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Systematic review

Does intra-articular injection of platelet-rich plasma/platelet-rich fibrin improve outcomes after temporomandibular joint arthrocentesis? A systematic review and meta-analysis

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Abstract

Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have been used as adjuncts to temporomandibular joint (TMJ) arthrocentesis but without any high-quality evidence. This systematic review collated data from published randomised controlled trials (RCTs) to provide level-1 evidence on its efficacy. Trials published on the databases of PubMed, Scopus, Embase, CENTRAL, and Web of Science up to 4 August 2023 and comparing intra-articular PRP/PRF with control after TMJ arthrocentesis were eligible. Primary outcomes were pain and maximal mouth opening (MMO). Twelve RCTs were included. Pooled analysis showed that pain scores were significantly reduced with the use of PRP/PRF as compared with control at one month (MD: −0.96 95% CI: −1.58 to −0.35 I^2 = 86%), three months (MD: −1.22 95% CI: −1.86 to −0.59 I^2 = 85%), and ≥six months (MD: −1.61 95% CI: −2.22 to −1.00 I^2 = 88%). Similarly, MMO was significantly improved in the PRP/PRF group at one month (MD: 2.40 95% CI: 1.02 to 3.77 I^2 = 88%), three months (MD: 3.17 95% CI: 1.63 to 4.72 I^2 = 91%), and ≥six months (MD: 2.98 95% CI: 1.86 to 4.10 I^2 = 75%) as compared with the control group. Subgroup analysis for PRP and PRF failed to show any difference in outcomes. Moderate quality evidence suggests that PRP and PRF may significantly improve pain and MMO when used as adjuncts to TMJ arthrocentesis. Due to the small effect size, the clinical significance of the results is questionable. The high heterogeneity in PRP/PRF preparation methods is a significant limitation.

Keywords: Temporomandibular joint; Lavage; Growth factors; Pain; Mouth opening

Introduction

Internal derangement (ID) of the temporomandibular joint (TMJ) refers to any condition that affects the smooth movement of the joint.[1] Internal derangement involves a spectrum of conditions ranging from disc displacement with reduction, disc displacement without reduction, to degenerative joint disease, all of which can cause significant pain, reduction in mouth opening, joint sounds, and reduced quality of life.[2] The management is usually aimed at converting a symptomatic joint into an adaptive state with minimal symptoms that do not interfere with daily activities.[3] Conservative therapy consisting of non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, stretching exercises, soft diet, and stabilisation splint therapy are usually combined as the first line of treatment in acute cases.[4] However, several cases fail to respond and TMJ arthrocentesis has become an effective second-line therapy.

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Arthrocentesis is a minimally invasive procedure that depends upon thorough lavage of the joint space to flush out inflammatory cytokines, pain mediators, and reactive oxygen species; break intra-articular adhesion; and re-establish the lubrication system of the joint.[5] Numerous studies have reported significant improvement in pain and maximal mouth opening (MMO) with the use of TMJ arthrocentesis.[6] Furthermore, several modifications of the procedure have also been proposed but with little change in patient outcomes.[7] In addition to changes in technique, there have also been reports of the use of intra-articular adjuncts after TMJ arthrocentesis. NSAIDs, opioids, steroids, hyaluronic acid, and platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) are being used to improve outcomes but with conflicting results.[8,9]

Platelet-rich therapies, namely, PRP and PRF both contain autologous blood products that are rich in growth factors and have anti-inflammatory and regenerative properties.[10] It is postulated that injection of PRP or PRF after complete lavage of the joint can aid joint healing and improve outcomes as compared to arthrocentesis alone.[11] In recent years, the use of PRP/PRF has been investigated by several trials but with variable results.[10–14] Past systematic reviews have either combined data from both arthrocentesis and arthroscopy[15,16] or included too few trials[17] on PRP/PRF to derive high-quality evidence. Hence, the current review was designed to investigate if the use of PRP/PRF as adjuncts to TMJ arthrocentesis improves patient outcomes.

Material and methods

Search strategy

As per established procedure, the protocol of the review was drafted and uploaded on the international register - PROSPERO (CRD42023425471). The study was performed based on the criteria of the Preferred Reporting Items for Statistic Reviews and Meta-Analyses statement.[18] English-language articles were searched on the databases of PubMed, Scopus, Embase, CENTRAL, and Web of Science. The search encompassed all studies published from 1991 to 4 August 2023. Conference proceedings and unpublished or non-peer-reviewed data were not considered during the search.

A search protocol was developed using the keywords: “PRP”, “PRF”, “Platelet-rich plasma”, “Platelet-rich fibrin”, “TMJ”, “temporomandibular joint”, “lavage”, and “arthrocentesis”. Boolean operators (AND, OR) were used to frame the search queries. Further details have been provided in detail in Supplementary Table 1 (online only).

Two reviewers (SN, VG) were involved in the search process which first began with title and abstract screening. Studies were excluded if the title or the abstract did not conform with the aims of this review. Full text was then obtained for all identified acceptable studies, or when the relevance of an article could not be determined. Disagreements were settled by discussions with the third author (VK). The same process was performed for the full-text review. The bibliography of included studies was cross-referenced to discover further eligible studies.

Inclusion criteria

Studies were included if they fulfilled the following PICOS criteria:

Population: Studies conducted on adult patients with TMJ ID
Intervention: TMJ arthrocentesis with intra-articular injection of PRP/PRF at the end of the procedure
Comparison: TMJ arthrocentesis without any intra-articular injection of any drug
Outcomes: Pain measured on a Visual Analogue Scale (VAS) and MMO measured in millimetres (mm)
Studies: Randomised controlled trials (RCT)

All retrospective studies, single-arm studies, editorials, and review articles were excluded.

Data extraction

Two reviewers (SN, HR) conducted the data extraction and collected information pertaining to the year of publication, the author’s first name, country, study type, diagnosis of patients, PRP/PRF preparation protocol, sample size, mean age of the population, gender details, arthrocentesis technique used, amount of irrigation solution, use of stabilisation splints, and follow up. Pain and MMO were the primary outcomes of the review.

Bias in the included RCTs was measured by the recommended Cochrane Collaboration risk of bias-2 tool.[19] Two reviewers examined the trials for the randomisation process, deviation from intended intervention, missing outcome data, measurement of outcomes, selection of reported results, and overall risk of bias. Each domain was marked with either low risk, high risk, or some concerns. Further, we also assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool based on the GRADEpro GDT software.

Statistical analysis

Pain and MMO were continuous outcomes presented as mean and standard deviation (SD) values. Since the same scale was used by all studies, data were collated to obtain mean difference (MD) with 95% confidence intervals (CI). Separate analysis was done for different follow-up intervals. Given the baseline difference amongst studies, meta-analysis was conducted in a random-effects model. Review Manager (RevMan, version 5.3) was used for the same. Outliers were assessed using a sensitivity analysis involving the removal of one study at a time. The chi squared-based Q statistics and I^2 statistics were the tools to examine inter-study heterogeneity. A p value of <0.10 for Q statistic and I^2 $>50\%$ meant sub-

stantial heterogeneity. Funnel plots were generated to judge publication bias. Subgroup analysis was conducted for PRP and PRF.

Results

Eight-six unique articles were searched from all databases (Fig. 1). Sixty-six of them were excluded following initial screening by the reviewers. Twenty articles underwent further screening and 12 made it to the final review.[10–14,20–26] The inter-reviewer rating for the selection of studies was high (kappa = 0.9).

Baseline data extracted from the studies are shown in Table 1. The RCTs were conducted in India, Spain, Turkey, Syria, and Egypt. Patients with disc displacement with and without reduction along with those with osteoarthritis were included in the trials. Four studies reported the use of PRF while remaining used PRP but with significant variations in PRP/PRF preparation technique. Most trials used the two-needle technique while only one reported the use of the single-needle technique. The amount of irrigation solution varied from 50-200ml. None of the studies reported the use of postoperative stabilisation splints. Maximum follow up varied from three to 24 months.

Pooled analysis showed that pain scores were significantly reduced with the use of PRP/PRF as compared with the control at one month (MD: −0.96 95% CI: −1.58 to −0.35 I^2 = 86%), three months (MD: −1.22 95% CI: −1.86 to −0.59 I^2 = 85%), and ≥six months (MD: −1.61 95% CI: −2.22 to −1.00 I^2 = 88%) (Fig. 2). Similarly, MMO was significantly improved in the PRP/PRF group compared with the control group at all follow-up intervals - one month (MD: 2.40 95% CI: 1.02 to 3.77 I^2 = 88%), three months (MD: 3.17 95% CI: 1.63 to 4.72 I^2 = 91%), and ≥six months (MD: 2.98 95% CI: 1.86 to 4.10 I^2 = 75%) (Fig. 3). The MD of all outcomes did not change in statistical significance on sensitivity analysis. There was no evidence of publication bias on funnel plots (Supplementary Figs. 1 & 2, online only).

Details of subgroup analysis for all outcomes based on the use of PRP or PRF are shown in Table 2. The results showed that MMO was significantly improved with the use of either PRP or PRF at all follow-up intervals. Pain scores at one and three months were not significant for the PRP group.

Table 3 shows the risk of bias assessment of included RCTs. Nine trials had a high risk of bias primarily due to a lack of allocation concealment and blinding of patients/outcome assessors. Two studies had some concerns due to a lack

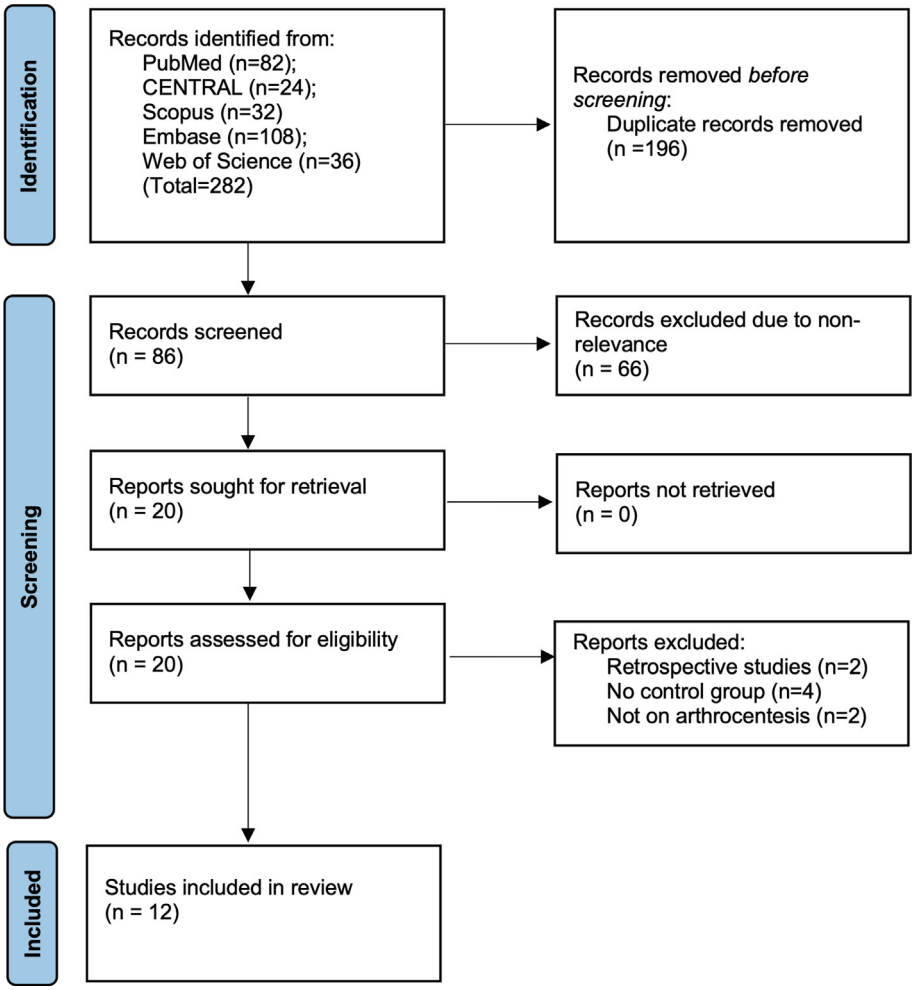

Fig. 1. Study flowchart.

Table 1
Details of included studies.

First author, year and reference	Location	Included patients	PRF/ PRP	Protocol of preparation	Groups	Sample size	Age	Male gender (%)	Arthrocentesis technique	Irrigation volume	Splint therapy	Follow up
Isik, 2023[10]	Turkey	DDwoR	PRF	10 mL venous blood centrifuged at 700 rpm for 3 minutes. 1 ml of i-PRF injected. Injections repeated once every week for 4 weeks	Study Control	38 38	47.2 46.8	10.5 7.9	2-needle	200 ml	NR	12 m
Ramakrishnan, 2022[12]	India	DDwoR	PRP	10 mL venous blood with anticoagulant centrifuged as per operator instructions. 1 ml PRP injected (activated)	Study Control	11 11	30.3 34.6	46 82	2-needle	100 ml	NR	3 m
Isik, 2022[11]	Turkey	OA	PRF	10 mL venous blood centrifuged at 700 rpm for 3 minutes. 1ml of i-PRF injected. Injections repeated once every week for 4 weeks	Study Control	18 18	44.7 45.7	11.1 5.5	2-needle	200 ml	NR	12 m
Dasukil, 2022[13]	India	DDwR, DDwoR	PRP	50 mL venous blood centrifuged at 200 G for 10min and 2000 G for 10 minutes. 1ml PRP injected twice after interval of one week	Study Control	30 30	37.7 37.5	23.3 33.3	1-needle	100 ml	NR	6 m
Abbadi, 2022[14]	Syria	OA	PRP	6 mL venous blood centrifuged at 1000 rpm for 10 minutes. 1ml of PRP injected	Study Control	11 11	26.5 27	36.3 36.4	2-needle	50 ml	NR	6 m
Singh, 2021[22]	India	DDwR, DDwoR	PRP	6 mL venous blood centrifuged at 2000 rpm for 8 minutes. 1ml of PRP injected	Study Control	12 12	34.7 36.4	33.3 66.6	2-needle	100 ml	NR	6 m
Karadayi, 2021[24]	Turkey	DDwoR, OA	PRF	10 mL venous blood centrifuged at 700 rpm for 3 minutes. 2ml of i-PRF injected	Study Control	18 18	39.9 39.6	55.5 50	2-needle	100 ml	NR	3 m
Jacob, 2021[23]	India	DDwR, DDwoR	PRP	1ml of PRP injected (non-activated). Protocol NR	Study Control	15 15	40.6 51.5	29.4 43.7	2-needle	100 ml	NR	6 m
Ghoneim, 2021[26]	Egypt	DDwR	PRF	Venous blood centrifuged at 700 rpm for 3 minutes. 1.5ml of i-PRF injected	Study Control	20 20	26.5 28.6	20 35	2-needle	100 ml	NR	6 m
Ansar, 2021[25]	India	NR	PRP	5 mL venous blood centrifuged at 2100 rpm for 15 minutes. Plasma separated and again centrifuged at 3500 rpm for 10 minutes. 0.8ml of PRP injected	Study Control	15 15	NR	NR	NR	200 ml	NR	6 m
Toameh, 2019[20]	Syria	DDwoR	PRP	13.5 mL venous blood centrifuged at 3400 rpm for 4 minutes. 1ml of PRP injected (activated)	Study Control	10 10	37.8 40.5	10 20	2-needle	100 ml	No	9 m
Kilic, 2015[21]	Turkey	OA	PRP	6 mL venous blood centrifuged at 100 rpm for 10 minutes. 1ml of PRP injected (non-activated). Injections repeated once every month for 4 months	Study Control	18 12	32.2 35.1	12 7	2-needle	100 ml	NR	24 m

PRF, platelet-rich fibrin; i-PRF, injectable PRF; PRP, platelet rich plasma; ml, millilitre; m, months; OA, osteoarthritis; DDwR, disc displacement with reduction; DDwoR, disc displacement without reduction; NR, not reported; rpm, revolutions per minute.

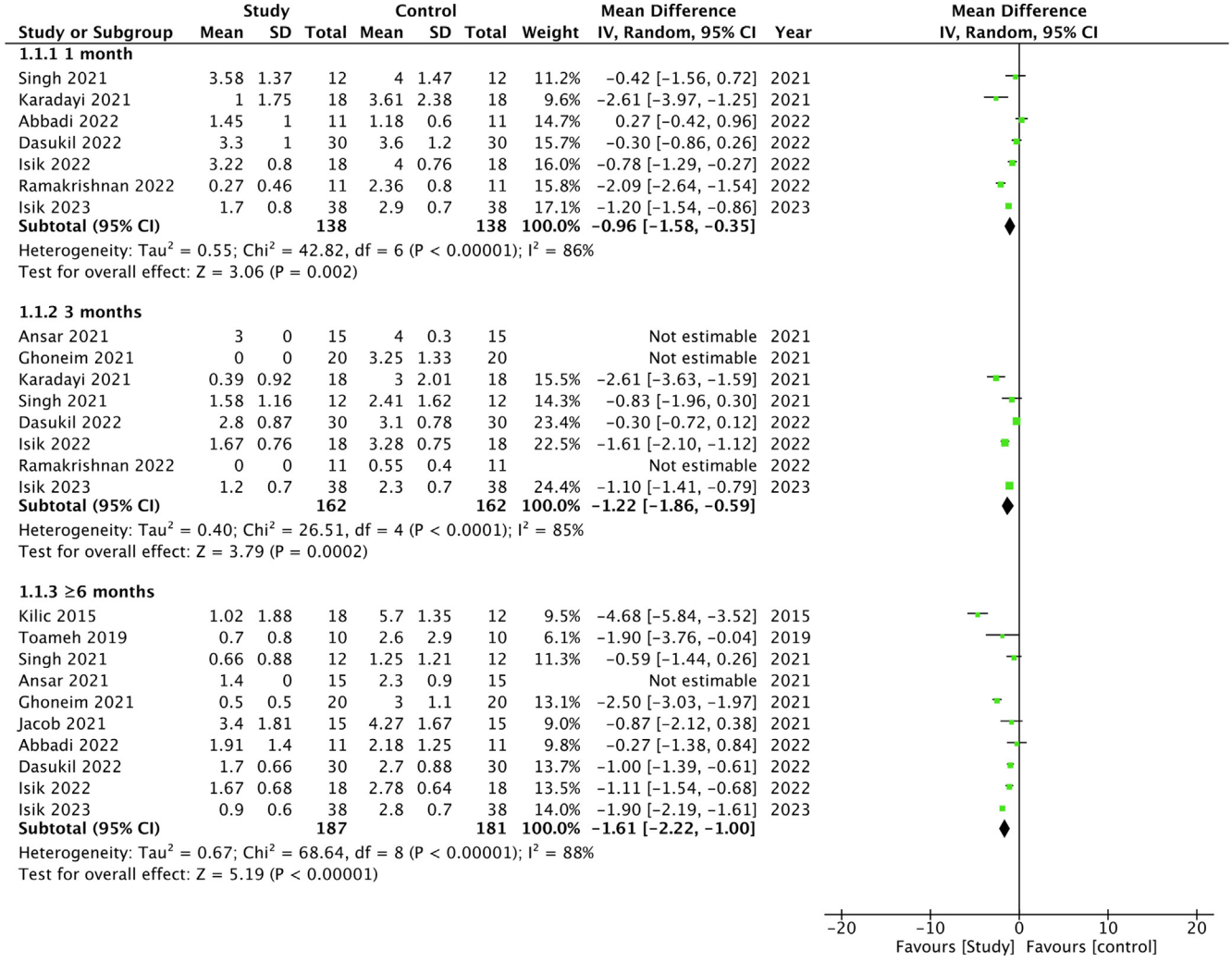

Fig. 2. Meta-analysis of pain scores between platelet-rich plasma/platelet-rich fibrin and control groups based on different follow-up periods.

of blinding of outcome assessment. Only one RCT[13] was considered to be high quality with a low risk of bias. Given the risk of bias in the included studies, the certainty of evidence based on GRADE was downgraded to 'moderate' for all outcomes (Supplementary Table 2, online only).

Discussion

Temporomandibular joint arthrocentesis has been advocated as an effective therapy for a range of joint problems namely anchored disc phenomenon, disc displacement with and without reduction, and osteoarthritis with high rates of success.[3] Nevertheless, in some cases, outcomes may not be favourable and patients may require reinterventions to improve function.[27] Since arthrocentesis involves only mechanical flushing of the joint without any pharmacological effects, it has been postulated that the use of intra-articular medications post-arthrocentesis may further enhance outcomes and reduce the rates of failure by direct action inside the joint.[8] While some individual trials have reported improved outcomes with intra-articular drugs, systematic reviews have failed to demonstrate a clear benefit of adjunctive measures over arthrocentesis alone. Gopalakrishnan et al[9] have reported inconclusive evidence on the effectiveness of intra-articular analgesics in improving pain outcomes after TMJ arthrocentesis. Derwich et al[8] in a review of 16 studies noted that the addition of hyaluronic acid or corticosteroids does not improve final clinical outcomes and arthrocentesis alone was effective in improving pain and MMO in TMJ osteoarthritis. In the same study, they noted that outcomes with the addition of PRP were questionable and not consistent. Gutierrez et al[16] in 2022, reviewed eight RCTs assessing PRP or PRF injections as adjuncts to TMJ arthrocentesis or arthroscopy and concluded that the use of PRP or PRF resulted in slightly better clinical outcomes but were of little significance compared with the control group. The evidence was found to be contradictory with a high risk of bias and the authors provided a grade C recommendation on the use of PRP/PRF based on evidence-based dentistry guidelines.

As compared with a previous review,[16] which included just six RCTs on arthrocentesis, the current updated review pooled data from 12 RCTs thereby presenting the most comprehensive evidence to date. Our meta-analysis found that

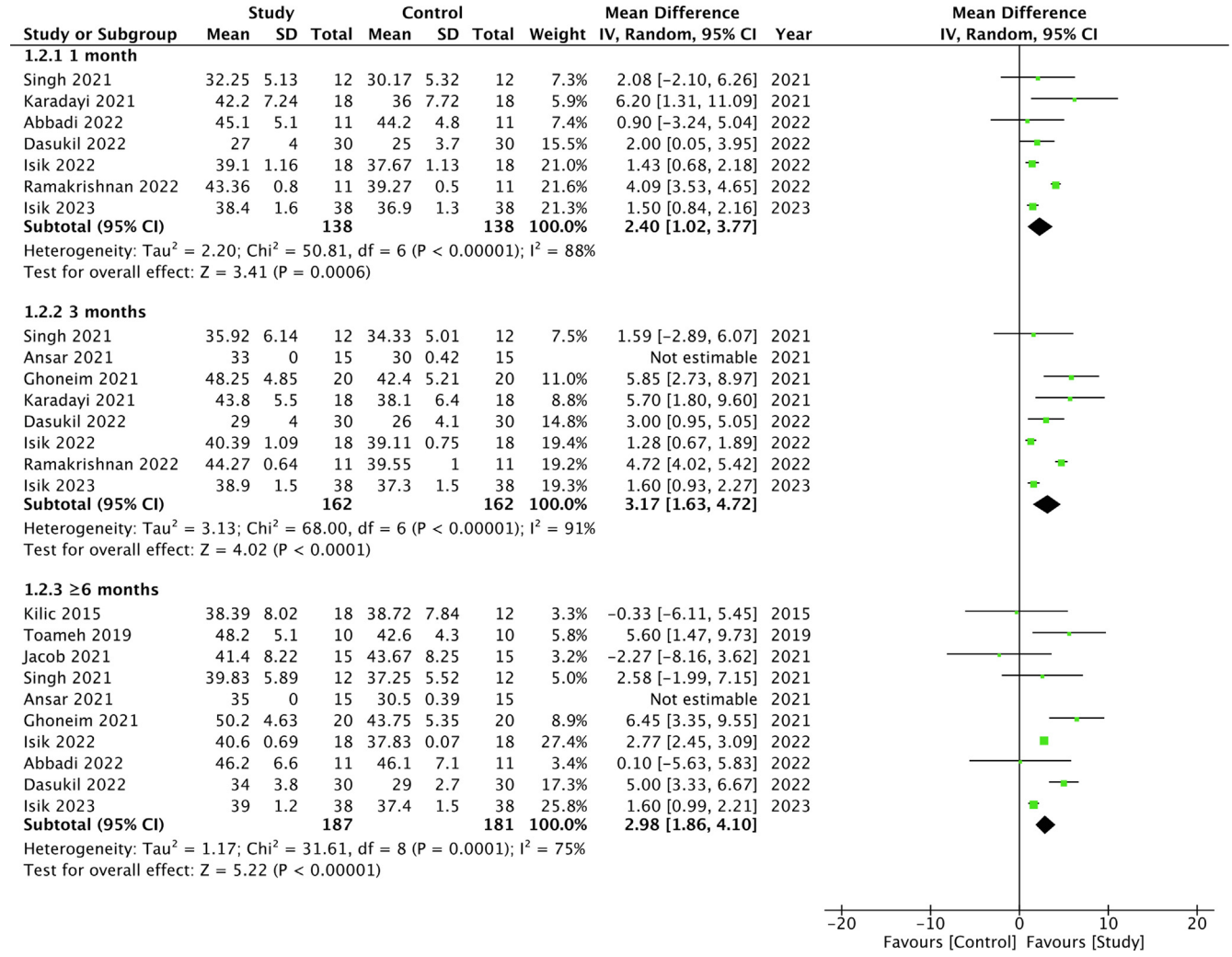

Fig. 3. Meta-analysis of maximal mouth opening scores between platelet-rich plasma/platelet-rich fibrin and control groups based on different follow-up periods.

Table 2
Subgroup analysis based on PRP vs PRF.

Outcome	Follow-up (months)	Number of studies	Mean difference [95% Confidence intervals]	I^2
Platelet rich plasma				
Pain	1	4	−0.65 [−1.80, 0.50]	91
	3	4	−0.36 [−0.76, 0.03]	0
	≥6	7	−1.51 [−2.61, −0.40]	88
Maximal mouth opening	1	4	2.86 [1.21, 4.51]	56
	3	4	3.84 [2.23, 5.45]	51
	≥6	7	2.61 [0.10, 5.11]	53
Platelet-rich fibrin				
Pain	1	3	−1.25 [−1.87, −0.62]	69
	3	4	−1.62 [−2.30, −0.95]	79
	≥6	3	−1.82 [−2.52, −1.13]	88
Maximal mouth opening	1	3	1.58 [0.80, 2.36]	44
	3	4	2.32 [1.07, 3.58]	76
	≥6	3	2.73 [1.46, 4.01]	88

Table 3
Risk of bias analysis.

First author, year and reference	Randomisation process	Deviation from intended intervention	Missing outcome data	Measurement of outcomes	Selection of reported result	Overall risk of bias
Isik, 2023[10]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Ramakrishnan, 2022[12]	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Isik, 2022[11]	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Dasukil, 2022[13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Abbadi, 2022[14]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Singh, 2021[22]	Some concerns	Low risk	Low risk	High risk	Low risk	High risk
Karadayi, 2021[24]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Jacob, 2021[23]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Ghoneim, 2021[26]	Some concerns	Low risk	Low risk	Some concerns	Low risk	High risk
Ansar, 2021[25]	Some concerns	Low risk	Low risk	High risk	Low risk	High risk
Toameh, 2019[20]	Some concerns	Low risk	Low risk	High risk	Low risk	High risk
Kilic, 2015[21]	Some concerns	Low risk	Low risk	High risk	Low risk	High risk

the use of PRP/PRF after TMJ arthrocentesis resulted in statistically significant improvement in pain scores and MMO at one month, three months and ≥six months as compared with no PRP/PRF injections. Adding to the credibility of the outcomes was the lack of change in the effect size on sensitivity analysis. This demonstrated that there was no outlier in the included studies, which significantly influenced the direction of the outcomes. Nevertheless, it is important to consider the resultant MD for both pain and MMO while interpreting the results. PRP/PRF reduced pain scores by only 0.96, 1.22, and 1.61 points and MMO was improved by only 2.4, 3.17, and 2.98 mm at one, three and ≥six months, respectively. These scores may have been statistically significant, but their clinical relevance is questionable. Clinical relevance of outcomes has been elucidated by the concept of 'Minimal Clinically Important Difference' (MCID), which is the smallest change in the outcome perceived by the patient as beneficial and which mandates a change in health-care protocols.[28] Literature is scarce on the MCID for pain and MMO for ID of TMJ. Calixtre et al[28] have shown that MCID for TMJ pain would be a reduction of 1.9 points on VAS for current pain and this may be less than a 1.5–3.2 point reduction needed for generalised chronic pain. MCID for MMO has been 6mm in cases of restricted mouth opening and 3mm in those with no limitation of MMO.[28] Therefore, the current evidence shows that while the use of intra-articular PRP/PRF compared with no drugs does significantly improve pain and MMO scores after TMJ arthrocentesis, the statistical difference may not translate into clinically relevant differences for the patient.

The improvement in outcomes with intra-articular PRP/PRF has been attributed to the high concentration of growth factors. Vascular endothelial growth factor, fibroblast growth factor, platelet-derived growth factor, epidermal growth factor, insulin-like growth factor, matrix metalloproteinases 2, 9, and interleukin 8 released by the platelets in PRP/PRF cause proliferation and differentiation of fibroblasts, osteoblasts, and chondrocytes leading to angiogenesis, and extracellular matrix synthesis. Three proteins namely, fibrin, fibronectin, and vitronectin present in PRP/PRF also stimulate osteoconduction and form a matrix for the migration of mesenchymal stem cells for tissue repair.[29] Both PRP and PRF are prepared from autologous blood just before the procedure but differ in their preparation methods. PRP is collected in anticoagulant vials while PRF uses no anticoagulant, which leads to the formation of a fibrin-rich clot that cannot be injected, unlike PRP.[30] Recently, injectable-PRF (i-PRF) formulations have been developed by low-speed centrifugation of blood in non-glass centrifugation tubes.[31] All four trials in this review using PRF used the i-PRF formulation. Compared with PRP, which shows early and bulk release of growth factors, i-PRF releases growth factors in a higher concentration over a longer duration of time and also demonstrates higher fibroblast activity.[31] Indeed, the early release of growth factors with PRP is a problem and some of the trials in this review even used inactivated PRP based on the theory that inactivated PRP results in better chondrogenic differentiation, mesenchymal stem cell proliferation, and osteoinductivity compared with activated PRP.[23,32] However, clinical studies have shown contrasting results when comparing PRP with PRF. Platelet-rich plasma has shown better healing in rotator cuff repair while PRF has shown better outcomes in facial lipostructure surgery.[33,34] Contrastingly, in a subgroup analysis of PRP and PRF for TMJ arthrocentesis, we noted no difference in MMO between the two platelet-rich therapies. However, with limited number of trials, PRP failed to improve pain scores at one and three months but had significant effect on pain scores at ≥six months.

The high heterogeneity in the meta-analysis is an important drawback. Major methodological variations were noted in the included trials pertaining to the included populations and the method of PRP/PRF preparation. Different systems of PRP/PRF vary in the procedure of collection and ability to concentrate platelets based on centrifugation speed and time. To date, there has been no consensus on the optimal centrifugation speed and time to obtain high-quality PRP/PRF.[29] However, these parameters affect the concentration of platelets and purity of the product obtained, which can have clinical implications.[35] Secondly, the number of injec-

tions of PRP/PRF and the dose also varied amongst the included trials. At this point, there is no clarity in the literature on the use of repeated PRP/PRF injections for TMJ ID. Thirdly, there were also slight variations in the amount of lavage fluid and the arthrocentesis technique. Research shows that the arthrocentesis technique (single puncture vs double puncture) and arthrocentesis lavage volumes (100 vs 250 ml) may not influence patient outcomes.[6,36]

There are other limitations of the review as well. First, there was a high risk of bias in the included trials. Only one RCT[13] was found to be of high quality with all others demonstrating bias in blinding of patients and/or assessment of outcomes. Lack of blinding of patients can have important implications on subjective outcomes such as pain wherein the patient may have a preconceived notion of better results with PRP/PRF. The high risk of bias led to a reduction of the certainty of evidence to moderate. Secondly, the follow-up duration was not consistent across studies, which reduced the number of studies in each analysis. Thirdly, due to overlapping inclusion criteria of disc displacement and osteoarthritis in the included trials, we were unable to perform a subgroup analysis for the same. Lastly, the trials were from a few select countries and may limit the generalisability of results.

Given these limitations, we believe that the use of PRP/PRF needs to be further validated by double-blinded rigorous multicentric clinical trials before they are routinely used in clinical practice. Such trials should have homogenous inclusion criteria, large sample size, uniform arthrocentesis, and PRP/PRF preparation protocol and long follow up to provide robust results. Further, a trial with multiple arms including other intra-articular drugs would further bring out evidence on the best intra-articular adjunct after arthrocentesis.

Conclusion

Moderate quality evidence suggests that PRP and PRF may significantly improve pain and MMO when used as adjuncts to TMJ arthrocentesis. Due to the small effect size, the clinical significance of the results is questionable. The high heterogeneity in PRP/PRF preparation methods is a significant limitation. Future trials should standardise inclusion criteria and preparation techniques to provide robust results.

Conflict of interest

We have no conflicts of interest.

Funding

No funding.

Ethics statement/confirmation of patient permission

Not required as it is a systematic review article.

Data availability statement

Publicly available datasets were analysed in this study. The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.bjoms.2024.06.007.

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