

Systematic Review and Meta-Analysis Oral Surgery

Platelet-rich fibrin in oral surgical procedures: a systematic review and meta-analysis

J. V. d. S. Canellas, P. J. D. Medeiros, C. M. d. S. Figueredo, R. G. Fischer, F. G. Ritto

Rio de Janeiro State University, Rio de Janeiro, Brazil

J. V. d. S. Canellas, P. J. D. Medeiros, C. M. d. S. Figueredo, R. G. Fischer, F. G. Ritto: Platelet-rich fibrin in oral surgical procedures: a systematic review and meta-analysis. Int. J. Oral Maxillofac. Surg. 2019; 48: 395–414. © 2018 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. The effect of platelet-rich fibrin (PRF) in enhancing the healing after oral surgical interventions is still a matter of debate. The purpose of this study was to identify instances where PRF has been shown to be effective in oral surgical procedures. A comprehensive literature search was performed up to 2017 on PubMed/MEDLINE, Cochrane Library, Web of Science, Scopus and LILACS databases and grey literature. The full-text of potentially relevant studies were reviewed and only randomized clinical trials (RCTs) were included. A total of 559 studies were found, of which 30 were included for qualitative analysis and 13 for quantitative analysis. Three review authors assessed the risk of bias independently. The available literature suggests that PRF has a positive effect in improving alveolar preservation on extraction sockets and around dental implants. The qualitative analysis showed a significantly better effect of PRF in promoting bone regeneration for alveolar cleft reconstruction. The meta-analysis for third molar surgery showed a decrease in prevalence of alveolar osteitis. PRF increased implant stability 1 week and 1 month after surgery ($P = 0.0005$ and 0.0003). Due to the lack of studies with low risk of bias and a limited number of patients available, further RCTs are needed to confirm these results.

Key words: platelet-rich fibrin; oral surgical procedures; oral surgery; bone healing.

Accepted for publication 10 July 2018
Available online 30 July 2018

Since the first description by Choukroun¹ in 2000, platelet-rich fibrin (PRF) has become an important surgical adjuvant in oral surgical procedures. In fact, only after the publication of five important articles^{2–6} in 2006 has this biomaterial

gained attention in the field of dental research. To date, more than 500 scientific articles have been published on this subject. Some of the possible recommendations for the use of this biomaterial in oral surgical procedures include third molar

surgery, alveolar ridge preservation after tooth extractions, sinus lift procedure, repair of alveolar cleft, dental implants, surgical treatment of medication-related osteonecrosis of the jaw and treatment of oroantral communications^{7–13}.

PRF is a second-generation platelet concentrate¹⁴ produced without biochemical blood manipulation, and is constituted of three key parameters: first, the presence of platelets and their activated growth factors that are substantially embedded into the fibrin matrix during the natural polymerization process⁵; second, the presence of leucocytes and their cytokines that contribute to anti-infectious action and immune regulation in the healing process^{6,15}; third, the density and complex organization of the fibrin matrix architecture produced by a natural polymerization, without the addition of any anticoagulant or gelling agent¹⁶.

The strong fibrin architecture distinguishes it from other kinds of platelet concentrates, like platelet-rich plasma (PRP). This fibrin matrix seems responsible for the slow release of growth factors during the proliferation stage of wound healing, over a period of 7–14 days, and it is composed of thin fibres with micropores that can serve as a scaffold for cell migration and differentiation. PRF is an important reservoir of numerous growth factors to promote angiogenesis, such as transforming growth factor β (TGF- β) and vascular endothelial growth factor (VEGF). There are still large amounts of platelet-derived growth factors (PDGFs) in platelet α -granules, which act as an essential regulator for collagen production and mesenchymal cell migration and proliferation^{5,16–18}.

Although many indications for the use of PRF in oral surgical procedures have been suggested, due to its biological potential to improve the wound-healing process, it is necessary to observe which of these oral surgical indications have been proven to be effective under an evidence-based analysis, leading to its recommended use in the enhancement of tissue/bone formation. The objective of this systematic review was to answer the following focused question: what indications has PRF shown to be effective in oral surgical procedures?

Materials and methods

The protocol for this systematic review was registered on PROSPERO (CRD42017078422)¹⁹. The PRISMA statement (Preferred Reporting Items for Systematic Review and Meta-Analyses) was used to ensure higher methodological quality of the article²⁰. The PICOS strategy was used for the research question construction: (P) patients or population: health patients requiring oral surgical procedures (orthognathic sur-

gery, mandibular third molar surgery, surgical treatment for medication-related osteonecrosis of the jaw, sinus lift procedure, treatment of oroantral communications, alveolar ridge preservation after tooth extractions, alveolar cleft reconstruction and dental implants); (I) intervention: use of autologous PRF combined or not with another biomaterial; (C) comparator or control group: no treatment or another biomaterial combination without PRF; (O) orthognathic surgery (pain, swelling, bone healing or postoperative complications), third molar surgery (pain, swelling, bone healing or alveolar osteitis (AO)), osteonecrosis of the jaw (prevalence of complete resolution), sinus lift procedure (bone regeneration, soft tissue healing or success rate of dental implants), oroantral communications (success rate, pain, swelling or time of surgery), alveolar ridge preservation (sockets dimensions, bone density, histomorphometric analysis or resorption of marginal bone), alveolar cleft grafting (bone volume, bone density or bone dimensions), dental implants (marginal bone change around a dental implant or implant stability); (S) study design: studies in humans, including only randomized control trials (RCTs). There were no language restrictions. An electronic search of the MEDLINE/PubMed database, Cochrane Library, Web of Science database, Scopus database and Latin American and Caribbean Health Sciences Literature database (LILACS) was conducted. The search strategy used both medical subject headings terms (MeSH) and free-text words. The search detailed PICOS framework is shown in the supplementary material to allow adequate reproduction of this study.

No language or time restrictions were applied for the screening process. The search was limited to human studies and the last electronic search was performed on the 16 September 2017. The following trial registry platforms were screened to find studies from the 'grey literature': ClinicalTrials.gov (<http://www.clinicaltrials.gov>) and EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu>). The reference lists of the articles identified were cross-checked. A manual search was performed in the following relevant journals of oral and maxillofacial surgery: *International Journal of Oral and Maxillofacial Surgery*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Cranio-Maxillofacial Surgery*, *Oral and Maxillofacial Surgery Clinics of North America*, *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and British Journal of Oral & Max-*

illofacial Surgery. Subsequently, the articles were imported into Endnote X7 software (Thompson Reuters, Philadelphia, PA, USA) where duplicates were removed.

Studies that used anticoagulants, gelling agents or any other biochemical blood handling to prepare the platelet concentrate were excluded. Additionally, controlled clinical trials, retrospective studies, duplicate studies, editorial letters, historical reviews, in vitro studies, cohort and observational studies were excluded. Finally, the articles were excluded when the full text was not found or, in the case of unpublished work, that the authors could not be contacted to provide more information.

Titles and abstracts of the screening studies were independently evaluated by two reviewers (J.V.C. and F.G.R.). The full-text articles were obtained for those studies that the authors considered relevant or those where they were uncertain regarding selection criteria. The level of agreement between the review authors was calculated by Kappa statistic. Value of Kappa between 0.40 and 0.59 is considered fair agreement, between 0.60 and 0.74 is a good agreement and 0.75 or more is considered excellent agreement. Disagreement regarding inclusion was resolved by discussion with third author (P.J.M.). The primary outcome for orthognathic surgery was bone healing; for mandibular third molar surgery it was AO; for surgical treatment of osteonecrosis of the jaw it was prevalence of complete resolution; for sinus lift procedure it was the percentage of new bone formation; for oroantral communications it was the success rate; for alveolar ridge preservation it was socket dimensions; for alveolar cleft grafting it was the percentage of newly formed bone and for dental implants it was the marginal bone resorption. The secondary outcomes for orthognathic surgery were pain, swelling and postoperative complications; for mandibular third molar they were pain, swelling and bone healing; for sinus lift procedure they were the success rate of dental implants installed and soft tissue healing; for oroantral communications they were pain, swelling and time of surgery; for alveolar ridge preservation they were bone density and marginal bone levels; for alveolar cleft grafting they were bone density, bone volume or bone dimensions and for dental implants it was implant stability.

The Cochrane Collaboration tool was used for assessing the risk of bias in included studies. Three review authors (J.V.C., F.G.R., P.J.M.) assessed inde-

pendently the risk of bias. The reviewers were blinded to information about the articles, such as the journal, the authors, the institution and direction of the results and the magnitude.

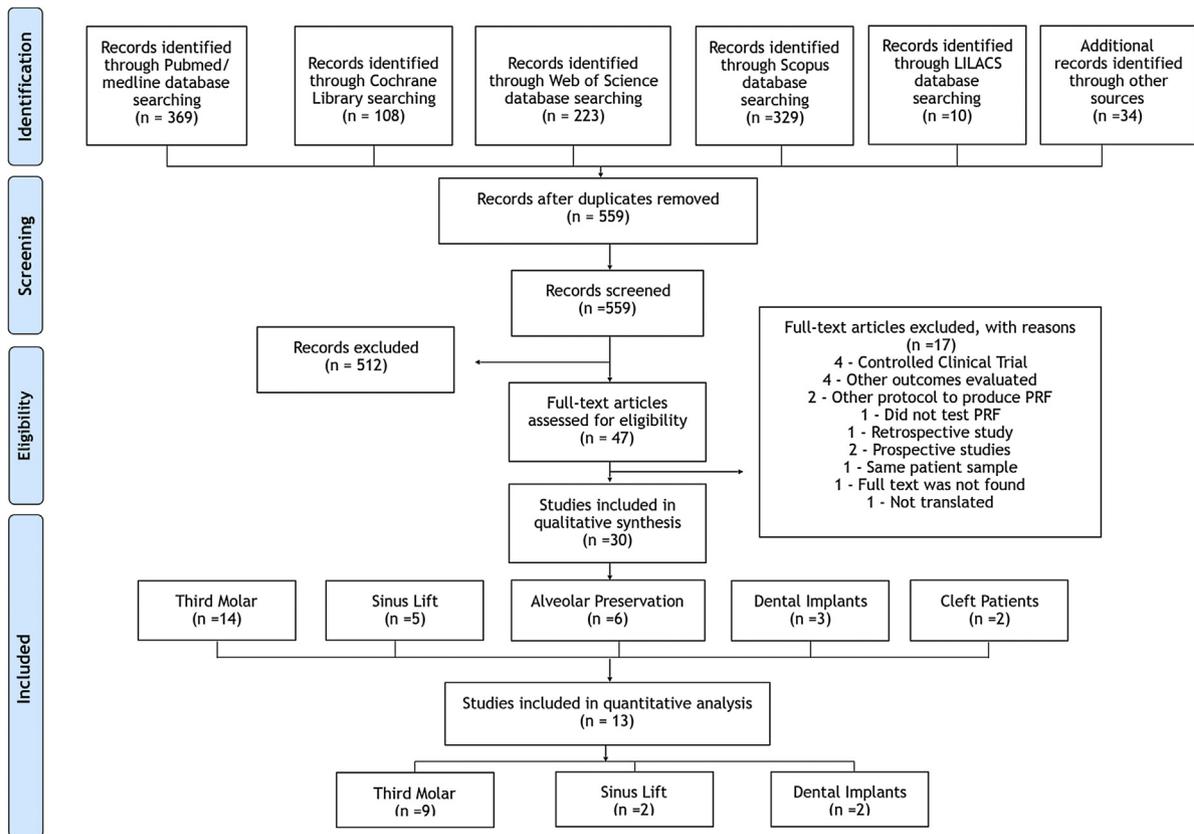
Any disagreements between the authors were resolved by discussion. In the risk of bias analysis, sequence generation was considered adequate if the method used to generate the allocation sequence was described in sufficient detail to allow an assessment of whether it should produce comparable groups. Allocation concealment was considered adequate if the method used to conceal the allocation sequence was sufficiently detailed to allow determination of whether intervention allocations could not have been foreseen in advance of, or during enrollment. The blinding of participants and outcome assessors were evaluated as well as the incomplete outcome, selective outcome reporting and other sources of bias. The assessment of the risk of bias was undertaken as follows: low risk of bias when all of the domains were judged to be at low risk of bias; unclear risk of bias, when one or more of the domains were judged to be at unclear risk of bias; and high risk of bias when one or more of the domains were judged to be at high risk of bias.

Qualitative and quantitative syntheses were performed and the meta-analysis was accomplished when the outcome variables were sufficiently homogenous. In the absence of statistical heterogeneity, Chi-square test (χ^2) > 0.10 and I-squared (I^2) < 50%, a fixed-effects model was used. The random-effect model was used to incorporate heterogeneity among studies and provide a more conservative pooled intervention effect when statistical heterogeneity was present. Review Manager version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014) was used for the meta-analysis computations. For the variables with considerable methodological and statistical heterogeneity, a meta-analysis could not be conducted, thus only a descriptive synthesis was performed.

Results

The PRISMA flow diagram of the screening and selection process is presented in Fig. 1. A total of 1073 articles were identified initially and after the exclusion of duplicates, 559 records remained. After the eligibility process 512 records were excluded and 47 full-text articles were

obtained. After full-text reading of these 47 articles, 30 randomized control trials (RCTs) fulfilled the inclusion criteria and were selected for qualitative analysis, 14 articles about third molar surgery^{8,21-33}, five articles about sinus lift procedure³⁴⁻³⁸, five articles^{12,39-42} and one conference abstract⁴³ about alveolar preservation, three articles about dental implants⁴⁴⁻⁴⁶ and two articles about the treatment of cleft patients^{11,47}. For quantitative analysis 13 articles were included, nine articles about third molar^{8,25,26,28,29,32,48-50}, two articles about sinus lift^{35,38} and two articles about dental implants^{45,46}. Seventeen articles were excluded and the reasons for exclusion were as follows: four non-randomized controlled clinical trial⁵¹⁻⁵⁴; four studies in which outcomes of interest were not reported⁵⁵⁻⁵⁸; two studies that used other PRF protocols^{59,60}; one study which did not test PRF⁶¹; one retrospective study⁶²; two prospective studies^{63,64}; one study that used the same patient sample as other studies⁶⁵; one where the full text was not found⁶⁶, and one study was written in Persian and not translated⁶⁷. The value of Kappa was 0.84, thus it was considered to be in excellent agreement. The characteristics of the included articles are shown in Tables 1 and 2.



Flow diagram (PRISMA) - screening and selection process.

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flow diagram of the screening and selection process.

Table 1. Characteristics of studies included.

Authors (year)	Surgical procedure	Country/ Language	Number of patients (n)	Number of interventions (n)	Treatment by group	Study designs	Gender	Mean age ± standard deviation (range), years	No. of drop-outs	PRF – production methods (protocol of centrifugation)	Outcome assessed (method of evaluation)					Follow-up
											Pain	Alveolar osteitis	Swelling	Bone healing	Implant stability	
Varghese et al. (2017)	Third molar surgery	India/English	30	60	30 PRF; 30 blood clot	RCT, split-mouth	(NR)	Mean ± SD (NR) (18–35)	0	3000 rpm × 10 min	–	–	–	Bone density (radiography evaluation)	–	Bone density: 1, 4 and 16 weeks
Gülşen et al. (2017)	Third molar surgery	Turkey/English	30	60	30 PRF; 30 blood clot	RCT, split-mouth	9 M, 21 F	20.03 ± SD (NR) (17–27)	0	3000 rpm × 10 min	Pain score (VAS), verbal scale (VRS)	–	(Horizontal and vertical guide with flexible rule)	–	–	Pain: 6/12 h and 1/2/3/7 days; swelling: 2/7 days
Al-Hamed et al. (2017)	Third molar surgery	Egypt/English	47	50	25 PRF; 25 blood clot	RCT, parallel-group	13 M, 34 F	25.24 ± 7.04 (18–48)	0	3000 rpm × 10 min	Pain score (VAS)	(Clinical evaluation)	–	–	–	Pain: 2/3/4/5/6/7 days; AO: 1 week
Kumar et al. (2016)	Third molar surgery	India/English	42	84	34 PRF; 34 blood clot	RCT, split-mouth	(NR)	(NR) (18–40)	8	3000 rpm × 10 min	Pain score (numerical pain score)	–	–	Osseous regeneration (radiographic evaluation by fractal analysis)	–	Pain: 1/3/7 days and 4 weeks; osseous regeneration: immediately and 2/4/6 months
Dutta et al. (2016)	Third molar surgery	India/English	40	40	10 PRF; 10 PRP; 10 HA; 10 control	RCT, parallel-group	13 M, 27 F	27 ± 5 (17–36)	0	3000 rpm × 10 min	Pain score (VAS)	(Clinical evaluation)	(Horizontal and vertical guide)	Bone healing (lamina dura, bone density and trabecular pattern)	–	Pain: 3/7/14 days; swelling: 1 day/1 month/3 months; bone healing: 1/2/6 months
Bilginaylar et al. (2016)	Third molar surgery	Cyprus/English	59	80	20 TS + blood clot; 20 TS + PRF; 20 PS + blood clot; 20 PS + PRF	RCT, split-mouth	22 M, 37 F	(NR)	0	3000 rpm × 10 min	Pain score (VAS)	–	(Horizontal and vertical guide)	–	–	Pain: 1/2/3/7 days; swelling: 1/2/3/7 days
Yelamali et al. (2015)	Third molar surgery	India/English	20	40	10 PRF; 10 PRP	RCT, split-mouth	12 M, 8 F	25.5 ± 1.60 (18–28)	0	3000 rpm × 10 min	–	–	–	Bone density (radiography evaluation)	–	Bone density: 4 months
Uyanik et al. (2015)	Third molar surgery	Cyprus/English	20	40	10 TS + blood clot; 10 TS + PRF; 10 PS + PRF; 10 TS + blood clot	RCT, split-mouth	10 M, 10 F	(NR) (19–31)	0	3000 rpm × 10 min	Pain score (VAS)	–	(Horizontal and vertical guide with flexible rule)	–	–	Pain: sum of 1, 2, 3 and 7 days; swelling: 1/2/3/7 days
Ozgul et al. (2015)	Third molar surgery	Turkey/English	56	112	56 PRF; 56 blood clot	RCT, split-mouth	23 M, 33 F	(NR) (18–28)	0	3000 rpm × 10 min	Pain score (VAS)	–	(Horizontal and vertical guide with flexible rule)	–	–	Pain: 1/3/7 days; swelling: 1/3/7 days
Kumar et al. (2015)	Third molar surgery	India/English	31	31	16 PRF; 15 blood clot	RCT, parallel-group	(NR)	26.1 ± SD (NR) (19–35)	0	3000 rpm × 10 min	Pain score (VAS)	–	(VAS scale for swelling according to Pasqualini)	Bone density (radiography evaluation)	–	Pain: 1 day/1 month/3 months; swelling: 1 day/1 month/3 months; bone density: 1/3 months
Baslarli et al. (2015)	Third molar surgery	Turkey/English	20	40	20 PRF; 20 blood clot	RCT, split-mouth	7 M, 13 F	23.9 ± SD (NR) (19–34)	0	3000 rpm × 10 min	–	–	–	Bone healing (scintigrams and radiographs)	–	Bone healing: 30/90 days
Eshghpour al. (2014)	Third molar surgery	Iran/English	85	170	78 PRF; 78 blood clot	RCT, split-mouth	33 M, 45 F	25 ± SD (NR) (18–35)	7	3000 rpm × 10 min	–	(Clinical evaluation)	–	–	–	AO: 2/7 days
Ruga et al. (2011)	Third molar surgery	Italy/English	14	28	14 PRF; 14 control	RCT, split-mouth	6 M, 8 F	29.5 ± SD (NR) (17–42)	0	2700 rpm × 12 min	Pain score (VAS)	–	–	Alveolar socket fulfillment	–	7 days and 6 months
Gurbuzer et al. (2010)	Third molar surgery	Turkey/English	20	40	14 PRF; 14 blood clot	RCT, split-mouth	7 M, 7 F	24.92 ± 4.69 (19–33)	6	2030 rpm × 10 min	–	–	–	Bone healing (scintigrams)	–	4 weeks
Oncu et al. (2007)	Dental implants	Turkey/English	26	60	30 IMI + PRF; 30 IMI	RCT, split-mouth	16 M, 10 F	40.2 ± 11.5 (NR)	0	2700 rpm × 12 min	–	–	–	Marginal bone levels (intraoral radiographs)	ISQ	Marginal bone levels: baseline/1 year; ISQ: baseline/1 week and 1/3 months
Oncu et al. (2015)	Dental implants	Turkey/English	20	64	31 DI + PRF; 33 DI	RCT, parallel-group	14 M, 16 F	44.2 ± 12.5 (NR)	0	2700 rpm × 12 min	–	–	–	–	ISQ	ISQ: baseline and 1/4 week
Boora et al. (2015)	Dental implants	India/English	20	20	10 PRF; 10 control	RCT, parallel-group	15 M, 5 F	24.6 ± NR (18–33)	0	3000 rpm × 10/12 min	–	–	–	Marginal bone levels (intraoral radiographs)	–	Marginal bone levels: baseline and 3 months

AO, alveolar osteitis; DI, dental implants; F, female; HA, hydroxyapatite; IMI, immediate implant; ISQ, implant stability quotient; M, male; NR, not reported; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; PS, piezosurgery; RCT, randomized clinical trial; rpm, rotations per minute; TS, traditional surgery; VAS, visual analog scale; VRS, verbal rate scale.

Table 2. Characteristics of studies included.

Authors (year)	Surgical procedure	Country/ language	Number of patients (n)	Number of Interventions (n)	Treatment by group	Study designs	Gender	Mean age ± standard deviation (range), years	No. of drop-outs	PRF: production methods (protocol of centrifugation: rpm × time = G force)	Outcome assessed (method of evaluation)	Follow-up
Cömert et al. (2017)	Sinus lift	Turkey/ English	26	26	9 β-TCP; 9 P-PRP; 8 PRF	RCT, parallel-group	17 M, 9 F	β-TCP: 31.51 ± 8.52; β-TCP + P-PRP: 34.01 ± 9.59; β-TCP+ PRF: 35.48 ± 9.53 (22–51)	0	3000 rpm × 10 min	Bone healing (histological and histomorphometric analysis)	Bone healing: 6 months
Gurler et al. (2016)	Sinus lift	Turkey/ English	24	24	ABG: 12; L-PRF: 12	RCT, parallel-group	14 M, 10 F	47.8 ± NR (23–66)	4	2700 rpm × 12 min	Soft tissue (numerical score)	Soft tissue: 7/14 days
Gassling et al. (2013)	Sinus lift	Germany/ English	6	12	6 AG + BDX + CM; 6 AG + BDX + PRF	RCT, split-mouth	NR	61 ± NR (54–69)	0	NR: rpm × 12 min; 400 g	Bone healing (histomorphometric analysis)	Bone healing: 5 months
Zhang et al. (2012)	Sinus lift	China/ English	10	11	6 BDX + PRF; 5, BDX	RCT, parallel-group	8 M, 2 F	BDX + PRF: 43.5 ± NR (30–49); BDX: 46.2 ± NR (37–53)	0	NR: rpm × 10 min; 300g	Bone healing (histological and histomorphometric analysis)	Bone healing: 6 months
Tatullo et al. (2012)	Sinus lift	Italy/ English	60	72	30 BDX; 42 BDX + PRF	RCT, cluster-sampling	12 M, 48 F	52.2 ± 6.15 (43–62)	0	3000 rpm × 10 min	Bone healing (histological and histomorphometric analysis)	Bone healing: 106/120/150 days
Sununliganon et al. (2017)	Alveolar preservation	Thailand/ English	19	32	?	?	?	?	0	?	Bone density and alveolar dimensions (CBCT)	Bone healing: 1/2/4/14 weeks
Thakkar et al. (2016)	Alveolar preservation	India/ English	NR	36	18 DFDBA + PRF; 18 DFDBA	RCT, parallel-group	RF	NR ± NR (20–55)	0	3000 rpm × 10 min	Alveolar dimensions (radiographic analysis)	Bone healing: baseline, 90/180 days

Table 2 (Continued)

Authors (year)	Surgical procedure	Country/language	Number of patients (n)	Number of Interventions (n)	Treatment by group	Study designs	Gender	Mean age \pm standard deviation (range), years	No. of drop-outs	PRF: production methods (protocol of centrifugation: rpm \times time = G force)	Outcome assessed (method of evaluation)	Follow-up
Temmerman et al. (2016)	Alveolar preservation	Belgium/English	22	22	22 L-PRF; 22 blood clot	RCT, split-mouth	15 M, 7 F	54 \pm 11 (NR)	0	2700 rpm \times 12 min	Bone healing, alveolar dimensions (CBCT)	Bone healing: baseline, 3 months
Das et al. (2016)	Alveolar preservation	India/English	26	30	15 PRF; 15 β -TCPCl	RCT, parallel-group	13 M; 13 F	31.22 \pm 8.51 (19–55)	0	3000 rpm \times 10 min	Alveolar dimensions (clinical and tomographic analysis)	Bone healing: baseline, 6 months
Suttapreyasri et al. (2013)	Alveolar preservation	Thailand/English	8	20	10 PRF; 10 Blood clot	RCT, parallel-group	3 M; 5 F	22.62 \pm 2.44 (20–27)	0	3000 rpm \times 10 min	Alveolar dimensions (clinical and radiographic analysis)	Bone healing: baseline, 1/2/4/6/8 weeks
Hauser et al. (2013)	Alveolar preservation	Switzerland/English	23	23	9 PRF; 6 PRF + FLAP; 8 blood clot	RCT, parallel-group	9 M; 14 F	47.43 \pm 2.30 (22–75)	0	2700 rpm \times 12 min	Bone healing (histomorphometric analysis), alveolar dimensions (clinical, radiography and μ CT)	Bone healing: 8 weeks; alveolar dimensions: 8 weeks
Movahedian et al. (2017)	Cleft patients	Iran/English	20	20	20 ICB; 20 ABG + AG + PRF	RCT, parallel-group	11 M; 9 F	ICB: 9.5 \pm 1.50; ABG + AG + PRF: 9.9 \pm 1.90 (8–14)	0	3000 rpm \times 10 min	Bone healing, alveolar dimensions (CBCT)	Bone healing: baseline, 1 year
Shawky et al. (2016)	Cleft patients	Egypt/English	24	24	12 ICB + PRF; 12 ICB	RCT, parallel-group	16 M; 8 F	10.91 \pm 1.69 (9–14)	0	3000 rpm \times 10 min	Bone healing, alveolar dimensions (CT scan)	Bone healing: baseline, 6 months

β -TCP, beta-tricalcium phosphate; β -TCPCl, Beta-tricalcium phosphate with type I collagen; μ CT, microcomputed tomography; ABG, allogeneous bone graft; AG, autogenous bone; BDX, bovine-derived xenograft; CBCT, cone-beam computed tomography; CM, collagen membrane; CT, computed tomography; DFDBA, demineralized freeze-dried bone allograft; F, female; FLAP, mucosal flap surgery; Hx, hydroxyapatite; ICB, iliac crest bone; L-PRF, Leucocyte-platelet-rich fibrin; M, male; NR, not reported; P-PRP, pure platelet-rich fibrin; PRF, platelet-rich fibrin; RCT, randomized clinical trial; rpm, rotations per minute.

None of the trials included in this review were assessed as at low risk of bias for all the domains. Sixteen trials were assessed as unclear risk of bias. The remaining 14 trials were assessed as high overall risk of bias because each of these trials was at high risk of bias in one or more domains (Fig. 2).

Mandibular Third Molar Surgery

In the primary outcome (AO) three studies were analysed (Table 3)^{8,29,50}. There were 226 extractions (113 test, 113 control) in 172 patients. No relevant clinical heterogeneity was observed among the studies, the values of Chi-squared test (χ^2) and I-squared (I^2) were 0.84 and 0%, respectively. The quantitative analysis showed a decrease in prevalence of AO (odds ratio 0.33, 95% confidence interval (CI) 0.14, 0.76; Z = 2.61, $P = 0.009$) presented in Fig. 3. Three secondary outcomes were analysed, pain (Table 4), swelling (Table 5) and bone healing (Table 6). The level of pain after surgery included nine articles^{22,24-26,28-30,32,50} of which six showed a favourable effect of PRF ($P < 0.05$) to reduce postoperative pain^{24,26,28-30,50}. A meta-analysis was applied for the first, second and third days and for the sum of the first 7 days. A favourable effect of PRF in the third day (Fig. 4) and in the sum of values in the first week (Fig. 5) was observed, and no difference between groups on the first (Fig. 6) and second days (Fig. 7) was found. The values of Chi-squared test (χ^2) and I-squared (I^2) demonstrated a high heterogeneity among the studies for the first, second and third days of analysis, and a low heterogeneity for the sum of the first 7 days of the analysis. To evaluate post-operative swelling, six articles were included^{24-26,28,29,32} of which three showed a favourable effect of PRF ($P < 0.05$) to reduce edema^{24,25,29} (Table 5). The meta-analysis to evaluate swelling after 1, 2 and 3 days (Figs 8-10, respectively) showed low heterogeneity among the studies, and only a beneficial overall effect of PRF on facial swelling after 3 days was noted (Fig. 10).

Lastly, regarding the effect of PRF on bone healing, seven studies were included in the qualitative analysis^{24,27,29,30,33,48,49}, five studies^{24,27,29,30,33} evaluated the bone healing through radiographs, of which four studies^{27,29,30,33} showed that PRF was significantly better at promoting bone regeneration after third molar ex-



Fig. 2. Risk of bias summary: review authors' judgements. CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

traction ($P < 0.05$) (Table 7). Due to the high methodological heterogeneity, it was not possible to perform a meta-analysis for these studies. Two studies^{48,49}

evaluated bone healing through scintigraphy, and for these studies a meta-analysis did not find any difference in osteoblastic activity when PRF was used

Table 3. Primary outcomes.

Authors (year)	Indication to use PRF	Outcome measured	Method of evaluation	Site of evaluation	Results	P-value*	Meta-analysis
Al-Hamed et al. (2017)	Mandibular third molar	Prevalence of alveolar osteitis	Clinical	Third molar	PRF (0) 0%; control (4) 16%	$P = 0.037^*$	Yes
Dutta et al. (2016)	Mandibular third molar	Prevalence of alveolar osteitis	Clinical	Third molar	PRF (1) 2.5%; control (2) 5%	NR	Yes
Eshghpour al. (2014)	Mandibular third molar	Prevalence of alveolar osteitis	Clinical	Third molar	PRF (7) 8.9%; control (16) 20.5%	$P = 0.042^*$	Yes
Oncu et al. (2017)	Dental implants	Peri-implant marginal bone resorption	Intraoral radiographs	Vertical bone level adjacent to the implants	PRF 0.7 (0.5) mm; control 1.3 (0.6) mm	$P < 0.05$	No
Boora et al. (2015)	Dental implants	Peri-implant marginal bone resorption	Intraoral radiographs	Mesial implant surface Distal implant surface	PRF $0.25 \pm (0.06)$ mm; control $0.57 \pm (0.22)$ mm PRF $0.27 \pm (0.07)$ mm; control $0.65 \pm (0.28)$ mm	$P = 0.0004^*$ $P = 0.0006^*$	No
Cömert et al. (2017)	Sinus lift	Percentage of new bone formation		Histomorphometric analysis	Bone graft biopsies after sinus lift procedure prior implant placement	PRF $32.03 \pm (6.34)$ %; control 33.40 $\pm (10.43)$ %	$P = 0.825$
Yes Gassling et al. (2013)	Sinus lift	Percentage of new bone formation		Histomorphometric analysis	Bone graft biopsies after sinus lift procedure prior implant placement	PRF 17.0 (NR); Bio-Gide 17.2 (NR)	$P > 0.05$
No Zhang et al. (2012)	Sinus lift	Percentage of new bone formation		Histomorphometric analysis	Bone graft biopsies after sinus lift procedure prior implant placement	PRF 18.35	$P = 0.138$
Yes Tatullo et al. (2012)	Sinus lift	Percentage of new bone formation		Histomorphometric analysis	Bone graft biopsies after sinus lift procedure prior implant placement	PRF $22.79 \pm (NR)$; control 26.44 $\pm (NR)$	$P = NR$
PRF $26.15 \pm (NR)$; control $28.7 \pm (NR)$ PRF $37.06 \pm (NR)$; control $38.97 \pm (NR)$						No	
Sununliganon et al. (2017)	Alveolar preservation	Sockets dimensions	CBCT	?	?	?	No
Thakkar et al. (2016)	Alveolar preservation	Sockets dimensions	Intraoral radiographs	Width Height	PRF + DFDBA $0.75 \pm (0.49)$; DFDBA $1.36 \pm (0.70)$ PRF + DFDBA: 1.08 $\pm (0.42)$; DFDBA: 1.38 $\pm (0.50)$	Width $P = 0.001^*$ Height $P > 0.05$	No

Author (Year)	Intervention	Outcome	Control	Significance
Temmerman et al. (2016)	Alveolar preservation	Sockets dimensions	CBCT	No
		Height: PRF 0.5 ± (2.3); Control	PRF 2.4 (2.3)/0.6 (0.7)/0.4 (0.5); control 5.4 ± (4.4)/1.2 ± (1.1)/0.5 ± (0.5)	Width H1 P = 0.0004*; width H3 P = 0.007*; width H5 P = 0.02*; height B P = 0.0002*; height V P > 0.05 P = NR
Das et al. (2016)	Alveolar preservation	Sockets dimensions	Multi-slice CT	No
		Buccal cortical height; PRF 1.55 ± (NR); β-TCP	PRF 1.52 (NR)/1.02 (NR)/1.43 (NR); β-TCP 0.86 ± (NR)/0.18 ± (NR)/0.36 ± (NR)	P < 0.05
Hauser et al. (2013)	Alveolar preservation	Sockets dimensions	Clinical analysis	No
		Width 4 mm under gingiva of adjacent teeth	PRF 0.06 ± (NR)/PRF + Flap 0.42 ± (NR)/Control 0.43 ± (NR)	P < 0.05
Movahedian et al. (2017)	Cleft patients	Percentage of new bone formation	CBCT	No
		Unilateral alveolar cleft	ABG + AG + PRF = 69.57 ± 10.13% ICB 73.86	P = 0.156
Shawky et al. (2016)	Cleft patients	Percentage of new bone formation	CT	No
		Unilateral alveolar cleft	PRF 82.6% ± (3.91); control 68.38% ± (6.67)	P < 0.05

β-TCP, beta-tricalcium phosphate; ABG, allogeneous bone graft; AG, autogenous bone; CT, computed tomography; Flap, dental extraction with mucosal flap; ICB, iliac crest bone; POD, postoperative day; PRF, platelet-rich fibrin group; SD, standard deviation; VAS, visual analog scale.
*P < 0.05.

or not (mean difference -0.03, 95% CI -0.53, 0.46; Z = 0.13, P = 0.90) (Fig. 11).

Sinus Lift Procedure

In the primary outcome (percentage of new bone formation) four studies were analysed (Table 2)^{34-36,38}. Two studies^{35,38} showed no difference between the use of PRF mixture with bone substitute or bone substitute alone, one study³⁶⁻³⁸ showed similar effects of PRF membrane and conventional collagen membrane (Bio-Gide) when they were used as a membrane at the lateral osteotomy window, and one study³⁴ showed that PRF reduced the healing time, favouring optimal bone cicatrization (Table 3). In the secondary outcome, one study evaluated the soft tissue and showed the favourable effects of PRF on wound healing, however this difference was not statistically significant (Table 7). The values of Chi-squared test (χ²) and I-squared (I²) demonstrated a moderate heterogeneity among the studies, P = 0.20 and I² = 40%. The quantitative analysis showed that there was no significant difference in the mean percentage of new bone formations when PRF was added or not added to bone substitute (standard mean difference 0.29, 95% CI -0.73, 1.30; Z = 0.55, P = 0.58) (Fig. 12).

Alveolar Ridge Preservation

Three studies showed a positive effect after comparing PRF (alone or combined with graft material) to control groups (no filling material or graft without PRF) and found that PRF improved the preservation of the alveolus and resulted in less bone resorption^{2,39,42}. One study compared PRF with beta-tri-calcium phosphate and showed similar effects in alveolar ridge preservation for both biomaterials⁴¹. Only one study⁶⁸ did not find statistical significance between PRF and control groups, although the PRF group demonstrated faster bone healing compared with the control in this study. The authors also concluded that PRF accelerated soft-tissue healing in the first 4 weeks⁶⁸. The primary outcomes are presented in Table 3 and secondary outcomes in Table 7. Due to the high methodological heterogeneity, it was not possible to perform a meta-analysis for these studies. One conference abstract⁴³ concluded that bone density was not statistically significantly different after comparing PRF and control groups, however

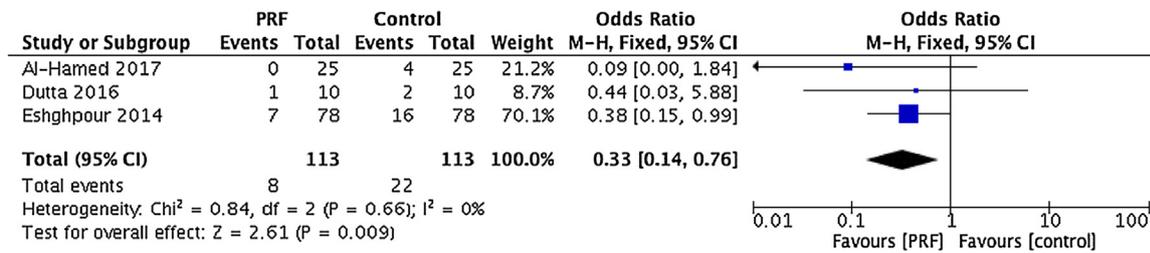


Fig. 3. Forest plot comparing platelet-rich fibrin versus control in the prevention of alveolar osteitis. CI, confidence interval; PRF, platelet-rich fibrin.

the PRF group demonstrated superiority in maintaining bone width. The authors were contacted to provide detailed information about the unpublished work, but unfortunately we did not receive the data in time to include it in this systematic review.

Dental Implants and Cleft Patients

Only one RCT¹¹ evaluating the use of PRF in the treatment of cleft patients was found. In this study, the mean percentage of newly formed bone, after unilateral maxillary alveolar cleft reconstruction, was significantly higher in patients that received PRF combined with autogenous bone graft than in those that received autogenous bone graft alone (Table 3). The mean bone density of the newly formed bone was similar in both groups ($P > 0.05$).

Two articles evaluated the effect of PRF on peri-implant marginal bone resorption^{44,46}. These studies confirmed the beneficial effect of PRF in reducing the peri-implant bone resorption following dental extraction with immediate implant placement, and following implant placement in partially edentulous patients. Due to the high methodological heterogeneity, it was not possible to perform a meta-analysis for these studies (Table 3). The secondary outcome for dental implants evaluation, the effect of PRF on implant stability quotient (ISQ), measured by resonance frequency analysis, was evaluated for two articles^{45,46}. Both studies found that the use of PRF increases implant stability during initial healing period. The overall effects of PRF on ISQ after 1 week and 1 month are presented in Figs 13 and 14, respectively.

This systematic review did not find RCTs that evaluated the use of PRF in orthognathic surgery, osteonecrosis surgical treatment or for closure of oroantral communications.

Discussion

PRF has certainly gained tremendous attention in recent years due to its capacity to successfully regenerate either soft or hard tissues, enhancing new blood vessels (angiogenesis), and tissue formation during healing. Some advantages of PRF over PRP are the lack of blood anti-coagulants, which results in a strong fibrin matrix, and considerable growth factor that may be released over a 10- to 14-day period. The theory is that the combination of host cells, strong fibrin matrix, and growth factors, acts to result in faster wound healing. The objective of this systematic review was to evaluate which indications of PRF have been shown to be effective for oral surgical procedures.

A total of eight types of surgical interventions routinely performed in oral and maxillofacial surgery were analysed in this systematic review. Currently, the use of PRF in mandibular third molar surgery has been broadly studied, and three recent systematic reviews⁶⁹⁻⁷¹ showed a beneficial effect of PRF in preventing dry sockets within the first 7 days. However, the study by He et al.⁷¹ included one article⁴⁹ that presented two cases of infection after surgery (3 weeks and 2 months), that should not have been included in the meta-analysis to evaluate AO. Furthermore, the authors mixed RCT and retrospective studies to estimate the effect size, thus decreasing the accuracy of the analysis. The present meta-analysis included only RCT, and found that PRF can be used to reduce the incidence of AO in the first week after mandibular third molar surgery, diminishing the risk of AO by 62% when compared with no treatment.

Other outcomes evaluated in mandibular third molar surgery were pain, swelling and bone healing. The pain evaluation should be analysed with caution because this meta-analysis showed an important heterogeneity among the included studies.

Some of the possible reasons that we should consider before interpreting the results are: sex-based differences in pain perception, type of analgesic therapy utilized in each study, ethnic disparities in progression of pain-related conditions, carry-across effect in pain analysis when the authors used a split-mouth design, and difficulty in measuring pain due to its multifaceted and subjective nature. The results of this meta-analysis showed a positive effect of PRF on postoperative pain confirming the results of other recent systematic reviews^{70,71}.

Our results showed that PRF was more effective in reducing swelling on the third day although only three studies were included and more studies are required to confirm the real effect. In the bone healing evaluation, the qualitative analysis observed a favourable effect of PRF on hard tissue cicatrization, similarly to other systematic reviews that evaluated platelets concentrates⁷²⁻⁷⁴. Only one systematic review showed no beneficial role of PRF in bone healing after extraction of mandibular third molars, however this study presented some limitations in the methodology and needs to be cautiously interpreted^{75,76}. The methodological differences among studies made it impossible to perform a meta-analysis of bone density, although the qualitative analysis showed a beneficial effect of PRF. The meta-analysis regarding the effect of PRF on osteoblastic activity was performed and no difference between PRF and the control group was observed. Osteoblastic activity failed to assess the real effect of PRF in bone-healing because it is not sensitive to bone mass evaluation. This is a surrogate endpoint which can lead to misinterpretation⁷⁶.

Currently, PRF has been used in sinus lift procedures, either in combination with another biomaterial or as a sole filling material^{63,77}. The release of

Table 4. Secondary outcome (pain).

Authors (year)	Method of pain evaluation	Pain – Scores (SD)					Sum	P	Meta-analysis
		1st POD	2nd POD	3rd POD	7th POD	Sum			
Gülşen et al. (2017)	VAS	25.0 (26.3) PRF; 20.9 (26.1) control	15.8 (20.9) PRF; 13.8 (18.4) control	7.9 (12.1) PRF; 8.0 (30.9) control	1.0 (3.0) PRF; 0.8 (2.7) control	Not reported	1st: 0.398/2nd: 0.655/ 3rd: 0.864/7th: 0.681	Yes	
Al-Hamed et al. (2017)	VAS	Not reported	3.08 (2.75) PRF; 4.24 (2.86) control	1.92 (2.27) PRF; 2.88 (2.36) control	0 (0) PRF; 0.52 (1.41) control	Not reported	2nd: 0.152/3rd: 0.078/ 4th: 0.057/5th: 0.041/ 6th: 0.031 /7th: 0.005 1st: 0.00*/3rd: 0.00*/7th: 0.00	Yes	
Kumar et al. (2016)	Numerical pain score	3.0 PRF; 6.0 control	Not reported	1.0 PRF; 4.0 control	0 PRF; 1.0 control	Not reported	3rd: <0.05*/7th: <0.05*	No	
Dutta et al. (2016)	VAS	Not reported	Not reported	2.4 (0.75) PRF; 5.4 (1.7) control	0.8 (0.25) PRF; 3.6 (1.13) control	Not reported	1st: 0.0001*/2nd: 0.032*/3rd: 0.002*/Sum: 0.001	Yes	
Bilginaylar et al. (2016)	VAS	22.93 (17.05) PRF; 43.05 (19.70) control	5.98 (6.09) PRF; 19.20 (16.67) control	1.30 (2.70) PRF; 9.85 (10.52) control	0 (0) PRF; 0 (0) control	30.28 (22.75) PRF; 72.30 (38.94) control	Sum: 0.079	Yes	
Uyanik et al. (2015)	VAS	Not reported	Not reported	Not reported	Not reported	5.6 (3.02) PRF; 9.4 (4.81) control	1st: 0.413/3rd: 0.296/ 7th: 0.503	Yes	
Ozgul et al. (2015)	VAS	47.16 (30.59) PRF; 42.84 (29.77) control	Not reported	25.50 (29.95) PRF; 26.48 (30.36) control	10.21 (19.75) PRF; 9.41 (16.57) control	Not reported	0.017*	No	
Kumar et al. (2015)	VAS	Not reported	Not reported	Not reported	Not reported	4.92 (not reported)	Not reported	No	
Ruga et al. (2015)	VAS	Not reported	Not reported	Not reported	Not reported	PRF; 5.42 (not reported) control	Not reported	No	

POD, postoperative day; PRF, platelet-rich fibrin group; SD, standard deviation; VAS, visual analog scale.
* $P < 0.05$.

blood-derived growth factors facilitates angiogenesis and increases blood flow into the sinus cavity favouring and accelerating bone healing. This systematic review did not find any RCT evaluating PRF as the sole filling material. The qualitative analysis showed three studies that compared the use of xenograft materials with or without PRF^{34,35,38}, and no statistically significant difference was detected. Nonetheless, two of these studies^{35,38} demonstrated a higher percentage of newly formed bone when PRF was used in combination with xenograft material in sinus augmentation. This was probably due to the limited quantity of patients evaluated in the meta-analysis (only 14 patients). Tatullo et al.³⁴ showed, through histological analysis of 72 sinus lift procedures, that PRF reduces the healing time favouring faster bone cicatrization. According to these authors, it is possible to obtain good stability of endosseous implants installed 106 days after sinus augmentation.

PRF has also been utilized to cover the lateral maxillary window during sinus augmentation. One RCT⁷⁸ investigating 12 sinuses from six patients compared PRF membrane with conventional collagen membrane (Bio-Gide®). The authors concluded that similar amounts of bone formation could be achieved after 5 months, when both types of membranes were utilized to cover the lateral window. The main advantages of using PRF in this situation are the low cost, the easy of obtainment, and the total biocompatibility of the membrane.

PRF has been suggested to treat Schneiderian membrane perforations during sinus elevation⁷⁹. PRF is recommended due to it is resorption period of 10–14 days, total biocompatibility, and adequate size to cover most common small perforations. No RCT evaluating PRF for this treatment is available for ethical reasons, because it would be necessary to either create intentional tears in the membrane, or to have an enormous sample to analyse the few cases that would suffer unintentional tears.

The use of PRF has been most frequently studied for alveolar ridge preservations after tooth extractions. Nowadays, we know that no single therapy can completely prevent the alveolar changes after dental extractions, and some amount of bone loss is always expected^{80,81}. Pre-clinical studies showed the negative effect of tooth extraction in alveolar dimensions, probably as a result of drastic initial loss of blood supply derived from periodontal ligaments^{82,83}. In this context, the pro-

Table 5. Secondary outcome (swelling).

Authors/year	Method of pain evaluation	Swelling: scores (SD)			P	Meta-analysis	
		1st POD	2nd POD	3rd POD			7th POD
Gülşen et al. (2017)	Distances from Go-Cl, Trg-Cl and Trg-Lc	Not reported	9.5 (1.0)/11.3 (0.9)/10.1 (0.8) PRF; 9.5 (0.8)/11.3 (0.7)/10.0 (0.7) control	Not reported	8.8 (0.8)/10.9 (0.8)/9.7 (1.3) PRF; 8.7 (0.8)/10.8 (0.7)/9.7 (0.8) control	2nd: 0.930/ 0.744/0.778; 7th: 0.408/ 0.845/0.896	No
Dutta et al. (2016)	Three line measurement AC/AD/BE	Not reported	Not reported	3.9 (0.23) PRF; 6.2 (0.24) control	2.7 (0.21) PRF; 3.6 (0.26) control	3rd: <0.05/ 7th: <0.05	No
Bilginaylar et al. (2016)	Gabka and Matsumara method	2.36 (1.28) PRF; 2.98 (1.80) control	1.86 (1.07) PRF; 2.44 (1.51) control	1.06 (0.77) PRF; 1.65 (1.26) control	0 (0) PRF; 0.01 (0.06) control	1st: 0.452/ 2nd: 0.437/ 3rd: 0.179/ 7th: 0.392	Yes
Uyanik et al. (2015)	Gabka and Matsumara method	2.10 (1.37) PRF; 2.20 (1.80) control	1.40 (0.96) PRF; 1.66 (1.71) control	0.80 (0.63) PRF; 1.15 (1.33) control	0 (0) PRF; 0 (0) control	1st, 2nd and 3rd: >0.05	Yes
Ozgul et al. (2015)	Distances from Trg-Lc and Cl-Go	3.28 (3.02) PRF; 4.64 (4.27) control	Not reported	1.83 (2.52) PRF; 3.62 (3.51) control	0.57 (1.87) PRF; 0.73 (1.89) control	1st: 0.041* / 3rd: 0.001* / 7th: 0.634	Yes
Kumar et al. (2015)	VAS: Pasqualini method	M/S/Se: (13/3/0) PRF; M/S/Se: (7/5/3) control	Not reported	Not reported	Not reported	0.022*	No

AC, horizontal line joining the outer corner of the mouth to the midline of the tragus of the ear lobe; AD, horizontal line joining the pogonium to the midline of the tragus of the ear lobe; BE, vertical line joining the outer canthus of the eye and point on mandibular angle; Cl, commissura labiorum; Go, gonion; Lc, lateral canthus; M, mild swelling; POD, postoperative day; PRF, platelet-rich fibrin group; S, slight swelling; SD, standard deviation; Se, severe swelling; Trg, tragus; VAS, visual analog scale.
*P < 0.05.

angiogenic cytokines and growth factors of PRF may improve alveolar bone preservation.

In this systematic review most studies confirmed that PRF decreased the alveolar resorption after dental extractions when used alone or combined with other biomaterials. This result is similar to other recent systematic reviews^{73,74,84}, although these findings should be cautiously interpreted due to the limited amount of available evidence. Two RCTs^{12,39} evaluating the ridge preservation properties of PRF showed a positive effect on alveolar dimensions preservation. The quantity of bone resorption was similar to that expected for other biomaterials, around 1 mm of bone loss horizontally and vertically^{82,80}. Hauser et al. showed that the positive effect of PRF disappeared when a more invasive surgery was performed, thus, the extraction with mucosal flap elevation should be avoided. Suttapreyasri et al.⁶⁸ did not find a statistically significant difference between PRF and control groups in alveolar ridge preservation. Possible factors for this result are some limitations of their study, such as two-dimensional image analysis (radiography), absence of histological analysis, measurement of the resorption of marginal bone at the extraction site without a reliable assessment method for measurement.

One recent conference abstract⁴³ confirmed the effect of PRF on bone width preservation, however it was not possible to assess the risk of bias in this study. We contacted the corresponding author for clarification and additional information to assess the risk of bias, however she did not respond in time for the data to be included in this analysis.

Only two RCTs^{11,47} assessing the use of PRF in alveolar cleft reconstruction were found. The first study¹¹ analysed 24 patients with unilateral alveolar cleft submitted to bone reconstruction. Two groups of 12 subjects were analysed: the first received autologous bone graft plus PRF, and the second received only autologous bone graft. PRF significantly increased the percentage of newly formed bone, but no statistical difference was observed when bone density was analysed. Nonetheless, despite the statistical result, bone density was higher in the PRF group. The authors believed that the fibrin matrix could aid the increase of bone formation after surgery.

The second study⁸⁵ assessed two treatment methods in alveolar cleft reconstruction. The combination of chin symphysis bone, allogeneic bone material and PRF

Table 6. Secondary outcome (bone healing).

Authors (year)	Method of pain evaluation	Bone healing: scores (SD)	P	Meta-analysis
Varghese et al. (2017)	(Radiological assessment)	Bone density 64.73 (24.41) PRF; 53.67 (16.52) control Percentage of bone fill 57.90 (26.78) PRF; 46.74 (17.71) control	0.000* 0.001*	No
Kumar et al. (2016)	(Radiological assessment)	Quantity of bone 0.13(0.12)/0.19(0.13)/0.23(0.12) PRF; 0.11(0.10)/0.16(0.11)/0.19(0.12) control	<0.05*	No
Dutta et al. (2016)	(Radiological assessment)	Bone density -0.4 ± 0.16/0.4 ± 0.16/1.2 ± 0.13 PRF; -1.9 ± 0.10/-1.3 ± 0.21/0.1 ± 0.23 control	<0.05*	No
Yelamali et al. (2015)	(Radiological assessment)	Bone density 156.1095 ± 9.74862 PRF; 145.2115 ± 11.37617	<0.05*	No
Kumar et al. (2015)	(Radiological assessment)	Bone density M/S increase (68.8%)/(31.3%) PRF; M/S (93.3%)/(6.7%) control	0.083	No
Baslarli et al. (2015)	Scintigraphy	Osteoblastic activity 1st month: 4.6 (0.95) PRF; 4.71 (1.16) control 3rd month: 3.96 (1.0) PRF; 4.1 (1.1) control	>0.05	Yes
Gurbuzer et al. (2010)	Scintigraphy	Osteoblastic activity 1st month: 4.544 (1.02) PRF; 4.614 (1.02) control	>0.05	Yes

M, moderate increase of overall density; PRF, platelet-rich fibrin group; S, severe increase of overall density; SD, standard deviation.
*Statistical significance.

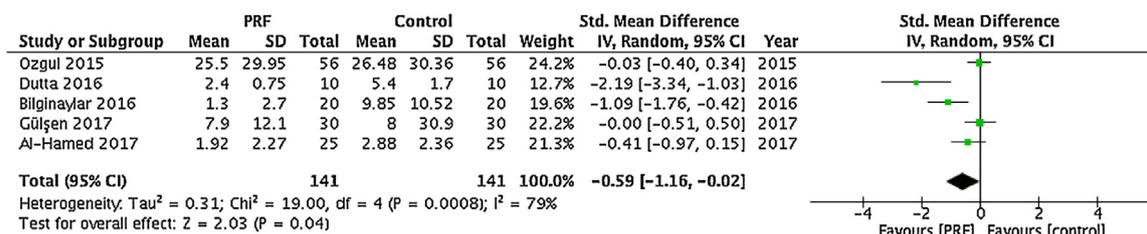


Fig. 4. Forest plot and meta-analysis of pain (third day). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

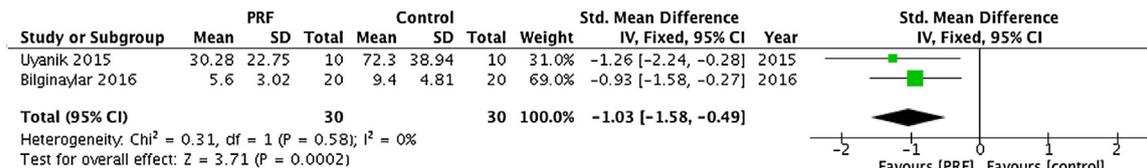


Fig. 5. Forest plot and meta-analysis of pain (sum of values in the first week). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

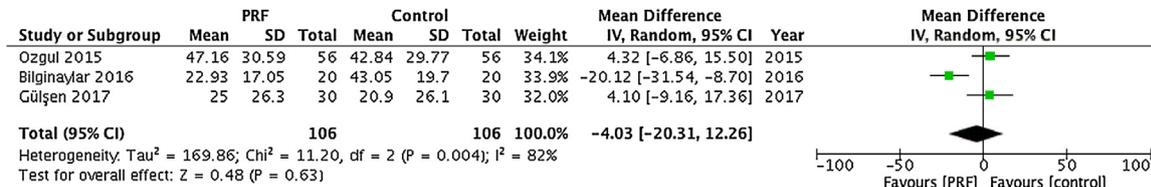


Fig. 6. Forest plot and meta-analysis of pain (first day). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

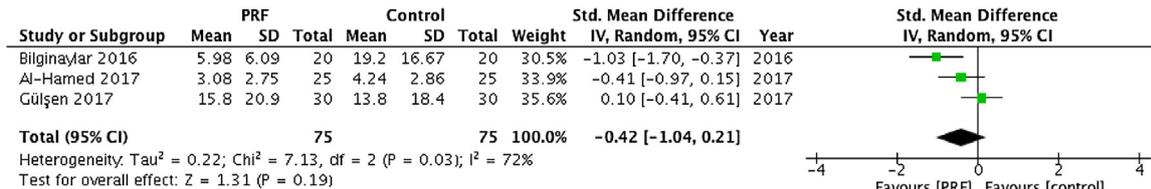


Fig. 7. Forest plot and meta-analysis of pain (second day). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

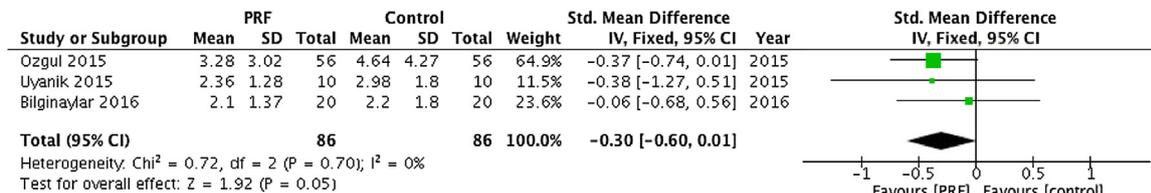


Fig. 8. Forest plot and meta-analysis of swelling (first day). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

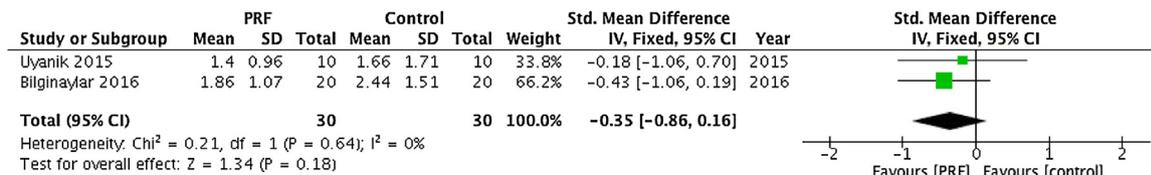


Fig. 9. Forest plot and meta-analysis of swelling (second day). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

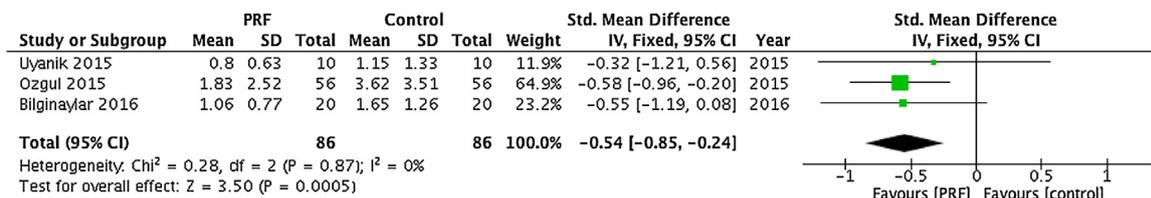


Fig. 10. Forest plot and meta-analysis of swelling (third day). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

showed similar results compared with the iliac bone graft. In this study the real contribution of PRF in bone healing cannot be measured. In theory, PRF works as a source of growth factors, increasing the vascularization and osteoblastic differentiation. More studies evaluating this effect are necessary to confirm these results.

A frequent topic of discussion regarding PRF is its potential to accelerate osteointegration in dental implant surgery. Although some studies have shown a beneficial effect of PRF, an evidence-

based validity to determine the real effect is necessary. The assessment of marginal bone level is one of the most important indicators of implant health. Two studies^{44,79} included in the qualitative analysis confirmed the positive effect of PRF on peri-implant marginal bone resorption. Some limitations of these studies are radiographic analysis and short follow-up period.

The present meta-analysis showed increased ISQ values during the early healing (first week and 1 month) when PRF

was utilized inside the osteotomy. However, it is necessary to cautiously interpret these results. Only two studies, with limited sample sizes and performed by the same group were included in this meta-analysis. Furthermore, the subgroup analysis of Oncu et al.⁴⁵ found statistically significant differences between PRF and control groups only in type 2 bone, and there were no difference between groups with other types of bone. The question of whether PRF can augment the value of ISQ during the osteointegration period

Table 7. Secondary outcome.

Authors (year)	Indication to use PRF	Outcome measured	Method of evaluation	Results	P^*	Meta-analysis
Gurler et al. (2017)	Sinus lift	(HI)	Clinical evaluation of soft tissue healing	HI: 7th day 4.2 ± 0.9 PRF/ 3.6 ± 0.7 control; HI: 14th 4.7 ± 0.4 PRF/ 4.4 ± 0.5 control	7th $P = 0.127$; 14th $P = 0.189$	No
Sununliganon et al. (2017)	Alveolar ridge preservation	(Bone density)	CBCT	?	Not statistically significant	No
Das et al. (2016)	Alveolar ridge preservation	(Bone density) coronal/middle and apical third (HU)	CT SCAN	842.43 ± 52.64 / 895.82 ± 186.67 / 727.34 ± 115.40 PRF; 695.45 ± 157.31 / 740.02 ± 173.06 / 735.54 ± 212.41 β -TCPC1	$P = 0.152/0.944/0.624$	No
Suttapreyasri et al. (2013)	Alveolar ridge Preservation	Marginal bone level (mesial and distal sites)	Intraoral radiographs	Mesial = PRF $2.22 \pm (0.51)$ /control $2.86 \pm (0.65)$; distal = PRF $2.08 \pm (0.09)$ /control $2.10 \pm (0.50)$	$P > 0.05$	No
Hauser et al. (2013)	Alveolar ridge Preservation	Marginal bone level (mesial and distal sites)	Intraoral radiographs	Mesial = PRF $1.21 \pm (0.40)$ /PRF + flap $0.86 \pm (0.34)$ / control $0.77 \pm (0.17)$; distal = PRF $0.76 \pm (0.25)$ /PRF + Flap $2.15 \pm (1.05)$ / control $2.07 \pm (0.81)$	$P < 0.05$	No
Movahedian et al. (2017)	Cleft patients	Volume of new bone formed (cm^3)	CBCT	ABG + AG + PRF = 0.61 ± 0.19 ; ICB 0.69 ± 0.19	$P = 0.409$	No

Table 7 (Continued)

Authors (year)	Indication to use PRF	Outcome measured	Method of evaluation	Results	P*	Meta-analysis
Shawky et al. (2016)	Cleft patients	(Bone density) Three points in axial cuts (HU)	CT SCAN	PRF = 360.82 ± (NR); control 384.03 ± (NR)	$P > 0.05$	No
Oncu et al. (2017)	Dental implants	ISQ	Osstell device	1st wk: 54.39 ± 15.88 PRF/48.67 ± 13.61 control; 1st Mo: 69.99 ± 11.87 PRF/61.03 ± 12.02 control; 3rd Mo: 71.19 ± 10.31 PRF/70.08 ± 11.2 control	$P = 0.002^*/0.002^*/0.682$	No
Oncu et al. (2015)	Dental implants	ISQ	Osstell device	1st wk: 69.29 ± 10.51 PRF/60.03 ± 12.2 control; 1st Mo: 77.19 ± 6.06 PRF/61.03 ± 12.02 control	$P = 0.002; P = 0.001$	No

β-TCP, beta-tricalcium phosphate; β-TCP/Cl, Beta-tricalcium phosphate with collagen; ABG, allogeneous bone graft; Flap, dental extraction with mucosal flap; ICB, iliac crest bone; HI, healing index; β-TCP/Cl, Beta-tricalcium phosphate with collagen; ISQ, implant stability quotient; POD, postoperative day; PRF, platelet-rich fibrin group; SD, standard deviation; VAS, visual analogue scale.

*P < 0.05.

remains unanswered, and more RCTs with adequate methodological designs are necessary.

A limitation of this systematic review was that the majority of studies showed insufficient information to permit judgment of ‘yes’ or ‘no’ regarding the sequence generation process and allocation concealment. Therefore, the unclear status could introduce selection bias, and in this case, systematic differences between baseline characteristics of the compared groups may be present. Another problem of this systematic review was that all included studies showed no trial registration, the only exception was the study of Gülşen et al.³² One of the concerns about no registrations is that results with statistically non-significant might have been selectively withheld from the final publication, thus introducing a reporting bias. The results should be interpreted with caution because a total of 14 studies (out of 30) showed a high risk of bias, therefore the plot of intervention effect estimates may be imprecise. Finally, the method used to estimate bone density and new bone formation were too diverse to allow good comparison. To analyse these variants, more studies using histomorphometry and tomography instead of radiography are required.

A total of 12 meta-analyses were performed in this study and the majority of these were a mixture of split-mouth design and parallel design. A more appropriate analysis of cross-over trials should take the individual correlation into account using a paired analysis⁸⁶, measuring the difference for each participant between the intervention and control, and taking the mean of these within-person differences. However, the limited amount of information in the primary studies made this approach impossible and the precision of results might be a little compromised. A unit-of-analysis error can arise from this approach leading to overestimation or underestimation of each study’s weight. Future RCTs with split-mouth design are encouraged to provide more information about paired analysis and correlation coefficient, thus permitting a more precise meta-analysis.

In summary, the available literature found suggest that PRF may perform better wound healing when it is used in oral surgical procedures. The most consistent indications found in this systematic review are: (1) to preserve alveolar dimensions after tooth extractions; and (2) to reduce dry sockets incidence after mandibular third molar surgery. PRF is very a promising biomaterial to enhance alveolar

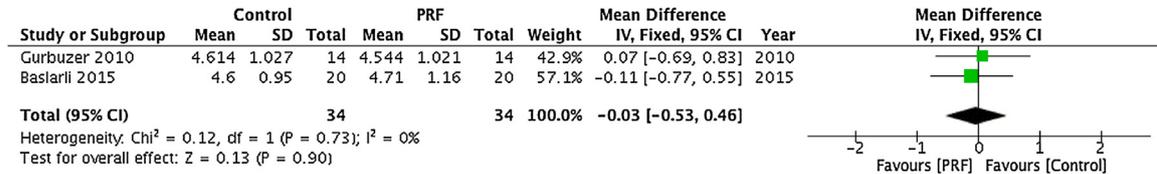


Fig. 11. Forest plot and meta-analysis of osteoblastic activity (first month). CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

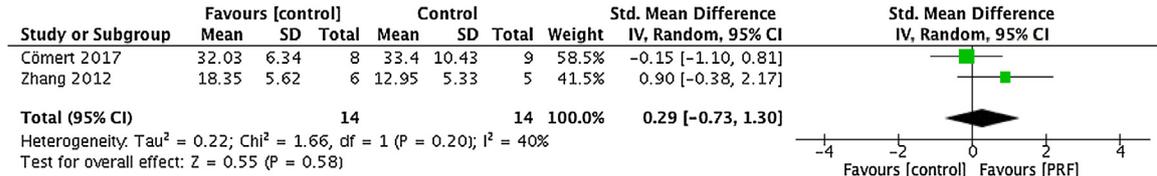


Fig. 12. Forest plot of percentage of new bone formation in sinus lift procedure. CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

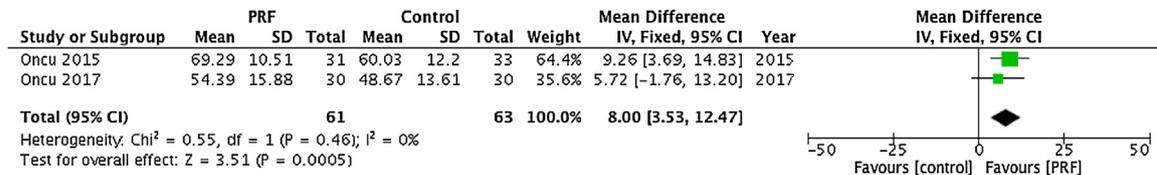


Fig. 13. Forest plot of implant stability quotient (ISQ) value after 1 week. CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

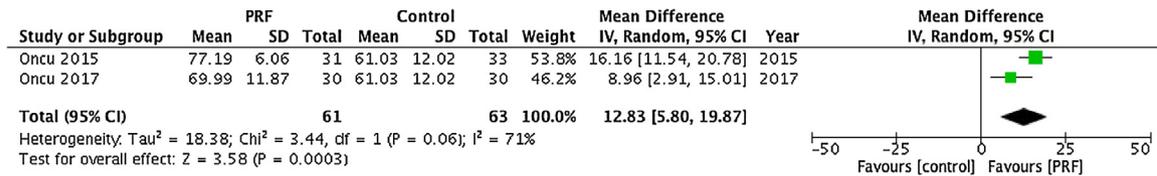


Fig. 14. Forest plot of implant stability quotient (ISQ) value after 1 month. CI, confidence interval; PRF, platelet-rich fibrin; SD, standard deviation.

cleft reconstruction and to reduce peri-implant marginal bone resorption, although only a limited quantity of information regarding these indications is available. The effect of PRF in sinus augmentation showed no advantage in percentage of final new bone formation, however the healing time might be reduced when PRF is added. Due to the lack of studies with low risk of bias and homogeneous methodology to permit a more precise meta-analysis, further RCTs are needed to confirm the evidence for these surgical indications.

Funding

None.

Competing interests

None declared.

Ethical approval

Not required.

Patient consent

Not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ijom.2018.07.007>.

References

1. Choukroun J, Adda F, Schoeffler C, Vervelle A. Une opportunité en paro-implantologie: le PRF. *Implantodontie* 2000;42:55–62.

2. Choukroun J, Diss A, Simonpieri A, Girard MO, Schoeffler C, Dohan SL, Dohan AJ, Mouhyi J, Dohan DM. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part V: histologic evaluations of PRF effects on bone allograft maturation in sinus lift. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101(3):299–303.
3. Choukroun J, Diss A, Simonpieri A, Girard MO, Schoeffler C, Dohan SL, Dohan AJ, Mouhyi J, Dohan DM. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part IV: clinical effects on tissue healing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101(3):e56–60.
4. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, Gogly B. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101(3):e37–44.
5. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, Gogly B. Platelet-rich

- fibrin (PRF): a second-generation platelet concentrate. Part II: platelet-related biologic features. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;**101**(3):e45–50.
6. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, Gogly B. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;**101**(3):e51–5.
 7. Mazor Z, Horowitz RA, Del Corso M, Prasad HS, Rohrer MD, Ehrenfest DMD. Sinus floor augmentation with simultaneous implant placement using Choukroun's platelet-rich fibrin as the sole grafting material: a radiologic and histologic study at 6 months. *J Periodontology* 2009;**80**(12):2056–64.
 8. Eshghpour M, Dastmalchi P, Nekooei AH, Nejat A. Effect of platelet-rich fibrin on frequency of alveolar osteitis following mandibular third molar surgery: a double-blinded randomized clinical trial. *J Oral Maxillofac Surg* 2014;**72**(8):1463–7.
 9. Kim JW, Kim SJ, Kim MR. Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study. *Br J Oral Maxillofac Surg* 2014;**52**(9):854–9.
 10. Boora P, Rathee M, Bhorla M. Effect of platelet rich fibrin (PRF) on peri-implant soft tissue and crestal bone in one-stage implant placement: a randomized controlled trial. *J Clin Diagn Res* 2015;**9**(4):Zc18–21.
 11. Shawky H, Seifeldin SA. Does platelet-rich fibrin enhance bone quality and quantity of alveolar cleft reconstruction? *Cleft Palate Craniofac J* 2016;**53**(5):597–606.
 12. Temmerman A, Vandessel J, Castro A, Jacobs R, Teughels W, Pinto N, Quirynen M. The use of leucocyte and platelet-rich fibrin in socket management and ridge preservation: a split-mouth, randomized, controlled clinical trial. *J Clin Periodontol* 2016;**43**(11):990–9.
 13. Bilginaylar K. The use of platelet-rich fibrin for immediate closure of acute oroantral communications: an alternative approach. *J Oral Maxillofac Surg* 2018;**76**(2):278–86.
 14. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol* 2009;**27**(3):158–67.
 15. Pirraco RP, Reis RL, Marques AP. Effect of monocytes/macrophages on the early osteogenic differentiation of hBMSCs. *J Tissue Eng Regen Med* 2013;**7**(5):392–400.
 16. Dohan Ehrenfest DM, Del Corso M, Diss A, Mouhyi J, Charrier JB. Three-dimensional architecture and cell composition of a Choukroun's platelet-rich fibrin clot and membrane. *J Periodontol* 2010;**81**(4):546–55.
 17. Kobayashi E, Fluckiger L, Fujioka-Kobayashi M, Sawada K, Sculean A, Schaller B, Miron RJ. Comparative release of growth factors from PRP, PRF, and advanced-PRF. *Clin Oral Investig* 2016;**20**(9):2353–60.
 18. Fujioka-Kobayashi M, Miron RJ, Hernandez M, Kandalam U, Zhang Y, Choukroun J. Optimized platelet-rich fibrin with the low-speed concept: growth factor release, biocompatibility, and cellular response. *J Periodontol* 2017;**88**(1):112–21.
 19. Canellas JV, Medeiros PJ, Figueredo CM, Fischer R, Ritto F. Has platelet-rich fibrin been shown effective for oral and maxillofacial surgical procedures? A systematic review and meta-analysis. *PROSPERO* 2017. CRD42017078422. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017078422.
 20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.
 21. Gurbuzer B, Pikkoken L, Tunali M, Urhan M, Kucukodaci Z, Ercan F. Scintigraphic evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. *J Oral Maxillofac Surg* 2010;**68**(5):980–9.
 22. Ruga E, Gallesio C, Boffano P. Platelet-rich fibrin and piezoelectric surgery: a safe technique for the prevention of periodontal complications in third molar surgery. *J Craniofac Surg* 2011;**22**(5):1951–5.
 23. Baslarli O, Tumer C, Ugur O, Vatankulu B. Evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. *Med Oral Patol Oral Cir Bucal* 2015;**20**(1):e111–6.
 24. Kumar N, Prasad K, Ramanujam L, Ranganath R, Dexith J, Chauhan A. Evaluation of treatment outcome after impacted mandibular third molar surgery with the use of autologous platelet-rich fibrin: a randomized controlled clinical study. *J Oral Maxillofac Surg* 2015;**73**(6):1042–9.
 25. Ozgul O, Senses F, Er N, Tekin U, Tuz HH, Alkan A, Kocuyigit ID, Atil F. Efficacy of platelet rich fibrin in the reduction of the pain and swelling after impacted third molar surgery: randomized multicenter split-mouth clinical trial. *Head Face Med* 2015;**11**:37.
 26. Uyanik LO, Bilginaylar K, Etikan I. Effects of platelet-rich fibrin and piezosurgery on impacted mandibular third molar surgery outcomes. *Head Face Med* 2015;**11**:25.
 27. Yelamali T, Saikrishna D. Role of platelet rich fibrin and platelet rich plasma in wound healing of extracted third molar sockets: a comparative study. *J Maxillofac Oral Surg* 2015;**14**(2):410–6.
 28. Bilginaylar K, Uyanik LO. Evaluation of the effects of platelet-rich fibrin and piezosurgery on outcomes after removal of impacted mandibular third molars. *Br J Oral Maxillofac Surg* 2016;**54**(6):629–33.
 29. Dutta SR, Passi D, Singh P, Sharma S, Singh M, Srivastava D. A randomized comparative prospective study of platelet-rich plasma, platelet-rich fibrin, and hydroxyapatite as a graft material for mandibular third molar extraction socket healing. *Natl J Maxillofac Surg* 2016;**7**(1):45–51.
 30. Kumar YR, Mohanty S, Verma M, Kaur RR, Bhatia P, Kumar VR, Chaudhary Z. Platelet-rich fibrin: the benefits. *Br J Oral Maxillofac Surg* 2016;**54**(1):57–61.
 31. Al-Hamed FS, Al-Saleh MAQ, Tawfik MA, Abdelfadil E. Efficacy of platelet-rich fibrin after mandibular third molar extraction: a systematic review and meta-analysis reply. *J Oral Maxillofac Surg* 2017;**75**(8):1577–8.
 32. Gulsen U, Senturk MF. Effect of platelet rich fibrin on edema and pain following third molar surgery: a split mouth control study. *BMC Oral Health* 2017;**17**(1):79.
 33. Varghese MP, Manuel S, Kumar S. Potential for osseous regeneration of platelet-rich fibrin-A comparative study in mandibular third molar impaction sockets. *J Oral Maxillofac Surg* 2017;**75**(7):1322–9.
 34. Tatullo M, Marrelli M, Cassetta M, Pacifici A, Stefanelli LV, Scacco S, Dipalma G, Pacifici L, Inchingolo F. Platelet Rich Fibrin (P.R.F) in reconstructive surgery of atrophied maxillary bones: clinical and histological evaluations. *Int J Med Sci* 2012;**9**(10):872–80.
 35. Zhang Y, Tangl S, Huber CD, Lin Y, Qiu L, Rausch-Fan X. Effects of Choukroun's platelet-rich fibrin on bone regeneration in combination with deproteinized bovine bone mineral in maxillary sinus augmentation: a histological and histomorphometric study. *J Craniomaxillofac Surg* 2012;**40**(4):321–8.
 36. Gassling V, Purcz N, Braesen JH, Will M, Gierloff M, Behrens E, Acil Y, Wiltfang J. Comparison of two different absorbable membranes for the coverage of lateral osteotomy sites in maxillary sinus augmentation: a preliminary study. *J Craniomaxillofac Surg* 2013;**41**(1):76–82.
 37. Gurler G, DelilbaSi C. Effects of leukocyte-platelet rich fibrin on postoperative complications of direct sinus lifting. *Minerva Stomatol* 2016;**65**(4):207–12.
 38. Cömert Kiliç S, Güngörmüş M, Parlak SN. Histologic and histomorphometric assessment of sinus-floor augmentation with beta-tricalcium phosphate alone or in combination with pure-platelet-rich plasma or platelet-rich fibrin: a randomized clinical trial. *Clin Implant Dent Relat Res* 2017;**19**(5):959–67.
 39. Hauser F, Gaydarov N, Badoud I, Vazquez L, Bernard JP, Ammann P. Clinical and histological evaluation of postextraction platelet-rich fibrin socket filling: a prospective randomized controlled study. *Implant Dent* 2013;**22**(3):295–303.
 40. Suttapreyasri S, Leepong N. Influence of platelet-rich fibrin on alveolar ridge preservation. *J Craniofac Surg* 2013;**24**(4):1088–94.
 41. Das S, Jhingran R, Bains VK, Madan R, Srivastava R, Rizvi I. Socket preservation by beta-tri-calcium phosphate with collagen

- compared to platelet-rich fibrin: a clinico-radiographic study. *Eur J Dent* 2016;**10**(2):264–76.
42. Thakkar DJ, Deshpande NC, Dave DH, Narayanar SD. A comparative evaluation of extraction socket preservation with demineralized freeze-dried bone allograft alone and along with platelet-rich fibrin: a clinical and radiographic study. *Contemp Clin Dent* 2016;**7**(3):371–6.
 43. Sununliganon L, Jiumkim A, Narkbuakaew W. Effect of platelet-rich fibrin in healing socket using cone beam computed tomography analysis. *J Oral Maxillofac Surg* 2017;**46**(Suppl. 1):352.
 44. Boora P, Rathee M, Bhorla M. Effect of Platelet Rich Fibrin (PRF) on peri-implant soft tissue and crestal bone in one-stage implant placement: a randomized controlled trial. *J Clin Diagn Res* 2015;**9**(4):ZC18–21.
 45. Öncü E, Alaaddinoglu EE. The effect of platelet-rich fibrin on implant stability. *Int J Oral Maxillofac Implants* 2015;**30**(3):578–82.
 46. Oncu E, Erbeyoglu AA. Enhancement of immediate implant stability and recovery using platelet-rich fibrin. *Int J Periodontics Restorative Dent* 2017. <http://dx.doi.org/10.11607/prd.2505>. [Epub ahead of print].
 47. Movahedian Attar B, Naghdi N, Etemadi Sh M, Mehdizadeh M. Chin Symphysis bone, allograft, and platelet-rich fibrin: is the combination effective in repair of alveolar cleft? *J Oral Maxillofac Surg* 2017;**75**(5):1026–35.
 48. Gurbuzer B, Pikkoken L, Tunali M, Urban M, Kucukodaci Z, Ercan F. Scintigraphic evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. *J Oral Maxillofac Surg* 2010;**68**(5):980–9.
 49. Baslarli O, Tumer C, Ugur O, Vatankulu B. Evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. *Med Oral Patol Oral Cir Bucal* 2015;**20**(1):e111–6.
 50. Al-Hamed FS, Tawfik MAM, Abdelfadil E. Clinical effects of platelet-rich fibrin (PRF) following surgical extraction of lower third molar. *Saudi J Dent Res* 2017;**8**(1–2):19–25.
 51. Singh A, Kohli M, Gupta N. Platelet rich fibrin: a novel approach for osseous regeneration. *J Maxillofac Oral Surg* 2012;**11**(4):430–4.
 52. Anwandter A, Bohmann S, Nally M, Castro AB, Quirynen M, Pinto N. Dimensional changes of the post extraction alveolar ridge, preserved with Leukocyte- and Platelet Rich Fibrin: a clinical pilot study. *J Dent* 2016;**52**:23–9.
 53. Doiphode AM, Hegde P, Mahindra U, Santhosh Kumar SM, Tenglikar PD, Tripathi V. Evaluation of the efficacy of platelet-rich plasma and platelet-rich fibrin in alveolar defects after removal of impacted bilateral mandibular third molars. *J Int Soc Prev Community Dent* 2016;**6**(Suppl. 1):S47–52.
 54. Asaka T, Ohga N, Yamazaki Y, Sato J, Satoh C, Kitagawa Y. Platelet-rich fibrin may reduce the risk of delayed recovery in tooth-extracted patients undergoing oral bisphosphonate therapy: a trial study. *Clin Oral Investig* 2017;**21**(7):2165–72.
 55. Marenzi G, Riccitiello F, Tia M, di Lauro A, Sammartino G. Influence of Leukocyte- and Platelet-Rich Fibrin (L-PRF) in the healing of simple postextraction sockets: a split-mouth study. *Biomed Res Int* 2015;336927. <http://dx.doi.org/10.1155/2015/369273>.
 56. Du Toit J, Siebold A, Dreyer A, Gluckman H. Choukroun platelet-rich fibrin as an autogenous graft biomaterial in preimplant surgery: results of a preliminary randomized, human histomorphometric, split-mouth study. *Int J Periodontics Restorative Dent* 2016;**36**(Suppl):s75–86.
 57. Chakravarthi S. Platelet rich fibrin in the management of established dry socket. *Korean Assoc Oral Maxillofac Surg* 2017;**43**(3):160–5.
 58. Hussain I, Singh S, Jain H, Kumar S, Anand KR, Batool N, Saikia J. A prospective randomised clinical study on evaluation of platelet-rich fibrin versus zinc oxide eugenol in the management of alveolar osteitis. *Oral Surg* 2018;**11**(1):41–9. <http://dx.doi.org/10.1111/ors.12299>.
 59. Girish Rao S, Bhat P, Nagesh KS, Rao GH, Mirle B, Kharbhari L, Gangaprasad B. Bone regeneration in extraction sockets with autologous platelet rich fibrin gel. *J Maxillofac Oral Surg* 2013;**12**(1):11–6.
 60. Cheng Y, Liu M. Osteogenic effects of concentrated growth factors applied in maxillary sinus floor elevation via a lateral window approach with simultaneous implant placement: study protocol for a single-center randomized controlled trial. *Chinese J Tissue Eng Res* 2017;**21**(4):574–9.
 61. Park JH, Kim JW, Kim SJ. Does the addition of bone morphogenetic protein 2 to platelet-rich fibrin improve healing after treatment for medication-related osteonecrosis of the jaw? *J Oral Maxillofac Surg* 2017;**75**(6):1176–84.
 62. Hoaglin DR, Lines GK. Prevention of localized osteitis in mandibular third-molar sites using platelet-rich fibrin. *Int J Dent* 2013;875380.
 63. Tajima N, Ohba S, Sawase T, Asahina I. Evaluation of sinus floor augmentation with simultaneous implant placement using platelet-rich fibrin as sole grafting material. *Int J Oral Maxillofac Implants* 2013;**28**(1):77–83.
 64. Norholt SE, Hartlev J. Surgical treatment of osteonecrosis of the jaw with the use of platelet-rich fibrin: a prospective study of 15 patients. *Int J Oral Maxillofac Surg* 2016;**45**(10):1256–60.
 65. Oncu E, Alaaddinoolu E. Effect of platelet-rich fibrin on osseointegration. *Int J Oral Maxillofac Surg* 2013;**42**(10):1265–6.
 66. Kim JH, Lee DW, Ryu DM. Effect of platelet-rich fibrin on pain and swelling after surgical extraction of third molars. *Tissue Eng Regen Med* 2011;**8**(4):80–6.
 67. Amini P, Milani A, Rahmani N. Radiological assessment of using allograft in combination with platelet-rich fibrin in alveolar cleft grafting. *J Mazandaran Univ Medi Sci* 2016;**26**(142):175–85.
 68. Suttapreysari S, Leepong N. Influence of platelet-rich fibrin on alveolar ridge preservation. *J Craniofac Surg* 2013;**24**(4):1088–94.
 69. Al-Hamed FS, Tawfik MAM, Abdelfadil E, Al-Saleh MAQ. Efficacy of platelet-rich fibrin after mandibular third molar extraction: a systematic review and meta-analysis. *J Oral Maxillofac Surg* 2017;**75**(6):1124–35.
 70. Canellas JV, Ritto FG, Medeiros PJD. Evaluation of postoperative complications after mandibular third molar surgery with the use of platelet-rich fibrin: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg* 2017;**46**(9):1138–46.
 71. He Y, Chen J, Huang Y, Pan Q, Nie M. Local application of platelet-rich fibrin during lower third molar extraction improves treatment outcomes. *J Oral Maxillofac Surg* 2017;**75**(12):2497–506.
 72. Del Fabbro M, Bortolin M, Taschieri S. Is autologous platelet concentrate beneficial for post-extraction socket healing? A systematic review. *Int J Oral Maxillofac Surg* 2011;**40**(9):891–900.
 73. Del Fabbro M, Corbella S, Taschieri S, Francetti L, Weinstein R. Autologous platelet concentrate for post-extraction socket healing: a systematic review. *Eur J Oral Implantol* 2014;**7**(4):333–44.
 74. Del Fabbro M, Bucchi C, Lolato A, Corbella S, Testori T, Taschieri S. Healing of post-extraction sockets preserved with autologous platelet concentrates. A systematic review and meta-analysis. *J Oral Maxillofac Surg* 2017;**75**(8):1601–15.
 75. Brignardello-Petersen R. Platelet-rich fibrin might not provide a benefit in healing and complications after third-molar extraction. *J Am Dent Assoc* 2017;**148**(6)e73.
 76. Dos Santos Canellas JV, Ritto FG, Medeiros PJD. Efficacy of platelet-rich fibrin after mandibular third molar extraction: a systematic review and meta-analysis. *J Oral Maxillofac Surg* 2017;**75**(8):1576–7.
 77. Mazor Z, Horowitz RA, Del Corso M, Prasad HS, Rohrer MD, Dohan Ehrenfest DM. Sinus floor augmentation with simultaneous implant placement using Choukroun's platelet-rich fibrin as the sole grafting material: a radiologic and histologic study at 6 months. *J Periodontol* 2009;**80**(12):2056–64.
 78. Gassling V, Douglas T, Warnke PH, Açil Y, Wiltfang J, Becker ST. Platelet-rich fibrin membranes as scaffolds for periosteal tissue engineering. *Clin Oral Implants Res* 2010;**21**(5):543–9.
 79. Oncu E, Kaymaz E. Assessment of the effectiveness of platelet rich fibrin in the treatment of Schneiderian membrane perforation. *Clin Implant Dent Relat Res* 2017;**19**(6):1009–14.

80. Morjaria KR, Wilson R, Palmer RM. Bone healing after tooth extraction with or without an intervention: a systematic review of randomized controlled trials. *Clin Implant Dent Relat Res* 2014;**16**(1):1–20.
81. Iocca O, Farcomeni A, Pardinás Lopez S, Talib HS. Alveolar ridge preservation after tooth extraction: a Bayesian Network meta-analysis of grafting materials efficacy on prevention of bone height and width reduction. *J Clin Periodontol* 2017;**44**(1):104–14.
82. Araujo MG, Sukekava F, Wennstrom JL, Lindhe J. Ridge alterations following implant placement in fresh extraction sockets: an experimental study in the dog. *J Clin Periodontol* 2005;**32**(6):645–52.
83. Scala A, Lang NP, Schweikert MT, de Oliveira JA, Rangel-Garcia Jr I, Botticelli D. Sequential healing of open extraction sockets: an experimental study in monkeys. *Clin Oral Implants Res* 2014;**25**(3):288–95.
84. Castro AB, Meschi N, Temmerman A, Pinto N, Lambrechts P, Teughels W, Quirynen M. Regenerative potential of leucocyte- and platelet-rich fibrin. Part B: sinus floor elevation, alveolar ridge preservation and implant therapy. A systematic review. *J Clin Periodontol* 2017;**44**(2):225–34.
85. Movahedian Attar B, Naghdi N, Etemadi Sh M, Mehdizadeh M. Chin symphysis bone, allograft, and platelet-rich fibrin: is the combination effective in repair of alveolar cleft? *J Oral Maxillofac Surg* 2017;**75**(5):1026–35.
86. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;**31**(1):140–9.

Address:
João Vitor dos Santos Canellas
Rio de Janeiro State University
Rua Boulevard 28 de Setembro
157 Vila Isabel
Rio de Janeiro
RJ 20551-030
Brazil
Tel.: +5521971507053
E-mail: drcanellas@icloud.com