally, patients who drop out of the study could have a different outcome than those studied till the end of the trial.

4.1. Limitations and future scope

Lack of well-designed RCTs with uniform PRP preparation protocol and implant placement protocol could be noted as a limitation. Further, three included studies in the present review had some concerns for risk of bias for at least two domains in the Cochrane risk of bias tool.

Due to the limited availability of published evidence that compares PRP in immediate and delayed implant placement protocol, the use of PRP in immediate implant placement could not be justified. Well-designed RCTs should focus on analysing the effects of PRP in immediate placement and comparing with delayed implant placement protocols could add further evidence to the use of PRP.

5. Conclusion

This systematic review revealed that the effect of platelet-rich plasma is uncertain on the survival of dental implants. The risk of bias associated with selective reporting of outcome data was considered as some concern for bias. Further, well-designed RCTs with uniform PRP preparation protocol and implant placement protocols are required to provide substantial evidence.

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Conflicts of interest

The authors declare no conflict of interest.

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