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Comparative efficacy of arthrocentesis combined with different drug injections for arthrogenic temporomandibular disorders: a network meta-analysis of randomized trials

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Abstract

Objective To compare the efficacy of intra articular injectable agents following arthrocentesis for arthrogenous TMDs and assess evidence certainty using GRADE.

Methods Systematic searches of 6 databases up to July 9, 2025 identified RCTs comparing injectable agents after arthrocentesis. Risk of bias was assessed with RoB 2 and evidence certainty with CINeMA/GRADE. Network meta analyses were performed at 1, 3, 6, and 12 months for pain (VAS) and MMO.

Results Nineteen RCTs (783 patients) were included. For VAS, iPRF was associated with greater pain reduction than placebo at 1 month (MD = 1.36, 95% CI: 0.51 to 2.21), 3 months (MD = 1.59, 95% CI: 0.66 to 2.52), and 12 months (MD = 1.60, 95% CI: 0.14 to 3.07), though confidence intervals were wide and the 12 month estimate barely reached significance. PRP showed a similar benefit at 3 months. For MMO, only high molecular weight HA was associated with improvement at 6 months vs placebo (MD = -8.07, 95% CI: -11.14 to -5.00) and PRP (MD = 5.62, 95% CI: 2.78 to 8.45).

Conclusions iPRF showed statistically significant pain reduction at 1, 3, and 12 months, but the clinical importance remains uncertain given marginal effect sizes and wide confidence intervals.

Keywords Temporomandibular disorders, Arthrocentesis, Network meta-analysis, Injectable platelet-rich fibrin, Hyaluronic acid

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Introduction

Temporomandibular joint disorders (TMD) is a general term for a group of diseases involving partial or overall functional disorders of the temporomandibular joint (TMJ), masticatory muscles, and adjacent structures. Its clinical manifestations include pain in the temporomandibular joint area, joint murmurs, limited mouth opening, and deviation of mandibular movement [1]. Based on the etiology, TMD can be classified into two types: myogenous temporomandibular joint disorders and arthrogenous temporomandibular joint disorders (arthrogenous TMDs). Approximately 80% of the clinical symptoms are related to arthrogenous TMDs [2, 3].

Arthrogenous TMDs refer to pathological changes derived from the structure of the TMJ itself, mainly including intra-articular disorders, joint pain, osteoarthritis and condylar resorption, etc. [1, 3]. Although the natural course of arthrogenous TMDs is usually good and symptoms in most cases resolve over time, some patients may require treatment. Cytokines, matrix metalloproteinases, proteolytic enzymes, proteoglycans and other molecular markers exist in the temporomandibular joint structure of arthrogenous TMDs. The release and interaction of these molecular markers are of great significance in tissue degeneration, increased inflammation degree and the occurrence and development of clinical symptoms. Therefore, timely intervention can prevent the aggravation of the disease [4, 5].

At present, the intervention of arthrogenous TMDs includes three stages: conservative treatment, minimally invasive treatment and surgical treatment. Firstly, conservative treatment, including health education and publicity, psychotherapy, oral medication therapy, physical therapy (manual reduction, photobiological regulation, transcutaneous electrical stimulation, etc.) and Bite plate treatment [6–11]. Secondly, minimally invasive treatment includes arthrocentesis (joint cavity irrigation) with or without drug injection [12]. Third, surgical treatment, including arthroscopic surgery or open joint surgery [13, 14]. Conservative treatment is regarded as the preferred treatment for relieving arthrogenous TMDs pain due to its lower risk of side effects, while minimally invasive and invasive surgeries are often used in cases where the disease is irreversible and accompanied by acute or chronic pain [15]. Recent evidence suggests that when patients do not benefit significantly from initial conservative treatment, it is recommended to implement minimally invasive treatments such as intra-articular injection and/or arthrocentesis as early as possible [16, 17].

Temporomandibular joint arthrocentesis is a procedure performed under local anesthesia, involving irrigation of the upper joint space using either a single-needle or double-needle technique with Ringer's solution or normal saline, followed by injection or non-injection of therapeutic agents. This process aims to remove inflammatory mediators and fibrous adhesions from the joint cavity, reduce surface friction, and maintain adequate synovial fluid viscosity [18]. Currently, intra-articular injection following TMJ arthrocentesis is widely used in the sequential management of TMJ disorders. Among the commonly injected agents, hyaluronic acid (HA) and corticosteroids have been supported by relatively extensive clinical research. Studies on platelet-rich plasma (PRP) and injectable platelet-rich fibrin (iPRF) are also maturing, while emerging agents such as bone marrow aspirate concentrate (BMNc) and microfragmented adipose tissue (FAT) demonstrate promising therapeutic potential [19–24].

In 2025, Kelemen et al. conducted an NMA of 13 RCTs and reported that saline-PRP ranked highest for improving mouth opening and pain at 1 to 3 months, while saline-HA and saline-steroids were more effective for long-term mouth opening [25]. However, their analysis included only one RCT on iPRF and did not stratify HA by concentration or molecular weight. More recently, Zou et al. published a larger NMA of 38 RCTs (1533 patients) showing that iPRF ranked first for mouth opening (SUCRA 99.1%) and lateral/protrusive movements, and they did compare iPRF with PRP (MD = 12.85, 95% CI: 6.24 to 19.46) [26]. Nevertheless, all HA studies were pooled regardless of concentration, and no subgroup analysis based on HA concentration was performed. Thus, no prior NMA has specifically addressed whether different HA concentrations affect clinical outcomes. Moreover, the limited number of iPRF trials in Kelemen et al. restricted the comparison between iPRF and PRP.

To fill these gaps, the present NMA introduces two novel features. First, we specifically evaluate iPRF as a distinct intervention and directly compare it with PRP and other injectables. Second, we perform subgroup analyses according to HA concentration (low, high) to determine whether concentration influences efficacy. These analyses have not been reported in previous NMAs, including Kelemen and Zou.

Therefore, to address these evidence gaps, we performed a network meta-analysis to compare and rank the efficacy of different intra-articular injectables following arthrocentesis in patients with arthrogenous TMDs.

Materials and methods

This systematic review and network meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. The protocol was registered with PROSPERO under registration number CRD42024499883.

Eligibility criteria

Inclusion and exclusion criteria

Based on the PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework, the following eligibility criteria were applied:

(P) Population: Patients diagnosed with arthrogenous temporomandibular disorders (TMD) according to the Diagnostic Criteria for TMD (DC/TMD) [28], the Research Diagnostic Criteria for TMD (RDC/TMD), or other similar diagnostic systems, and/or confirmed by medical history, prior treatment history, clinical examination supplemented with imaging findings if necessary, and who were not undergoing concurrent conservative treatments (including physical therapy, oral NSAIDs, stabilization splint therapy, etc.). (I) Intervention and (C) Comparison: Patients use normal saline or lactated Ringer's solution for simple temporomandibular joint arthrocentesis irrigation, or irrigation followed by injection of drugs, such as Platelet-rich plasma (PRP), Hyaluronic acid (HA), injectable platelet-rich fibrin (iPRF), Bone marrow aspirate concentrate (BMNc), Triamcinolone acetonide (TA), microfragmented adipose tissue (FAT). (O) Outcomes: At least one of the following primary outcomes had to be reported: pain intensity measured using a visual analog scale (VAS), or maximum mouth opening (MMO). A follow-up duration of at least 1 month was required. (S) Study design: RCTs.

Studies were excluded if they met any of the following criteria:

> Participants had other TMJ disorders (e.g., ankylosis, tumor, trauma), previous TMJ surgery, polyarthritis or other rheumatic diseases, congenital deformities, or neurological disorders;
> Non-RCTs or animal studies;
> Non-English publications.

Research strategy

This study conducted a systematic search across six major electronic databases (PubMed, Embase, Web of Science, Cochrane Library, ClinicalTrials.gov and WHO ICTRP) to identify RCTs investigating the efficacy of arthrocentesis irrigation combined with various intra-articular drug injections for the treatment of arthrogenous TMDs. The search covered the period from the inception of each database up to July 9, 2025. The search strategy combined Medical Subject Headings (MeSH) with free-text terms tailored to the specific features of each database. Supplementary searches were also performed by screening reference lists of relevant reviews and meta-analyses. Emphasis was placed on optimizing the specificity of the search strategy to minimize the inclusion of irrelevant literature. The detailed search strategy is provided in Supplementary Material. 1.

Screening and data extraction

EndNote X9 was used to identify duplicate records among the initially identified literature. Two authors (DSW and TG) first removed duplicates through both automated and manual processes, and then performed an initial screening based on titles and abstracts. Two authors (DSW and TG) independently screened titles and abstracts. Inter-rater agreement was assessed using Cohen's κ based on initial independent decisions. Disagreements were resolved by consensus. This was followed by a full-text review of the remaining articles for further eligibility assessment. For the included studies, the same two authors (XYQ and YW) independently assessed the risk of bias using the Cochrane Risk of Bias Tool (ROB 2.0) [29]. Finally, they independently extracted data and cross-verified the results. The extracted data encompassed basic study information, participant characteristics, as well as detailed descriptions of interventions and outcomes. Any disagreements were resolved through discussion or, when necessary, by arbitration from a third author (HBL).

Outcome assessment

At least one of the following effectiveness outcomes of interest was reported: visual analog scale (VAS) for pain assessment and maximum mouth opening (MMO), with a follow-up period of ≥ 1 month. The effect measure of interest was the mean change from baseline to each follow-up time point, expressed as mean ± standard deviation (SD). For VAS pain scores, data reported on a 0–100 scale were linearly rescaled to a 0 to 10 scale by dividing the mean and standard deviation by 10, ensuring a uniform metric across studies. As the outcome measures were continuous and consistently scaled after conversion, mean differences (MD) in change-from-baseline values were calculated between treatment groups. Thus, MD along with its 95% confidence interval (95% CI) was used as the effect size measure. Clinical significance was interpreted against a pre-specified MCID of 1.4 points for VAS pain and 5 mm for MMO, based on TMD-specific literature [30].

Network meta-analysis

For studies with missing data, we contacted the corresponding authors via email to request complete data; those that could not be provided were excluded. For studies that reported only baseline and follow-up endpoint values without the corresponding change-from-baseline standard deviations, we calculated the change score standard deviation using the formula recommended in the Cochrane Handbook [31]:

$$SD\ \text{change} = \sqrt{SD_{\text{baseline}}^2 + SD_{\text{final}}^2 - 2r \cdot SD_{\text{baseline}} \cdot SD_{\text{final}}}$$

. This study followed the Cochrane Handbook guidelines to weight outcome variables based on sample size [32]. Statistical analyses were performed using the "network" and "mvmeta" packages in STATA 18.0. A global inconsistency model was fitted. If the p-value exceeded 0.05, a consistency model was applied; otherwise, an inconsistency model was used. Local inconsistencies were examined using the node-splitting method. For networks containing closed loops, loop-specific inconsistency was evaluated. Consistency between direct and indirect evidence was assumed if the 95% confidence interval of the inconsistency factor (IF) included or was close to zero. League tables were used to present pairwise comparison results. Furthermore, the surface under the cumulative ranking (SUCRA) curve was applied to evaluate the relative efficacy of treatments; higher SUCRA values indicate a greater probability of the treatment being the optimal intervention [33]. Subsequently, adjusted funnel plots generated with Stata 18.0 were used to assess between-study bias. Symmetrical funnel plots suggested no significant publication bias. The confidence in network meta-analysis (NMA) results for each outcome was evaluated using the open-source software CINeMA based on the GRADE framework [34].

Results

Study selection

The initial search yielded 619 studies. After removing 208 duplicates, 411 studie underwent title and abstract screening. The independent screening by two authors demonstrated substantial agreement, with a Cohen's κ of 0.81 (95% CI: 0.76 to 0.85), exceeding the commonly accepted threshold for good reliability. A 2×2 contingency table detailing the independent judgments is provided in Supplementary Material. 2.

Following resolution of disagreements through discussion, 214 studies were excluded, leaving 197 studies for further assessment. Of these, 178 were excluded after detailed title/abstract screening due to ineligible PICO, unavailable data, or non-randomized controlled trial design. Finally, 19 full-text articles were assessed and all 19 were included in the quantitative synthesis [23, 24, 35–51].The process of study inclusion and exclusion is illustrated in Fig. 1.

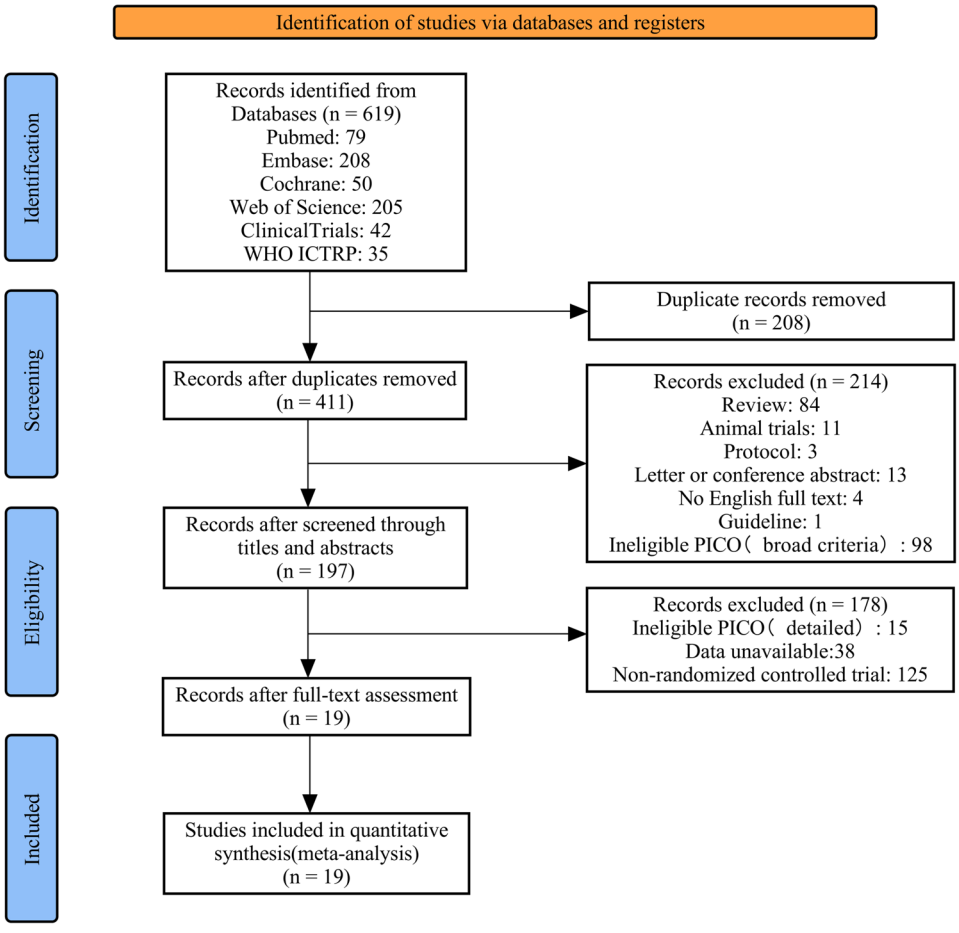


Fig. 1 Flowchart of the selection process

Characteristics of included studies

This network meta-analysis included 19 RCTs, involving a total of 783 patients and 819 TMJs, with 241 patients (258 TMJs) in the control group and 542 patients (561 TMJs) in the experimental group. Among the 19 studies, 1 was a four-arm trial, 3 were three-arm trials, and the remainder were two-arm trials [41, 45, 46, 49]. The basic characteristics of the included studies are presented in Table 1.

Adverse events

A total of 12 studies reported on adverse events [23, 36–39, 43–47, 49, 50]. Among them, 6 studies explicitly stated that no adverse events occurred [36, 39, 44, 45, 49, 50]. 3 studies reported postoperative swelling and pain [37, 38, 49], 2 studies reported transient facial palsy [23, 46], and 2 studies reported postoperative ipsilateral open bite or transient malocclusion [43, 49].

Risk of bias assessment

1 study was rated as having a low risk of bias in the randomization domain. They clearly described using a computer software program (Random Allocation 2.0) to generate the random sequence and sequentially numbered, opaque, sealed envelopes to ensure allocation concealment [48]. Studies were rated as having "some concerns" in the randomization domain if allocation concealment was inadequately described, or if baseline imbalances raised concerns despite a reported random sequence. 4 studies were rated as low risk for deviations from intended interventions for both VAS and MMO outcomes, with no evidence of major protocol violations or imbalanced attrition [23, 38, 40, 46]. 1 study was rated as having some concerns for missing outcome data for both VAS and MMO, owing to imbalanced post-randomization exclusions without intention-to-treat analysis [40]. 4 studies were rated as having a low risk of bias in the measurement-of-outcome domain for both VAS and MMO, owing to blinded outcome assessment or the use of objective measures [23, 40–42]. 10 studies reported their pre-specified outcomes, and no other significant sources of bias were identified; thus, they were judged to have low risk of reporting bias and other biases [35–39, 42, 48–51]. Risk of bias assessments for pain VAS and MMO yielded identical overall judgments. The predominance of 'some concerns' ratings for allocation concealment, the absence of blinding in most trials, and incomplete outcome reporting in several studies are reflected in the moderate-to-low GRADE certainty ratings. The RoB 2 summary plot is shown in Fig. 2.

Results of the network meta-analysis

Curative effects in arthrogenous TMDs (1-month follow-up)

A total of 12 RCTs, involving 9 interventions and 530 patients (568 TMJs), used the pain VAS score as an outcome measure. For MMO, 12 RCTs were included, encompassing 9 interventions and 530 patients (568 TMJs). Consistency checks and NMA were performed on the incorporated data. All global inconsistency tests yielded p-values greater than 0.05, indicating no significant overall inconsistency. For the pain VAS score and the 1-month MMO outcomes, no significant inconsistency was detected in any node comparisons or loop tests. Further details will be discussed in the Discussion section.(see Fig. 4A and 4D) Summary of Node-Splitting Methods and Loop Inconsistency Tests (see Supplementary Material. 3).

The network geometry was structured around PRP, HA, GCS, and placebo, forming six triangular closed loops (Fig. 3A and 3E). The network meta-analysis of VAS scores indicated that iPRF was the only intervention for which the difference from placebo reached statistical significance (MD = 1.36, 95% CI: 0.51 to 2.21). No other pairwise comparisons were significant. The SUCRA-based efficacy rankings are illustrated in Fig. 5A and 5E.

For MMO, the NMA comprising 36 pairwise comparisons yielded no significant findings for any of the evaluated interventions. SUCRA efficacy results are presented in Fig. 6A and 6E.

Curative effects in arthrogenous TMDs (3-month follow-up)

A total of 9 RCTs, involving 6 interventions and 390 patients (429 TMJs), used the pain VAS score as an outcome measure. For MMO, 10 RCTs were included, encompassing 6 interventions and 430 patients (469 TMJs). Consistency checks and NMA were performed on the incorporated data. All global inconsistency tests yielded p-values greater than 0.05, indicating no significant overall inconsistency. The node-splitting method showed that good local consistency overall. The IF values from loop inconsistency tests ranged from 0.01 to 0.97. Notably, the lower bounds of the 95% CI for most closed loops were either equal to or close to zero, indicating no significant inconsistency among these loops. For the 3-month MMO outcomes, no significant inconsistency was detected in any node comparisons or loop tests ($p > 0.05$). Further details will be discussed in the Discussion section.(see Fig. 4B and 4E).

The network geometry was structured around PRP, HA, and placebo, forming four triangular closed loops (Fig. 3B and 3F). In the network meta-analysis of VAS scores comprising 15 pairwise comparisons, statistically significant differences were observed for iPRF versus placebo (MD = 1.59, 95% CI: 0.66 to 2.52), PRP versus placebo (MD = 1.02, 95% CI: 0.02 to 2.02), iPRF versus GCS (MD = 2.45, 95% CI: 0.63 to 4.28), PRP versus GCS (MD = 1.88, 95% CI: 0.12 to 3.64), and iPRF versus HA (MD = 1.64, 95% CI: 0.22 to 3.06). No significant differences were detected for the remaining comparisons.

Table 1 Main characteristics of included studies

Auhor	Participants					Intervention					Adverse Events	
	Diagnosis/Wilkes stage	Group	Male/Female	No. of joints	Age(years)	Method	Treatment	Arthro-centesis / Injection (n)	Injection timing	Follow-up(month)	Adverse Event Description	Incidence
Tabriz 2014 [35]	ID	Placebo	8/22	30	28 ± 7.17	2-needle	200ml Linger solution	1/0		1,6	NR	NR
		Dexamethasone	5/25	30	27.07 ±7 .42		200ml Linger solution + 8.0mg Dexamethasone	1/1	After arthrocentesis			
Hanci 2015 [37]	DDWR	Placebo	3/7	15	25.4 ± 1.7	2-needle	100ml Linger solution	1/0		1, 3, 6	Transient swelling/ Soreness	NR
		PRP	2/8	17	27.2 ± 13.4		100ml Linger solution + 0.6ml PRP	1/1	After arthrocentesis			
Hegab 2015 [38]	OA	HA	11/14	25	38.2 ± 4.368	2-needle	50ml Linger solution + 1.0ml HA	1/3	After arthrocentesis, then once weekly for 3 weeks	1,3,6,12	Injection pain; Postoperative pain	PRP: 88%/76%; HA: 60%/32%
		PRP	10/15	25	39 ± 4.975		50ml Linger solution + 1.0ml PRP	1/3	After arthrocentesis, then once weekly for 3 weeks			
Cömert 2015 [36]	OA	Placebo	1/11	15	35.08 ± 14.84	2-needle	100ml Linger solution	1/0		12	None	0%
		PRP	2/16	32	32.22 ± 14.33		100ml Linger solution+1.0ml PRP	1/5	After arthrocentesis, then once monthly for 4 months			
Cömert 2016 [39]	OA	HA	3/10	17	32.22 ± 14.33	2-needle	100ml Linger solution + 1.0ml HA	1/1	After arthrocentesis	12	None	0%
		PRP	2/16	32	28.08 ± 11.12		100ml Linger solution + 1.0ml PRP	1/5	After arthrocentesis, then once monthly for 4 months			
Ozdamar 2017 [40]	ID/Wilkes III	Placebo	4/6	10	26.8 ± 8.07	1-needle	2.0ml Saline solution	2/1		3,6	NR	NR
		HA	3/11	14	26.93 ± 7.76		2.0ml Saline solution + 2.0ml HA	2/1	After arthrocentesis			
Yapici-Yavuz 2018* [41]	DDWOR	Placebo	6/38	44	NR	2-needle	200ml Linger solution	1/0		1,3,6	NR	NR
		HA					200ml Linger solution + HA	1/1	After arthrocentesis			
		Methylprednisolone acetate					200ml Linger solution + Methyl-prednisolone acetate	1/1	After arthrocentesis			
		Tenoxicamum					200ml Linger solution + Tenoxicamum	1/1	After arthrocentesis			
Bergstrand 2019 [23]	OA	Placebo	6/11	17	55 ± 14.5	2-needle	Linger solution	1/0		6	Transient facial palsy	NR
		HA	1/19	20	47 ± 15.7		Linger solution + 1.0ml HA	1/1	After arthrocentesis			
De Riu 2019 [42]	ID/Wilkes III, IV	HA	1/14	15	44.5 ± 12.6	2-needle	200-250ml Linger solution + 2.0ml HA	1/1	After arthrocentesis	1,6,12	NR	NR
		BMNc	0/15	15	48.2 ± 10.2		200-250ml Linger solution + 2.0ml BMNc	1/1	After arthrocentesis			
Karadayi 2021 [24]	ID	Placebo	9/9	18	39.67	2-needle	100ml Linger solution	1/0		1,3	NR	NR
		iPRF	8/10	18	39.97		100ml Linger solution + 2.0ml iPRF	1/1	After arthrocentesis			
Sembronio 2021* [43]	ID, OA	HA	9/31	25	50.7 ± 17.4	2-needle	200ml Saline solution	1/0		1,6	Mild abdominal hematoma; Ipsilateral open bite	7.5%; NR
		FAT		26	43.3 ± 21.4		200ml Saline solution + 2.0ml FAT	1/1	After arthrocentesis			
Singh 2021 [44]	ID/WilkesII, III	Placebo	2/10	12	34.75 ± 10.83	2-needle	100ml Linger solution	1/0		1,3,6	None	0%
		PRP	4/8	12	36.41 ± 11.15		100ml Linger solution + 1.0ml PRP	1/1	After arthrocentesis			
Asadpour 2022 [45]	OA	PRP	5/5	10	29.5 ± 8.9	2-needle	100ml Linger solution + 1.0ml PRP	1/1	After arthrocentesis	1,6	None	0%
		HA	5/5	10	29.5 ± 8.5		100ml Linger solution + 1.0ml HA	1/1	After arthrocentesis			
		PRP+HA	5/5	10	29.9 ± 8.5		100ml Linger solution + 1.0ml PRP+HA	1/1	After arthrocentesis			

Table 1 (continued)

Auhor	Participants					Intervention					Adverse Events	
	Diagnosis/Wilkes stage	Group	Male/Female	No. of joints	Age(years)	Method	Treatment	Arthrocentesis / Injection (n)	Injection timing	Follow-up(month)	Adverse Event Description	Incidence
Dasukil 2022 [46]	ID/WilkesII, III	Placebo	10/20	30	37.5 ± 4.2	1-needle	100ml Linger solution	1/0		1,3,6	Transient facial palsy	13.3% (PRP:13.3%, HA:20%, Control:6.7%)
		HA	9/21	30	36.9 ± 5.9		100ml Linger solution + 1.0ml HA	1/2	After arthrocentesis and again at 2 weeks.			
		PRP	7/23	30	37.7 ± 4.7		100ml Linger solution + 1.0ml PRP	1/2	After arthrocentesis and again at 2 weeks.			
Ghoneim 2022 [47]	DDWR	Placebo	7/13	20	26.45 ± 8.21	2-needle	100ml Linger solution	1/0		3,6	Transient malocclusion (iPRF)	10% (iPRF group)
		iPRF	4/16	20	28.60 ± 8.42		100ml Linger solution + 1.5ml iPRF	1/1	After arthrocentesis			
Işık 2022 [48]	OA	Placebo	1/17	21	44.67 ± 12.13	2-needle	200ml Saline solution	1/0		1,2,3,6,12	NR	NR
		iPRF	2/16	22	45.72 ± 13.12		200ml Saline solution + 1.0ml iPRF	1/4	After arthrocentesis, then once weekly for 3 weeks			
Jacob 2022* [49]	DDWR, DDWOR	Placebo	7/9*	15	51.50 ± 12.80	2-needle	100ml Linger solution	1/0		6	Swelling/Tenderness; Infection (1 case, PRP); Vertigo (1 case); Open surgery required	NR
		HA	6/9	15	46.53 ± 19.15		100ml Linger solution + 1.0ml HA	1/1	After arthrocentesis			
		PRP	4/12*	15	40.56 ± 9.72		100ml Linger solution + 1.0ml PRP	1/1	After arthrocentesis			
Işık 2023 [50]	DDWOR	Placebo	3/35	44	47.2 ± 9.1	2-needle	200ml Saline solution	1/0		1,2,3,6,12	None	0%
		iPRF	4/34	43	46.8 ± 10.2		200ml Saline solution + 1.0ml iPRF	1/4	After arthrocentesis, then once weekly for 3 weeks			
Dharamsi 2024 [51]	ID/Wilkes Ⅰ-Ⅳ	HA	7/13	24	34.25	2-needle	100ml Saline solution	1/0		1,3	NR	NR
		TA	10/10	25	39.74		100ml Saline solution + 1.0ml TA	1/1	After arthrocentesis			

ID Internal derangements, *OA* Osteoarthritis, *DDWR* Disc displacement with reduction, *DDWOR* Disc displacement without reduction, *PRP* Platelet-rich plasma, *HA* Hyaluronic acid, *iPRF* injectable platelet-rich fibrin, *BMNc* Bone marrow aspirate concentrate, *TA* Triamcinolone acetonide, *FAT* microfragmented adipose tissue, *NR* Not report, *None* No adverse events observed

Jacob 2022* [49]: One patient each in Group Placebo and Group PRP was lost to follow-up. Yapici-Yavuz 2018* [41] and Sembronio 2021* [43]: No group specific sex or joint counts were provided (unilateral/bilateral involvement not specified)



Fig. 2 Summary of risk of bias of all included studies

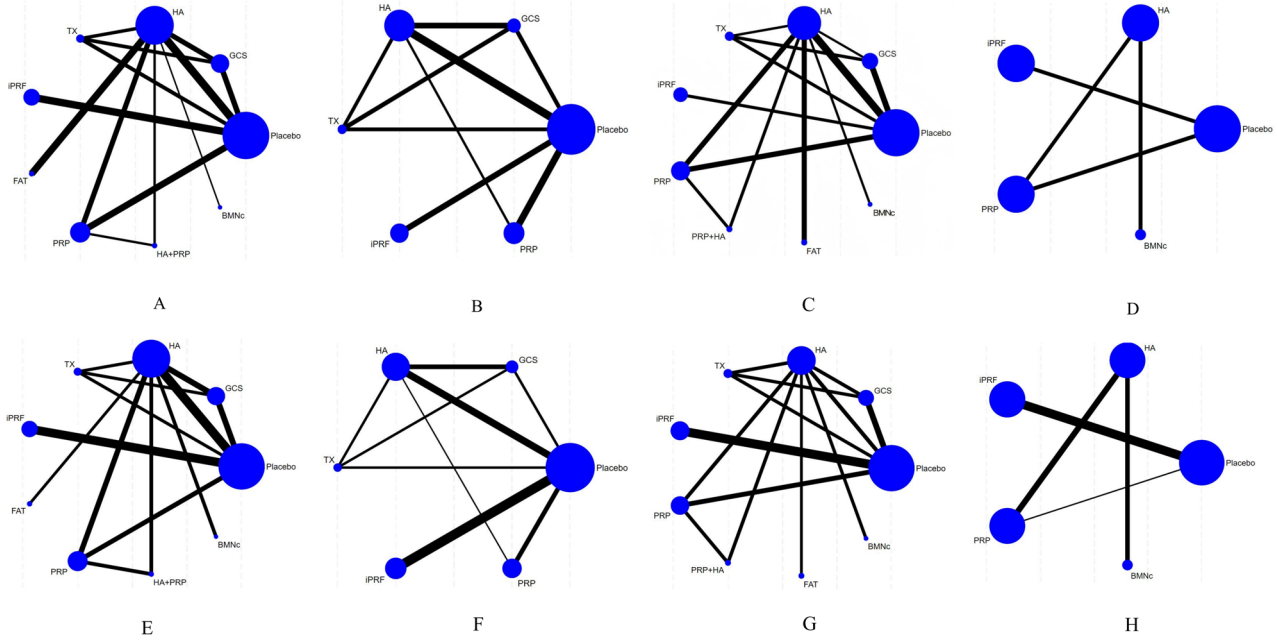


Fig. 3 Network plot. Network plots at 1-month follow-up, (**A**) (VAS), (**E**) (MMO); At 3-month follow-up, (**B**) (VAS), (**F**) (MMO); At 6-month follow-up, (**C**) (VAS), (**G**) (MMO); At 12-month follow-up, (**D**) (VAS), (**H**) (MMO); PRP, platelet-rich plasma; HA, hyaluronic acid; GCS, glucocorticoids; BMNc, bone marrow nucleated cell concentrate; iPRF, injectable platelet rich fibrin; TX, tenoxicam; FAT, microfragmented adipose tissue; VAS, visual analog scale; MMO, maximal mouth opening

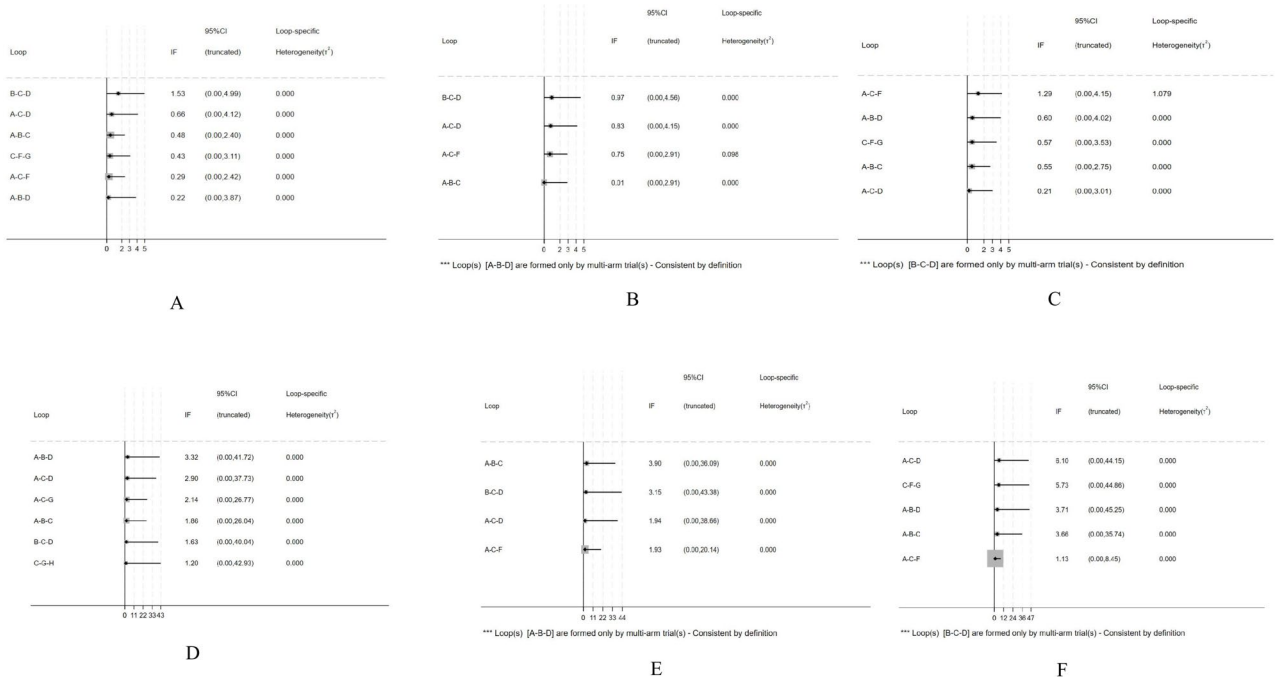


Fig. 4 Inconsistency factor values of the meta-analysis. **A**: A-G (Placebo GCS HA TX iPRF FAT PRP), **B**: A-F (Placebo GCS HA TX iPRF PRP), **C**: A-G (Placebo GCS HA TX iPRF PRP PRP+HA), **D**: A-H (Placebo GCS HA TX iPRF FAT PRP PRP+HA), **E**: A-F (Placebo GCS HA TX iPRF PRP), **F** A-G (Placebo GCS HA TX iPRF PRP PRP+HA)

The SUCRA-based efficacy rankings are illustrated in Fig. 5B and 5F.

For MMO outcomes, the NMA comprising 15 pairwise comparisons yielded no significant findings for any of the evaluated interventions. SUCRA efficacy results are presented in Fig. 6B and 6F.

Curative effects in arthrogenous TMDs (6-month follow-up)

A total of 11 RCTs, involving 9 interventions and 442 patients (498 TMJs), used the pain VAS score as an outcome measure. For MMO, 11 RCTs were included, encompassing 9 interventions and 445 patients (486 TMJs). Consistency checks and NMA were performed on the incorporated data. All global inconsistency tests yielded p-values greater than 0.05, indicating no significant overall inconsistency. The node-splitting analysis revealed no evidence of local inconsistency, with all p-values exceeding 0.05 across the evaluated comparisons. The IF values from loop inconsistency tests ranged from 0.21 to 1.29. The lower bounds of the 95% CI for most closed loops were either equal to or close to zero, indicating no significant inconsistency among these loops. For the 6-month MMO outcomes, no significant inconsistency was detected in any node comparisons or loop tests ($p > 0.05$). Further details will be elaborated in the Discussion section (see Fig. 4C and 4F).

The network relationship was structured around PRP, HA, and placebo, forming five triangular closed loops (Fig. 3C and 3F). The NMA comprising 36 pairwise comparisons yielded no significant findings for any of the evaluated interventions. SUCRA efficacy results are illustrated in Fig. 5C and 5G.

For MMO outcomes, the network meta-analysis of 36 pairwise comparisons indicated that HA was associated with greater improvement than placebo (MD = -7.96, 95% CI: -11.00 to -4.92) and PRP (MD = 5.52, 95% CI: 2.70 to 8.33). No significant differences were observed for the remaining comparisons. The SUCRA-based efficacy rankings are presented in Fig. 6C and 6G.

Curative effects in arthrogenous TMDs (12-month follow-up)

A total of 6 RCTs, involving 5 interventions and 253 patients (306 TMJs), used the pain VAS score as an outcome measure. For MMO, 6 RCTs were included, encompassing 5 interventions and 253 patients (306 TMJs).For the 12-month follow-up data, the network geometry did not contain any closed loops (Fig. 3D and 3H); all treatment comparisons were informed solely by direct evidence. Consequently, neither global nor local inconsistency tests were applicable, as inconsistency arises only when direct and indirect evidence can be contrasted within a closed loop. The network structure inherently satisfies the consistency assumption, and all reported effect estimates were derived directly from pairwise meta-analyses of the available head-to-head studies.

The NMA comprising 10 pairwise comparisons indicated that iPRF showed a statistically significant difference from placebo (MD = 1.60, 95% CI: 0.14 to 3.07), with

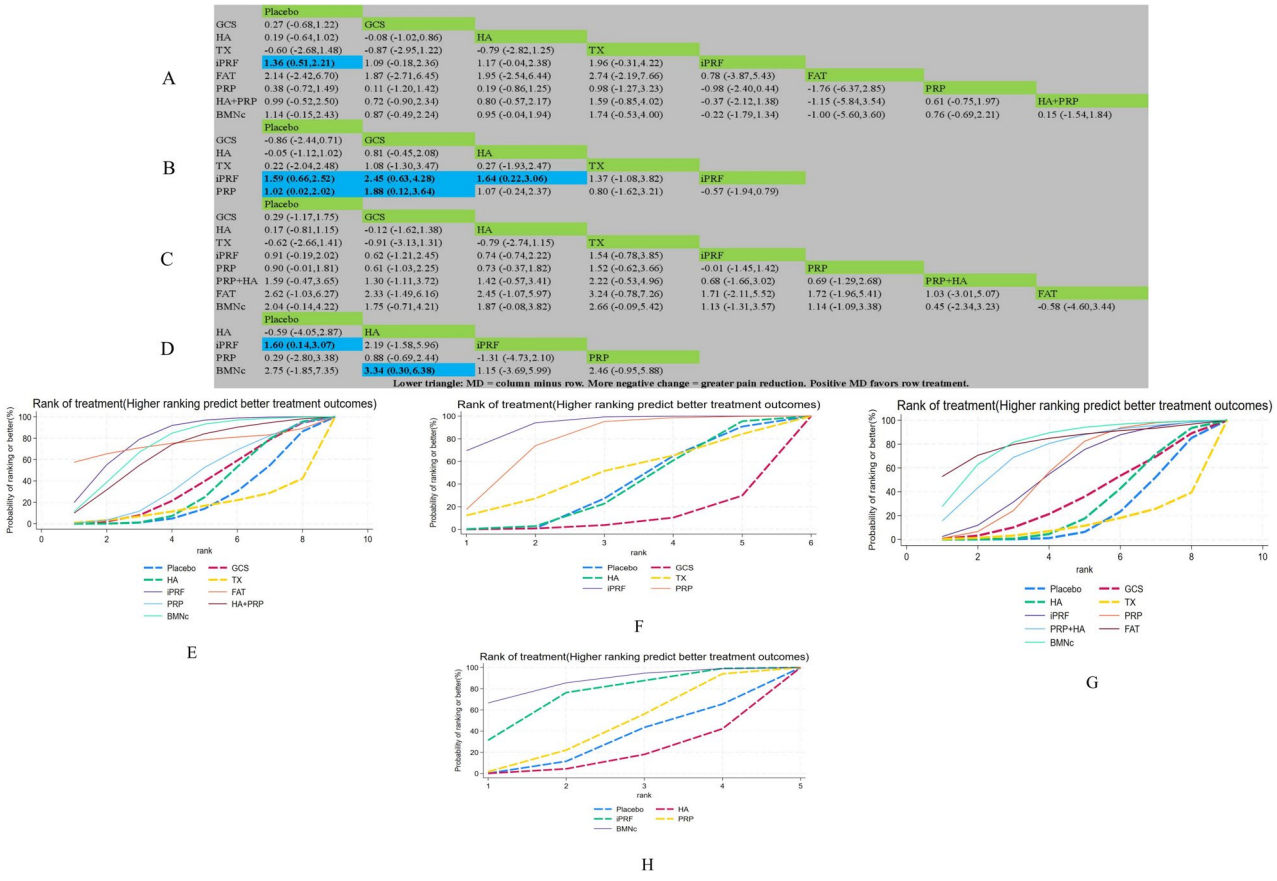


Fig. 5 Network meta-analysis of VAS. SUCRA of VAS at **A**, **E** 1-month follow-up; **B**, **F** 3-month follow-up; **C**, **G** 6-month follow-up; **D**, **H** 12-month follow-up; PRP, platelet-rich plasma; HA, hyaluronic acid; GCS,glucocorticoids; BMAc, bone marrow nucleated cell concentrate; iPRF, injectable platelet rich fibrin; TX, tenoxicam; FAT, microfragmented adipose tissue

the lower confidence limit approaching zero. BMNC also differed significantly from HA (MD = 3.34, 95% CI: 0.30 to 6.38). No other comparisons reached statistical significance. The SUCRA-based efficacy rankings are illustrated in Fig. 5D and 5H.

For MMO outcomes, the NMA comprising 10 pairwise comparisons yielded no significant findings for any of the evaluated interventions. SUCRA efficacy results are illustrated in Fig. 6D and 6H.

Publication bias

However, some outcome measures showed an asymmetric scatter distribution, suggesting probable publication bias. Funnel plot interpretation in this context is constrained by the small number of studies per comparison, but the asymmetry nonetheless warrants acknowledgment rather than dismissal, as shown in Fig. 7.

GRADE evidence assessment

Evidence certainty was assessed using GRADE for NMA, implemented via CINeMA, and disaggregated by comparison, outcome, and follow-up time point (Supplementary Material. 4 and 5). "Inconsistency" encompasses both heterogeneity and incoherence; no downgrading was warranted for any comparison at 1 or 3 months, and the 12-month network contained no closed loops precluding inconsistency assessment.

For VAS at 1 month, iPRF versus placebo was rated moderate (risk of bias); all other comparisons were low owing to imprecision. For VAS at 3 months, iPRF versus placebo, PRP versus placebo, iPRF versus GCS, PRP versus GCS, and iPRF versus HA were moderate; remaining comparisons were low. For VAS at 12 months, iPRF versus placebo and BMNC versus HA were moderate; other comparisons were low. For MMO at 6 months, HA versus placebo and PRP versus HA were moderate; other comparisons were low due to imprecision.

Discussion

Consistency and heterogeneity tests were satisfactory across all time points, with only minor heterogeneity in isolated loops. The certainty of evidence, assessed via GRADE, ranged from moderate to low across comparisons, driven mainly by imprecision and risk of bias.

Currently, there is no universally accepted quantitative classification for HA molecular weight. In this analysis,

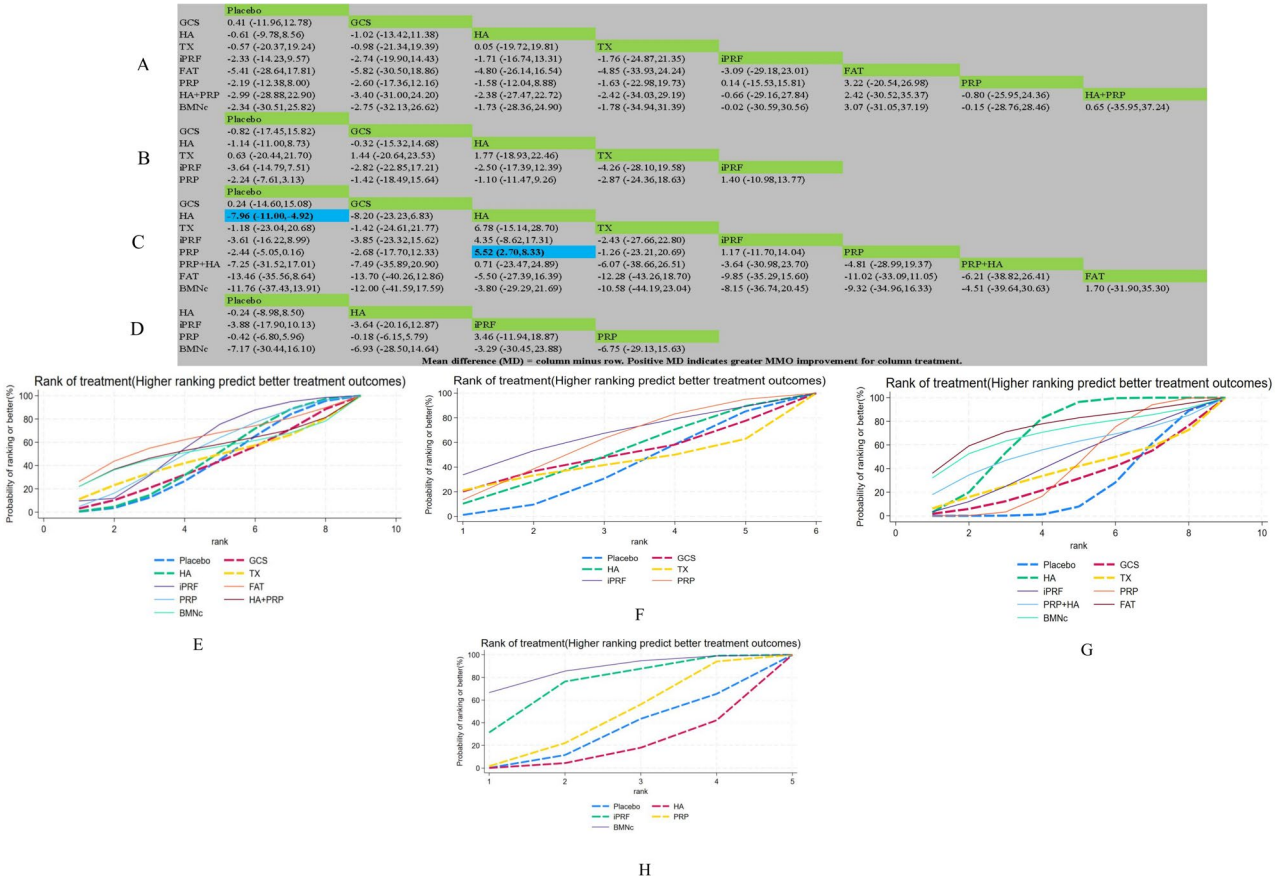


Fig. 6 Network meta-analysis of MMO. SUCRA of MMO at **A**, **E** 1-month follow-up; **B**, **F** 3-month follow-up; **C**, **G** 6-month follow-up; **D**, **H** 12-month follow-up; PRP, platelet-rich plasma; HA, hyaluronic acid; GCS, glucocorticoids; BMAc, bone marrow nucleated cell concentrate; iPRF, injectable platelet rich fibrin; TX, tenoxicam; FAT, microfragmented adipose tissue

we adopted the framework proposed by de Campos et al., which categorizes linear HA into low (< 1MDa), intermediate (1 to 2 MDa), and high (> 2 MDa) molecular weight, to explore potential differences in treatment effect across the included HA formulations. For the 6-month MMO outcome, disaggregating HA by molecular weight according to this classification revealed that high-molecular-weight HA was significantly superior to both placebo (MD = -8.07, 95% CI: -11.14 to -5.00) and PRP (MD = 5.62, 95% CI: 2.78 to 8.45), whereas low-molecular-weight HA showed no difference (Supplementary Material. 6). Evidence for these comparisons was of moderate quality. However, subgroup analyses within network meta-analyses are inherently exploratory, and the absence of a consensus definition for HA molecular weight further limits the stability of these findings. These results should therefore be interpreted with caution and considered hypothesis-generating rather than confirmatory [52].

For VAS outcomes, a clear temporal pattern emerged. At 1 month, only iPRF showed significantly greater pain reduction than placebo (MD = 1.36, 95% CI: 0.51 to 2.21; moderate certainty). By 3 months, both iPRF and PRP showed significant analgesic benefits over placebo, GCS, and HA (moderate certainty). At 6 months, no intervention retained significance (low certainty). At 12 months, iPRF again showed a significant difference from placebo (MD = 1.60, 95% CI: 0.14 to 3.07) and BMNC showed a significant difference from HA (MD = 3.34, 95% CI: 0.30 to 6.38), both with moderate certainty. Collectively, iPRF was associated with pain reduction at 1, 3, and 12 months, though the 6-month result did not reach significance and the effect sizes were modest. PRP showed benefit primarily at 3 months. The lack of sustained effects may reflect waning platelet concentrate activity without repeated injections.

MMO outcomes showed sparse significant findings. Apart from moderate-certainty evidence favoring HA over placebo and PRP at 6 months, no other intervention improved mouth opening at 1, 3, or 12 months (all low certainty). This suggests that a single arthrocentesis procedure, regardless of adjunctive agent, may be insufficient for durable functional gains.

Against the pre-specified MCID (VAS 1.4, MMO 5 mm), no treatment effect consistently met the criterion

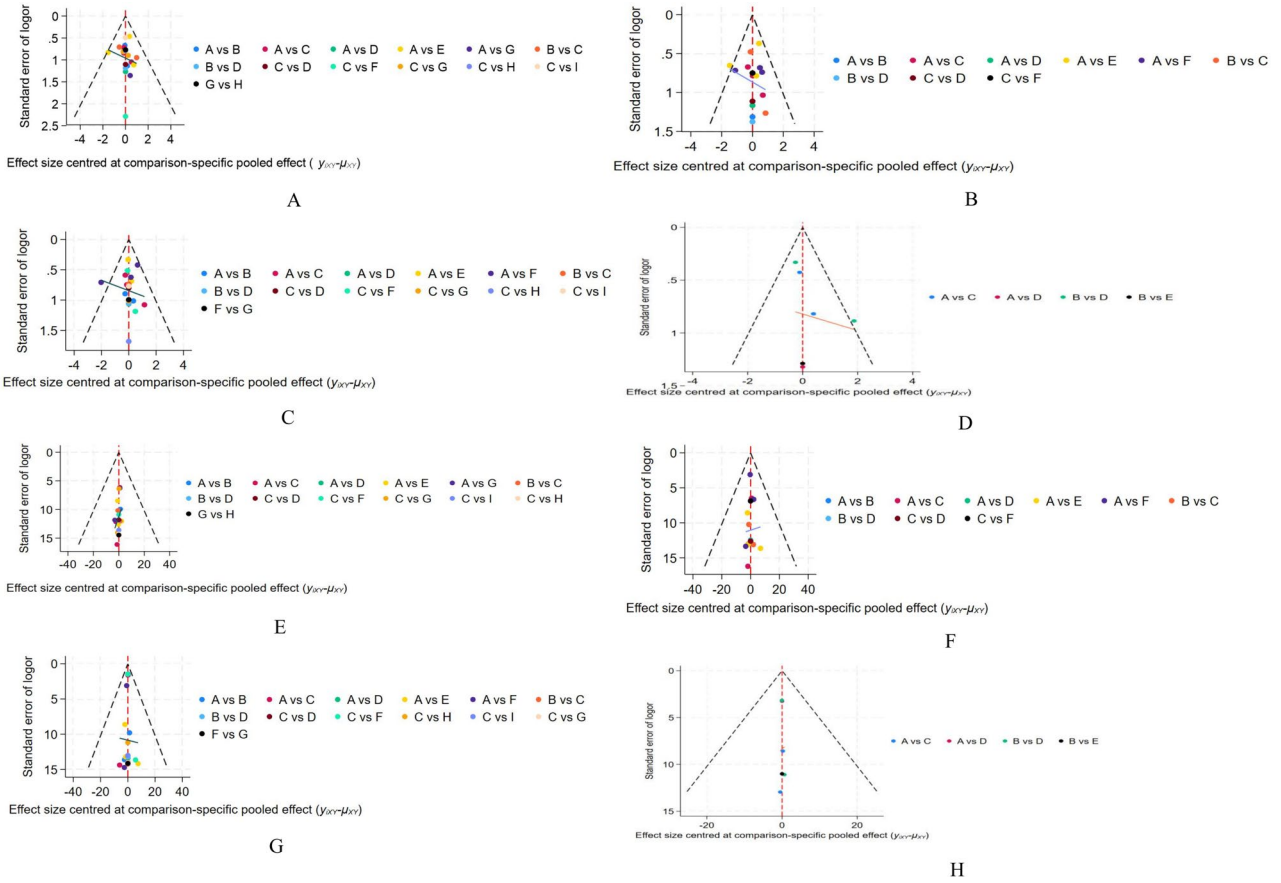


Fig. 7 Funnel plots. **A**: A-I (Placebo, GCS, HA, TX, iPRF, FAT, PRP, HA+PRP, BMNc); **B**: A-F (Placebo, GCS, HA, TX, iPRF, PRP); **C**: A-I (Placebo, GCS, HA, TX, iPRF, PRP, PRP+HA, FAT, BMNc); **D**: A-E (Placebo, HA, iPRF, PRP, BMNc); **E**: A-I (Placebo, GCS, HA, TX, iPRF, FAT, PRP, HA+PRP, BMNc); **F** A-F (Placebo,GCS, HA, TX, iPRF, PRP); **G**: A-I (Placebo, GCS, HA, TX, iPRF, PRP, PRP+HA, FAT, BMNc); **H**: A-E (Placebo, HA, iPRF, PRP, BMNc)

of both a point estimate exceeding the MCID and a 95% CI entirely beyond the threshold. For iPRF versus placebo, point estimates at 1 month (MD = 1.36, 95% CI 0.51 to 2.21), 3 months (MD = 1.59, 95% CI 0.66 to 2.52), and 12 months (MD = 1.60, 95% CI 0.14 to 3.07) were near or slightly above the MCID, but the lower confidence bounds encompassed trivial values, rendering clinical significance uncertain. The exploratory finding for high-molecular-weight HA versus placebo at 6 months (MMO MD = -8.07, 95% CI -11.14 to -5.00) exceeded 5 mm with a CI entirely above it, but this derives from a subgroup analysis and requires confirmation. Overall, statistical significance did not translate into confirmed clinical significance, consistent with the chronic nature of TMD where small group-level differences may not be individually perceptible.

Overall, no intervention demonstrated a consistent and unequivocal clinically meaningful advantage. The marginal effect sizes and wide confidence intervals preclude any treatment recommendation at this stage, and the choice of agent should remain individualized and guided by further evidence.

The DC/TMD diagnostic system provides a standardized framework for TMD classification, though it continues to evolve through ongoing empirical refinement [53–55].Although adjunctive imaging may refine diagnosis, the present analysis focuses on the comparative efficacy of injectable agents rather than on imaging-based selection [54–61].

Arthrocentesis technique varied across the included studies in terms of needle approach, irrigation volume, and injection site. Both single-needle and double-needle approaches have shown efficacy, though standardization of protocols would enhance future comparability [62–66].

HA plays a well-established role in joint lubrication and cartilage protection, and intra-articular HA injection has been shown to alleviate clinical symptoms of arthrogenous TMDs [67–70]. However, the optimal molecular weight and injection frequency remain unresolved, with some evidence suggesting that higher molecular weight and repeated injections may yield greater benefits [71–74]. In the present analysis, only high-molecular-weight HA was associated with MMO improvement at

6 months, whereas low-molecular-weight HA showed no significant effect. These findings align with the notion that HA molecular weight may influence clinical outcomes. However, the subgroup analysis is exploratory, the classification of molecular weight varied across the included trials, and no consensus definition exists in the literature. The results should therefore be viewed as hypothesis-generating. Future studies should standardize molecular weight definitions and injection protocols.

Advances in regenerative medicine have enabled the application of autologous biologics such as PRP, iPRF, BMNc, and FAT in arthrogenous TMDs [75–77]. Although clinical studies for BMNc and FAT remain limited [42, 43, 78, 79], both PRP and iPRF have shown improvements in clinical symptoms [80, 81]. In this NMA, iPRF was associated with pain reduction at multiple time points, while PRP showed benefit primarily at 3 months. Further investigations are needed to clarify long-term benefits, and the considerable research interest in these autologous biologics should be kept in mind as a potential source of selective publication when appraising the aggregated evidence.

Although corticosteroids (particularly glucocorticoids) can markedly reduce pain in arthrogenous TMDs, their clinical use has declined due to potential long-term adverse effects such as osteoporosis [82]. Similarly, while tenoxicam has demonstrated benefits in improving mouth opening and reducing pain, larger controlled trials are necessary to confirm its clinical value [83].

Recent NMAs by Kelemen et al. and Zou et al. reported broadly comparable findings regarding the analgesic efficacy of PRP and iPRF [25, 26]. The present analysis extends this work by incorporating more recent trials and disaggregating HA by molecular weight.

Limitations

Several limitations of this network meta analysis warrant careful consideration, each with potential implications for the interpretation and generalizability of the findings.

Clinical heterogeneity from diagnostic criteria

The included trials used varying diagnostic frameworks and enrolled heterogeneous TMD subtypes. This diagnostic variability may not be fully captured by statistical heterogeneity metrics. For instance, patients with early-stage osteoarthritis may respond differently to viscosupplementation or regenerative therapies than those with advanced degenerative changes or chronic disc displacement, which may dilute or exaggerate treatment effects for specific subgroups and limit the precision of the estimated effect sizes. Future network meta-analyses would benefit from stratification by specific TMD subtypes or by disease severity, contingent on more granular reporting in primary trials.

Technique heterogeneity in arthrocentesis

As summarized in Table 1, the included studies varied substantially in arthrocentesis methodology: single-needle versus double-needle approaches, irrigation volumes ranging from 2 mL to 250 mL, use of Ringer's solution versus normal saline, and injection protocols ranging from a single intra-articular injection to five serial injections over several months. These technical differences are not trivial. Irrigation volume and needle configuration influence the clearance of inflammatory medsdiators and the mechanical disruption of adhesions; the type and timing of adjunctive agent injection affect intra-articular residence time and bioavailability. Consequently, the efficacy of a given adjunctive agent may be confounded by the specific arthrocentesis technique with which it was paired. This heterogeneity complicates the isolation of agent-specific effects and may contribute to the variability observed across trials. Standardization of arthrocentesis protocols (including needle approach, irrigation volume, and injection frequency) would greatly enhance the comparability of future RCTs and strengthen the evidence base for adjunctive therapies.

Absence of robust safety data

Only 12 of the 19 included RCTs reported adverse events, and among those that did, the definitions, ascertainment methods, and granularity of reporting were inconsistent. While transient facial palsy, postoperative swelling, and transient malocclusion were noted in a subset of studies, the absence of standardized safety reporting precludes a reliable comparative assessment of the harm profiles of different adjunctive agents. This is particularly relevant for autologous biologics such as PRP and iPRF, which are generally considered safe but for which rare or long-term adverse events may be under-reported. Similarly, the potential for corticosteroid-related adverse effects (such as local tissue atrophy or accelerated cartilage degeneration) cannot be adequately evaluated from the available data. Future trials should adopt standardized adverse event definitions and reporting frameworks (e.g., CONSORT Harms) to enable meaningful comparisons of both efficacy and safety.

Uncertainty in MCID thresholds

The interpretation of clinical significance in this analysis relied on established minimal clinically important difference (MCID) thresholds for VAS pain scores and MMO in TMD populations. However, MCID estimates vary considerably across the TMD literature: for VAS, reported values range from 0 to 1.90 points depending on the population, measurement context, and anchoring method; for MMO, thresholds range from approximately 2.5 mm to 9 mm. The choice of a specific MCID benchmark can materially influence whether a given effect size

is deemed clinically meaningful. We pre-specified an MCID of 1.4 points for VAS and 5 mm for MMO based on TMD-specific literature [30]; however, published MCID estimates vary widely (VAS 0.9 to 1.9, MMO 2.5 to 9 mm), and the choice of threshold inevitably influences clinical interpretation. Future research should seek to establish consensus MCID values for TMD interventions through dedicated anchor-based studies in well-defined patient populations.

Overlap with previous network meta-analyses

Recent NMAs by Kelemen et al. and Zou et al. have similarly evaluated intra-articular therapies for TMDs, with partially overlapping study inclusion and broadly comparable conclusions regarding the analgesic efficacy of PRP and iPRF. The present analysis extends prior work by incorporating more recent trials, disaggregating HA by molecular weight, and evaluating multiple follow-up time points. Nevertheless, differences in study selection criteria, statistical models, and handling of heterogeneity across these NMAs underscore the sensitivity of network meta-analytic results to methodological choices. The consistency of core findings across independent analyses lends credibility to the observed treatment effects, but the remaining discrepancies highlight the need for standardized reporting and individual participant data meta-analysis to resolve residual uncertainties.

Structural limitations of the evidence network

Finally, the 12-month follow-up network lacked closed loops, precluding formal inconsistency testing at this time point. Effect estimates at 12 months therefore rely solely on direct evidence, and the consistency assumption cannot be empirically verified. This structural limitation, combined with the smaller number of studies with extended follow-up, reduces confidence in the long-term comparative estimates and underscores the need for trials with longer follow-up and broader intervention coverage.

Future trials should adopt standardized diagnostic criteria, harmonized arthrocentesis protocols, routine adverse event reporting, and follow-up of at least 12 months to strengthen the evidence base for intra-articular therapies in arthrogenous TMDs.

Conclusions

This network meta-analysis aimed to compare the efficacy of different intra-articular injectable agents following arthrocentesis for arthrogenous TMDs. Although iPRF was associated with statistically significant pain reduction, the effect sizes only marginally reached the pre-specified MCID, and confidence intervals included trivial values; thus, clinical benefit remains uncertain. However, the evidence is limited by few iPRF trials, small samples, and moderate certainty. No agent can be considered consistently superior. High-molecular-weight HA was associated with MMO improvement at 6 months, but this derives from an exploratory subgroup analysis limited by inconsistent molecular weight definitions across the literature. Further high-quality randomized controlled trials with standardized protocols and extended follow-up are needed before any agent can be definitively recommended.

Abbreviations

TMD	Temporomandibular joint disorders
TMJ	Temporomandibular joint
NMA	Network meta-analysis
RCTs	Randomized controlled trials
VAS	Visual analog scale
MMO	Maximum mouth opening
SUCRA	Surface under the cumulative ranking
IF	Inconsistency factor
CI	Confidence interval
MRI	Magnetic resonance imaging
CBCT	Cone Beam Computed Tomography
RDC/TMD	Research Diagnostic Criteria for Temporomandibular Disorders
DC/TMD	Diagnostic Criteria for TMD
PRP	Platelet-rich plasma
HA	Hyaluronic acid
GCS	Glucocorticoids
BMAC	Bone marrow aspirate concentrate
iPRF	Injectable platelet rich fibrin
TX	Tenoxicam
FAT	Microfragmented adipose tissue

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-026-09013-y.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

Supplementary Material 8.

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Authors' contributions

DSW was responsible for the design of the article concept and the writing of the manuscript; DSW and TG were responsible for the literature search and screening of literature that fulfilled the inclusion criteria; DSW, CFL, WY and HBL were responsible for the extraction of data and quality evaluation of the included literature; CFL, DSW and XYQ were responsible for interpreting the key results of the NMA. All authors contributed to the article and approved the submitted version. All authors gave their final approval and agree to be accountable for all aspects of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study is a secondary literature study and does not require ethical approval. Therefore, Clinical Trial Number is not applicable to this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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