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Platelet-rich fibrin in third molar surgery: a systematic review and meta-analysis

Fibrina rica en plaquetas en cirugía de terceros molares: revisión sistemática y metanálisis

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ABSTRACT: The aim was to summarize the evidence on the effectiveness and safety of platelet-rich fibrin (PRF) use for patients undergoing third molar surgery. Eligible studies were randomized controlled trials (RCT) that evaluated the use of PRF in third molar surgery. Searches in CENTRAL, MEDLINE, Embase, LILACS, the International Clinical Trials Registry Platform, ClinicalTrials.gov and grey literature were performed. Two reviewers evaluated potentially eligible studies and extracted data. We performed meta-analyses using random-effect models and assessed overall certainty using GRADE. Search strategy yielded 134 studies. We included 28 RCTs, 24 were assessed quantitatively. Overall risk of bias was low for 10,4 % of the outcomes. Recent RCTs generated pooled statistically significant results for the use of PRF in: alveolar osteitis (RR=0.39, IC95 % 0.21 to 0.72); postoperative pain day 1 (SMD=1.19, 95 %CI 1.89 to 0.48) and day 3 (SMD=1.31, 95 %CI 2.07 to 0.55); soft tissue healing day 7 (SMD=0.17, 95 %CI 1.61 to 1.27); oedema day 3 (SMD=1.95, 95 %CI 3.45 to 0.45); and wound infection (RR=0.29, 95 %CI 0.06 to 1.37). Contrasting previous reviews, PRF benefited bone healing at month 2 (SMD=5, 95 %CI 1.02 to 8.98). Certainty of evidence increased from previous reviews to moderate for alveolar osteitis and pain day 3. All other outcomes remained with low and very low confidence in results, thus, the use of PRF may result in little to no difference for these. No adverse events were reported. Recent RCTs have improved the precision and potency of previous reviews' results, increasing their certainty. PRF likely reduces the risk of alveolar osteitis and pain at day 3 after third molar surgery. Regarding oedema, trismus, infection, soft tissue and bone healing, certainty of evidence remains very uncertain due to small samples and high or unclear risk of bias. Thus, further well-designed RCTs are needed to confirm and expand these results.

KEY WORDS: Platelet-rich fibrin, third molars, wound healing, systematic review, meta-analysis.

INTRODUCCIÓN

Prevalence of third molars impaction rounds 24 % (Carter & Worthington 2015) which can be due to obstruction by another structure or abnormal path of development (Ventä *et al*., 1999). Specifically, impacted ones have been linked with diverse conditions such as pericoronitis, root resorption, periodontal disease, caries, cysts and tumors (Celikoglu *et al*., 2010). Assessment of impacted mandibular third molars is generally based on clinical and radiographic examination (Bienstock *et al*., 2011).

In the last stages of third molar surgery, prior to closure, the socket may be conditioned in several ways. Multiple techniques have been proposed to aid and enhance wound healing in order to assess postoperative pain, discomfort, bleeding, dehiscence, trismus and others; these

techniques may include the use of hemoderivatives (Bienstock *et al*., 2011).

Platelet-rich fibrin (PRF) is a blood derivative and second generation platelet concentrate, conceived in 2001 by Choukroun *et al*., (2001), to accelerate the healing of soft and hard tissue. It has the advantages of being completely autologous, not requiring any biochemical modification prior to its use and fast as only one centrifugation cycle is needed. This translates into a simple and highly manageable biomaterial to use in the receptor site (Ham *et al*., 2010; Karnieli *et al*., 2017).

Although the use of PRF is widely accepted for several oral surgery procedures, no high-quality and up-to-date SR about its use in third molar surgery is available for an evidence-based analysis. Recently published randomized controlled trials (RCTs), not included in prior reviews, add information on whether the intervention modifies several outcomes of clinical relevance. Therefore, this review aims to assess the effectiveness and safety of PRF use during third molar surgery on several outcomes.

MATERIAL AND METHOD

The protocol for this SR was registered in PROSPERO (CRD42020183827) and previously published (Salas *et al*., 2021). The PRISMA statement and the Cochrane Handbook for Systematic Reviews of Intervention(Lefebvre *et al*., 2021) was used to ensure higher methodological quality of the article.

Eligibility criteria

Study designs. RCTs of both parallel and split-mouth designs were included. Non-randomized and quasi randomized controlled trials were excluded. This selection is justified since RCTs correspond to the primary study design with the highest level of evidence, as they are designed to be unbiased and have less risk of systematic errors.

Population. Male and female patients of all ages, with partially or fully erupted, impacted or not, third molars undergoing third molar surgery. Participants with pathological signs (cysts, tumors), ectopic localization or aberrant anatomy, concomitant systemic disease andhistory of alcohol, tobacco or drug abuse were excluded.

Intervention. PRF placement in the surgical wound prior to closure.

Comparison. Placebo or standard rinse and suture closure of the residual socket. Trials that allowed concomitant use of pain medication were also included only if co-interventions were identical in both groups.

Outcomes. Primary outcomes were alveolar osteitis, postoperative pain, soft tissue healing, swelling and infection. Secondary outcomes were restricted mouth opening or trismus and post-operative bleeding. Bone healing, clinical attachment level, probing depth, analgesic consumption, and reports of adverse events were also scouted.

Literature search

A comprehensive search strategy (see Appendix 1 – Search strategy) was used to identify all relevant RCTs, regardless of language or publication status. Databases searched include Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, Embase, LILACS, WHO, International Clinical Trials Registry Platform (WHO-ICTRP) and ClinicalTrials.gov. Grey literature searches were in OpenGrey and NICE. Reference lists of all included studies and relevant SRs were reviewed. Authors of eligible studies and researchers with expertise relevant to this topic were contacted. Abstracts and oral presentations of specialty meetings and congress were reviewed.

Data collection and analysis

Review authors screened independently and in duplicate titles and abstracts of articles obtained through the searches according to inclusion criteria, followed by screening of full texts. Disagreements were solved through a third party. The selection process was documented in a PRISMA flow chart (Moher *et al*., 2009). Level of agreement between the review authors was calculated by Kappa statistic.

Data extraction and management

Review authors extracted data independently and in duplicate using a standardized form (RevMan, 2021). Any disagreements were resolved by consensus or by a third author. Multiple reports of the same study were collated. Outcomes and variables for which data were sought are presented in detail in the published protocol (Salas *et al*., 2021).

Risk of bias (RoB) assessment

Included studies were assessed independently in duplicate by authors using the Cochrane risk of bias tool 2 (Sterne *et al*., 2019). We tabulated the RoB for each included study, along with a judgement of low, high, or unclear RoB for each domain.

Statistical analysis

To measure treatment effect in dichotomous outcomes, the estimate is expressed as risk ratios (RR) or odds ratios (OR) along with 95% confidence intervals (CI). For continuous outcomes, mean difference, and standard deviation (SD) to summarize the data using a 95% CI were used. Continuous outcomes were measured using different scales, the treatment effect is expressed as a standardized mean difference (SMD) with 95% CI. Risk ratios for dichotomous data and mean differences for continuous data using the inverse variance method were combined with the random-effects model. When combining outcome data was not feasible due to differences in the reported outcomes, a narrative summary is presented.

Visual inspection of forest plots, Chi-squared test and the I2 statistic were used to assess statistical heterogeneity. Any level of heterogeneity greater than 40% was explained according to the covariates collected, by sensitivity analysis, subgroup analysis and/or meta-regression. When heterogeneity could not be explained, the results of the meta-analysis performed were excluded. Sensitivity analysis was also performed excluding studies with high RoB. In cases where the primary analysis effect estimates and the sensitivity analysis effect estimates significantly deferred, data was either presented as low RoB- adjusted sensitivity analysis estimates - or presented the primary analysis estimates but downgrading the certainty of the evidence because of RoB. Publication bias was assessed for outcomes that were reported for 10 or more RCTs by visual inspection of the symmetry of the funnel plot assessment (Higgins *et al*., 2021).

Certainty assessment

Review authors independently assessed the certainty of the evidence using the five GRADE (GRADEpro, 2022) considerations. Disagreements on certainty ratings were resolved by discussion, providing justification for decisions regarding the ratings using footnotes in the table.

RESULTS

Search results

We identified 152 studies through database searching and 14 studies from other sources. After removing duplicates, 88 articles were screened by title and abstract, excluding 56 references. 32 articles were assessed by full text, resulting in 28 articles. From the search update, 2 additional references met the inclusion criteria and passed full text analysis, therefore included in this review. A total of 28 articles were included for qualitative synthesis (Gürbüzer *et al*., 2010; Eshghpour *et al*., 2014; Baslarli *et al*., 2015; Kumar *et al*., 2015; Niyombandith & Pisarnpan, 2015; Ozgul *et al*., 2015; Uyanık *et al*., 2015; Wageeh *et al*., 2015; Bilginaylar & Uyanik, 2016; Kumar *et al*., 2016; Asutay *et al*., 2017; Esen *et al*., 2017; Güls¸en & S¸entürk, 2017; Varghese *et al*., 2017; Daugela *et al*., 2018; Jeyaraj & Chakranarayan, 2018; Revathy *et al*., 2018; Unsal & Erbasar, 2018; Afat *et al*., 2019; Kapse *et al*., 2019; Ritto *et al*., 2019; Singha *et al*., 2019; Zahid & Nadershah, 2019; Gasparro *et al*., 2020; Sybil *et al*., 2020; Torul *et al*., 2020; Gupta & Agarwal, 2021; Nourwali, 2021). 24 trials from the prior selected studies were included for quantitative synthesis and meta-analysis. The PRISMA flow diagram of the screening and selection process is presented in Fig. 1. We excluded a total of 4 studies (Girish Rao *et al*., 2013; Dutta *et al*., 2016; Dar *et al*., 2018; Harsh, 2018) after full-text assessment. The reasons for exclusion were study found not to be an RCT after review of the full published reports; intervention done in teeth other than third molars; study design unclear and attempts to contact the authors for clarification were unsuccessful; full-report publication was not found. The value of Kappa was 0.88, thus it was considered excellent agreement.

Study characteristics

All of the included studies took place in hospital settings, and no commercial sponsorships were reported or identified in the published report, although three studies declared receiving financial support from government (Kumar *et al*., 2016) or university funds (Baslarli *et al*., 2015; Singha *et al*., 2019). Nevertheless several studies did not report funding sources and/or conflict of interest declaration (Gürbüzer *et al*., 2010; Eshghpour *et al*., 2014; Baslarli *et al*., 2015; Kumar

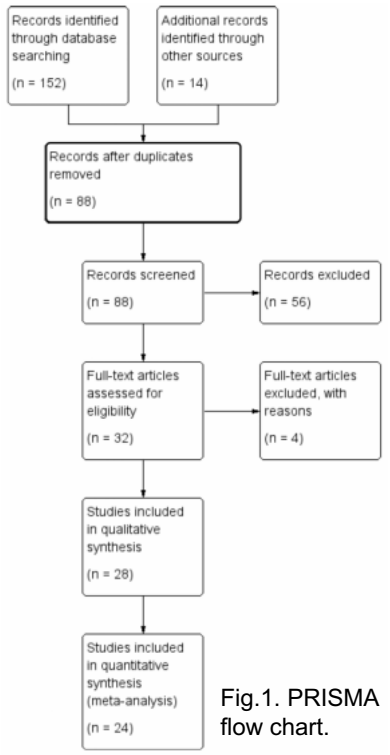

Fig.1. PRISMA flow chart.

et al., 2015; Niyombandith & Pisarnpan, 2015; Ozgul *et al*., 2015; Uyanık *et al*., 2015; Wageeh *et al*., 2015; Bilginaylar & Uyanik, 2016; Güls¸en & S¸entürk, 2017; Varghese *et al*., 2017; Daugela *et al*., 2018; Kapse *et al*., 2019; Zahid & Nadershah, 2019).

Nine of 28 included studies had parallel-group design (Kumar *et al*., 2015; Wageeh *et al*., 2015; Bilginaylar & Uyanik, 2016; Esen *et al*., 2017; Jeyaraj & Chakranarayan, 2018; Afat *et al*., 2019; Singha *et al*., 2019; Torul *et al*., 2020; Nourwali, 2021) and the remaining 19 studies had split-mouth design(Gürbüzer *et al*., 2010; Eshghpour *et al*., 2014; Baslarli *et al*., 2015; Kumar *et al*., 2015; Niyombandith & Pisarnpan, 2015; Ozgul *et al*., 2015; Uyanık *et al*., 2015; Asutay *et al*., 2017; Güls¸en & S¸entürk 2017; Varghese *et al*., 2017; Daugela *et al*., 2018; Revathy *et al*., 2018; Unsal & Erbasar, 2018; Kapse *et al*., 2019; Ritto *et al*., 2019; Zahid & Nadershah, 2019; Gasparro *et al*., 2020; Sybil *et al*., 2020; Gupta & Agarwal, 2021). The included studies involved a total of 1002 participants, with individual studies recruiting between 10 and 100 participants (mean of 35 participants per study). In all included studies, participants were systemically healthy and without any indication of infection or inflammation surrounding the mandibular third molars. In most included studies, the mean age was not reported, but the inclusion criteria specified an age range of approximately 16 to 40 years, except for one study with a high-end range of 60 years, with mean ages ranging from 20 to 32 years old. Characteristics of the included articles are shown in Table I.

Risk of bias assessment

Trials included in this SR were analysed for RoB at study and outcome level, depending on the domain observed of RoB 2 tool. Overall bias pertains to outcome level assessment. 10.4% of outcomes assessed were found to have low RoB, 60.4% with some concerns and 29.5% showed high RoB. RoB assessment is presented in Fig. 2.

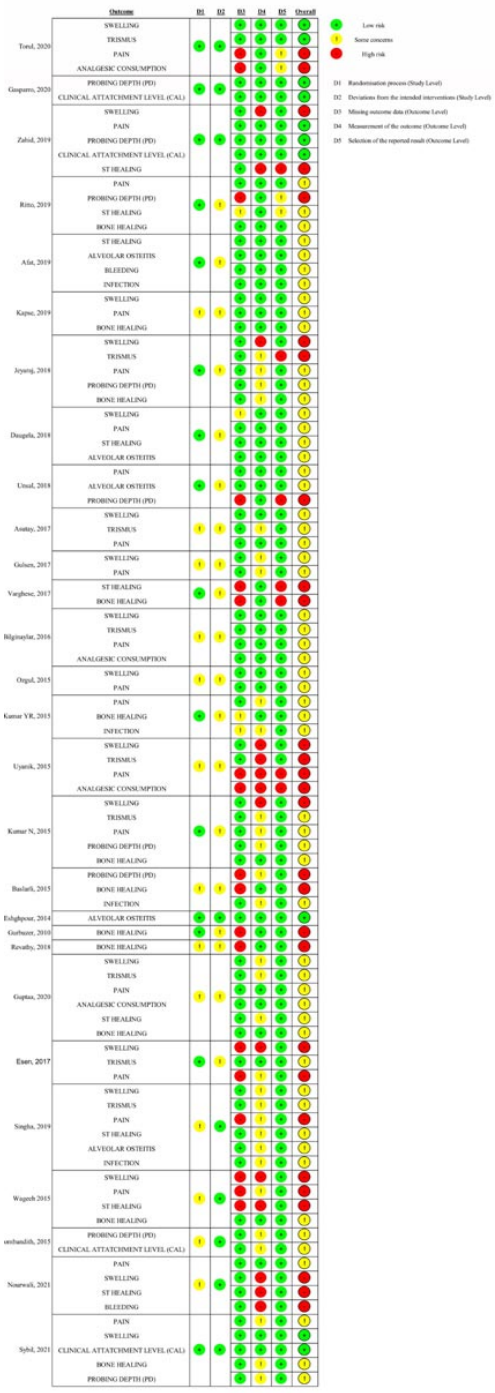

Fig. 2. Risk of Bias assessment graph for the randomized trials included in the study.

Table I. Characteristics of included studies.

Nº	Author/Year	Age mean ± SD/range	Sex	RCT design	PRF (n)	Control (n)	Follow-up (D)	RPM x Min	Cointervention	Outcomes Assessed
1	Gürbüzer *et al.*, 2010	24.92 ± 4.69	7 male, 7 female	Sm	14	14	D30	2030 RPM x 10 min/400g	Yes	Bh
2	Eshghpour *et al.*, 2014	25.09 ± 4.25	33 male, 45 female	Sm	78	78	D2, D7	3000 RPM x 10 min	Yes	Ao
3	Baslarli *et al.*, 2015	23.9 (19-34)	7 male, 13 female	Sm	20	20	D30, D90	3000 RPM x 10 min	Yes	Bh, Pd
4	Kumar *et al.*, 2015	26.1 (19-35)	Ni	Pa	16	15	D1, D30, D90	3000 RPM x 10 min	Yes	P, Sw, Rmo, Pd, Bh
5	Uyanik *et al.*, 2015	22.5 (19-31)	10 male, 10 female	Sm	10	10	D1, D2, D3, D7	3000 RPM x 10 min/400g	Yes	P, Sw, Ac, Rmo
6	Kumar *et al.*, 2016	Ni (18-40)	Ni	Sm	34	34	D1, D3, D7, D30, D60, D120, D180	Ni	Yes	Bh, Sth, P
7	Ozgul *et al*., 2015	Ni (18-28)	23 male, 33 female	Sm	56	56	D1, D3, D7	3000 RPM x 10 min	Yes	Sw, P
8	Wageeh, 2015	Ni (20-30)	8 male, 12 female	Pa	10	10	D2, D4, D7, D30, D60, D90	3000 RPM x 10 min	Yes	Sth, P, Sw, Rmo, Bh
9	Niyombandith & Pisarnpan, 2015	24.9 ± 2.64 (21-30)	10 males	Sm	10	10	D60	3000 RPM x 10 min	Yes	Pd
10	Bilginaylar & Uyanik, 2016	21.98 (18-31)	22 male, 37 female	Pa	20	20	D1, D2, D3, D7	3000 RPM x 10 min/400g	Yes	P, Sw, Ac
11	Varghese *et al.*, 2017	Ni (18-35)	Ni	Sm	30	30	BL, D7, D30, D120	3000 RPM x 10 min	Ni	Bh, Sth
12	Gül_en & _entürk, 2017	20.03 (17-27)	9 male, 21 female	Sm	30	30	6HR, 12 HR, D1, D2, D3, D7	3000 RPM x 10 min	Yes	P, Sw
13	Asutay *et al.*, 2017	20.32 (18-29)	6 male, 24 female	Sm	30	30	6HR, 12 HR, D1, D2, D3, D7	2700 RPM x 12 min	Yes	P, Rmo, Sw
14	Esen *et al*., 2017	23.3 ± 4.25 (18-33)	14 male, 26 female	Pa	20	20	D1, D3, D7	3000 RPM x 10 min	Yes	P, Sw, Rmo, QoL
15	Unsal & Erbasar, 2018	23.96 (15-53)	17 male, 33 female	Sm	50	50	6HR, 12 HR, D1, D2, D3, D7	3000 RPM x 10 min	Ni	Ao, P, Pd
16	Daugela *et al.*, 2018	22.76 ± 2.02	14 male, 20 female	Sm	30	30	D1, D2, D3, D4, D5, D6, D7	2800 RPM x 12 min	Yes	Sth, P, Sw, Ao
17	Jeyaraj & Chakranarayan, 2018	Ni	Ni	Pa	30	30	D3, D60, D120, D180	3000 RPM x 10 min	Yes	Sth, Bh, P, Sw, Rmo, Pd
18	Revathy *et al.*, 2018	± (18-35)	15 male, 10 female	Sm	20	20	D30, D90, D180	3000 RPM x 10 min	Yes	-
19	Kapse *et al*., 2019	25.47 ± 0.90 (18-40)	13 male, 17 female	Sm	30	30	D1, D3, D7, D14	2700 RPM x 12 min	Ni	P, Sw, Bh, Ao, Wi, Rmo
20	Afat *et al*., 2019	22.3 ± 2.44 (18-30)	22 male, 38 female	Pa	30	30	D7, D14, D21	3000 RPM x 10 min/400g	Yes	Sth, Bl, Ao, Wi
21	Ritto *et al*., 2019	21.8 (16-29)	10 male, 7 female	Sm	17	17	D1, D2, D7, D90	2700 RPM x 12 min/400g	Yes	Bh, Sth, P
22	Zahid & Nadershah, 2019	24	10 females	Sm	10	10	D7, D15, D30, D90	1300 RPM x 13 min	Yes	Pd, Cal, P, Sw, Sth
23	Gasparro *et al.*, 2020	23.3 ± 4.73 (18-35)	10 male, 8 female	Sm	18	18	D180	2700 RPM x 12 min/408g	Yes	Pd, Cal
24	Singha *et al.*, 2019	Ni (18-30)	Ni	Pa	100	100	D1, D3, D7	3000 RPM x 15 min	None	P, Sw, Rmo, Ao, Wi, Sth
25	Torul *et al*., 2020	22.31 ± 4.65	14 male, 36 female	Pa	25	25	6HR, 12 HR, D1, D2, D3, D7	1300 RPM x 13 min/198g	None	P, Sw, Rmo
26	Gupta & Agarwal, 2020	Ni (18-35)	8 male, 12 female	Sm	20	20	D1, D3, D7, D30, D90, D180	1500 RPM x 14 min	Ni	P, Ac, Sth, Sw, Rmo, Bh
27	Nourwali, 2021	Ni	Ni	Pa	10	10	1 HR D1, D2, D3, D7	3000 RPM x 10 min	Yes	Sw, P
28	Sybil *et al*., 2021	32.3 (18-55)	14 male, 11 female	Sm	25	25	D1, D3, D7, D30, D60, D90	3000 RPM x 10 min	Ni	Sw, P, Pd, Cal, Bh, Bl

Effects of interventions

Alveolar osteitis. Five trials reported this outcome: three split-mouth RCTs (Eshghpour *et al*., 2014; Daugela *et al*., 2018; Unsal & Erbasar, 2018) and two parallel-arm RCTs (Afat *et al*., 2019; Singha *et al*., 2019). The pooled estimate for all five trials was a RR of 0.39 (95% CI 0.21 to 0.72; n=376; p=0.003; I2=0%). Fig. 3.

Postoperative pain (PoP) day 1 and 3. 20 trials reported pain as a continuous outcome by visual analogue scale (VAS) (Kumar *et al*., 2015, 2016; Ozgul *et al*., 2015; Uyanık *et al*., 2015; Wageeh *et al*., 2015; Bilginaylar & Uyanik, 2016; Esen *et al*., 2017; Gülsen & Sentürk, 2017; Daugela *et al*., 2018; Jeyaraj & Chakranarayan, 2018; Unsal & Erbasar, 2018; Kapse *et al*., 2019; Ritto *et al*., 2019; Singha *et al*., 2019; Zahid & Nadershah, 2019; Sybil *et al*., 2020; Torul *et al*., 2020; Gupta & Agarwal, 2021; Nourwali, 2021) nevertheless, five studies (Uyanık *et al*., 2015; Wageeh *et al*., 2015; Esen *et al*., 2017; Singha *et al*., 2019; Torul *et al*., 2020) were excluded from quantitative analysis as data was not available, incomplete, or authors did not respond to requests. At day 1 the pooled estimate SMD from the 11 RCTs was -1.19 (95% CI -1.89 to -0.48; n=567; p<0.00001; I2= 93%). For day 3 SMD was -1.31 (95% IC -2.07 to -0.55; n=578; p=0.00007; I2=94%). Figs. 4 and 5.

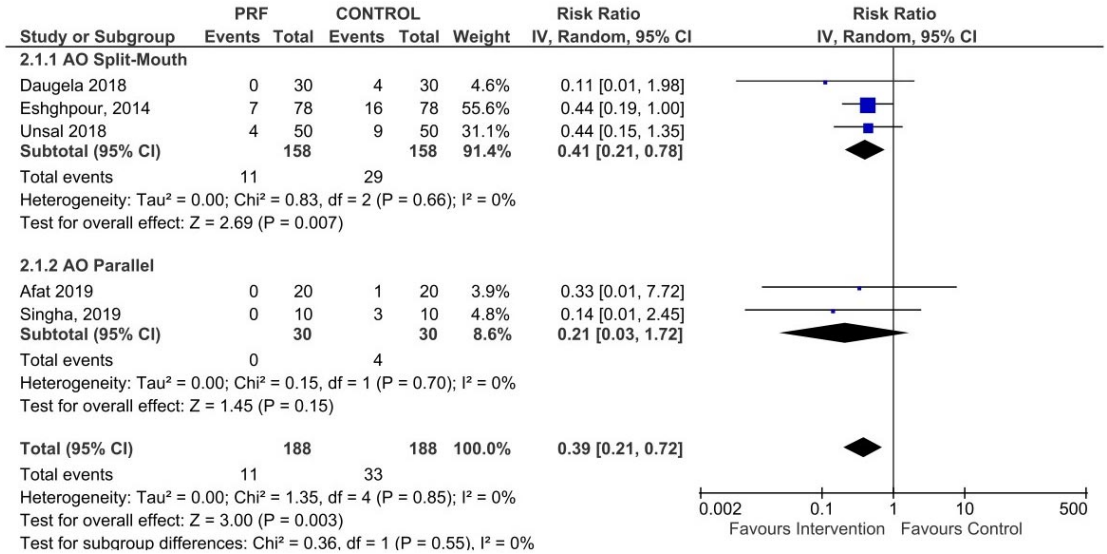

Fig. 3. Forest plot showing the effect of PRF vs. control after third molar surgery on alveolar osteitis.

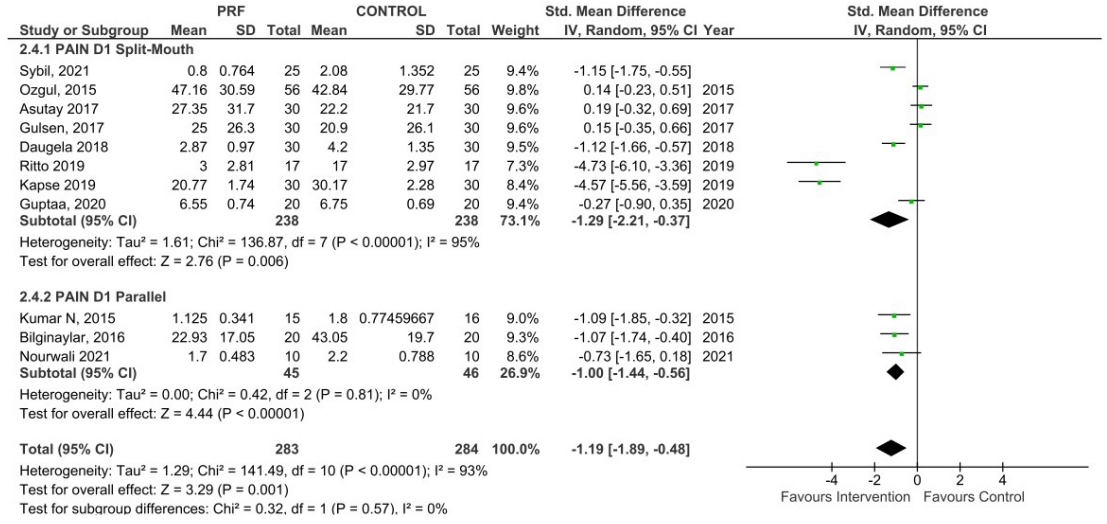

Fig. 4. Forest plot showing the effect of PRF vs. control after third molar surgery on pain, day 1.

Soft tissue healing (Sth) day 7. Regarding soft tissue healing, nine trials reported this outcome (Wageeh *et al*., 2015; Varghese *et al*., 2017; Daugela *et al*., 2018; Afat *et al*., 2019; Ritto *et al*., 2019; Singha *et al*., 2019; Zahid & Nadershah, 2019; Gupta & Agarwal, 2021; Nourwali, 2021). Five trials were excluded from analysis due to data not reported or presented as added scores from multiple assessment in different time frames (Wageeh *et al*., 2015; Varghese *et al*., 2017; Zahid & Nadershah, 2019; Nourwali, 2021), remaining three split-mouth (Daugela *et al*., 2018; Ritto *et al*., 2019; Gupta & Agarwal, 2021) and two parallel-arm trials (Afat *et al*., 2019; Singha *et al*., 2019) for analysis. For day seven, four trials (Daugela *et al*., 2018; Afat *et al*., 2019; Singha *et al*., 2019; Gupta & Agarwal, 2021) evaluated Sth. The pooled estimate SMD was -0.17 (95% IC -1.61 to 1.27; n=160; p=0.82; I2 = 94%). Fig. 6.

Swelling (Sw) day 3. Swelling was reported by seventeen trials (Kumar *et al*., 2015; Ozgul *et al*., 2015; Uyanık *et al*., 2015; Wageeh *et al*., 2015; Bilginaylar & Uyanik, 2016; Asutay *et al*., 2017; Esen *et al*., 2017; Güls¸en & S¸entürk, 2017; Daugela *et al*., 2018; Jeyaraj & Chakranarayan, 2018; Kapse *et al*., 2019; Singha *et al*., 2019; Zahid & Nadershah, 2019; Sybil *et al*., 2020; Torul *et al*., 2020; Gupta & Agarwal, 2021; Nourwali, 2021). Five studies were excluded from analysis due to not reporting any data (Wageeh *et al*., 2015; Esen *et al*., 2017; Güls¸en & S¸entürk, 2017; Daugela *et al*., 2018; Singha

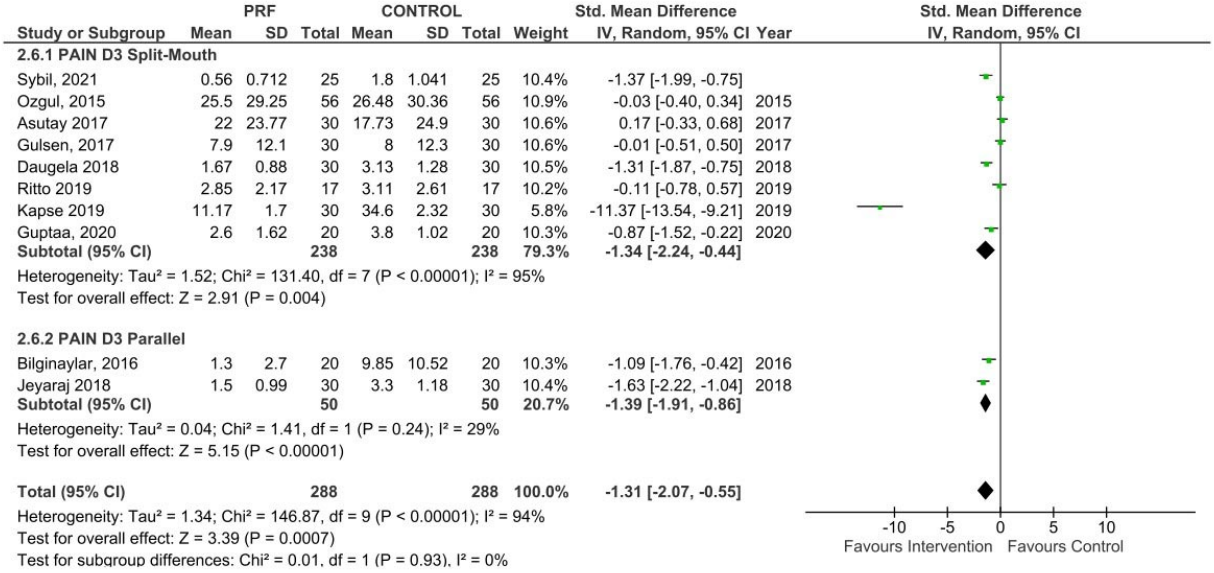

Fig. 5. Forest plot showing the effect of PRF vs. control after third molar surgery on pain, day 3.

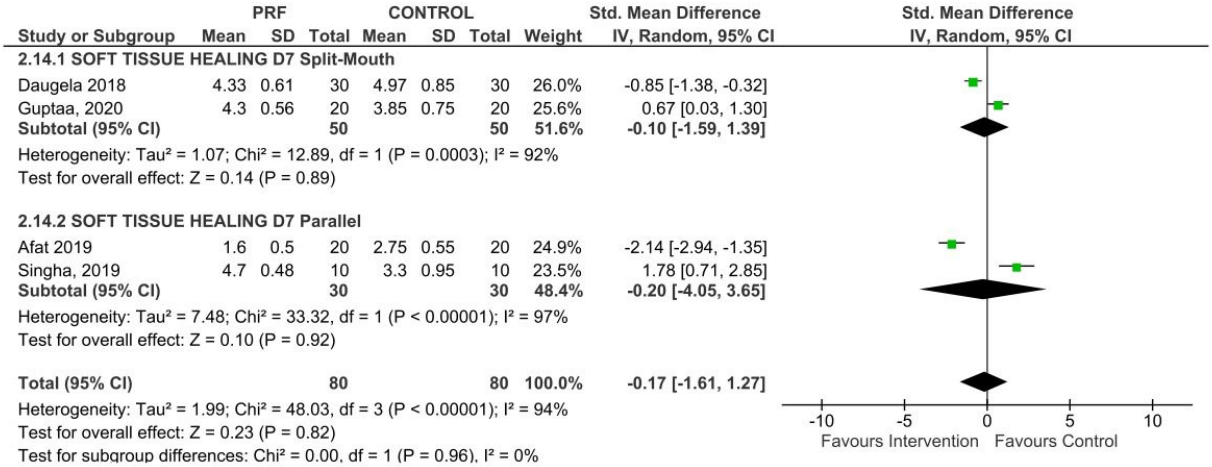

Fig. 6. Forest plot showing the effect of PRF vs. control after third molar surgery on soft tissue healing, day 7.

et al., 2019). Seven trials, five split-mouth(Ozgul *et al*., 2015; Uyanık *et al*., 2015; Kapse *et al*. 2019; Sybil *et al*., 2020; Gupta & Agarwal, 2021) and two parallel-arm design(Bilginaylar & Uyanik, 2016; Jeyaraj & Chakranarayan, 2018) reported the outcome of Sw at day 3, SMD was -1.52 (95% IC -2.62 to -0.43; n=402; p=0.0006; I2=95%). Fig. 7.

Wound Infection. The overall pooled estimate relative risk (RR), from two split-mouth (Baslarli *et al*., 2015; Kumar *et al*., 2016) and two parallel-arm (Afat *et al*., 2019; Singha *et al*., 2019) RCTs that reported the outcome of wound infection, was RR 0.29 (95% CI 0.06 to 1.37; n=208; p=0.12; I2=0%). Fig. 8.

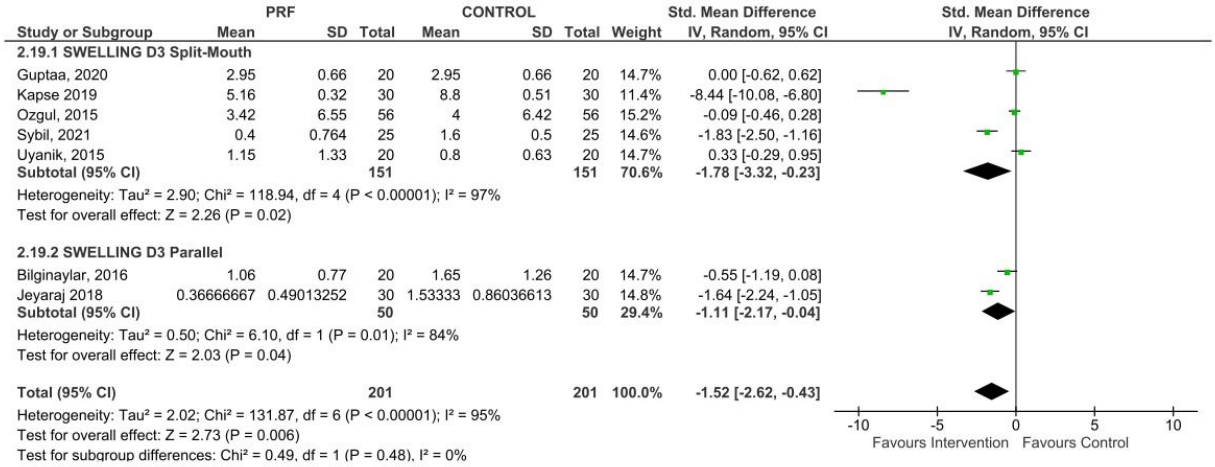

Fig. 7. Forest plot showing the effect of PRF vs. control after third molar surgery on oedema, day 3.

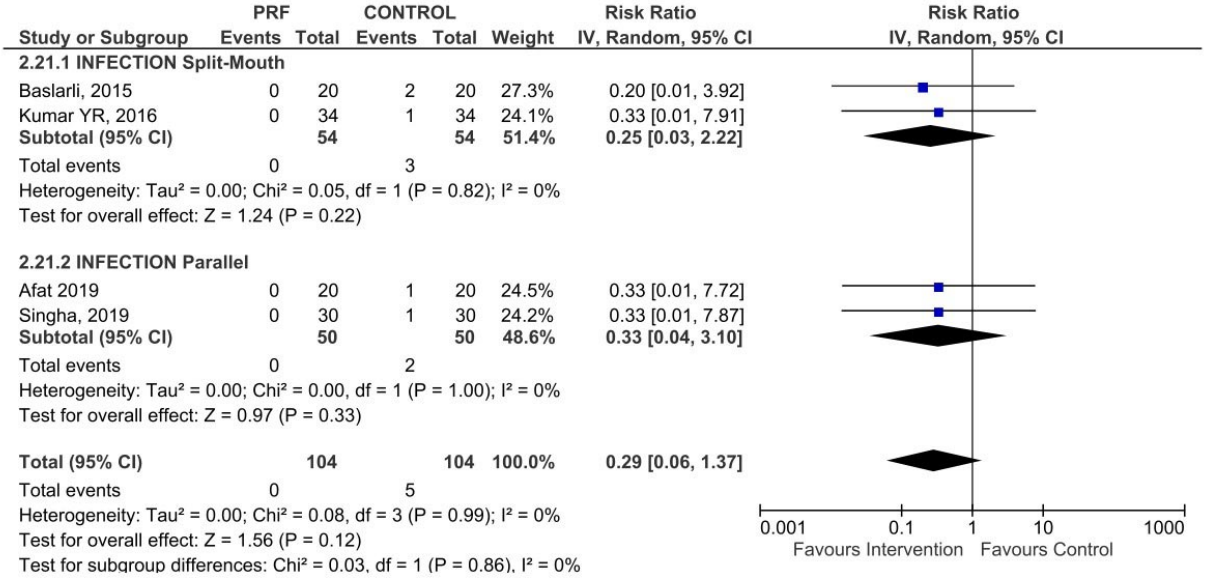

Fig. 8. Forest plot showing the effect of PRF vs. control after third molar surgery on wound infection.

Secondary outcomes

Effect of interventions on secondary outcomes are presented in supplementary material.

Subgroup analysis

No study included reported adverse events in the use of PRF (Fig. 9). Due to absence of data, it was not feasible to carry

subgroup analysis neither for type of PRF, gender, position of third molar or protocols/equipment used to harvest, process PRF, neither was possible to observe differences in intra alveolar placement of PRF mainly plugs, membranes or exudate. Summary of findings with certainty of the evidence using GRADE considerations (Schünemann *et al*., 2021) is described in Table II.

Table II. Summary of Findings Table (SoF) for Platelet-rich fibrin in third molar surgery.

Patients: Patients undergoing third molar surgery

Intervention: Platelet-rich fibrin (PRF) (as defined by the studies)

Comparison: Placebo or no treatment ± standard treatment (as defined by the studies)

Outcomes	Relative effect (95% CI) Patients/Studies	Absolut effect*			Certainty of evidence (GRADE)	Key messages
		WITHOUT PRF	WITH PRF	Difference (CI 95%)		
Alveolar osteitis	RR 0.39 (0.21 to 0.72) 376 patients/5 RCTs	18 per 1000	7 per 1000	11 less (14 to 5 less)	⊕⊕⊕O Moderate (1)	Platelet-rich fibrin likely reduces the risk of alveolar osteitis.
Postoperative pain (day 1)	567 patients/11 RCTs	SMD 1.19 lower (1.89 lower to 0.48 lower)			⊕OOO Very low (1,2,3)	The evidence is very uncertain about the effect of platelet-rich fibrin on postoperative pain at day 1.
Postoperative pain (day 3)	576 patients/10 RCTs	SMD 1.31 lower (2.07 lower to 0.55 lower)			⊕⊕⊕O Moderate (1)	Platelet-rich fibrin likely reduces the postoperative pain at day 3.
Soft tissue healing (day 7)	160 patients/4 RCTs	SMD 0.17 lower (1.61 lower to 1.27 higher)			⊕⊕OO Low (1,2)	Platelet-rich fibrin may result in little to no difference in soft tissue healing.
Swelling (day 3)	302/5 RCTs	SMD 1.95 lower (3.45 lower to 0.45 lower)			⊕OOO Very low (1,2,3)	The evidence is very uncertain about the effect of platelet-rich fibrin on oedema.
Wound infection	RR 0.29 (0.06 to 1.37) 208 patients/4 RCTs	5 Per 1000	1 per 1000	4 less (5 less to 2 more)	⊕⊕OO Low (1,2)	Platelet-rich fibrin may result in little to no difference in the risk of wound infection.
RMO (day 3)	140 patients/4 RCTs	SMD: 1.06 more (-0.03 fewer to 2.16 more)			⊕OOO Very Low (1,2,3)	The evidence is very uncertain about the effect of platelet-rich fibrin on Rmo at D3.

CI: confidence interval; RR: Risk ratio; SMD: Standard mean difference, GRADE: Grading of Recommendations Assessment, Development and Evaluation, RMO: Restricted mouth opening.

*The risk WITHOUT intervention is based on the risk in the control group of the trials. The risk WITH intervention (and its margin of error) is calculated from relative effect.

***Standard mean difference is used when the outcome has been measured in different scales and it is hard to interpret clinically. A general rule is that values near 0.2 have little clinical relevance, values of 0.5 have moderate relevance and values over 0.8 have an important clinical relevance.

1 ,2, 3 The certainty of the evidence is based in the following judgments: Risk of bias: downgraded in one level since the overall risk of bias for studies was evaluated as 'high' and 'some concerns'; Inconsistency: downgraded in one level for inconsistency since the studies show contradictory results; Indirectness: no concerns; Imprecision: downgraded in one level for imprecision since each end of the confidence interval would lead to different conclusions; Publication bias: no concerns.

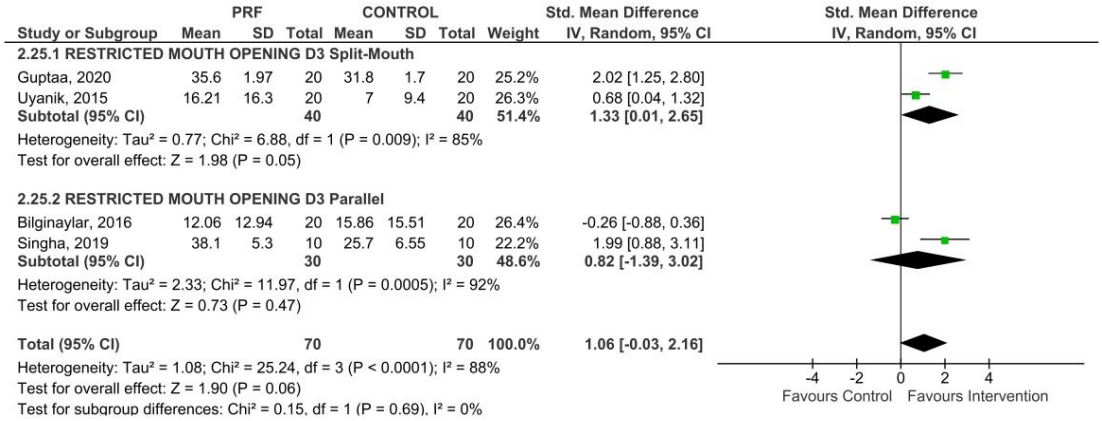

Fig. 9. Forest plot showing the effect of PRF vs. control after third molar surgery on restricted mouth opening, day 7.

Publication bias

Two outcomes were assessed for publication bias, as they were the only ones reported by 10 or more RCTs.

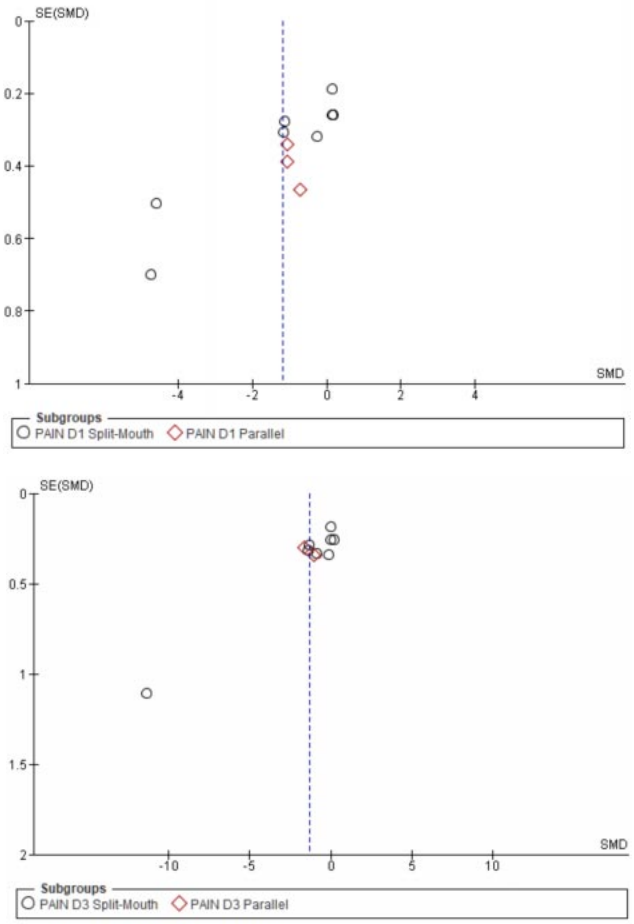

Fig. 10. Funnel plots for publication bias test. A: Postoperative pain day 1; B: Postoperative pain day 3.

Nevertheless, the power of the tests was too low to distinguish chance from real asymmetry in the funnel plots (Fig. 10).

DISCUSSION

The main objective of this review was to assess the effectiveness and safety of PRF use during third molar surgery. To answer this objective, a SR was conducted, identifying 28 RCTs, which showed a beneficial effect of PRF likely reducing alveolar osteitis risk and postoperative pain (day 3). Nevertheless, regarding the other outcomes assessed, certainty of evidence remains low or very low due to the small number of trials and participants and the high or unclear risk of bias in the trials. After inspection of data on the matter of trial design (parallel vs split-mouth) there is no clear difference, asymmetry, or heterogeneity in outcome results.

Risk of bias was low for only 10.5% of all outcomes observed across all studies. Although, participant blinding was unrealistic in many studies due to the surgery being carried out under local anaesthetic. We considered blinding of outcome assessment was both possible and important to reduce the risk of detection bias. Where the person assessing the outcomes was the same surgeon who performed the procedure, or where blinded outcome assessment was not mentioned, the risk of detection bias was considered high. Previous reviews on the topic have certain limitations, as they included moderate to high RoB RCTs with a high heterogeneity, combined results from RCTs and retrospective

studies decreasing their accuracy (He *et al*., 2017), and others did not perform meta-analysis at all (Miron *et al*., 2017). In contrast with previous reviews (Niyombandith & Pisarnpan, 2015; Al-Hamed *et al*., 2017; Dos Santos Canellas *et al*., 2017; Xiang *et al*., 2019), our results showed a statistically significant reduction of pain at day 1, and oedema at days 1, 3 and 7. Xiang *et al*. (2019) and He *et al*. (2017) results were not statistically significant for pain at day 1 (Xiang *et al*., 2019), oedema at day 1 (He *et al*., 2017), 3 (Xiang *et al*., 2019), and 7 (Xiang *et al*., 2019). Discrepancies in the results are explained as new eligible studies emerged and were included in our review, which increased the potency and precision of these results. Various forms of measurement of facial oedema used in the RCTs, as well as the high RoB of the former (Uyanık *et al*., 2015; Wageeh *et al*., 2015; Kumar *et al*., 2016; Esen *et al*., 2017; Jeyaraj & Chakranarayan, 2018; Zahid & Nadershah, 2019; Nourwali, 2021), translate into this outcome having a low certainty of evidence. Alveolar osteitis and pain were defined to have low level of certainty in the most recent and largest review (Xiang *et al*., 2019). Though, as our review included more recently published studies with low and unclear RoB, our results increased the level of certainty from low to moderate. Thus, we can now assert that PRF likely reduces the risk of alveolar osteitis and pain at day three. Regarding wound infection, this is the first review that meta-analysed the outcome, which resulted in not statistically significant, due to the low number of studies and events. Similar to our findings, other authors (Al-Hamed *et al*., 2017; He *et al*., 2017; Xiang *et al*., 2019) reported no statistical difference regarding trismus in patients who were administered with PRF. Respecting bone healing assessment, a meta-analysis performed by Al Hamed *et al*. (2017) concluded that there was no differential effect when administering PRF in the extraction socket. These findings do not correlate with our results, as they showed a beneficial effect of PRF at the second month postoperative, however, discrepancies can be explained due to the high heterogeneity of measurement methods for this outcome and small sample sizes.

As for the strengths in this review, a comprehensive search strategy was used to identify all relevant RCTs, regardless of language or publication status. Additionally, selection process, data extraction, and quality assessment were performed independently and in duplicate. Therefore, the process provides confidence in the results. This review has also some limitations. First, because of the different study scales of measurement and surgical protocols, high clinical heterogeneity between studies was found. Second, due to mainly high risks of bias, inconsistency and imprecision of the primary studies, results of this review must be taken with caution.

Studies of a split-mouth design may be appropriate for comparing effects of the use of PRF for third molar removal, but trialists need to consider which outcomes can be accurately measured and analysed. It would be helpful to have a consensus agreement on the criteria for the measurement of different outcomes such as trismus and pain, this is also needed in the cases of soft tissue and bone healing for both split-mouth and parallel design trials.

CONCLUSION

Our review provides a description and analysis of relevant evidence regarding the use of PRF in third molar surgery. Our results conclude that the use of PRF likely reduces the risk of alveolar osteitis and pain (at day 3) after third molar surgery. Yet, regarding oedema, trismus, infection, soft tissue and bone healing, certainty of evidence remains low or very low due to the small number of trials and participants and the high or unclear RoB in the trials. Thus, further well-designed RCTs, with better adherence to the CONSORT statement for reporting of RCTs.

Authors' contributions. G.S.: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. J.B.: Data curation; Formal analysis; Investigation; Roles/Writing - original draft; Writing - review & editing. F.V.P.: Validation; Formal analysis; Investigation; Writing - review & editing. R.R., C.P., and G.R.: Methodology; Supervision; Validation; Writing - review & editing.

Ethics and dissemination. As researchers will not access information that could lead to the identification of an individual participant, obtaining ethical approval was waived.

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SALAS-BARRERA G, BENDERSKY J, VERDUGO-PAIVA F, REQUENA R, PRATS C, RADA G. Fibrina rica en plaquetas en cirugía de terceros molares: revisión sistemática y metanálisis. *Craniofac Res. 2022*; 1(2):143-158.

RESUMEN: El objetivo fue resumir la evidencia sobre la efectividad y seguridad del uso de fibrina rica en plaquetas (PRF) para pacientes sometidos a cirugía del tercer molar. Los estudios elegibles fueron ensayos controlados aleatorios (ECA) que evaluaron el uso de PRF en la cirugía del tercer molar. Se realizaron búsquedas en CENTRAL, MEDLINE, Embase, LILACS, International Clinical Trials Registry Platform, ClinicalTrials.gov y literatura gris. Dos revisores evaluaron los estudios potencialmente elegibles y extrajeron los datos. Realizamos metanálisis mediante modelos de efectos aleatorios y evaluamos la certeza general mediante GRADE. La estrategia de búsqueda produjo 134 estudios. Se incluyeron 28 ECA, 24 se evaluaron cuantitativamente. El riesgo general de sesgo fue bajo para el 10,4% de los resultados. ECA recientes generaron resultados estadísticamente significativos agrupados para el uso de PRF en: osteítis alveolar (RR = 0,39, IC95% 0,21 a 0,72); dolor posoperatorio día 1 (DME=1,19, IC del 95%: 1,89 a 0,48) y día 3 (DME=1,31, IC del 95%: 2,07 a 0,55); curación de tejido blando día 7 (DME = 0,17, IC del 95 %: 1,61 a 1,27); edema día 3 (DME = 1,95, IC del 95 %: 3,45 a 0,45); e infección de la herida (RR = 0,29; IC del 95%: 0,06 a 1,37). En contraste con las revisiones anteriores, la PRF benefició la cicatrización ósea en el mes 2 (DME = 5, IC del 95 %: 1,02 a 8,98). La certeza de la evidencia aumentó a moderada desde las revisiones anteriores para la osteítis alveolar y el dolor el día 3. Todos los demás resultados permanecieron con una confianza baja y muy baja en los resultados, por lo tanto, el uso de PRF puede dar lugar a poca o ninguna diferencia para estos. No se reporto ningún evento adverso. Los ECA recientes han mejorado la precisión y la potencia de los resultados de las revisiones anteriores, aumentando su certeza. PRF probablemente reduce el riesgo de osteítis alveolar y dolor en el día 3 después de la cirugía del tercer molar. Con respecto al edema, el trismo, la infección, la cicatrización de los tejidos blandos y los huesos, la certeza de la evidencia sigue siendo muy incierta debido a las muestras pequeñas y al riesgo de sesgo alto o incierto. Por lo tanto, se necesitan más ECA bien diseñados para confirmar y ampliar estos resultados.

PALABRAS CLAVE: Fibrina rica en plaquetas, terceros molares, cicatrización de la herida, revisión sistemática, metanálisis.

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APPENDIX

1. Search strategies

· PubMed (NIH)

((third* AND molar*) OR (wisdom* AND (tooth* OR teeth*)) AND ((("platelet-rich" OR "platelet rich") AND fibrin*) OR prf)) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

· Central (Cochrane)

o Filters:

§ Trials

o ((third* AND molar*) OR (wisdom* AND (tooth* OR teeth*)) AND ((("platelet-rich" OR "platelet rich") AND fibrin*) OR prf))

· Embase

o Filters:

§ Meta-analysis

§ Controlled clinical trial

§ Randomized controlled trial

o ((third* AND molar*) OR (wisdom* AND (tooth* OR teeth*)) AND ((("platelet-rich" OR "platelet rich") AND fibrin*) OR prf)

· Lilacs

o tw:((("third" AND "molar") AND (("PRF") OR ("Platelet" AND "RICH" AND "FIBRIN"))) AND (db:("LILACS" OR "BBO" OR "CUMED" OR "BDENF" OR "SES-SP" OR "BRISA" OR "colecionaSUS" OR "INDEXPSI" OR "SMS-SP" OR "BINACIS" OR "ARGMSAL") AND type_of_study:("clinical_trials"))

· ICTPR (WHO)

o Condition field: “third” and “molar”

o Intervention field: “PRF” OR “platelet rich fibrin” OR “Platelet-rich fibrin”

o Filters:

§ Recruitment status: ALL

§ Phases: ALL

· Clinical Trial (NIH)

o Recruiting, Not yet recruiting, Available, Active, not recruiting, Completed, Enrolling by invitation, Suspended, Terminated, Withdrawn, No longer available, Temporarily not available, Approved for marketing, Unknown status Studies | Interventional Studies | third molar | Platelet rich fibrin | Child, Adult, Older Adult

· Open Grey

o ("third" AND "molar") AND ("PRF" OR ("Platelet-rich" AND "fibrin") OR ("platelet" AND "rich" AND "fibrin"))

· NICE

o Platelet rich fibrin AND third molar

o Filters:

§ Evidence type: primary research, ongoing trials

§ Area of interest: Clinical

SUPPLEMENTARY MATERIAL

Effects of interventions of secondary outcomes

Bleeding. Two of the included studies reported the outcome bleeding during the post-operative period with an 1.33 RR of bleeding in the presence of PRF (95% CI 0.40 to 4.49; n=60; p=0.64; I2 not applicable).

Restricted mouth opening (Rmo). Nine of the included trials reported the outcome of restricted mouth opening, one was excluded for not reporting data necessary for analysis. Four trials reported Rmo as an outcome at day 1 (Kumar *et al*., 2015; Bilginaylar & Uyanik, 2016; Singha *et al*., 2019; Gupta & Agarwal, 2021), SMD for day 1 was 0.77 (95% IC 0.01 to 1.53; n=171; p=0.05; I2=0%). Four trials reported Rmo at Day 2 (Uyanık *et al*., 2015; Bilginaylar & Uyanik, 2016; Asutay *et al*., 2017; Torul *et al*., 2020), SMD for day 2 was 0.03 (95% IC -0.43 to 0.50; n=150; p=0.89; I2 = 0%). Four trials (Uyanık *et al*., 2015; Bilginaylar & Uyanik, 2016; Singha *et al*., 2019; Gupta & Agarwal, 2021) reported Rmo on day 3, SMD for day 3 was 1.06 (95% IC -0.03 to 2.16; n=140; p=0.06; I2=88%). See Figure 9. At day seven, six RCTs reported the outcome of restricted mouth opening (Uyanık *et al*., 2015; Bilginaylar & Uyanik, 2016; Asutay *et al*., 2017; Esen *et al*., 2017; Singha *et al*., 2019; Torul *et al*., 2020; Gupta & Agarwal, 2021), SMD was 0.29 (95% IC -0.10 to 0.67; n=290; p=0.14; I2=0%).

Bone healing (Bh). Twelve trials reported the outcome of bone healing (Gürbüzer *et al*., 2010; Baslarli *et al*., 2015;

Kumar *et al*., 2015, 2016; Wageeh *et al*., 2015; Varghese *et al*., 2017; Jeyaraj & Chakranarayan, 2018; Revathy *et al*., 2018; Kapse *et al*., 2019; Ritto *et al*., 2019; Sybil *et al*., 2020; Gupta & Agarwal, 2021), three trials (Baslarli *et al*., 2015; Varghese *et al*., 2017; Revathy *et al*., 2018) were excluded due to missing data. Multiple methods for measuring this outcome were observed. Ritto *et al*. (2019) were the only ones that used grey scale values for comparison. Kapse *et al*. (2019) evaluated this outcome using three different parameters; lamina dura, bone density and trabecular pattern score. Jeyaraj *et al*. (Jeyaraj & Chakranarayan, 2018) also used the former two. Another two studies used bone density (Kumar *et al*., 2015; Wageeh *et al*., 2015; Gupta & Agarwal, 2021) and two other studies used bone height (Wageeh *et al*., 2015; Sybil *et al*., 2020) to assess the outcome of bone healing. Three trials (Gürbüzer *et al*., 2010; Wageeh *et al*., 2015; Gupta & Agarwal, 2021) reported this outcome at the first month post-surgery. Pooled SMD was 0.41 (95% CI -0.25 to 1.08; n=88; p=0.22; I2=57%). For the second month post-surgery, three trials showed results for this outcome (Wageeh *et al*., 2015; Jeyaraj & Chakranarayan, 2018; Kapse *et al*., 2019). Pooled SMD was 5.00 (95% CI 1.02 to 8.98; n=140; p=0.01; I2: 97%). Four studies (Kumar *et al*., 2015; Wageeh *et al*., 2015; Sybil *et al*., 2020; Gupta & Agarwal, 2021) reported bone healing at month 3. The pooled estimate was 0.56 (95% CI -0.19 to 1.31; n=141; p=0.14; I2=78%). Only one study assessed Bh at month 4 (Kapse *et al*., 2019), therefore meta-analysis was not feasible. Two studies with a split-mouth design reported this outcome for month 6 post surgery (Sybil *et al*., 2020; Gupta & Agarwal, 2021). The pooled estimate for these studies was 0.43 favouring intervention, this result was also not statistically significant (95% CI -1.21 to 2.08; n=90; p=0.61; I2=93%).

Clinical attachment level/loss (Cal). Clinical attachment level or loss was evaluated by four trials (Niyombandith & Pisarnpan, 2015; Zahid & Nadershah, 2019; Gasparro *et al*., 2020; Sybil *et al*., 2020), all of them with a split-mouth design. At the first postoperative month only one study assessed Cal (Zahid & Nadershah, 2019). For second month this was also the case (Niyombandith & Pisarnpan, 2015), thus, metanalysis was not feasible. Two RCTs (Zahid & Nadershah, 2019; Sybil *et al*., 2020) reported results for this outcome at the third postoperative month. MD was -0.76 mm (95% IC -2.66 to 1.14; n=70; p=0.44; I2=82%). At sixth month two trials reported results for this outcome (Gasparro *et al*., 2020; Sybil *et al*., 2020). MD was -1.39 mm (95% IC -2.15 to -0.62; n=86; p=0.0004; I2=81%).

Probing depth (Pd). Nine trials reported assessing probing depth (Kumar *et al*., 2015; Niyombandith & Pisarnpan, 2015; Jeyaraj & Chakranarayan, 2018; Ritto *et al*., 2019; Zahid & Nadershah, 2019; Gasparro *et al*., 2020; Sybil *et al*., 2020). Nevertheless, three of them were excluded from quantitative analysis due to no available data (Baslarli *et al*., 2015; Unsal & Erbasar, 2018; Ritto *et al*., 2019). Of the six remaining studies, four had a split-mouth design (Niyombandith & Pisarnpan, 2015; Zahid & Nadershah, 2019; Gasparro *et al*., 2020; Sybil *et al*., 2020), whereas two had a parallel-arm design (Kumar *et al*., 2016; Jeyaraj & Chakranarayan, 2018). Pd at the first postoperative month was evaluated by two trials (Kumar *et al*., 2015; Zahid & Nadershah, 2019), pooled MD was -0.29 mm (95% CI -0.81 to 0.23; n=51; p=0.27; I2: 0%). Also two trials evaluated this outcome at month two (Niyombandith & Pisarnpan, 2015; Jeyaraj & Chakranarayan, 2018), MD was -0.58 mm (95% CI -1.11 to -0.12; n=80; p=0.02 I2: 14%). Three RCTs reported results for Pd at month three (Kumar *et al*., 2015; Zahid & Nadershah, 2019; Sybil *et al*., 2020). The pooled MD was -0.69 mm (95% CI -1.61 to 0.24; n=101; p=0.15; I2: 82%). For month 6, two trials evaluated the outcome of probing depth(Gasparro *et al*. 2020; Sybil *et al*. 2020). Pooled MD was -0.64 mm (95% CI -0.87 to -0.42; n=86; p<0.00001; I2: 0%).

Analgesic consumption (Ac). Ac was evaluated by four trials (Uyanık *et al*., 2015; Bilginaylar & Uyanik, 2016; Torul *et al*., 2020; Gupta & Agarwal, 2021), two of them with a parallel-arm design (Bilginaylar & Uyanik, 2016; Torul *et al*., 2020) and the other two with split-mouth (Uyanık *et al*., 2015; Gupta & Agarwal, 2021). Two of the above mentioned studies did not report data (Uyanık *et al*., 2015; Torul *et al*., 2020), therefore excluded from analysis. Both trials included in analysis (Bilginaylar & Uyanik, 2016; Gupta & Agarwal, 2021) evaluated Ac on day one. The pooled MD was -0.03 (95% CI -0.31 to 0.25; n=40; p=0.84; I2=0%). Only one trial (Bilginaylar & Uyanik, 2016) reported Ac on day two. In the absence of other trials evaluating this outcome at this day, meta-analysis was not feasible for this time frame. The two trials included in analysis (Bilginaylar & Uyanik 2016; Gupta & Agarwal, 2021) evaluated Ac on day three. MD for day three was -0.9 (95% CI -1.84 to 0.01; n=40; p=0.051; I2=81%). The same two trials (Bilginaylar & Uyanik ,2016; Gupta & Agarwal, 2021) evaluated this outcome at day seven. The pooled estimate was not available as one study(Bilginaylar and Uyanik 2016) reported that neither control or intervention group had any analgesic consumption at day seven.

Swelling (Sw) days 1, 2, and 7. Seven trials, five split-mouth (Ozgul *et al*., 2015; Uyanık *et al*., 2015; Bilginaylar & Uyanik, 2016; Kapse *et al*., 2019; Gupta & Agarwal, 2021) and two parallel-arm design (Kumar *et al*., 2015; Bilginaylar & Uyanik, 2016) reported the day 1, SMD was -0.99 (95% IC -2.09 to 0.11; n=372; p=0.08; I2=95%). Four trials, two split-mouth (Uyanık *et al*., 2015; Asutay *et al*., 2017) and two parallel-arm design (Bilginaylar & Uyanik, 2016; Torul *et al*., 2020) reported Sw at day 2, SMD was -0.04 (95% IC -0.33 to 0.24; n=190; I2=0%). Nine trials, seven split-mouth (Ozgul *et al*., 2015; Uyanık *et al*., 2015; Asutay *et al*., 2017; Kapse *et al*., 2019; Zahid & Nadershah, 2019; Sybil *et al*., 2020; Gupta & Agarwal, 2021) and two parallel-arm design (Bilginaylar & Uyanik, 2016; Torul *et al*., 2020) reported the outcome of Sw at day 7, SMD was -1.05 (95% CI -2.17 to 0.06; n=472; p=0.06; I2=96%).

Soft tissue healing (Sth) days 1, 7, 14 and 21. At first day after surgery (Daugela *et al*., 2018; Gupta & Agarwal, 2021)

SMD was -0.26 (95% IC -1.76 to 1.25; n=100; p=0.74; I2=92%). At day three (Daugela *et al*., 2018; Gupta & Agarwal, 2021) SMD was -0.35 (95% IC -2.26 to 1.57; n=100; p=0.74 I2=95%). Two trials (Daugela *et al*., 2018; Afat *et al*., 2019) reported the outcome of soft tissue healing at day 14, the pooled estimate SMD was -1.17 (95% IC -2.52 to 0.18; n=100; p=0.09; I2= 88%). One study reported Sth for day 21 (Afat *et al*., 2019) so metanalysis was not feasible.

Postoperative pain (PoP) at 6 and 12 hours, days 4, 5, 6, 7, and 14. At day 0, 6 hours, the pooled estimate resulted in a SMD of 0.10 (95% CI -0.23 to 0.43; n=140; p=0.55; I2=0%). At day 0, 12 hours, the pooled estimate SMD was -0.14 (95% IC -0.74 to 0.46; n=140; p=0.65; I2=64%). On day 2 the pooled estimate was - 0.39 (95% IC -0.91 to 0.13; n=220; p=0.002; I2 49%). See Figure 5. Two RCTs (Asutay *et al*., 2017; Daugela *et al*., 2018) reported pain results on day four the pooled estimate resulted in a SMD of -0.85 (95% CI -2.44 to 0.74; n=120; p=0.29; I2=94%). At day 5 two trials (Asutay *et al*., 2017; Daugela *et al*., 2018) reported results with a pooled estimate SMD of -0.05 (95% CI -0.41 to 0.31; n=120; p=0.79; I2=0%). Two RCTs reported pain results on day six (Asutay *et al*., 2017; Daugela *et al*., 2018) the pooled estimates for this studies showed a SMD of -0.51 (95% CI -2.62 to 1.61; n=120; p=0.64; I2=97%). Nine trials reported pain results on day seven (Ozgul *et al*., 2015; Bilginaylar & Uyanik, 2016; Asutay *et al*., 2017; Güls¸en & S¸entürk, 2017; Daugela *et al*., 2018; Kapse *et al*., 2019; Ritto *et al*., 2019; Sybil *et al*., 2020; Gupta & Agarwal, 2021) the pooled SMD was -1.46 (95% CI -2.45 to -0.47; n=476; p=0.004; I2=95%). One study (Kapse *et al*., 2019) reported pain scores for day 14 metanalysis was not feasible.