Effect of Autologous Growth Factors in Maxillary Sinus Augmentation: A Systematic Review

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ABSTRACT

Purpose: The aim of the present study was to systematically evaluate the effect of autogenous platelet concentrates on the clinical and histomorphometric outcomes of maxillary sinus augmentation.

Materials and Methods: MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched using a combination of specific search terms. Furthermore, a hand searching of the relevant journals and of the bibliographies of reviews was performed. Prospective comparative clinical studies were included. Implant survival and histomorphometric outcomes were evaluated.

Results: Twelve studies were included. Four hundred forty-five sinus floor augmentation procedures were considered. No difference in implant survival was reported between test and control groups. Six studies reported a beneficial effect of platelet concentrates based on histomorphometric outcomes, while another six studies found no significant effect. A large heterogeneity was found regarding study design, surgical techniques, graft materials, clinical and histomorphometric outcome variables, and methods for preparing platelet concentrates. Favorable effects on soft tissue healing and postoperative discomfort reduction were often reported but not quantified.

Conclusions: A clear advantage of platelet concentrates could not be evidenced. Standardization in the experimental design is needed in order to detect the true effect of platelet concentrates in maxillary sinus augmentation procedure, especially regarding postoperative quality of life.

KEY WORDS: dental implants, growth factors, implant survival, maxillary sinus augmentation, platelet concentrate

INTRODUCTION

An inadequate bone quantity and quality have been considered for many years as absolute contraindications for implant-supported rehabilitation. The risk of implant failure in the posterior maxilla is generally high, because of the low bone density and the progressive ridge resorption caused by edentulism. Implant treatment in the atrophic posterior maxilla must be carefully planned and may require a pre-prosthetic surgical intervention of bone grafting. Maxillary sinus floor augmentation is often performed to create conditions adequate for implant placement.

The implant success rate and the predictability of maxillary sinus augmentation procedure depend on numerous factors. However, because of the improvement of surgical techniques and the progress of research in the field of biomaterials, excellent outcomes have been reported in the last years. Recent systematic reviews of the literature have demonstrated that sinus floor augmentation procedure is well documented with an overall implant survival rate well beyond 90%.[1–7]

Many different types of graft materials have been used over the years in the sinus lift procedure, but autogenous bone has long been considered the "gold standard" because of its osteogenic, osteoconductive, and osteoinductive properties.[8–10] Autogenous bone contains all the elements of organic and inorganic matrix, as well as part of the viable cell component in the cancellous

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portion. The use of autogenous bone, however, may imply a certain degree of discomfort for the patient because of the need for a harvesting site. In order to reduce the patient's morbidity, autogenous bone graft can be replaced, completely or partially, by a variety of bone substitutes with a highly predictable graft and implant survival rate.[1,2,4] Bone substitutes however generally possess only osteoconductive property. This implies that cells, and soluble growth and differentiation factors from the surrounding host bone tissue must be recruited and directed toward the graft site, in order to achieve new bone formation. In this case, the surgical procedure itself represents the main stimulus for activating the healing process leading to graft integration and maturation.

Growth factors have been shown to modulate the wound healing response in both hard and soft tissues.[11–14] During the past years, many studies demonstrated that specific growth factors (such as platelet-derived growth factor [PDGF], transforming growth factor-β1 [TGF-β1], epidermal growth factor [EGF], vascular endothelial growth factor [VEGF], insulin-like growth factor-I [IGF-I], basic fibroblast growth factor [bFGF], hepatocyte growth factor [HGF]) may promote bone regeneration of oral and maxillofacial bone defects.[14–17] Because most of these factors are released by platelets, locally delivered platelet concentrates are supposed to increase proliferation of osteoprogenitor cells, to stimulate osteoblast activity and to enhance angiogenesis, all of which are fundamental to graft survival.[16–18]

In the recent years, several clinical studies of different evidence level, follow-up time, and sample size have been performed to evaluate the effect of platelet concentrates in the sinus augmentation procedure, reporting contrasting results.[19–40] Furthermore, different techniques have been adopted to obtain platelet concentrates. Taken together, the results of these studies can be confounding for the practitioner as also suggested by some reviews published in the last years.[41–46]

The main aim of the present systematic review was to determine if the use of autogenous platelet-derived growth factors may affect the survival rate of implants placed in the grafted maxillary sinus. A secondary aim was to determine if a correlation between graft quality (based on histomorphometric data) and clinical outcome (based on implant survival) could be established.

MATERIALS AND METHODS

Literature Search

A search was performed on electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials), using the following search terms, alone and in combination by means of Boolean operators: "platelet-rich plasma" (PRP), "platelet concentrate," "platelet growth factors," "autologous platelet concentrate," "plasma rich growth factors," "platelet-rich fibrin" (PRF), "PRP," "PRGF," "PRF," "maxillary sinus lift," "maxillary sinus augmentation," "maxillary sinus floor elevation," "maxillary sinus graft," and "dental implants." The search was limited to controlled trials involving human subjects. No language or time restrictions were applied. The last electronic search was performed on April 30, 2010.

A further hand search was carried out on the major international journals in the field of implant dentistry, and of oral and maxillofacial surgery (*British Dental Journal*, *British Journal of Oral and Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Clinical Periodontology*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Periodontology*, and *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, and *Endodontology*).

The reference list of the review articles was also checked for possible additional studies. Finally, the authors of the identified studies and the implant manufacturing companies producing devices for concentrating platelets were contacted in order to identify ongoing or unpublished studies pertinent to this review.

Inclusion and Exclusion Criteria

All randomized clinical trials (RCTs) and controlled clinical trials (CCTs) assessing the efficacy of platelet concentrates on sinus augmentation procedures were included. Other types of study design, like case series, single case reports, technical studies, animal studies, and reviews were excluded. No limitation was placed regarding the number of patients treated.

Studies were selected according to the following inclusion criteria: (1) a test group using platelet concentrates was compared with a control group non-utilizing

platelet concentrates; (2) treatment outcomes (implant survival or histomorphometric results) were clearly reported or provided by the authors; and (3) when reporting implant survival, the mean follow-up was no less than 6 months after placement.

Data Extraction

The titles and abstracts of the retrieved articles were screened by two reviewers (M.D.F., M.B.), and publications meeting the inclusion criteria were identified. When the title and abstract of an article did not provide sufficient information to make a decision, the full text was obtained and examined. Publications that did not meet the inclusion criteria were excluded. In case of disagreement between examiners, a third reviewer was consulted (S.T.), and a decision was made by collegial discussion.

The characteristics of the included studies were examined by the reviewers, and the articles were sorted into two groups:

1. studies reporting the survival of implants placed in grafted maxillary sinus; and
2. studies reporting results of histologic and histomorphometric analysis.

For each study, the method of platelet concentrate preparation (with regard to commercial system, anticoagulant and activator used, and the number, speed, and duration of centrifugations) was recorded.

RESULTS

The search provided 28 articles, of which 17 reported on comparative studies investigating the effect of platelet concentrates in maxillary sinus augmentation procedures.[20,22–27,29–35,37,38,40] Three articles were excluded after review of the full text.[25,30,33] The study by Steigmann and Garg[25] was excluded because of inadequate reporting, the Lindeboom and colleagues study[30] was excluded because the only outcome provided was the capillary density of the oral mucosa, while in the study by Lee and colleagues,[33] the platelet concentrate was used in all study groups. Fourteen articles reporting on 12 studies fulfilled all inclusion criteria and were included in the present analysis (Table 1). Ten studies were RCT, and two were CCT; most of them had a split-mouth design. The study by Torres and colleagues[40] had a hybrid split-mouth parallel study design, in which 87 patients were followed clinically and radiographically up to 2 years, and five patients with symmetrical severely resorbed maxilla underwent bone biopsy 6 months after sinus grafting, for histologic and histomorphometric analysis. The included articles were published in a period ranging from 2002 to 2010. Overall, 445 sinus floor elevation procedures were performed on 269 patients. Residual ridge height before surgery varied between 1 and 7 mm. A lateral approach to the sinus was used in all cases. Various materials were used for grafting the sinus: freeze-dried bone allograft, β-tricalcium phosphate, anorganic bovine bone (Bio-Oss®, Geistlich Söhne AG, Wolhusen, Switzerland), and autogenous bone from the iliac crest or the mandibular ascending ramus. A membrane was used to cover the graft in six studies.[20,23,27,32,37,38] In three studies, reported in five articles,[24,26,31,34,35] an additional ridge augmentation procedure was performed.

The articles provided a broad range of variable outcomes to assess the regenerative potential of platelet concentrates and its possible benefits to the treatment: radiographic bone density, bone level around implants, implant survival rates, and various types of histomorphometric measures.

Effect of Platelet Concentrates on Implant Survival

Seven articles reported sinus augmentation in combination with dental implant placement (Table 2). Overall, 862 implants were placed in 191 patients. Some studies did not report the exact number of implants for each treatment group.[32,35,38] Healing time of graft before implant placement varied from 3 to 6 months. The mean follow-up for the analysis of implant survival ranged from 6 months after placement[35] to 60 months of function.[32] Nineteen implants (8 test and 11 control implants) failed in 15 patients, yielding an overall implant survival of 98.26%. Seventeen implants failed during the healing phase, while two implants (one test and one control[40]) were lost during the first year of prosthetic loading. No significant difference was reported by the single studies between test and control groups regarding implant survival. A formal meta-analysis could not be performed because of the high level of heterogeneity among the studies for experimental design, clinical protocol, patients' selection criteria, graft material, and follow-up duration.

TABLE 1 Studies Assessing the Efficacy of Platelet Concentrates on Sinus Augmentation Procedures

Author, Publication Year	Study Type	N° Patients	N° Sinuses	PC Category	Graft Material	Membrane	Outcome Measure
Froum and colleagues (2002)[20]	RCT (sm)	3	6	PRP	Bio-Oss	Yes (resorbable in two cases and nonresorbable in one)	Histomorphometric analysis
Wiltfang and colleagues (2003)[22]	RCT	35	35	PRP	β-TCP	No	Histomorphometric analysis
Kassolis and Reynolds (2005)[23]	RCT (sm)	10	20	PRP	FDBA	Yes (control group only)	Histomorphometric analysis
Raghoebar and colleagues (2005)[24]	RCT (sm)	5	10	PRP	ABG	No	Radiographic bone density, histomorphometric analysis, implant survival
Thor and colleagues (2005, 2007)[26,31]	CCT (sm)	19	38	PRP	ABG	No	Implant survival rate, marginal bone level, implant stability using RFA, histomorphometric analysis (11 patients)
Choukroun and colleagues (2006)[27]	CCT	9	9	PRF	FDBA	Yes (autologous fibrin)	Histomorphometric analysis
Consolo and colleagues (2007)[29]	RCT (sm)	16	32	PRP	ABG	No	Radiographic bone density, histomorphometric analysis
Aimetti and colleagues (2008)[32]	RCT (sm)	4	8	PRP	ABG	Yes (resorbable)	Histomorphometric analysis, implant survival, marginal bone level
Schaaf and colleagues (2008)[34,35]	RCT (sm)	53	87	PRP	ABG	No	Radiographic bone density, implant survival, histomorphometric analysis (34 patients)
Bettega and colleagues (2009)[38]	RCT (sm)	18	36	PRP	ABG	Yes (biologic glue)	Radiographic bone density, implant survival, histomorphometric analysis
Torres and colleagues (2009)[40]	RCT	87	144	PRGF	Bio-Oss	No	Implant survival
	RCT (sm)	5	10	PRGF	Bio-Oss	No	Histomorphometric analysis
Anitua and colleagues (2010)[37]	RCT (sm)	5	10	PRGF	Bio-Oss	Yes (autologous fibrin)	Histomorphometric analysis

ABG = autogenous bone; CCT = controlled clinical trial; FDBA = freeze-dried bone allograft; PC = platelet concentrate; PRF = platelet-rich fibrin; PRGF = plasma rich in growth factors; PRP = platelet-rich plasma; RCT = randomized clinical trial; RFA = resonance frequency analysis; sm = split mouth; β-TCP = β-tricalcium phosphate.

TABLE 2 Studies Reporting Sinus Augmentation in Combination with Dental Implant Placement

Author, Publication Year	Graft Material	sim/del	N° Total Implants (Test/Control)	Implant Survival (%)			FU (Months)	N° Failures (Time of Failure)
				Total	Test	Control		
Raghoebar and colleagues (2005)[24]	ABG	del	30 (15/15)	96.67	93.33	100.00	20.2*	1 (test) before prosthetic loading
Thor and colleagues (2005)[26]	ABG	del	152 (76/76)	98.68	100.00	97.37	18†	2 (control) before prosthetic loading
Aimetti and colleagues (2008)[32]	ABG	del	20 (NR)	100.00	100.00	100.00	60	0
Schaaf and colleagues (2008)[35]	ABG	del	245 (NR)	96.33	NR	NR	6†	5 test and 4 control implants before loading
Bettega and colleagues (2009)[38]	ABG	del	111 (NR)	100.00	100.00	100.00	12†	0
Torres and colleagues (2009)[40]	Bio-Oss	sim/del	282 (153/129)	97.50	98.60	96.20	24	1 (test) + 4 (control) before prosthetic loading and 1 (test) + 1 (control) during first year of loading
Anitua and colleagues (2010)[37]	Bio-Oss	del	22 (11/11)‡	100.00‡	100.00‡	100.00‡	30.5*‡	0

*Mean value.
†Time since implant placement.
‡Unpublished data, information provided by the authors.
ABG = autogenous bone; del = implant placement delayed with respect to grafting procedure; FU = follow-up; NR = not reported; sim = implant placement simultaneous to grafting procedure; test = platelet concentrate group.

Effect of Platelet Concentrates on Histomorphometric Parameters

Twelve articles reported histologic and histomorphometric analysis (Table 3). Overall, 274 sinuses were analyzed (138 test and 136 controls). Bone biopsies for histologic and histomorphometric analysis were obtained from 3 to 12 months after grafting procedure. In three studies,[20,31,32] the biopsy included a mini-implant. In the study by Aimetti and colleagues,[32] the mini-implants were placed 6 months after grafting and retrieved 6 months later. Different histomorphometric parameters were evaluated in different studies. Parameters were defined as the amount of bone in relation to the amount of tissue in the sample (bone area/tissue area, %). Three articles evaluated the total bone area, while five articles assessed the percentages of newly formed bone and of old bone (when the grafting material used was autogenous bone), or residual graft material (in case of bone substitutes). Torres and colleagues also evaluated the amount of connective tissue. One study[27] reported vital and non-vital bone percentages. Aimetti and colleagues[32] evaluated the bone-implant contact (BIC) in all patients, while Froum and colleagues provided BIC for one patient (two test implants and one control implant placed at the time of grafting).

Six studies claimed a positive effect of platelet concentrates on bone regeneration assessed through histomorphometric analysis. However, two of these articles[29,31] found significant differences between test and control groups only for biopsies taken at the shortest healing times. Anitua and colleagues[37] reported the highest difference between test (plasma rich in growth factors [PRGF] + Bio-Oss) and control (Bio-Oss alone) biopsies, showing about 300% more new bone formation in the cases in which PRGF had been used. This result was based on biopsies from two patients only. They also reported that platelet concentrates reduced tissue inflammation after surgery and promoted the vascularization of bone tissue. Six studies found no significant difference between the test and control group. However, better handling of particulate grafts, reduction of graft healing time, and reduction of the amount of autogenous bone used to fill the sinus cavity were often reported.

Platelet Concentrate Preparation

Most of platelet concentrates used in the included articles were referred to as PRP, the same name as the original transfusion platelet concentrate.[18] One study[27] used Choukroun and colleagues' PRF, while two studies[37,40] used Anitua and colleagues' PRGF® (BTI Biotechnology Institute, Alava, Vitoria, Spain).

Several techniques for platelet concentrate preparation were used, as shown in Table 4. Automated systems (e.g., cytopheresis, Sequestra 1000® [Medtronic, Minneapolis, MN, USA], PCCS® [3i/Implant Innovations, Palm Beach Gardens, FL, USA], and SmartPreP® [Harvest Technologies Corporation, Plymouth, MA, USA]) as well as manual protocols (e.g., Curasan® [Curasan, Kleinostheim, Germany] and PRGF) were employed, either performing one-step or two-step centrifugation procedures. Duration and speed of centrifugations varied, according to the instructions of each device's manufacturer.

Various anticoagulants (citrate dextrose, citrate phosphate dextrose, and sodium citrate) were used to collect blood before centrifugation. Bovine thrombin, autologous thrombin, or calcium chloride was used to trigger platelet activation and fibrin polymerization. PRF preparation did not require anticoagulants or activators.[27]

The final volume of usable platelet concentrate (depending on the initial blood harvest, which varied from 60 to 450 mL) differed among articles. In most studies, platelet concentrations ranged from 2.6 to 11.5 times the value of peripheral blood. In one study, the authors declared that they used a platelet concentration over 60 times higher than the baseline concentration in peripheral blood.[38]

DISCUSSION

Very few clinically controlled studies have been found concerning the effect of platelet concentrates in the sinus augmentation procedure. The results of the present literature analysis demonstrate a substantial heterogeneity among different studies regarding study design, surgical technique, graft material, outcome assessment variables, histological and histomorphometric outcomes, healing time for biopsies, healing time for implant placement, follow-up duration, and type and method of preparation of the platelet concentrate.

Furthermore, in three studies,[24,26,31,34,35] the patients underwent an additional ridge augmentation procedure (buccal onlays). It is difficult to interpret the results of these studies because the effect of the additional graft on the final outcome cannot be quantified.

TABLE 3 Studies Reporting Histomorphometric Analysis

Author, Publication Year	N° Sinuses Analyzed	Graft Material	Biopsy Time (Months)	Histomorphometry (%)	Effect of PC
Froum and colleagues (2002)[20]	6	Bio-Oss	7, 7.5, 11	Vital bone 23.3 ± 9.7 (test); 21.3 ± 9.7 (ctr) BIC*: 38.2% (test); 33.8% (ctr)	None
Wiltfang and colleagues (2003)[22†]	35	β-TCP	6	New bone: 38 (test); 29 (ctr) Residual graft: 13.8 (test); 15.0 (ctr)	None
Kassolis and Reynolds (2005)[23]	20	FDBA	4.5 to 6	New bone: 33.3 ± 11.3 (test); 26.5 ± 6.8 (ctr) Residual graft: 21.2 ± 8.3 (test); 37.0 ± 15.7 (ctr)	Positive
Raghoebar and colleagues (2005)[24]	10	ABG	3	Total bone: 38.4 ± 11.3 (test); 41.1 ± 8.3 (ctr)	None
Choukroun and colleagues (2006)[27]	9	FDBA	4 (test)/8 (ctr)	Vital bone: 21.0 (test); 20.3 (ctr) Non-vital bone: 9.4 (test); 10.9 (ctr)	None
Thor and colleagues (2007)[31]	18	ABG	3 and 6	New bone at 3 months: 22 ± 9 (test); 11 ± 3 (ctr) Old bone at 3 months: 13 ± 7 (test); 20 ± 11 (ctr) New bone at 6 months: 14 ± 7 (test); 13 ± 6 (ctr)* Old bone at 6 months: 19 ± 10 (test); 23 ± 11 (ctr)*	Positive (significant only at 3 months)
Consolo and colleagues (2007)[29]	32	ABG	4/5/6/7	Total bone at 4 months: 43.3 ± 9.1 (test); 26 ± 5.2 (ctr) Total bone at 5 months: 39.3 ± 5.7 (test); 29.2 ± 4.0 (ctr) Total bone at 6 months: +29 (test vs ctr) Total bone at 7 months: +20 (test vs ctr)	Positive (significant only at 4 and 5 months)
Aimetti and colleagues (2008)[32]	8	ABG	6	BIC*: 46.75% ± 13.6% (test); 20.5% ± 5.57% (ctr)	Positive
Schaaf and colleagues (2008)[34]	36	ABG	4	Total bone: ~18 to 55‡ (test); ~15 to 58‡ (ctr)	None
Bettega and colleagues (2009)[38†]	24	ABG	6	Total bone: 43.2 (test); 50.0 (ctr)	None
Torres and colleagues (2009)[40]	10	Bio-Oss	6	New bone: 31 ± 5 (test); 21.3 ± 4.5 (ctr) Residual graft: ~47‡ (test); ~50‡ (ctr) Connective tissue: ~22‡ (test); ~29‡ (ctr)	Positive
Anitua and colleagues (2010)[37]	4	Bio-Oss	5	New bone: 24.9 (test); 8.3 (ctr)	Positive

Data are reported as mean (±standard deviation) values.
*Around mini-implants.
†Median values.
‡Data extrapolated from a graph.
ABG = autogenous bone; BIC = bone-implant contact; ctr = control group; FDBA = freeze-dried bone allograft; PC = platelet concentrate; test = platelet concentrate group; β-TCP = β-tricalcium phosphate.

TABLE 4 Platelet Concentrate Preparation

Author, Publication Year	PC Category	System	Anticoagulant	Centrifugation			Activator	Platelet Yield
				Times	Speed†	Time (Minutes)		
Froum and colleagues (2002)[20]	PRP	(a)	NR	2×	5,600 rpm; 2,400 rpm	NR	Bovine thrombin	NR
Wiltfang and colleagues (2003)[22]	PRP	Curasan	NR	2×*	2,400 rpm; 3,600 rpm*	10; 15*	NR	4.1-fold over PB
Kassolis and Reynolds (2005)[23]	PRP	SmartPreP	Citrate dextrose	2×*	2,400 rpm; 3,600 rpm*	10; 15*	Calcium chloride	NR
Raghoebar and colleagues (2005)[24]	PRP	PCCS	Citrate dextrose	2×*	3,000 rpm; 3,000 rpm*	3:45; 13*	Calcium chloride	NR
Thor and colleagues (2005, 2007)[26,31]	PRP	(a)	Citrate phosphate dextrose	2×	5,600 rpm; 2,400 rpm	NR	Autologous thrombin	2.6 ± 1.3-fold over PB
Choukroun and colleagues (2006)[27]	PRF	PRF	No	1×	2,500 rpm (~280 g)	10	No	NR
Consolo and colleagues (2007)[29]	PRP	(b)	Citrate dextrose	2×	1,200 g; 440 g	6; 6	Autologous thrombin	>3-fold over PB
Aimetti and colleagues (2008)[32]	PRP	PCCS	Citrate dextrose	2×*	3,000 rpm; 3,000 rpm*	3:45; 13*	Calcium chloride	4-fold over PB
Schaaf and colleagues (2008)[34,35]	PRP	(c)	Citrate phosphate dextrose	2×	1,000 g; 2,900 g	10; 9	NR	11.5-fold over PB
Bettega and colleagues (2009)[38]	PRP	Cytopheresis (d)	Citrate dextrose	1×	1,700 g	15	NR	62.58-fold over PB
Torres and colleagues (2009)[40]	PRGF	PRGF	Sodium citrate	1×	460 g	8	Calcium chloride	2.97 ± 0.7-fold over PB
Anitua and colleagues (2010)[37]	PRGF	PRGF	Sodium citrate	1×	580 g	8	Calcium chloride	2 to 3-fold over PB‡

*Data from the manufacturer's instructions (user manual).
†The two consecutive values under the "speed" and "time" columns refer to the first and the second centrifugation in the order. (a) 450-mL whole blood processed with Sequestra 1000 gradient density cell separator; (b) 450-mL whole blood processed with RC3C (Sorvall, Thermoelectron Corp., Waltham, MA, USA); (c) 450-mL whole blood processed by differential centrifugation; (d) Trima Accel, Vers. 5.1 (Gambro BCT, Lakewood, CO, USA).
‡Information provided by the authors.
NR = not reported; PB = peripheral blood; PC = platelet concentrate; PRF = platelet-rich fibrin; PRGF = plasma rich in growth factors; PRP = platelet-rich plasma.

The sinus lift procedure has evolved considerably over time, and the implant survival rate has achieved excellent results, as testified by the most recent systematic reviews, reporting overall values well higher than 90%.[1,2,4] The overall implant survival resulting from the present review is in line with the results of the recent literature. It could be speculated that the absence of difference between test and control groups regarding implant survival could be because of the extremely low number of failures recorded, which could as well be due to confounding factors other than the use of platelet concentrates. For example, in the study by Raghoebar and colleagues,[24] implants with machined surface were used, which are known to be associated with low survival rates.[1,2,4] In the study by Torres and colleagues, five out of the seven failures reported occurred in patients with smoking habits.[40] In the same study, six of the failures occurred in patients that underwent a two-stage procedure, meaning that their residual bone height at the time of grafting surgery was lower than 4 mm. It has been shown that the lack of initial bone support can be detrimental to implant survival.[47,48] In the Torres and colleagues study, of the six failures recorded in the two-stage group, only one occurred in a patient of the group using platelet concentrates, suggesting that in critical clinical conditions, the addition of growth factors could be beneficial. In the study by Schaaf and colleagues,[35] a single patient of the PRP group lost three implants before loading. Unfortunately, not much detail was provided in this study regarding the causes related to implant failure. Furthermore, in three studies, no implant failure was recorded independent of the use of the platelet concentrate.[32,37,38]

In summary, regarding clinical outcomes in terms of implant survival, no evident benefit of the use of platelet concentrates can be evinced from these studies.

The analysis of histomorphometric data suggested a possible advantage of using platelet-derived growth factors. Such benefit however is limited to the early phases (first 3–6 months) of graft maturation. The positive effect of growth factors on the graft maturation process could be particularly relevant when they are associated to osteoconductive scaffolds with a slow healing dynamics like anorganic bovine bone, as suggested by the studies of Torres and colleagues[40] and Anitua and colleagues.[37] In these cases, the use of platelet-derived growth factors could allow a significant reduction of the total treatment time. In the study by Anitua and colleagues,[37] radiographic evaluation of bone density using the Hounsfield scale also revealed significantly higher values for cases in which PRGF was used as compared with those grafted with anorganic bovine bone alone.

Because of the heterogeneity in data reporting, no aggregation of histomorphometric results from different studies was attempted.

Because of the small amount of implant failures recorded and to the heterogeneity of study protocols, histomorphometric data reporting, and follow-up duration among studies, no relation could be established between the graft quality and the clinical outcome. In other words, no consistent data are available to make clear if the possible advantage of platelet concentrate in enhancing the early phases of graft healing is also reflected in a better treatment outcome in the medium-long term.

In theory, the use of particulate grafts combined with an autogenous blood derivative rich in growth factors should represent an effective mixture for sinus augmentation procedure. In fact, according to previous systematic reviews, the former is associated with the highest implant survival rates, independent of the graft material.[1,2,4] The additional regenerative potential provided by platelet-derived growth factors should enhance the early healing phase, allowing to reduce the time elapsing between grafting and implant placement and loading. Furthermore, aside from any effect that platelet concentrates might have on wound healing, because of their mechanical features, the handling properties of the particulate graft material can be dramatically improved by the addition of the activated platelet concentrate.[20,27,37,38,49,50] The resultant fibrin formation allows a consolidation and a much better shaping of the graft that can be easily molded into the desired position.[20] There is not the need for compaction of the graft, leaving room between granules for angiogenesis. The graft enriched with growth factors could have a stimulating effect on the schneiderian membrane as well, which was recently shown to possess regenerative properties because of the presence of osteoprogenitor cells.[51] After activation, the platelet concentrates can also be easily flattened and successfully used, mixed or not with the graft material, as a covering membrane rich in growth factors, acting as a substitute of conventional resorbable collagen membrane.[27,37,38,49,50] In addition to

regenerative and mechanical properties, other possible benefits of the platelet-derived growth factors have been reported for the early postoperative phase, such as reduction of bleeding, edema, scarring, pain levels, and other unwanted side effects.[15,21,37] Unfortunately, these effects have not been evaluated quantitatively to date. Lindeboom and colleagues[30] confirmed the favorable effects of PRP on the soft tissues, reporting a significant acceleration of wound healing in PRP-treated mucosal wounds. In that study, in patients undergoing a bilateral sinus floor augmentation, platelet-derived growth factors showed a strong stimulating effect on the microvascular capillary density of the oral mucosa, particularly in the early days post-surgery.[30]

The main drawbacks of the present review, as also underlined by previous literature analyses,[41–46] include: lack of standardization of study design, relatively low sample size of the single studies, and, above all, the lack of a consistent single outcome variable for evaluating the efficacy of platelet concentrates in sinus augmentation studies. Some studies suggest some beneficial effects, but the result is often statistically insignificant or borderline in its significance. There is not a definite trend. Although the angiogenic and rapid tissue regenerative potential of platelet-derived growth factors has been previously demonstrated in other medical fields like trauma surgery and transplantation,[52] the same benefits are not as evident in the field of implant dentistry. One might speculate that the contact area available for regeneration at the graft site during sinus augmentation procedures is limited and might mask the true effect of PRP by restricting cellular infiltration, as compared with an area of a larger trauma site. Thus, there is the need for targeted RCTs to further evaluate the benefits of platelet-derived growth factors in sinus augmentation procedures. Such trials should not be restricted to the assessment of faster hard and soft tissue healing, but should also quantitatively evaluate the possible benefits for the patient in terms of satisfaction and reduced discomfort in the postoperative phase, which can be related to the quality of life. In addition, there is a need for a standardized protocol to extract and prepare platelet concentrates that yields a specific platelet concentration, possibly identifying a threshold concentration to be used safely and with certain benefits, as this may affect the success rate of all procedures involving platelet concentrates. All these factors may have a direct influence on the clinical choice for using or not the platelet concentrates in the treatment, as it all depends on the evidence-based balance among safety, efficacy, and patient's acceptance, as well as on the added cost of preparation.

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