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Review Article

Efficacy of platelet-rich fibrin on socket healing after mandibular third molar extractions

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ABSTRACT

Objective: To investigate the efficacy of platelet-rich fibrin (PRF) for the socket healing after removal of mandibular third molars when compared to natural wound healing.
Methods: This systematic review and meta-analysis were conducted according to PRISMA guidelines. The eligibility criteria comprised randomized controlled trials (RCTs) comparing the clinical outcomes of PRF with that of natural healing. Outcomes measured include post-operative pain, analgesics taken, swelling, soft tissue healing, bone healing, complication rates, as well as incidence of alveolar osteitis (AO, dry socket).
Results: From 194 articles identified, 18 RCTs were included. Overall, 15 of 18 RCTs demonstrated significantly better outcomes in terms of reduced complication rates, healing rates, or patient reported pain scores in the PRF group when compared to control. Data from all studies demonstrated that PRF was able to significantly lower the rate of AO from 15.9 % in the control group to 5.8 % in the PRF group, representing a ~3-fold reduction. All studied investigating soft tissue healing with PRF demonstrated better outcomes in favor of PRF group.
Conclusions: PRF was shown to decrease post-op pain/morbidity, have favored soft tissue healing, and possess lower complication rates or AO incidence. PRF therefore proves to be a viable treatment adjunct following removal of mandibular third molars.

Contents

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Introduction

Extraction of mandibular third molars is one of the most frequently performed dental surgical procedures [1]. While various surgical techniques and materials have been designed to accelerate the healing process after extraction [1–6], to date extractions specific to mandibular third molars remain those associated with the highest rate of potential complications. Specifically, alveolar osteitis (AO, dry socket) has been a well-known side effect following removal of mandibular third molars (especially those impacted) with well-known clinical manifestations including a partial or total disintegrated blood clot within the healing socket, resulting in prolonged inflammation, exposed bone, delayed healing, and gradually increasing severity of pain [7].

Reports from the literature suggests that while the incidence of AO has been reported relatively low in routine dental extractions, this rate has been reported much higher (3.9–29.6 %) when focused specifically on mandibular third molars [8,9]. Therefore, precautions and effective strategies should be employed to minimize patient discomfort and improve clinical outcomes with many predisposing factors, including pre-existing systemic diseases, operative technique, smoking, oral contraceptives, anticoagulant medication, and poor oral hygiene and/or pre-existing local infection, being identified as risk factors increasing the rate of occurrence [7,10–12].

One strategy that has gained popularity in recent years has been the use of platelet concentrates [13–15]. While platelet rich plasma (PRP) was first utilized in regenerative medicine and dentistry owing to its supra-physiological doses of platelets and accompanying growth factors, more recently, its incorporation of anticoagulants has since been shown to interfere with the angiogenic and regenerative responses mediated by platelets [16]. For these reasons, a second generation platelet concentrate termed platelet rich fibrin (PRF) has been more favorably utilized with anticoagulant removal [17]. A number of randomized clinical studies in various avenues of dentistry have further demonstrated its ability to either promote hard or soft tissues [13–15].

PRF offers one main advantage over PRP in that a fibrin scaffold is formed following centrifugation which can then serve as a scaffold to place in the healing socket post-extraction. Furthermore, its inclusion of supra-physiological concentrations of leukocytes allows some immune defense against a potential bacterial invasion.

The aim of this systematic review and meta-analysis was therefore to investigate the effectiveness of PRF for the management of mandibular third molar extractions from randomized clinical trials (RCTs). As a primary outcome, PRF was investigated for its ability to reduce the rate of alveolar osteitis. Secondary outcomes included post-operative pain, analgesics taken, swelling, soft tissue healing, bone healing, and additional complication rates.

Methods

Protocol

This systematic review (SR) followed the recommendations of the PRISMA guidelines [18]. The protocol for this SR was based on PRISMA-P [19]. A protocol including all aspects of a systematic review methodology was developed prior to initiation of this review. This included definition of the focused question; a PICO (patient, intervention, comparison, outcome) question, a defined search strategy; study inclusion criteria; determination of outcome measures; screening methods, data extraction and analysis; and data synthesis. There were no deviations from the initial protocol.

Focused question

Is there an advantage for using PRF to enhance socket healing and reduce associated complications after removal of mandibular third molars when compared to natural wound healing.

Eligibility criteria and study selection process

The inclusion criteria were based on the PICOS strategy [20]. The search-and-screening process was conducted by two independent reviewing authors (M.F.K and R.J.M), commencing with the analysis of titles and abstracts. Next, full papers were selected for careful reading and matched with the eligibility criteria for future data extraction. Disagreements between the reviewing authors were resolved through careful discussion. Only studies meeting the following criteria were included:

- Population: Systemically healthy humans in need of tooth extraction.
- Intervention: Use of PRF to promote socket healing and reduce associated complication sequelae after removal of mandibular third molars with a follow-up period of at least 6 months.
- Comparison: PRF vs. natural wound healing
- Outcomes: The outcome variable was post-operative pain, analgesics taken, swelling, soft tissue healing, bone healing, complication rates, as well as incidence of AO.
- Study design: RCTs with a minimum of 10 patients.

Search strategy

PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, Scopus, Embase, and Lilacs were used to search for articles that were published before June 2020 without other restrictions regarding date or language. A search of the gray literature using the Literature Report [21] and OpenGrey [22] databases was also conducted. Finally, the study reference lists were evaluated (cross-

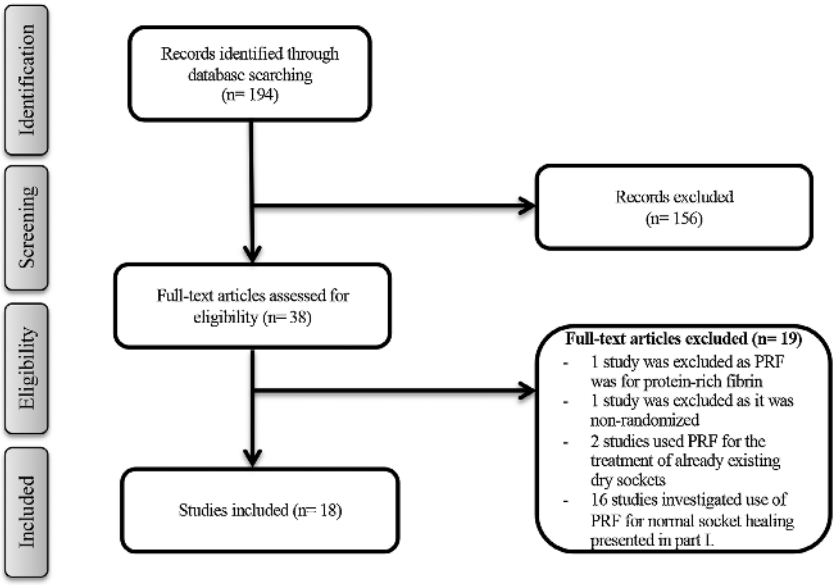

Fig. 1. Flow diagram (PRISMA format) of the screening and selection process.

referenced) to identify other studies for potential inclusion. A combination of several search terms and search strategies were applied to identify appropriate studies (Supplemental Tables 1, 2). Reference lists of review articles and of the included articles in the present review were screened. Finally, a hand search of the *Journal of Clinical Periodontology*, *Journal of Dental Research, Journal of Periodontal Research*, *Journal of Periodontology*, *Clinical Oral Implants Research, Clinical Implant Dentistry and Related Research, Clinical Oral Investigations* and the *International Journal of Periodontics and Restorative Dentistry* was performed from January 2000 till June 2020.

Criteria for study selection and inclusion

Study selection considered only articles published in English, describing the human clinical evaluation of PRF for the above-indicated search strategies. Only human studies of more than 10 patients evaluating the comparative effects of PRF to an appropriate control for at least 6 months follow-up were included. All human studies evaluating PRF in a case report or case series or retrospective clinical studies as well as animal and in vitro studies were excluded. In addition, papers with incomplete data collection were also excluded.

Assessments of the risk of bias

Two reviewing authors (V.M. and R.J.M.) analyzed the risk of bias. The RoB 2 (a revised Cochrane risk-of-bias tool for randomized trials) [23] was used to analyze the risk of bias in RCTs. Each study was analyzed in relation to five domains: risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions, missing outcome data, risk of bias in the measurement of the outcome, and risk of bias in the selection of the reported research. Studies were classified as having a low risk, some concerns, or high risks of bias for each domain. The overall risk of biased judgment used the following criteria: low risk, when the five areas of the study were judged as low risk; some concerns, when the study is judged as raising some concerns in at least one area; and high risk, when the study is judged to be at high risk in at least one domain or when the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Data synthesis

The study data were extracted by M.F.K. and R.J.M. The following data, when available, were extracted from the included studies: authors, study design, follow-up, number of treated cases, number of subjects, age range, gender, number of smokers, surgical technique, conclusions, incidence rate of AO (%), pain VAS score, soft tissue healing response, bone response, centrifugation system, volume of blood drawn, and centrifugation parameters. Due to the heterogenicity of the investigated parameters in the studies, no meta-analysis could be performed. Instead, the data was reported in a systematic fashion with an overview of all studies fitting the search descriptions. Thereafter, data was extracted from the collection of articles and summarized in separate tables and discussed accordingly.

Statistical analysis

The binary variables of the included studies were meta-analyzed when at least two studies assessed had the same data types. For the binary outcomes (e.g. AO), the intervention effects estimated were expressed as a percentage risk ratio (RR) with a 95 % confidence interval (CI). The inverse-variance method was used for the random effects model or the fixed effects model. Heterogeneity was assessed using the Chi-squared test and any impact on the meta-analysis was quantified via I^2. Values of $\leq$ 25 % were classified as low heterogeneity, and values of up to 50 % and above 70 % were classified as medium and high heterogeneity, respectively. When a significant heterogeneity was found ($P < 0.10$), the results of the random effects model were validated. When low heterogeneity was verified, the fixed effects model was considered. The level of statistical significance was set as $P < 0.05$. The data were analyzed using a statistical software Review Manager (version 5.2.8; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). A funnel plot was drawn to assess publication bias across studies.

Results

Literature search

The process of the search including the selection and reasons for excluding potential studies are shown in Fig. 1. In total, of the 194

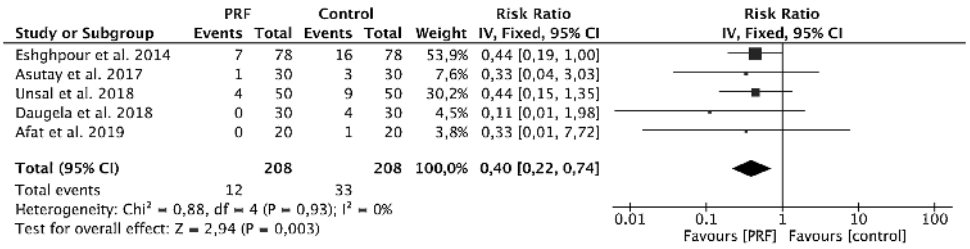

Fig. 2. Forest plot for the event reduction in AO (reported in %) for mandibular third molars.

articles originally screened, 18 RCTs [24–41], published between 2010 and 2019, were included meeting the inclusion criteria.

Study characteristics

In total, 1097 mandibular third molar sites were compared with/without PRF in 643 research participants (mean age of 23.6 ± 2.41). The most common protocol utilized was a 3000 RPM for 10 min protocol (10 of 18 studies = 56 % of studies).

PRF versus natural wound healing for the management of extraction socket after removal of mandibular third molars

Table 1 demonstrates the accumulation of 18 RCTs evaluating the use of PRF post-extraction of mandibular 3rd molars when compared to natural wound healing [24–41]. Most studies (15 of 18 studies) showed PRF improved either the rate of AO development, improved soft tissue healing and/or decreased post-operative pain and/or number of analgesics taken when compared to control group (Table 1).

Out of all 18 RCTs, PRF was most frequently investigated for its ability to decrease post-operative pain and lower the number of analgesics. In a study by Uyanik and colleagues, patients were assessed for pain, the number of analgesics taken, trismus, and swelling on days 1, 2, 3, and 7 following removal of impacted 3rd molars [27]. A significant reduction in pain on days 1, 2, and 3, and in the number of analgesics taken on days 2 and 3 was reported in the PRF groups. Overall, PRF was shown to reduce post-operative pain largely due to the improvements in soft tissue healing while reducing infections due to presence of microbial-fighting immune cells (leukocytes) [27]. This has now been shown in over a dozen RCTs with accompanying lower analgesics taken by patients post-op (Table 1).

One study examined the amount of additional time required to manage complications post-op in patients with/without PRF after removing the mandibular third molars [41]. It was found that an additional 6.5 h of surgical time was needed to manage local infections necessitating extra costs to resolve the problems [42]. The findings suggest a low cost, autogenous, soluble, biologic material (PRF) could prove to be an effective strategy to minimize localized AO in all cases requiring mandibular third-molar socket healing [42].

Meta-analysis

Only the AO parameter was analyzed through pairwise meta-analysis. The fixed effect model was used to access the occurrence of AO between the PRF and control groups due to the absence of heterogeneity found (P = 0.93; I^2 = 0 %). The sockets that received PRF had a significantly (P = 0.003) lower incidence of AO when compared to the control groups, with a RR of 0.40 (95 % CI: 0.22–0.74) (Fig. 2). The funnel plot demonstrated a fairly symmetrical distribution indicating low risk of publication bias (Fig. 3). The overall

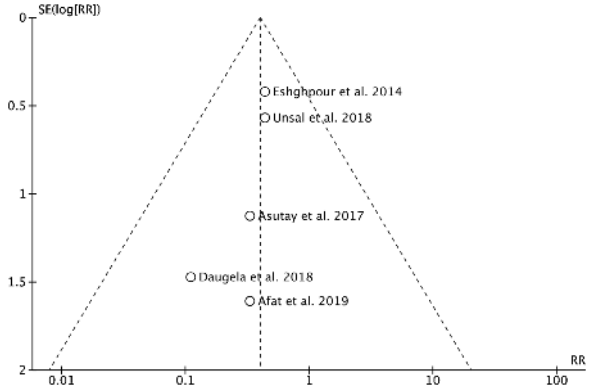

Fig. 3. Funnel plot for the studies reporting AO (reported in %) for mandibular third molars.

rate of AO from all studies was 15.9 % in the control group and 5.8 % in the PRF group, representing a close to 3-fold decrease.

Assessment of the risk of bias

The overall risk of biased judgment from six studies [26,28,30,32,38,41] was classified as "some concerns." These studies showed the possibility of bias in the randomization process or bias due to deviations from intended interventions. All other studies were classified as "low risk of bias." The ROB 2 analysis is shown in Supplemental Table 2.

Discussion

The present SR investigated the use of PRF to facilitate healing of mandibular third molars extraction socket. Surprisingly, this area has been one of the most frequently investigated in RCTs specific to PRF. Recently, various SRs performed by our group investigating the use of PRF for various clinical applications in regenerative dentistry found that 17 RCTs were gathered investigating the use of PRF for gingival recession coverage, 27 RCTs investigated its use for intrabony defect regeneration, and 16 RCTs investigated its use for extraction sites. Herein, we presented 18 RCTs that investigated the use of PRF when compared to natural healing for the management of mandibular third molars. Thus, many conclusions could be reached owing to the array of data available on this topic spanning roughly 1000 cases grafted with/without PRF for the management of mandibular third molars.

Of the 18 studies, 5 RCTs investigated the rate of AO development post extraction. While the advantages of utilizing PRF following 3rd molars varied substantially, the following studies highlight the use of PRF to reduce the rate of AO. In the majority of studies, significant improvements were observed as follows: Eshghpour et al. (20.5 % down to 9.0 %), Asutay et al. (10 % down to 3.3 %), Unsal et al. (18 % down to 8 %), Daugela et al. (13.3 % down to 0 %) (Table 1). Noteworthy within these studies were the fact that 1)

Table 1
Main characteristics of the included studies investigating the use of PRF for mandibular third molar removal versus natural wound healing.

Authors (year)	Study design Follow-up	No. of participants Gender Mean age	Groups	Smokers (No, Yes)	Conclusions
Gürbüzer 2010	RCT, Split mouth study 4 weeks	14 (28 sites) ♂7 / ♀7 24.9	C: 14, clot T: 14, PRF	No	PRF might not lead to enhanced bone healing in soft tissue impacted mandibular third molar extraction sockets 4 weeks after surgery.
Ruga 2011	RCT, Split-mouth study Pain at 1 week Healing at 6 months	14 (28 sites) ♂6 / ♀8 29.5	C: 14, Piezo + clot T: 14, Piezo + PRF	Yes Less than 20 cigarettes/day	Combined action of PRF and piezoelectric surgery can be considered a safe and fine technique for third molar surgery and alveolar socket healing.
Eshghpour 2014	double-blinded RCT, Split-mouth study 1 week	78 (156 sites) ♂33 / ♀45 25.1	C: 78, clot T: 78, PRF	No	The overall frequency of AO was 14.74 % for all surgeries. The frequency of AO in the PRF group was significantly lower than in the non-PRF group.
Kumar 2015	RCT, 1 day, 1 and 3 months	31 (31 sites) ♂NR/ ♀NR 26.1	C: 15, clot T: 16, PRF	NR	The application of PRF lessens the severity of immediate postoperative sequelae, decreases preoperative pocket depth, and hastens bone formation.
Uyanik 2015	RCT, 1, 2, 3, and 7 days	20 (40 sites) ♂10 / ♀10 22.5	C1: 10 traditional T1: 10 traditional + PRF C2: 10 traditional T2: 10, Piezo + PRF	No	The use of PRF with traditional surgery and PRF combined with piezosurgery significantly reduced pain during the postoperative period. In addition, PRF in combination with piezosurgery significantly decreased the number of analgesics taken.
Ozgul 2015	RCT, Split-mouth study 1, 3, and 7 days	56 (112 sites) ♂23 / ♀33 18–28	C: 56, clot T: 56, PRF	NR	Horizontal and vertical measurements showed more swelling at the control side (without PRF) in 3th day postoperatively ($p < 0.05$). There were no statistically significant differences regarding pain among the groups.
Baslarli 2015	RCT, Split-mouth study 30 and 90 days	20 (40 sites) ♂7 / ♀13 23.9	C: 20, clot T: 20, PRF	No	PRF might not lead to enhanced bone healing in impacted mandibular third molar extraction sockets 30 and 90 days post-surgery.
Bilginaylar 2016	RCT, 1, 2, 3, and 7 days	59 (80 sites) ♂22 / ♀37 18–31	C1: 20 traditional T1: 20 traditional + PRF T2: 20 Piezo T3: 20, Piezo + PRF	No	There was a significant reduction in pain on days 1, 2, and 3, and in the number of analgesics taken on days 2 and 3 in both PRF groups.
Varghese 2017	RCT, Split-mouth study 1, 4, and 16 weeks	30 (60 sites) ♂NR / ♀NR 18–35	C: 30, clot T: 30, PRF	NR	In general, there was markedly greater bone formation in sockets treated with PRF. Soft tissue healing as evaluated by the healing index also was found to be better at the PRF test site.
Gülşen 2017	RCT, Split mouth study 6, 12 h and 1, 2, 3 and 7 days	30 (60 sites) ♂9 / ♀21 20.0	C: 30, clot T: 30, PRF	NR	Both groups recorded significant improvement compared to the baseline levels in almost all of the outcome variables. There was no statistically significant difference between the study and control groups.
Asutay 2017	Double-blinded RCT, Split-mouth study 6, 12 h and 1, 2, 3, 4, 5, 6 and 7 days	30 (60 sites) ♂6 / ♀24 20.3	C: 30, clot T: 30, PRF	No	No significant differences between the control and study groups regarding postoperative pain, swelling, and trismus. 10 % AO reported in the control group versus 3.3 % in the PRF group.
Unsal 2018	RCT, Split-mouth study AO development at 7 days Pain at 6, 12 h and 1, 2, 3 and 7 days Periodontal probing depth at 3 months	50 (100 sites) ♂17 / ♀33 24.0	C: 50, clot T: 50, PRF	Yes	PRF did not significantly change the AO incidence among nonsmokers, but it positively affected postoperative pain levels. None of the smokers in the PRF group and 37.5 % smokers in the control group were diagnosed with AO.
Jeyaraj 2018	RCT, Parallel study, 8 weeks	60 (60 sites) NR NR	C: 30, clot T: 30, PRF	NR	The PRF group exhibited quick and complication-free soft tissue healing as well as a much quicker reossification and bone fill of the extraction socket when compared to control.

Table 1 (*Continued*)

Authors (year)	Study design Follow-up	No. of participants Gender Mean age	Groups	Smokers (No, Yes)	Conclusions
Dar 2018	Split-mouth study, Postoperative pain, swelling at 1, 3, 7, and 14 days Bone healing at 4 and 12 weeks	30 (60 sites) ♂13 / ♀17 23.6	C: 30, clot T: 30, PRF	No	The mean postoperative VAS pain score and swelling were lower for the PRF group at all points of time.
Daugela 2018	RCT, Split-mouth study, 1, 3, 7, and 14 days	34 (68 sites) ♂14 / ♀20 22.8	C: 30, clot T: 30, PRF	No	Sites treated with PRF resulted in improved pain VAS scores in the first post-op week and significant reduction in facial swelling. 13.3 % AO in the control group vs 0 in the PRF group.
Zahid 2019	Double-blinded RCT, Split-mouth study, Periodontal regeneration at 1, 3 months Pain, swelling, and healing at 7 days	10 (20 sites) ♂0 / ♀10 24.0	C: 10, clot T: 10, PRF	No	The findings of this study demonstrate PRF as a potential biomaterial for lessening the severity of pain and swelling after third molar surgery.
Ritto 2019	Double-blind RCT, Split-mouth study Bone regeneration and soft tissue healing at 3 months Pain at 1, 3, and 7 days	17 (34 sites) ♂10 / ♀7 21.8	C: 17, clot T: 17, PRF	No	The application of PRF improved bone density, which was significantly higher in test. There was no statistical difference related to pain or soft tissue between the groups.
Afat 2019	Double-blind RCT, Parallel study, Healing score at 7, 14, and 21 days	60 (60 sites) ♂22 / ♀38 22.3	C: 20, clot T1: 20, PRF T2: 20, PRF + HA	No	Mean healing scores for the mucosa on the 7th, 14th, and 21 st days for both the PRF group and the HA + PRF group. There were no cases of AO or wound infection in either of the test groups with PRF.

Methods for PRF preparation

Authors (year)	AO (%)	VAS Scores/Pain	Bone / Soft Tissue Healing	Centrifugation system	Volume of tubes for blood drawn	Centrifugation parameters speed (RPM) x time (min)
Gürbüzer 2010	NR	NR	Scintigraphic analysis, 4 weeks, NS 4.61-fold ± 1.02 (C) 4.54-fold ± 1.03 (T)	Universal 320, Hettich, Tuttlingen, Germany	10 mL glass tubes (total 10 mL)	2030 RPM (400 g) for 10 min
Ruga 2011	NR	7 days (0–10) 5.42 (C) 4.92 (T)	Insufficient healing, 6 months 3/14 cases = 21.4 % (C) 0/14 cases = 0 % (T)	Process for PRF, Nice, France	9 mL glass-coated plastic tubes (total 18–54 mL)	2700 RPM for 12 min
Eshghpour 2014	~1 week, * 20.5 % (C) 9.0 % (T)	NR Slight/Severe Pain, 1 day, * 60.0 % (C) 12.5 % (T)	NR Overall density Severe Increase, 3 months, NS 6.7 % (C) 31.3 % (T)	Labofuge 400R centrifuge, Heraeus, Hanau, Germany	10 mL tubes (total 10 mL)	3000 RPM for 10 min
Kumar 2015	NR	Slight/Severe Swelling, 1 day, * 53.3 % (C) 18.8 % (T)		NR	Total 5 m L	3000 RPM for 10 min

Table 1 (*Continued*)

	Methods for PRF preparation					
Authors (year)	AO (%)	VAS Scores/Pain	Bone / Soft Tissue Healing	Centrifugation system	Volume of tubes for blood drawn	Centrifugation parameters speed (RPM) x time (min)
Uyanik 2015	NR	VAS Scores, 7 days, *(C vs T1, C2 vs T2) 74.60 ± 35.21 (C1) 25.00 ± 18.99 (T1) 48.51 ± 44.15 (C2) 24.45 ± 14.95 (T2) # of analgesics taken, 7 days, NS (C1 vs T1), * (C2 vs T2) 9.4 ± 4.81 (C1) 5.6 ± 3.02 (T1) 9.5 ± 6.11 (C2) 4.3 ± 2.94 (T2)	NR	Elektro-mag M415 P, Istanbul, Turkey	10 mL glass-coated plastic tubes (total 10 mL)	3000 RPM (400 g) for 10 min
Ozgul 2015	NR	VAS scores, 3 days, NS 26.48 ± 30.36 (C) 25.50 ± 29.95 (T) Swelling (horizontal), 3 days, * 3.62 ± 3.51 (C) 1.83 ± 2.52 (T)	NR	NR	10 mL glass-coated plastic coated (total 10 mL)	3000 RPM for 10 min
Baslarli 2015	NR	NR	Technetium-99 methylene diphosphonate uptake, 3-month, NS 3.96 ± 1.00 (C) 4.10 ± 1.10 (T)	NR	9 mL glass tubes (total 9 mL)	3000 RPM for 10 min
Bilginaylar 2016	NR	VAS Scores, sum of days 1, 2, 3 and 7, *(C vs T1, C vs T3) 72.30 ± 38.94 (C) 30.28 ± 22.75 (T1) 51.13 ± 16.76 (T2) 32.95 ± 27.30 (T3) # of analgesics taken, sum of days 1, 2, 3 and 7, *(C vs T1, C vs T3) 9.45 ± 5.36 (C) 5.75 ± 3.06 (T1) 6.70 ± 4.07 (T2) 5.00 ± 3.34 (T3)	NR	Elektro-mag M415 P, Istanbul, Turkey	10 mL glass-coated plastic tubes (total 10 mL)	3000 RPM (400 g) for 10 min
Varghese 2017	NR	NR	Bone fill, 16 weeks, * 46.74 % ± 17.71 (C) 57.90 % ± 26.79 (T)	Remi R 23, Remi Laboratories, Mumbai, India	Total 5–10 mL	3000 RPM for 10 min
Gülşen 2017	NR	VAS Scores, 3 days, NS 8.0 ± 12.3 (C) 7.9 ± 12.1 (T)	NR	NUVE NF 200, Turkey	10 mL tubes with clot activator (total 30 mL)	3000 RPM for 10 min
Asutay 2017	7 days, NS 3/30 = 10 % (C) 1/30 = 3.33 % (T)	VAS Scores, 3 days, NS 17.73 ± 24.90 (C) 22.00 ± 23.77 (T) Swelling, 2 days, NS 20.47 ± 10.63 (C) 19.85 ± 9.45 (T)	NR	NR	10 mL tubes (total 10 mL)	2700 RPM for 12 min

Table 1 (*Continued*)

	Methods for PRF preparation					
Authors (year)	AO (%)	VAS Scores/Pain	Bone / Soft Tissue Healing	Centrifugation system	Volume of tubes for blood drawn	Centrifugation parameters speed (RPM) x time (min)
Unsal 2018	7 days, NS 9/50 = 18 % (C) 4/50 = 8 % (T) 7 days, * In smokers 6/16 = 37.5 % (C) 0/16 = 0 % (T)	Pain [0–5], 3 days, NS 1.40 (C) 0.88 (T)	NR	NF 200 centrifuge; Nuve, Ankara, Turkey	10 mLglass-coated plastic tubes (total 10 mL)	3000 RPM for 10 min
Jeyaraj 2018	NR	Pain [0–10], 3 days 3.30 ± 1.18 (C) 1.50 ± 1.01 (T) VAS Scores, 3 days, *	Bone density [0–3], 8 weeks 0.87 ± 0.73 (C) 2.53 ± 0.57 (T) Bone healing, 4 weeks, *	NR	10 mL tubes (total 20 mL)	2700 RPM for 12 min or 30,000 RPM for 10 min
Dar 2018	NR	2.20 ± 1.86 (C) 0.50 ± 0.94 (T) Swelling, 3 days *	0.53 ± 0.90 (C) 2.43 ± 0.94 (T) Bone density, 4 weeks *	NR	10 mL tubes (total 10 mL)	3000 RPM for 12 min
Daugela 2018	3 days * 4/30 = 13.3 % (C) 0/30 = 0 % (T)	4.03 ± 2.16 (C) 1.87 ± 1.94 (T) VAS Scores, 3 days, * 3.13 ± 1.28 (C) 1.67 ± 0.88 (T) Swelling, 3 days, *	13.3 % (C) 83.3 % (T) Soft tissue healing, 7 days, * 4.97 ± 0.85 (C) 4.33 ± 0.61 (T)	EBA20, Andreas Hettich	9 mL glass-coated tubes (total 18 mL)	2800 RPM for 12 min
Zahid 2019	NR	91.07 ± 7.51 (C) 87.27 ± 7.16 (T) VAS Scores, 7 days, * 5.0 [4.25–6.75] (C) 2.5 [2–4.75] (T) Swelling score, 7 days, *	Healing score, 7 days, NS 0.2 [0–1] (C) 0.5 [0–3] (T)	Duo, Process for PRF, France	10 mL tubes (total 20 mL)	1300 RPM for 13 min
Ritto 2019	NR	1.2 [0–3] (C) 0.6 [0–2] (T) Pain, 3 days, NS 3.11 ± 2.61 (C) 2.85 ± 2.17 (T)	Bone density, 3 months, * 522.5 ± 352.3 (C) 954.1 ± 500.8 (T)	NR	10 mL tubes	2700 RPM (400 g) for 12 min
Afat 2019	1/20 = 5 % (C) 0/20 = 0 % (T1) 0/20 = 0 % (T2)	NR	Wound healing, 7 days, * 2.75 ± 0.55 (C) 1.6 ± 0.50 (T1) 1.5 ± 0.51 (T2)	Elektro-mag® M615 P, Istanbul, Turkey	10 mL plastic tubes spray-coated with silica (total 20 mL)	3000 RPM (400 g) for 10 min

RCT, randomized clinical trial; NR, not reported; C, control group; T, test group, ♂, male; ♀, female; PRF, platelet-rich fibrin; RPM, rotation per minute; min, minute; VAS, visual analog scale; AO, alveolar osteitis (dry socket); HA, Hyaluronic acid; *, significant difference; NS, non-significant difference.

some studies such as the one conducted by Daugela and colleagues reduced the rate of AO from 13.3 % to 0 % (no reported cases out of 30) [43]. One other surprising finding from the study conducted by Unsal and colleagues [37] showed an extremely high rate of AO in smokers (37.5 %). Interestingly, when PRF was utilized specifically in the smokers' group, a 0 % rate of AO was reported post-op. Based on this data, it may be recommended that PRF should be considered, especially in high risk AO developing patients such as smokers. Additionally, in one of the first non-randomized comparative studies investigating PRF for mandibular third molars (excluded from Table 1 as it was non-randomized), Hoaglin and Lines investigated the number of alveolar infection including AO with/without PRF [42]. It was found that placement of PRF within the extraction site was associated with a 1.0 % rate of AO versus 9.5 % in the control site (nearly a 10 fold reduction) [42].

Moreover, Sharma and colleagues were one of the first to investigate the efficacy of PRF for the treatment of already present AO using a single arm non-randomized clinical trial [44]. There was a significant reduction in pain associated with AO at 3 and 7 days post-PRF placement, a marked decrease in the degree of inflammation at 3 days and better wound healing by the 2nd week [44]. Similarly, Yüce and colleagues found that PRF application in already existing AO cases demonstrated rapidly and continually reduced pain intensity at each respective time when compared to the control [45]. Faster healing rates of the overlaying epithelium was also significantly faster and this led to a reduction in the number of analgesics taken post-op (dropped from 13.05 ± 1.32 in the control group down to 3.6 ± 1.19 in the PRF group, a close to 3-fold difference) [45].

The most common investigated parameter in the present SR was that of pain scores (Table 1). Thirteen of the 18 studies investigated patient reported pain outcomes using a VAS scoring system typically up to 7 days post-op. Overall, the overwhelming majority of studies found that the use of PRF was shown to 1) reduce post-operative patient reported pain and 2) significantly and often reduce the number of post-operative analgesics taken.

Using PRF was also shown to favor the rate of soft tissue healing, thereby promoting a stable blood clot faster where overlaying epithelium was found formed more rapidly. For example, a split-mouth study by Ruga and co-workers found that of the 14 treated cases, 3 of 14 (21.4 %) did not demonstrate complete healing in the control group whereas all 14 cases healed completely in the PRF group for 6 months [36]. These findings re-iterate that PRF could improve soft tissue healing, lead to less post-operative complication, less pain scores as well as less analgesics taken by patients.

Another area that becomes relevant as well for post-extraction grafting with PRF is for patients that currently possess additional risk factors. As previously stated, these include patients with systemic diseases, the complexity of the operative technique, smokers, oral contraceptives, anticoagulant medication, as well as bisphosphonate users [7,10,11]. These conditions affect blood flow to the extraction site which may prove to be further advantageous using PRF. While one study did show a dramatic decrease in the rate of AO in smokers following mandibular third molar extractions, no other study has investigated the above-mentioned risk factors. Future studies could therefore investigate the added benefit for using PRF in specifically these more complex scenarios.

Conclusions

The present systematic review found strong evidence that support the use of PRF to reduce the rate of AO (nearly 3-fold), especially in medical or wound healing compromised patients such as smokers (though additional data is needed). PRF was further shown to improve soft tissue healing following removal of mandibular third molars which led to a decrease in patient reported post-operative pain as well as number of analgesics taken in all investigated studies. Future studies investigating the added benefit in patients with additional risk factors remains needed.

Ethical approval

Not applicable.

Declaration of Competing Interest

One author (R.J.M) holds intellectual property on PRF. All other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ajoms.2021.01.006.

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