

SYSTEMATIC REVIEW

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Arthrocentesis for temporomandibular joint disorders: a network meta-analysis of randomised controlled trials

Jun-Ming Zhang¹, Jie Yun^{2*}, Tian-Qi Zhou³, Ying Zhang¹ and Chao Gao¹

Abstract

Objective Clinical studies have demonstrated the effectiveness of arthrocentesis in managing temporomandibular joint disorders (TMDs). However, there is a lack of consensus among these studies regarding the selection of injectables. Furthermore, an increasing number of drugs have been tested for TMDs in recent years, complicating the decision-making process for clinicians. This study conducted a network meta-analysis of randomized controlled trials (RCTs) to compare the clinical efficacy of different arthrocentesis treatment regimens.

Methods We conducted a comprehensive search of Embase, PubMed, Cochrane Library, and Web of Science to gather articles on RCTs pertaining to the management of TMDs using arthrocentesis. This search spanned from inception of these databases up to July 29, 2024. We then performed a network meta-analysis using Stata 17.0 software. The outcome indicators used were VAS scores and changes in unassisted maximum opening. To determine the efficacy of each regimen, we employed surface-under the cumulative ranking curve (SUCRA) ranking.

Result Forty RCTs were included, encompassing 1904 temporomandibular joints (TMJs) cases. Treatment options encompass platelet-rich plasma (PRP), hyaluronic acid (HA), corticosteroids (CS), bone marrow concentrate (BMAC), injectable platelet-rich fibrin (i-PRF), concentrated growth factor (CGF), Tenoxicam (TX), microfragmented adipose tissue (FAT), and their combination regimens. The SUCRA ranking revealed that the most effective treatment options at 1-, 3-, and 6-months post-arthrocentesis were HA + PRP, i-PRF, and BMAC, respectively.

Conclusion HA + PRP, i-PRF and BMAC may represent the optimal arthrocentesis agents for the management of TMDs symptoms and restoration of TMJ function in the short, medium, and long term, respectively. Systematic Review Registration: <https://www.crd.york.ac.uk/PROSPERO/>, identifier CRD42024563975.

Keywords Temporomandibular joint disorders, Temporomandibular joint, Arthrocentesis, Biological products, Network meta-analysis

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Introduction

The temporomandibular joint (TMJ) plays a crucial role in coordinating various daily functions such as chewing, articulation, and breathing. It is one of the most frequently used and complex joints in the human body. Temporomandibular joint disorders (TMDs) are musculoskeletal disorders, affect 5–12% of the global population, with an average incidence of 34%, 47% in South America, 33% in Asia, 29% in Europe, and 26% in North America [1]. TMDs rank as the second most prevalent chronic musculoskeletal condition, trailing only behind chronic low back pain [2].

TMDs are a group of painful disorders that affect the masticatory muscles, temporomandibular joint and related structures. The etiology of TMDs is multifaceted, encompassing factors such as trauma, chronic pain syndromes, autoimmune diseases, sleep apnea, and psychiatric disorders. Notably, the potential for certain dental interventions to precipitate TMDs is frequently underemphasized. Diagnosis is achieved through a variety of methods including patient history, screeners, physical examination, and imaging. When gathering patient history, it is important for physicians to be empathetic and provide a comfortable environment with ample time to ensure a comprehensive understanding of the disease is achieved [3]. The original Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) has demonstrated reliability in numerous studies. However, its screening sensitivity is suboptimal. Consequently, Schiffman et al. made revisions to enhance its applicability in clinical settings and universality, resulting in the newly recommended Diagnostic Criteria for TMD (DC/TMD) [4]. Furthermore, physical indicators that support the diagnosis of TMDs encompass, but are not confined to, irregular jaw movements, a diminished range of motion, tenderness during mastication, evidence of bruxism, and joint noise. In instances where occlusal misalignment or intra-articular anomalies are suspected, supplementary imaging techniques may aid in the diagnosis of TMDs. Modalities such as magnetic resonance imaging (MRI), computed tomography (CT), X-ray plain film, and MRI can serve as supplementary diagnostic tools. Notably, MRI is deemed the most effective method for a comprehensive evaluation of joint conditions, albeit it may yield false positive results [5].

Patients diagnosed with TMDs often encounter a range of symptoms including joint pain, muscle discomfort, disc displacement, and restricted mouth movement [6]. According to statistical data, the prevalence of muscular disorders, disc displacement, and other joint conditions among TMDs patients in Poland was 56.9%, 48.9%, and 31% respectively [7]. Besides causing significant physical and psychological distress to patients, TMDs also negatively impact social and economic development. Research

[7] indicates that the average cost of treating and rehabilitating TMDs patients is 7,890 USD, with an annual global expenditure of 4 billion USD on TMDs management [8].

The vast majority of TMDs can be successfully managed with reversible, safe, and effective treatment modalities. Treatment options for TMDs can be broadly classified into non-pharmacological therapy and pharmacological therapy. Non-pharmacological treatment options typically encompass functional exercises, occlusal splint therapy, massage, acupuncture, biofeedback, ultrasound, and Transcutaneous Electrical Nerve Stimulation (TENS). Among these, ultrasound therapy is regarded as one of the most effective methods to alleviate pain and enhance muscle function [9]. Drug treatment for chronic TMDs typically includes muscle relaxants, non-steroidal anti-inflammatory drugs, analgesics, tricyclic antidepressants, benzodiazepines, corticosteroids, and various biologics. However, there is limited evidence supporting the efficacy of oral and topical drug treatments for chronic TMDs. In contrast, research on drug therapy combined with joint puncture is relatively abundant and provides a reasonable level of evidence. Consequently, Tran proposed a treatment pathway that progresses from conservative to invasive approaches [10]. There is increasing evidence to suggest that the initial treatment of TMDs with minimally invasive therapy may be more effective in alleviating clinical symptoms in patients compared to conservative treatments [11]. The procedure involves flushing and expanding the upper joint space with either normal saline or Ringer's solution under local anesthesia. This process aims to dissolve and clear the inflammatory fibrous tissue within the joint cavity through joint irrigation and injection, thereby addressing joint adhesions and significantly enhancing the mobility of the affected joint. Additionally, it alleviates muscle and bone pain, as well as abnormal joint closure and locking [12].

Clinicians have always been faced with a complex array of treatment options regarding the treatment of TMDs, and recent findings regarding TMJ puncture have not simplified this dilemma, but rather added to its complexity [13]. Currently, clinics widely utilize drugs such as platelet-rich plasma (PRP), hyaluronic acid (HA), corticosteroid (CS), among others. In previous retrospective studies, Turosz [14] suggested that injectable platelet-rich fibrin (i-PRF) was the preferred drug for arthrocentesis in TMDs. Conversely, Ulmner [15] concluded that PRP, used as an injection for arthrocentesis, was the most effective in managing TMDs patients. However, there were studies [8, 16] that concluded intra-articular injections of PRP, HA and CS had no effect on improving TMJ pain and functional outcomes compared to placebo. Given the existing retrospective studies, it's challenging to determine the optimal drug for TMJ injection.

Therefore, we undertook an innovative network meta-analysis to discern ambiguities in the management of TMDs.

Materials and methods

This systematic review and network meta-analysis were conducted in accordance with the A Measurement Tool to Assess Systematic Reviews and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. Go to the International Systematic Review Registration Platform website to enroll in the study and receive the registration number: CRD42024563975.

Database and search

RCTs investigating various arthrocentesis regimens for TMDs were identified through computer searches of PubMed, Embase, Cochrane Library, and Web of Science databases. The RCTs included in this study involved TMD patients who received intra-articular injections of PRP, HA, CS, bone marrow aspirate concentrate (BMAC), i-PRF, concentrated growth factor (CGF), tenoxicam (TX), microfragmented adipose tissue (FAT) or placebo. These interventions were compared independently. The primary outcome measure was pain management and TMJ function, assessed during follow-up. The main outcome was TMJ pain, while the secondary outcome was the patient's unassisted maximum opening. The search period extended from the creation of the databases to July 29, 2024. The search strategy employed a combination of Medical Subject Headings (MeSH) and free terms tailored to the characteristics of each database to ensure comprehensive and accurate results. Additionally, literature cited in reviews or meta-analyses on relevant topics was searched to supplement the information gathered. The keywords searched included platelet-rich plasma, hyaluronic acid, steroids, tenoxicam, morphine, granisetron, temporomandibular joint, and injections, intra-articular. For specific search formulas, see Supplement 1.

Inclusion and exclusion criteria

Inclusion criteria were as follows: Participants were diagnosed with TMDs through the Research Diagnostic Criteria for TMDs (RDC/TMD) or Diagnostic Criteria for TMD (DC/TMD) combined with a physical examination. The age and gender of the patients were not differentiated in detail. Moreover, the patients did not show a clear curative effect on conservative treatment methods such as soft food, wet hot compresses, analgesics, anti-inflammatory drugs, and splint treatment for TMDs. Patients with a history of TMJ surgery, polyarthrititis or other rheumatic diseases and neurological diseases were excluded. Interventions and controls: Included randomized

controlled trials should involve intra-articular injection of PRP, HA, CS, BMAC, i-PRF, CGF, TX, FAT or placebo (normal saline or Ringer's lactic acid solution), but the number of injections is not restricted during the experiment. Included studies did not necessarily need to include placebo injections or irrigation. Included RCTs must report pain improvement in patients with primary outcome (visual analogue scale, VAS), secondary outcome (unassisted maximum opening, UMO) and at least 1 month of follow-up.

Study selection

The EndNote 21 software facilitated the identification of duplicate title information among the documents considered for inclusion. Two independent researchers (JMZ and YZ) conducted a literature screening, extracted relevant data, and verified it through cross-checking. Discrepancies were resolved either through discussion or by seeking arbitration from a third researcher (JY). The initial screening involved reviewing article titles; irrelevant literature was excluded. Subsequently, abstracts and full texts were scrutinized to determine if an article met the inclusion criteria. In cases where data was incomplete, original study authors were contacted via email or phone to obtain the missing information.

Data extraction

Two researchers (JMZ and YZ) independently extracted and cross-verified the following information: (1) Basic study details: first author, publication date, country of study, and sample size. (2) Baseline characteristics of the study population: mean age, whether arthroarthrosis was performed, type of drugs (including drug name, dose, frequency, etc.) and follow-up duration. (3) Outcome measures (VAS, UMO). Any discrepancies in the data extraction process were resolved through discussion or mediation by a third researcher (JY). All data were sourced from the original studies included in the analysis.

Risk of bias assessment

The quality of RCTs were evaluated using the Cochrane Risk of Bias Tool 2.0 (ROB 2.0). Two authors (JMZ/YZ) used the Cochrane collaborative "risk of bias" tool sequence to generate results from six aspects: allocation hiding, blinding (or masking), incomplete data evaluation, evaluation report, and other sources of biased selective results. The methods of the articles included in the trial were independently evaluated. Each study was classified as low risk, high risk, or undefined risk, and differences in the evaluation process were resolved through discussion or negotiation with a third researcher (JY).

Data analysis

The efficacy of treatments was gauged by improvements in patients' pain status and UMO. These were assessed through changes in the VAS scores and precise tools before and after intervention. A significant score difference denotes a pronounced treatment effect. Since the outcome measure is continuous, we calculated the mean and its standardized mean difference (SMD) based on VAS scores and UMO. Consequently, SMD and its 95% confidence interval (95% CI) served as effect size indicators. Studies that used line charts for patient condition changes without providing exact data were excluded to ensure research accuracy.

In cases of missing data, authors were contacted via email to obtain complete datasets; otherwise, such articles were excluded. When raw data was sufficient, outcome variables were measured following original studies, weighted by sample size, adhering to the Cochrane Handbook [18]. Network Meta-Analysis (NMA) was conducted using the "network" package in Stata 17.0, resulting in a network diagram. Each node represented an intervention, with its size indicating the sample size involved. Lines between nodes signified direct comparisons, with line thickness denoting the number of these comparisons.

Transitivity and consistency are NMA prerequisites. Overall inconsistency was assessed using the inconsistency model; non-significant differences ($p > 0.05$) indicated consistency. Local inconsistencies were examined using the "node splitting method." Non-significant differences ($p > 0.05$) between split points warranted the use of the consistency model. For graphs with closed loops, the cyclic loop inconsistency determined inconsistencies. An inconsistency factors (IF) value's 95% CI lower bound close to or at 0 implied consistency between direct and indirect evidence. Intervention rankings were determined by comparing the surface under the cumulative ranking curve (SUCRA). Higher SUCRA values correlated with increased intervention effectiveness and higher rankings [19]. Top-ranked drugs at each stage were further analyzed to elucidate potential therapeutic mechanisms and impacts on treatment outcomes. Funnel plots, corrected for comparisons and created using Stata17, were used to detect inter-study biases. Symmetrical funnel plots suggested no significant publication bias; asymmetry indicated potential bias [20].

Results

Study selection

A total of 1664 articles were retrieved from the database. The EndNote 21 software was used to eliminate duplicates, resulting in 663 articles being removed. Of the remaining 1001 articles, 714 were excluded after reading the title and abstract as they did not meet the

inclusion criteria. For the remaining 287 articles, a full text reading and screening process was conducted. This resulted in the exclusion of 111 articles for meeting and trial registration, 36 for systematic review or review, 41 for research methods that did not meet the requirements, 9 for data that could not be extracted, 40 for animal experiments, and 10 for unreasonable intervention measures. After this process, a final total of 40 articles [21–59] were included in the study. The study included a total of 1904 TMJs, with 839 in the control group and 1065 in the experimental group. The literature screening process is illustrated in Fig. 1. Among the 40 studies, 2 were four-arm trials, 6 were three-arm trials, and the remainder were two-arm trials. The basic information of the included literature is presented in Table 1.

Risk of bias assessment

A total of 24 studies [21, 23–30, 32, 35, 38–44, 47, 49, 52, 55, 57, 59] reported specific randomized methods, with 14 being double-blind [26, 27, 29, 30, 39–42, 44, 47, 49, 52, 57, 60], 10 single-blind [21–23, 25, 28, 32, 33, 37, 38, 59], and 1 not mentioning blindness [53]. No bias from established interventions or missing outcome data was found in all studies, and no significant bias in selective reporting of results was found in any study. Overall, the quality of the included literature was generally high, and the risk of bias was low. Bias risk results were plotted using ROB 2.0, as shown in Fig. 2.

NMA results

The network relationships between the various treatments are depicted in Fig. 3. The letters denote the respective interventions, the circle size indicates the number of individuals utilizing the intervention, and the thickness of the lines connecting the different letters represents the number of studies.

Improvement of TMDs curative effect (1-month follow-up)

Studies utilizing VAS as an outcome measure encompassed 30 RCTs, incorporating 12 interventions and a cumulative total of 1436 TMJs. The evaluation of UMO as an outcome measure encompassed 24 RCTs, 11 interventions and a collective total of 1192 TMJs. Consistency testing and NMA were executed on the incorporated data. All inconsistent results yielded a p-value greater than 0.05, indicating an absence of overall inconsistency within the study. Node segmentation methodology revealed that the p-value was greater than 0.05 among each node, thereby suggesting generally favorable local consistency. The IF values derived from the cyclic inconsistency test results ranged from 0.02 to 2.24, with the lower limit of the 95% CI equal to or nearing zero, signifying an absence of substantial inconsistency between the closed loops (A and D in Fig. 4). The network

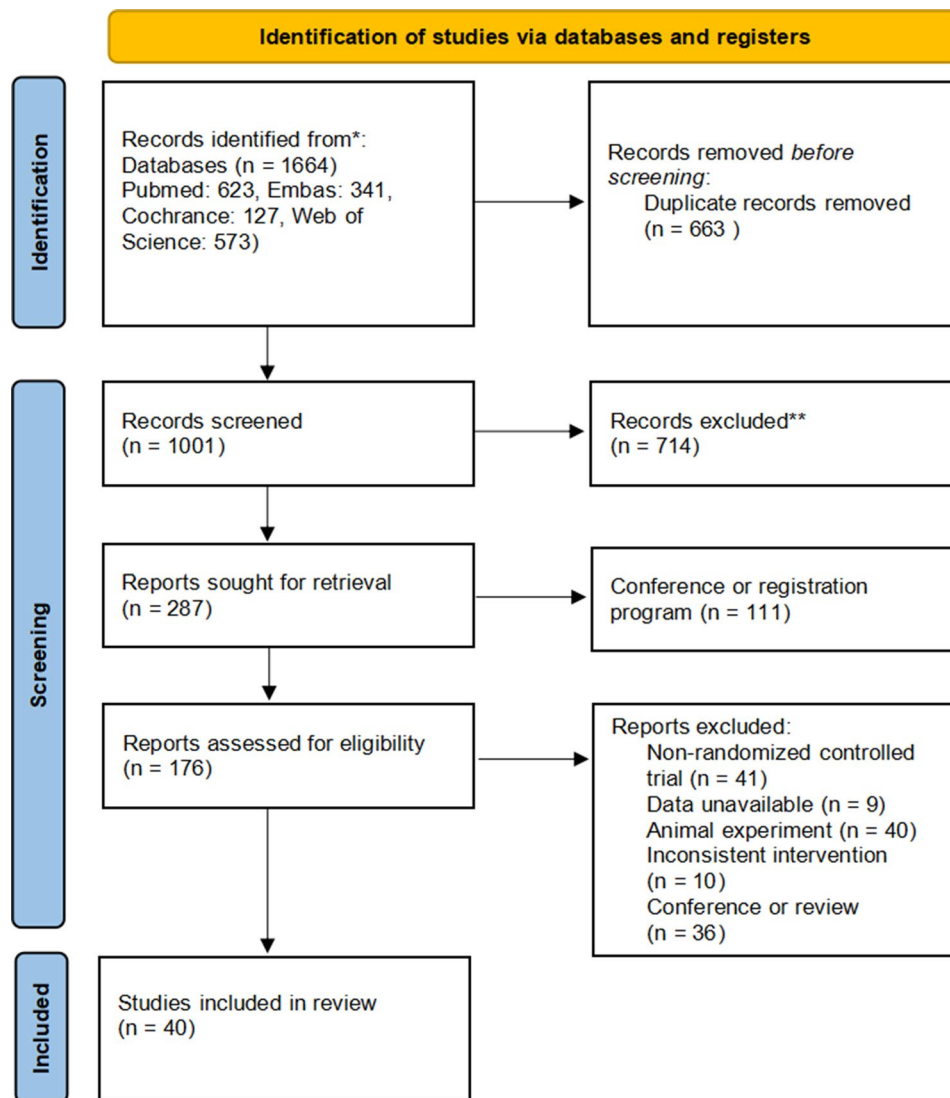


Fig. 1 Flowchart of selection of included studies. No map legends

relationships are centralized around PRP, HA, CS, and PLA, forming 8 and 9 trilateral closed loops, respectively (A and D in Fig. 3). NMA was conducted using the VAS as an outcome indicator. The results demonstrated that among the 66 two-on-two comparisons, only HA+PRP [MD=2.19, 95% CI (3.50, 0.88)], HA [MD=0.76, 95% CI (1.46, 0.06)] and PRP [MD=0.72, 95% CI (-1.42, -0.02)] were statistically significant when compared with PLA. There was no significant difference found when other drugs were used. The efficacy of the SUCRA is in Fig. 5A. NMA results using UMO as an outcome indicator showed that among 55 2-on-2 comparisons, i-PRF [MD=1.20, 95% CI (0.27, 2.12)], HA+PRP [MD=1.05, 95% CI (0.22, 1.88)], PRP [MD=0.52, 95% CI (0.07, 0.98)] was statistically significant when compared with PLA, but no significant difference was found when using other drugs. The efficacy of SUCRA is in Fig. 6A.

Improvement of TMDs curative effect (3-month follow-up)

Studies utilizing VAS as an outcome measure encompassed 23 RCTs, 12 interventions, and a cumulative total of 1062 TMJs cases. Conversely, research focusing on UMO as an outcome measure comprised 20 RCTs, 10 interventions and a combined total of 898 TMJs instances. Consistency testing and NMA were executed on the incorporated data. All inconsistent results yielded p-values greater than 0.05, suggesting an absence of overarching inconsistency within the study. Node segmentation methodology revealed that only one node produced a p-value less than 0.05, indicating generally acceptable local overall consistency. The IFs values from the cyclic inconsistency test fluctuated between 0.22 and 4.46. Notably, the lower threshold of the 95% CI in most closed loops either equaled or approached zero, signifying no substantial inconsistency among these loops.

Table 1 Characteristics of included studies

Author	N (C/T)	Age (mean ± sd)	Intra-articular lavage	Treatment	Method	Frequency	Follow-up (month)	Outcome
A. S. Ansar	15/15	/	200 mL NS	1: lavage 2: 0.8 mL PRP	2-needle	single injection	1, 3	①②
N. Asadpour	10/20	29.63 ± 8.33	100 mL RL	1: HA 2: PRP 3: HA + PRP	2-needle	single injection	1, 6	①②
S. Bergstrand	17/20	50.68 ± 12.49	RL	1: lavage 2: 0.8 mL HA	2-needle	single injection	6	①②
T. Bjørnland	20/20	51.7 ± 13.05	unclear	1: 0.7–1 mL HA 2: 0.7–1 mL betametason	single needle	2-injection	1, 6	①
L. Chandra	22/22	30.65 ± 9.45	50–60 mL RL	1: lavage 2: 0.6 mL PRP	2-needle	single injection	1, 3, 6	①②
N. I. Ghoneim	20/20	27.53 ± 8.28	100 mL RL	1: lavage 2: 1.5 mL i-PRF	2-needle	single injection	3, 6	①②
H. M. Fayed	24/24	43.7 ± 8.69	50 mL RL	1: lavage 2: 7–8 mL BMAC	2-needle	single injection	1, 3, 18	①②
A. Gupta	11/11	33.45 ± 12.88	10 mL RL	1: lavage 2: TX (20 mg/mL)	2-needle	single injection	1, 3	①②
M. Hanci	20/20	26.3 ± 9.34	100 mL RL + splint	1: lavage 2: 0.6 mL PRP	2-needle	single injection	3, 6	①②
A. N. Harba	12/12	/	unclear	1: 1 mL HA 2: 0.5 mL HA + 0.5 mL PRP	single needle	4-injection	1, 3, 6	①②
A. F. Hegab	30/60	31.53 ± 5.23	200 mL NS	1: 2 mL PRP 2: 2 mL HA 3: 1 mL HA + 1 mL PRP	2-needle	single injection	1, 3, 6, 12	①②
G. Isik ¹	38/38	47 ± 9.6	unclear	1: arthrocentesis 2: 1 mL i-PRF	2-needle	2-injection	1, 3, 6, 12	①②
S. G. Kutuk	20/40	36.1 ± 9.09	unclear	1: 1 mL PRP 2: 1 mL HA 3: 1 mL triamcinolone	2-needle	3-injection	1, 3	①
H. A. M. Marzook	8/8	/	50 mL RL	1: lavage 2: 0.5 mL HA + 0.5 mL triamcinolone (40 mg/mL)	2-needle	single injection	1, 3	①②
S. K. Mathpati	64/64	28.8 ± 3.35	NS	1: NS 2: PRP	unclear	single injection	1	①②
S. M. Mohammed	27/27	9.92 ± 33.39	splint	1: 1 mL betamethasone 2: 1 mL HA	unclear	single injection	12	①②
M. E. Onder	16/22	31.92 ± 13.99	50–100 mL RL + splint	1: lavage 2: HA	2-needle	single injection	1, 3, 6	①②
S. M. Ozdamar	15/15	26.87 ± 7.92	splint	1: 2 mL NS 2: 2 mL HA	unclear	single injection	1, 3	①②
A. Rajput	10/20	25 ± 8.95	100 mL RL	1: lavage 2: PRP	2-needle	single injection	3, 6, 12	①②
A. Sipahi	30/30	/	60–100 mL RL + splint	1: lavage 2: 0.01 g morphine 3: 50 mg tramadol	2-needle	single injection	1, 3, 6	①②
R. Tabrizi	11/33	27.54 ± 7.25	200 mL RL	1: lavage 2: 8 mg dexamethasone	2-needle	single injection	1, 6	①②
G. Yapici-Yavuz	11/11	/	200 mL RL	1: lavage 2: HA 3: methylprednisolone 4: TX	2-needle	single injection	1, 3, 6	①②
W. Abbadi	30/30	27.42 ± 6.59	50 mL NS	1: lavage 2: PRP	2-needle	single injection	1, 6	①②
A. Attia	14/16	25.37 ± 5.29	unclear	1: 1 mL HA + 1 mL PRP 2: 1 mL HA + 1 mL triamcinolone (40 mg/mL)	2-needle	single injection	1, 6	①②
Z. Bayramoglu	30/60	41.96 ± 11.5	100 mL RL	1: lavage 2: 2 mL TX (10 mg/mL)	2-needle	single injection	1, 3, 6	①②

Table 1 (continued)

Author	N (C/T)	Age (mean ± sd)	Intra-articular lavage	Treatment	Method	Frequency	Follow-up (month)	Outcome
S. Dasukil	15/15	37.4 ± 4.9	100 mL RL	1: lavage 2: 1 mL HA 3: 1 mL PRP	Single needle	2-injection	1, 3, 6	①②
G. De Riu	31/31	46.35 ± 2.19	200–250 mL RL	1: 2 mL HA (10 mg/mL) 2: 2 mL BMAC	2-needle	single injection	1, 6, 12	①②
H. Gorrela, J	14/14	/	100 mL NS	1: lavage 2: 1 mL HA	2-needle	single injection	6	①②
J. J. Hud-dleston Slater	24/25	33.25 ± 13.63	300 mL NS	1: lavage 2: 1 mL dexamethasone	2-needle	single injection	1, 6	①②
R. Dharamsi	25/27	/	unclear	1: 1 mL HA 2: 1 mL triamcinolone	2-needle	single injection	1, 3	①②
G. Isacson	21/22	51.85 ± 17.16	unclear	1: 1 mL NS 2: 1 mL methylprednisolone (40 mg/mL)	single needle	single injection	1	①
G. Isik ²	15/15	45.2 ± 12.46	200 ml NS	1: lavage 2: 1 mL i-PRF	2-needle	4-injection	1, 3, 6, 12	①②
S. M. Jacob	15/30	46.19 ± 14.72	100 mL RL	1: lavage 2: 1 mL HA 3: 1 mL PRP	2-needle	single injection	6	①②
X. Y. Jia	30/30	31.25 ± 7.07	unclear	1: 1 mL HA 2: 0.5 mL HA + 0.5 mL CGF	single needle	single injection	3, 6	①
S. C. Kiliç	17/32	30.48 ± 13.04	unclear	1: HA 2: PRP	2-needle	4-injection	12	①②
S. S. Liu	32/33	33.09 ± 7.53	unclear	1: 0.8 mL HA 2: 0.8 mL PRP	unclear	HA: 2-injection PRP: single injection	1, 3, 6	①②
S. Sembronio	28/35	47 ± 19.61	200 ml NS	1: 2 mL HA 2: 2 mL FAT	2-needle	single injection	1, 6	①②
Z. D. Shi	28/35	40.56 ± 16.21	unclear	1: 0.5 mL prednisolone 2: 0.6 mL HA	unclear	4-injection	1	①②
A. K. Singh	12/12	35.58 ± 10.78	100 mL RL	1: lavage 2: 1 mL PRP	2-needle	single injection	1, 3, 6	①②
B. M. Sousa	20/60	43.1 ± 17.7	splint	1: arthrocentesis 2: 1 mL betamethasone 3: 1 mL HA (10 mg/mL) 4: 2 mL PRP	2-needle	single injection	1, 6	①②

NS, 0.9% normal saline; RL, Ringer's Lactated Solution; PRP, platelet-rich plasma; HA, Hyaluronic acid; CS, corticosteroid; BMAC, bone marrow aspirate concentrate; i-PRF, injectable platelet rich fibrin; CGF, concentrated growth factor; TX, tenoxicam; FAT, microfragmented adipose tissue; ①VAS, visual analog scale; ②UMO, unassisted maximum opening

Nonetheless, two closed loops indicated loop inconsistency. Further details will be elucidated in the [discussion](#) section (B and E in Fig. 4). The network associations primarily revolve around PRP, HA and PLA, forming 8 and 6 trilateral closed loops respectively. In this context, the VAS network also incorporates 2 quadrilateral closed loops (B and E in Fig. 3). NMA results, using VAS as the outcome index, revealed that among 66 2-on-2 comparisons, only the efficacy of i-PRF [MD = -1.10, 95% CI (-2.12, -0.08)] was significantly superior to that of PLA, with the difference being statistically significant at the time of comparison. The efficacy of SUCRA is in Fig. 5B. The NMA results with the UMO as the outcome indicator showed that in 45 2-on-2 comparisons, only the efficacy of i-PRF [MD=1.30, 95% CI (0.69, 1.91)] was

significantly superior to that of PLA, with the difference being statistically significant at the time of comparison. The difference was statistically significant. The efficacy of SUCRA is in Fig. 6B.

Improvement of TMDs curative effect (more than 6-month follow-up)

Studies using VAS as an outcome measure included 31 RCTs, 13 interventions, and a total of 1465 TMJs. The study using UMO as an outcome measure included 28 RCTs, 12 interventions, and a total of 1315 TMJs. Consistency testing and NMA were conducted on the included data. All inconsistent results had a p-value greater than 0.05, indicating no overall inconsistency in the study. Node segmentation analysis revealed that no inter-node

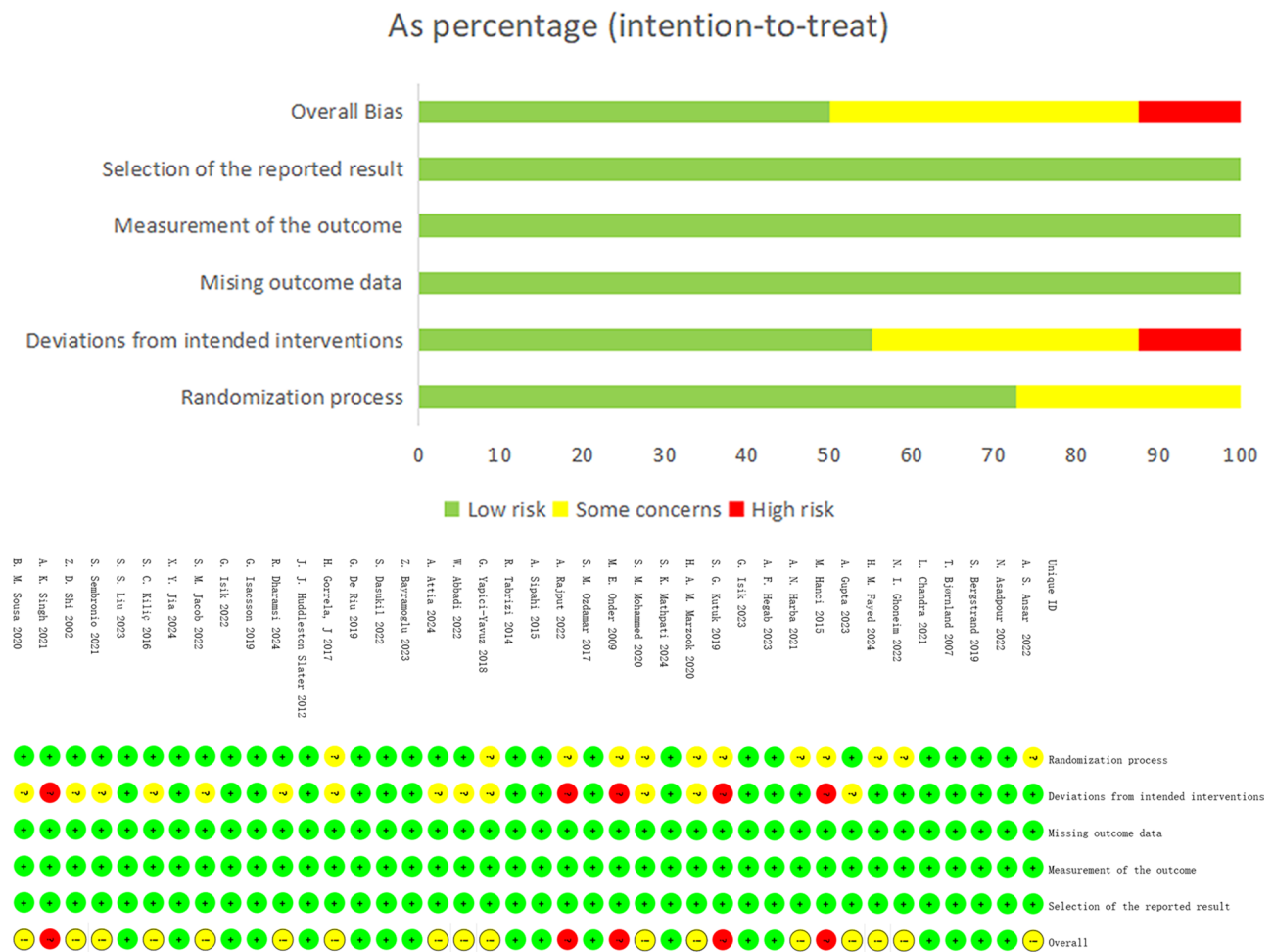


Fig. 2 Risk of bias summary. Risk of bias graph. No map legends

p-values were less than 0.05, indicating generally good local consistency. IFs values from the cyclic inconsistency test ranged from 0.01 to 7.51. Most closed loops had a lower limit of the 95% CI equal to or nearing zero, suggesting no significant inconsistency. However, one loop exhibited inconsistency. Details will be discussed in the discussion section (C and F in Fig. 4). Network relationships primarily involve PRP, HA, and PLA, forming 9 and 8 trilateral closed loops, respectively (C and F in Fig. 3). The results of the NMA using VAS as the outcome index revealed that out of 91 2-on-2 comparisons, HA+CGF [MD=9.53, 95% CI (14.10, 4.97)], HA+PRP [MD=8.66, 95% CI (13.25, 4.06)], FAT [MD=9.03, 95% CI (13.60, 4.47)], HA [MD=7.91, 95% CI (11.85, 3.97)], PRP [MD=8.26, 95% CI (12.83, 3.70)], HA+CS [MD=7.32, 95% CI (12.46, 2.18)], TX [MD=7.60, 95% CI (12.21, 2.18)], CS [MD=4.73, 95% CI(-9.04,-0.41)] were superior to that of PLA, and the differences were statistically significant. The specific efficacy differences of other treatment schemes are illustrated in Fig. 5C. The results of the NMA using the UMO as the outcome indicator

demonstrated that, among 66 2-on-2 comparisons, the effectiveness of i-PRF MD=1.85, 95%CI (1.24,2.47)] and FAT [MD=1.81, 95%CI (0.37,3.24)] were significantly different compared to that of PLA. The SUCRA ranking for efficacy in Fig. 6C.

SUCRA for all interventions are summarized in Table 2.

Publication bias

Funnel plots were constructed for the included literature based on outcome indicators. The majority of scatter points in these plots were symmetrically distributed. However, a few outcome indicators exhibited asymmetrical scatter points, indicating potential publication bias that could influence the results, as illustrated in Fig. 7.

Discussion

TMJ is a unique synovial joint essential for jaw movement and function. Distinct from most synovial joints, the TMJ’s joint surface is enveloped by a dense layer of fibrocartilage, rather than the standard hyaline cartilage.

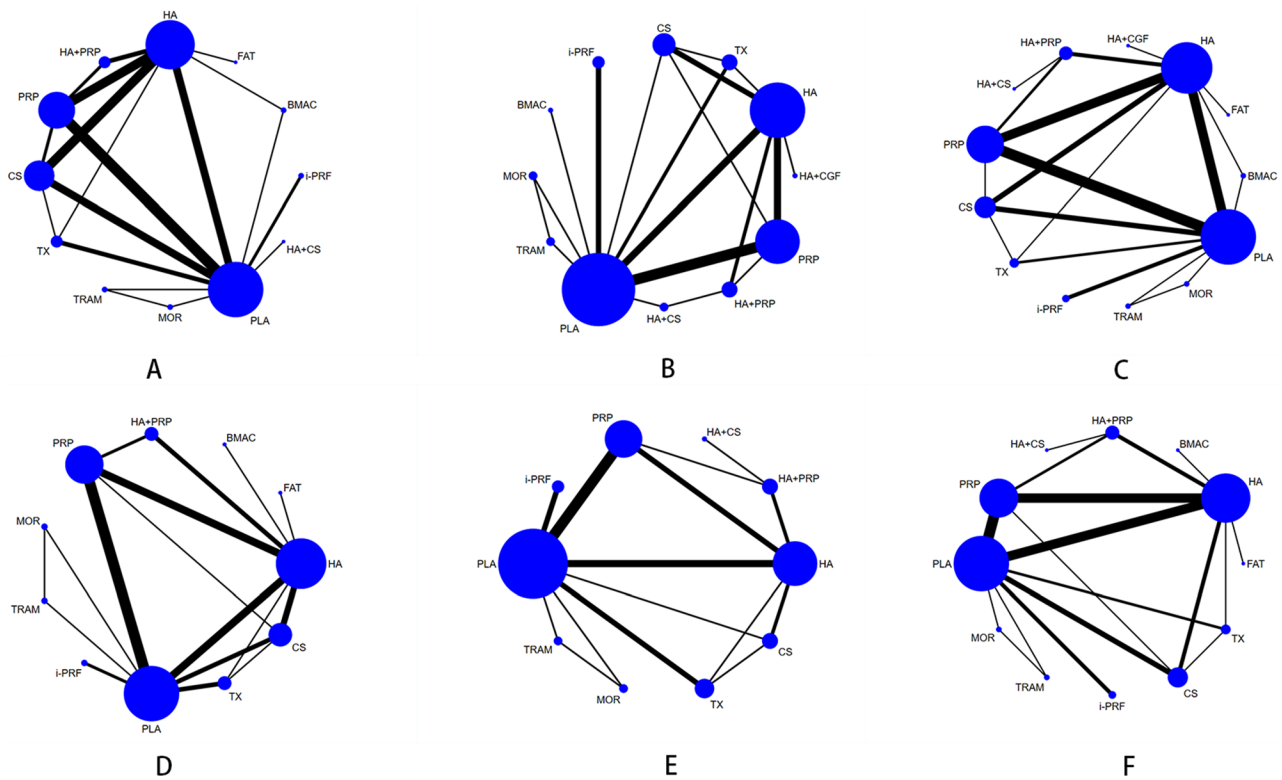


Fig. 3 Network plot. Network plots at 1-month follow-up, (A) (VAS), (D) (UMO); At 3-month follow-up, (B) (VAS), (E) (UMO); At 6-month follow-up, (C) (VAS), (F) (UMO); PRP, platelet-rich plasma; HA, hyaluronic acid; CS, corticosteroid; BMAC, bone marrow aspirate concentrate; i-PRF, injectable platelet rich fibrin; CGF, concentrated growth factor; TX, tenoxicam; FAT, microfragmented adipose tissue; VAS, visual analog scale; UMO, unassisted maximum opening

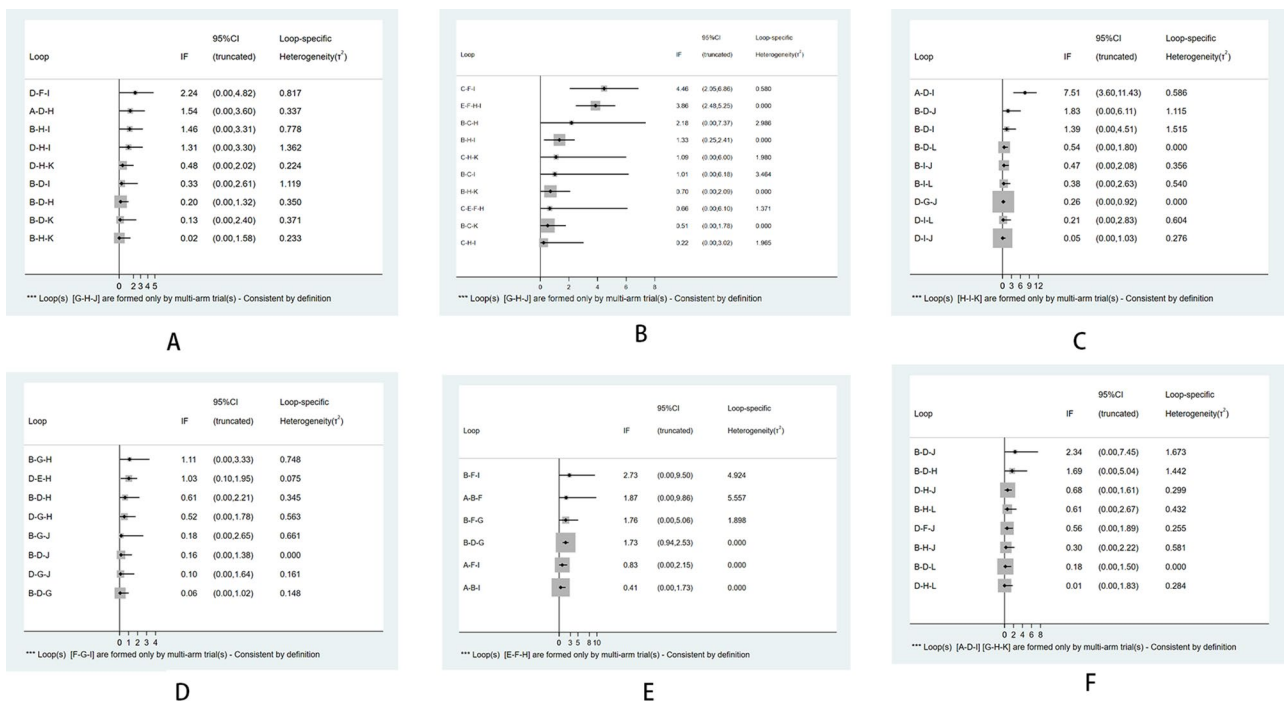


Fig. 4 Inconsistency factor values of the meta-analysis. **A:** A-L (BMAC, CS, FAT, HA, HA + CS, HA + PRP, MOR, PLA, PRP, TRAM, TX, i-PRF); **B:** A-L (BMAC, CS, HA, HA + CGF, HA + CS, HA + PRP, MOR, PLA, PRP, TRAM, TX, i-PRF); **C:** A-M (BMAC, CS, FAT, HA, HA + CGF, HA + CS, HA + PRP, MOR, PLA, PRP, TRAM, TX, i-PRF); **D:** A-K (BMAC, CS, FAT, HA, HA + PRP, MOR, PLA, PRP, TRAM, TX, i-PRF); **E:** A-J (CS, HA, HA + CS, HA + PRP, MOR, PLA, PRP, TRAM, TX, i-PRF); **F:** A-L (BMAC, CS, FAT, HA, HA + CS, HA + PRP, MOR, PLA, PRP, TRAM, TX, i-PRF)

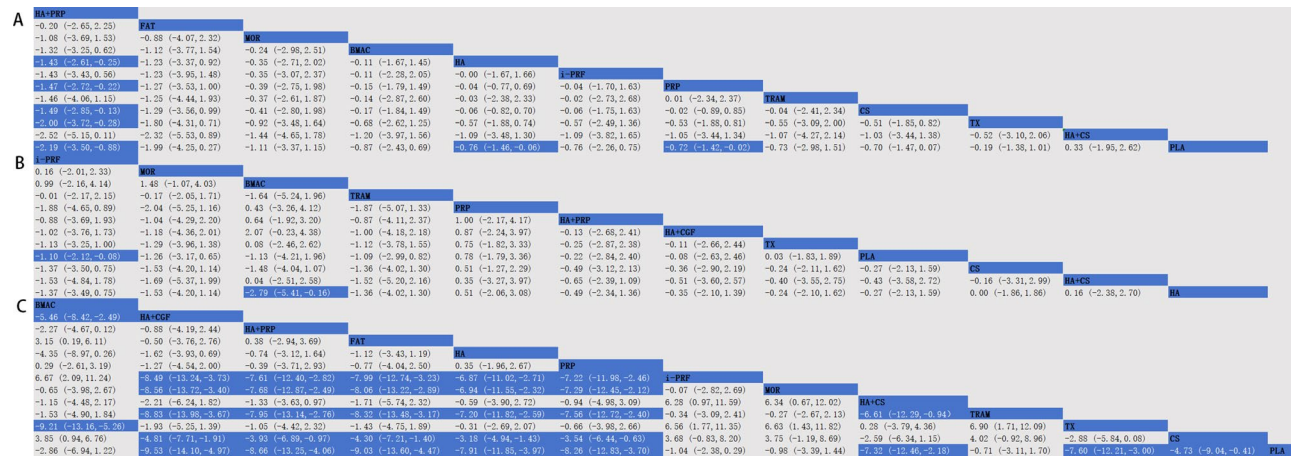


Fig. 5 Network meta-analysis of VAS. SUCRA of VAS at A, 1-month follow-up; B, 3-month follow-up; C, 3-month follow-up; PRP, platelet-rich plasma; HA, Hyaluronic acid; CS, corticosteroid; BMAC, bone marrow aspirate concentrate; i-PRF, injectable platelet rich fibrin; CGF, concentrated growth factor; TX, tenoxicam; FAT, microfragmented adipose tissue

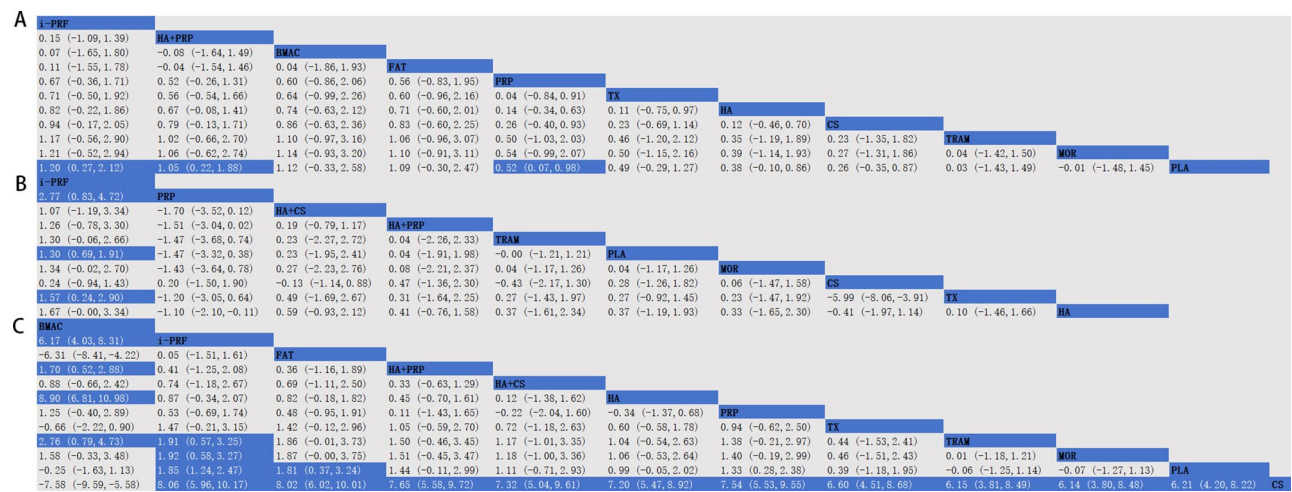


Fig. 6 Network meta-analysis of UMO. SUCRA of UMO at A, 1-month follow-up; B, 3-month follow-up; C, 3-month follow-up; PRP, platelet-rich plasma; HA, Hyaluronic acid; CS, corticosteroid; BMAC, bone marrow aspirate concentrate; i-PRF, injectable platelet rich fibrin; CGF, concentrated growth factor; TX, tenoxicam; FAT, microfragmented adipose tissue

Consequently, it is less vulnerable to age-related bone mineral density loss, which could diminish TMJ functionality. Moreover, the TMJ possesses an enhanced capacity for self-repair compared to other synovial joints [61]. When the mouth and face experience direct or indirect trauma, an occlusal relationship disorder or extracellular matrix degradation, the TMJ may exhibit dysfunction. The influence of TMDs on an individual's overall quality of life is substantial, potentially resulting in functional impairments such as difficulties in eating, speaking, sleeping, and, for some patients, tinnitus [62]. Furthermore, the symptom complex associated with TMDs can induce psychological distress, encompassing depression, anxiety, and social isolation. Apart from the physical and mental impacts on individuals, TMDs may also impose a considerable financial burden due to medical expenses and absenteeism from work [63]. Existing

research indicates that treatments for TMDs vary in effectiveness, from conservative approaches to surgical procedures. There are several treatment options for TMDs, most of which aim to alleviate the patient's painful experience. However, their effectiveness has been a subject of debate. Physicians in the United States and Australia typically employ a comprehensive combination of treatments, including various conservative approaches, joint puncture, and open surgery [64]. A consensus of 24 experts suggests that conservative treatment should be the initial approach, even for advanced TMDs, although this proposal lacks substantial research support [65]. Besides medication for moderate to severe pain, multidisciplinary conservative treatments such as educational counseling, exercise therapy, manual reduction, non-invasive physical therapy, and occlusal splints are deemed effective for many mild cases [66]. Ultrasound therapy,

Table 2 Summary results of all SUCRA values SCURA(%)

1-month follow-up			3-month follow-up			more than 6-month follow-up		
Treat	VAS	UMOD	Treat	VAS	UMOD	Treat	VAS	UMOD
HA + PRP	90.6	77.8	HA + PRP	48.1	49	HA + PRP	73	77.9
BMAC	54	75.1	BMAC	73.9	/	BMAC	99.6	95.8
i-PRF	50.1	81.4	i-PRF	74.2	95.6	i-PRF	45.8	80.6
PRP	49.4	51	PRP	55.4	65.1	PRP	47.2	45
CS	48.4	32.6	CS	30.6	34.8	CS	18.3	0
HA	51.6	40.7	HA	29.1	29	HA	52.2	54.1
MOR	59.9	26.3	MOR	74.2	44.4	MOR	43.7	24.9
TRAM	49.3	28.2	TRAM	69.5	49	TRAM	38	25.6
TX	27.5	48.4	TX	37.9	34.2	TX	28.3	24.7
FAT	81.1	73.6	FAT	/	/	FAT	71.4	79.5
HA + CGF	/	/	HA + CGF	43.4	/	HA + CGF	78.1	/
HA + CS	21.3	/	HA + CS	30.1	57.1	HA + CS	39.6	57.8
PLA	16.9	15	PLA	33.5	44.9	PLA	14.8	24.1

PRP, platelet-rich plasma; HA, Hyaluronic acid; CS, corticosteroid; BMAC, bone marrow aspirate concentrate; i-PRF, injectable platelet rich fibrin; CGF, concentrated growth factor; TX, tenoxicam; FAT, microfragmented adipose tissue; TRAM, tramadol; MOR, morphine

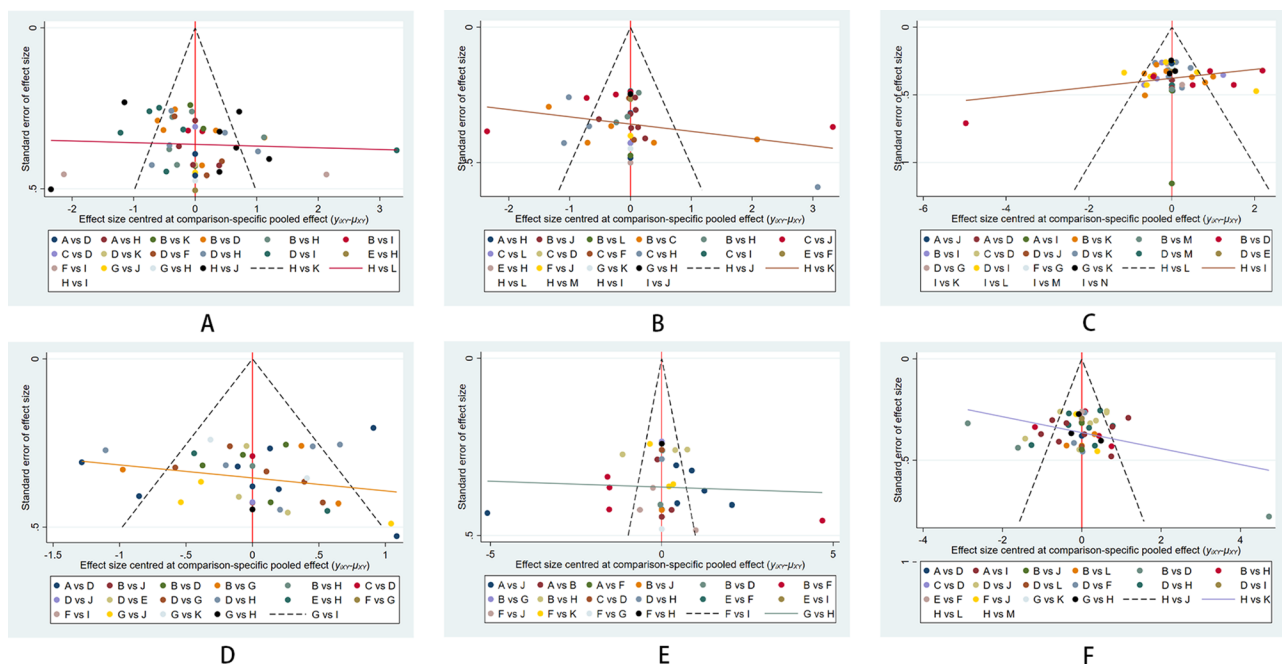


Fig. 7 Funnel plots. **A:** A-L (BMAC, CS, FAT, HA, HA + CS, HA + PRP, MOR, PLA, PRP, TRAM, TX, i-PRF); **B:** A-L (BMAC CS HA HA + CGF HA + CS HA + PRP MOR PLA PRP TRAM TX i-PRF); **C:** A-M (BMAC CS FAT HA HA + CGF HA + CS HA + PRP MOR PLA PRP TRAM TX i-PRF); **D:** A-K (BMAC CS FAT HA HA + PRP MOR PLA PRP TRAM TX i-PRF); **E:** A-J (CS HA HA + CS HA + PRP MOR PLA PRP TRAM TX i-PRF); **F:** A-L (BMAC CS FAT HA HA + CS HA + PRP MOR PLA PRP TRAM TX i-PRF)

a prime example of non-invasive physical therapy, can mitigate symptoms by enhancing blood circulation and modulating inflammatory responses [67]. Currently, the management of TMDs also encompasses the neurological domain, where neural regulation and biofeedback through appropriate electrical or magnetic stimulation can significantly alleviate the pain and tension in the masticatory muscle [68]. With the advent of precision medicine and minimally invasive techniques, joint injection strategies that promote regeneration have gained

prominence over alternatives like PRP, HA and mesenchymal stem cells (MSCs). These methods have demonstrated notable advancements in managing TMDs [69]. This study analyzed follow-up data at 1-, 3- and 6-months post-arthrocentesis, identifying HA + PRP, i-PRF and BMAC as the most effective treatments for postoperative recovery. All three are classified as regenerative therapies.

HA is a crucial component of the extracellular matrix that contributes to the viscoelastic properties of joints. Moreover, HA has been demonstrated to support cell

growth and chondrogenic differentiation of stem cells, as well as provide binding sites for growth factors [69], which are beneficial for tissue healing. Following the onset of TMDs, the friction coefficient of synovial fluid in the joint cavity increases by 3.5 times compared to normal conditions [70], and the volume of synovial fluid decreases, thereby affecting the nutritional support of TMJ cartilage. The combined effects of these changes accelerate TMJ wear, leading to tissue damage and functional decline. Consequently, the injection of HA into the TMJ lumen can not only lubricate and alleviate pain but also nourish articular cartilage to promote self-repair. PRP is a platelet concentrate derived from autologous whole blood following centrifugation. Its platelet concentration is at least twice the baseline concentration, rich in numerous growth factors and proteins, with its growth factor content reaching up to eight times the normal blood level. Numerous studies [71, 72] have shown that PRP may promote the proliferation of chondrocytes and MSCs, and it can serve as a biomolecular framework for tissue regeneration in cartilage defects to expedite damaged tissue repair. Therefore, intra-articular injection of PRP is widely employed in various diseases associated with joint tissue injury. Our study concluded that HA+PRP may be the most effective short-term management for TMDs. Among existing meta-analysis results, Al-Moraissi [73] and Li [74] concluded that HA and PRP had almost equivalent efficacy, but only in managing patients' pain, with no significant improvement in patients' temporomandibular activity and physiological function. However, neither of these two studies made a detailed distinction regarding follow-up time. Therefore, it remains unclear how well the drug is maintained. The combination of HA+PRP represents a highly innovative treatment program that maintains the normal physiological environment in the TMJ cavity through the physical and chemical properties of HA, reduces tissue friction loss, and relies on the regenerative capacity of PRP to repair damaged tissue structures, further alleviating TMDs symptoms and aiding patients in restoring normal TMJ physiological function. Unfortunately, no meta-analysis has been found to report on the combination of HA+PRP for TMDs.

Compared to PRP, the i-PRF offers several advantages including ease of processing, cost-effectiveness, and a higher concentration of regenerative cells, growth factors, and interleukin-10 at the same volume [75]. Furthermore, i-PRF can induce the proliferation and migration of MSCs. The use of i-PRF in regenerative dentistry has been extensively studied in both *in vitro* and *in vivo* studies. As a novel injectable biomaterial, i-PRF has been widely utilized in regenerative dentistry as a carrier for various biomolecules or in combination with other biomaterials. However, there are limited reports related

to TMDs. Sielski's review [76] obtained similar results as this paper, but their study did not conduct further subgroup analysis based on the follow-up period, leaving the phased efficacy of i-PRF uncertain. Additionally, due to the limitation of search terms, the drugs included were not comprehensive, which may have led to accidental results. Currently, no definitive meta-analysis of arthrocentesis combined with i-PRF in the treatment of TMDs has been published.

Bone marrow (BM) is located in the cancellous space of bone and the BM cavity of long bones, consisting of various cell types and reticular connective tissue. BM plays a crucial role in hematopoiesis, immunity, and defense mechanisms. BMAC is derived from the extraction of BM, which is then centrifuged and separated. Compared to BM, BMAC contains a higher concentration of MSCs, Hematopoietic Stem Cells and a variety of common blood cells at different stages of differentiation per unit volume. It is also rich in Transforming Growth Factor- β , Platelet-Derived Growth Factor and a range of bone morphogenetic proteins [77]. Among the many substances found in BMAC, the high concentration of MSCs and various growth factors significantly influence its regenerative capabilities. MSCs possess robust self-renewal and regeneration abilities, capable of differentiation into chondrocytes, bone cells, and adipocytes under specific conditions. Growth factors can protect cartilage tissue by reducing apoptosis, controlling inflammatory responses, and minimizing the degradation of cartilage matrix [78]. The combined effects of these components may positively impact injured TMJ. While there are limited reports on the application of BMAC in TMDs, Belk [79] has demonstrated that BMAC has at least similar effects to PRP in knee osteoarthritis studies. Notably, most current meta-analyses [79, 80] suggest PRP as the optimal long-term treatment for knee osteoarthritis, indicating significant potential for BMAC in TMD management.

In addition to prior studies, we examined various meta-analyses, including both paired and network meta-analyses. We identified that the research by Christidis [81] and Xu [82] exhibited certain similarities with our study. Christidis's research employed a NMA to assess the efficacy and ranking of different medications for managing pain symptoms associated with TMDs. However, it did not address improvements in TMJ activity among TMDs patients, hence excluded medications such as HA, PRP or CS. In contrast, Xu's study utilized NMA to evaluate the efficacy of HA, PRP, and i-PRF in managing TMDs pain and unassisted maximum opening (UMO). This approach closely resembled our methodology. Nonetheless, our study offers broader applicability by incorporating recently introduced medications for TMDs management and considering multi-drug combinations as separate interventions, which facilitates comparison

between singular and combined drug efficacy. Notably, while Xu's findings paralleled ours, our comprehensive analysis—encompassing a larger array of study protocols and demonstrating superior efficacy for certain treatments—led us to conclude that i-PRF was most effective three months post-arthrocentesis surgery. Conversely, Xu posited that i-PRF's efficacy spanned the entire duration. Aggregating our results, we discerned no significant overall score differences among HA+PRP, i-PRF, and BMAC when evaluating intervention efficacy across all stages. However, the absence of UMO data at the three-month follow-up for BMAC precluded further comparative analysis of these interventions. Future research necessitates multi-center participation, extensive sampling and prolonged follow-ups to derive more precise conclusions.

In this study, three inconsistent results were observed during the ring inconsistency test, indicating discrepancies between direct and indirect intervention comparisons. This finding was initially disconcerting; however, upon re-analysis of the original data and a meticulous review of each article, potential explanations for these inconsistencies emerged. Notably, at the third and sixth month follow-ups using VAS as the outcome measure, three inconsistent closed loops were identified (B and C in Fig. 4): C - F - I (HA - HA+PRP - PRP), E - F - H - I (CS - HA+PRP - PLA - PRP) and A - D - I (BMAC - HA - PLA). A comprehensive review of the literature revealed that the inconsistencies might stem from our classification approach to interventions, where specific drugs and their injection frequencies were not distinctly specified, nor were the sources and preparation methods of certain drugs clearly defined. For instance, the molecular weight of HA was not differentiated in detail, leading to a uniform categorization of all HA types under a single umbrella. Research [83] suggests that HA with a molecular weight less than 5 kDa could possess pro-inflammatory effects, while HA exceeding 800 kDa demonstrates anti-inflammatory properties and the efficacy of moderate molecular weight HA remains ambiguous. Although Nardini and Ferreira's study [84, 85] indicated no significant difference between medium and high molecular weight HA comparisons and varying injection frequencies of high molecular weight HA, the extensive sample size included might amplify minor differences, potentially skewing therapeutic outcomes. Similarly, CS such as methylprednisolone, dexamethasone and betametasone were grouped together without delineating specific types and injection frequencies. In the PRP studies, consistency in preparation processes was also not mandated. Given the variability and lack of unified nomenclature in PRP, along with poor standardization in evidence-based guidelines, differences in gravity and centrifugation times during preparation could result in varied PRP content concentrations across studies,

indirectly impacting outcome measures [86]. Furthermore, the specific intervention content for PLA was not confined, encompassing possibilities such as isolated arthrocentesis, arthrocentesis combined with irrigation (normal saline or Ringer's lactate solution), supplementation with placebo injections or even splint fixation assistance. Tsui and Moraissi's meta-analysis [87, 88] confirmed that both arthrocentesis and splint-assisted approaches can somewhat improve TMDs. These factors contributing to inconsistencies also represent limitations of this study. Regarding BMAC within the closed loop, our assessment showed similarities in both preparation schemes and puncture operations among original studies, with variations solely in the volume of solution used for irrigation. Moreover, BMAC's influence on VAS and unassisted maximum opening degree appeared relatively stable upon original data review. Hence, we provisionally conclude that BMAC is not a principal source of ring inconsistencies. Initially, the study aimed to distinguish various interventions minutely to pinpoint the most effective treatment regimen for TMDs via arthrocentesis, including dosage, injection frequency, and preparation methods. However, pre-grouping based on this premise revealed two main issues: an excess of indirect evidence, theoretically diminishing the level of evidence, and an inability to form complete network diagrams for some drugs, hindering comparisons. Consequently, we opted to aggregate drugs of similar categories.

Limitations

This study is not without its limitations. Initially, a preliminary investigation was undertaken to establish the definitive methodology. However, during the analysis of results, certain drugs were omitted due to discrepancies in study types or incomplete data, potentially leading to an inadequate representation of the drugs included in our study. Other issue may be the fact that some drugs are currently being tested or remain in clinical trials for TMDs, resulting in a paucity of research and insufficient evidence. Furthermore, we highlighted the limitations associated with the classification of interventions in our discussion as well.

Abbreviations

TMJ	Temporomandibular joint
TMDs	Temporomandibular joint disorders
PRP	Platelet-rich plasma
HA	Hyaluronic acid
CS	Corticosteroid
BMAC	Bone marrow aspirate concentrate
i-PRF	Injectable platelet rich fibrin
CGF	Concentrated growth factor
TX	Tenoxicam
FAT	Microfragmented adipose tissue
VAS	Visual analogue scale
UMO	Unassisted maximum opening
SMD	Standardized mean difference
CI	Confidence interval

NMA	Network Meta-Analysis
IF	Inconsistency factors
SUCRA	Surface under the cumulative ranking curve
MSCs	Mesenchymal stem cells
BM	Bone marrow
RDC/TMD	Research Diagnostic Criteria for Temporomandibular Disorders
DC/TMD	Diagnostic Criteria for TMD
MRI	Magnetic resonance imaging
CT	Computed tomography
TENS	Transcutaneous Electrical Nerve Stimulation

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12903-024-04858-7>.

Supplementary Material 1

Supplementary Material 2

Author contributions

JMZ was responsible for the design of the article concept and the writing of the manuscript; JMZ and YZ were responsible for the literature search and screening of literature that fulfilled the inclusion criteria; JMZ, YZ and JY were responsible for the extraction of data and quality evaluation of the included literature; TQZ and CG 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

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Declarations

Ethical approval

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

Human ethics and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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