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Review

The hierarchy of different treatments for arthrogenous temporomandibular disorders: A network meta-analysis of randomized clinical trials☆

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ABSTRACT

Purpose: Different treatment options for patients with arthrogenous Temporomandibular Disorders (TMDs) have been reported. However, evidence regarding the most effective intervention using network meta-analysis (NMA) has not been performed. Thus, we conducted a NMA of randomized clinical trials (RCTs) to identify the most effective treatment of arthrogenous TMDs with respect to pain reduction and improved mouth opening, and to generate a ranking according to their effectiveness.

Material and methods: An electronic search on three major databases was undertaken to identify RCTs published before August 2019, comparing up to fourteen different treatments against control/placebo patients for arthrogenous TMDs with respect to pain reduction and improved mouth opening. The treatment variables were controls/placebo, conservative treatment (muscle exercises and occlusal splint therapy), occlusal splint therapy alone, intraarticular injection (IAI) of hyaluronic acid (HA) or corticosteroid (CS), arthrocentesis with or without HA, CS and platelet-rich plasma (PRP), arthroscopy with or without HA and PRP, open joint surgery, and physiotherapy. Frequentist NMA was performed using STATA software. Studies meeting the inclusion criteria were divided according to the length of follow-up (short-term (≤5 months) and intermediate-term (≥6 months to 4 years) and type of TMJ arthrogenous disorders; internal derangement (ID) and TMJ osteoarthritis (OA). The standardized mean differences (SMD) in post-treatment pain reduction and maximum mouth opening (MMO) were analysed.

Results: Thirty-six RCTs were identified that performed comparative outcome assessments for pain and 33 RCTs for MMO. At the short term (≤5 months), IAI-HA (SMD = −2.8, CI: −3.7 to −1.8) and IAI-CS (SMD = −2.11, CI: −2.9 to −1.2) (all very low quality evidence) achieved a substantially greater pain reduction than control/placebo.

At intermediate term (≥6 months), a statistically significant decrease in posttreatment pain intensity was observed following Arthroscopy-PRP (SMD = −3.5, CI: −6.2 to −0.82), Arthrocentesis-PRP (SMD = −3.08, CI: −5.44 to −0.71), Arthroscopy-HA (SMD = −3.01, CI: −5.8 to −0.12), TMJ surgery (SMD = −3, CI: −5.7 to −0.28), IAI-HA (SMD = −2.9, CI: −4.9 to −1.09) (all very low quality evidence), Arthroscopy-alone (SMD = −2.6, CI: −5.1 to −0.07, low quality evidence) and Arthrocentesis-HA (SMD = −2.3, CI: −4.5 to −018, moderate-quality evidence) when compared to the control/placebo groups.

Relative to MMO, the most effective treatments for short- and intermediate-term improvement were the arthroscopy procedures (PRP > HA > alone, all very low-quality evidence) followed by Arthrocentesis-PRP (very low-quality evidence) and Arthrocentesis-HA (moderate-quality evidence).

The non-invasive procedures of occlusal splint therapy, physical therapy, conservative therapy, placebo/control provided significantly lower quality outcomes relative to pain and MMO.

Conclusion: The results of the present meta-analysis support a paradigm shift in arthrogenous TMJ disorder treatment. There is a new evidence (though on a very low to moderate quality level) that

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minimally invasive procedures, particularly in combination with IAI of adjuvant pharmacological agents (PRP, HA or CS), are significantly more effective than conservative treatments for both pain reduction and improvement of MMO in both short (≤5 months) and intermediate term (6 months–4 years) periods. In contrast to traditional concepts mandating exhaustion of conservative treatment options, minimally invasive procedures, therefore, deserve to be implemented as efficient first-line treatments (e.g. IAIs and/or arthrocentesis) or should be considered rather early, i.e. as soon as patients do not show a clear benefit from an initial conservative treatment.

1. Introduction

Temporomandibular joint disorders (TMDs) have been categorized based on the origin of the problem into myogenous TMDs which are composed of problems in the masticatory muscles associated with the TMJ, and arthrogenous TMDs which include disorders within components of the TMJ itself. Arthrogenous TMDs include internal derangements, arthralgias, osteoarthritis, and osteoarthrosis (Dworkin and LeResche, 1992). Displacement of the articular disc is a subgroup of arthrogenous TMDs that manifests with TMJ pain, TMJ clicking during jaw function, jaw deviation, and functional limitation of the jaw opening (Okeson, 1996). Chronic articular disc displacement could lead to osteoarthritis of the TMJ (Dimitroulis, 2005).

The prevalence of TMD has been reported around 3.7–12% and women have a greater prevalence rate than men (Magnusson et al., 2000). Additionally, among TMD patients, about 44.2% and up to 55.6% have TMJ disc displacement and degenerative disorders, respectively (Manfredini et al., 2006; Abrahamsson et al., 2009; Almoznino et al., 2015).

The main aim for management of arthrogenous TMDs is to reduce pain, reestablishing the normal mandibular movements and improve the quality of life for patients. The reported treatment strategies for arthrogenous TMDs involve three sequences. First, conservative treatment which includes medications, patient education and counselling, occlusal splints, physiotherapy (manual therapy or home muscle exercise) and low-level laser therapy. Second, less invasive treatment which includes intraarticular injection (IAI) of pharmacological agents: hyaluronic acid (HA), corticosteroid (CS), morphine, and/or growth factors as found in platelet-rich plasma (PRP), arthrocentesis with or without occlusal splint therapy or arthroscopy either alone or in combination with IAI of HA or CS or PRP, etc. Third, a surgical treatment which includes minimally invasive arthroscopic procedures or invasive open joint surgeries such as disc plication, discectomy and arthroplasty.

Currently, there is no consensus regarding the most effective treatment for patients with arthrogenous TMD. There are a large number of clinical studies that have investigated the efficacy of various treatment modalities for the management of arthrogenous TMDs. However, the best treatment modality with predictable outcomes based on solid evidence is still unclear. Conventional direct meta-analysis only compares head-to-head studies. So, comparisons have been limited to these direct clinical trials. Network meta-analyses (NMA) emerged as a suitable tool not only for comparing two interventions which have not been compared directly in a head-to-head clinical trial but also provides the opportunity to run a collective assessment of various interventions in a single study (Kanters et al., 2016).

For outcomes of posttreatment pain intensity and improved mouth opening following various treatments of arthrogenous TMDs, no randomized clinical trials (RCTs) have been compared between co-interventions: (1) Arthrocentesis with IAI of HA, CS or PRP versus arthroscopy plus IAI of HA or PRP. (2) Physiotherapy, open joint surgery or conservative treatments versus IAI of HA or CS, arthrocentesis with or without IAI of HA, CS or PRP, and arthroscopy with or without IAI of HA and PRP. (3) IAI of HA, CS or PRP vs arthrocentesis with or without IAI of HA, CS or PRP, arthroscopy with or without HA or PRP, and open joint surgery, physiotherapy, control and occlusal splints therapy.

Therefore, a NMA of randomized clinical trials (RCTs) is needed to compare different treatments of arthrogenous TMDs and to rank their effectiveness in pain reduction and improvement of jaw function. As we hypothesized that there would be no differences regarding maximal mouth opening and pain reduction between different treatment options for heterogeneous TMDs, the specific aims of this NMA were to challenge this H0 hypothesis and to identify the best treatment for adult patients with articular TMDs.

2. Materials and methods

2.1. Protocol and registration

This NMA was done based on the Preferred Reporting Items for The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions (the PRISMA-P checklist) (Online version 11) (Hutton et al., 2015) and has been registered in PROSPERO with No. CRD42018103671 (Al-Moraissi E, 2018).

2.2. Search strategy

All pertinent RCTs without language restriction were screened by comprehensive research in MEDLINE, EMBASE, CINAHL, the Cochrane Central Registry of Controlled Trials (CENTRAL) and SCOPUS from the commencement of each database to March 2019 (Online version 2).

2.3. Selection criteria

The following inclusion criteria were adopted based on the PICOTS process: (P) Patients: adult patients with arthrogenous TMDs based on the RDC/TMD or DC/TMD protocol (osteoarthritis and/or disc displacements of the TMJ) or clear clinical diagnosis including signs and symptoms of TMD. (I) Intervention: studies comparing 2 or more of the following treatment modalities for arthrogenous TMD; 1) Conservative treatments (which include flat stabilization splint or anterior repositioning splint, home muscles exercise and self-care); 2) Physical therapy (which includes manual therapy and low laser therapy); 3) Intra-articular injection (IAI) of hyaluronic acid (HA); 4) IAI of a corticosteroid (CS); 5) Arthrocentesis alone (which includes lysis and lavage using normal saline or ringer solution without injection of any medications); 6) Arthrocentesis plus IAI of HA; 7) Arthroscopy alone (which includes lysis and lavage with or without arthroscopic surgery using normal saline or ringer

solution without injection of any medications); 8) Arthrocentesis plus IAI of growth factors (PRP); 9) Arthrocentesis plus IAI of CS; 10) Arthroscopy with IAI of growth factors (PRP); 11) Arthroscopy with IAI of HA; 12) Open joint surgery (which includes discectomy, high condylectomy, disc repositioning and arthroplasty). (C) Comparator: control group which included patients who did not receive any treatments and/or placebo (which includes intraarticular injection of normal saline, application of inactive laser). (O) Outcomes: primary outcomes were pain intensity scores using a visual analogue scale (VAS) and a numerical pain rating scale. The secondary outcome was the maximal mouth opening. (T) Time: short time (≤5 months) and intermediate-term (≥6 months to 4 years). (S) Study design: RCTs that reported the outcomes of interest.

2.4. Exclusion criteria

The following exclusion criteria were applied: (1) Studies with missing data required to perform a meta-analysis such as the post-treatment mean and standard deviation for the outcomes of interest; 2) RCTs that assessed myogenous or mixed TMDs; 3) Non-randomized clinical studies, case series, and cohort studies. 4) Review articles. 5) Publications using duplicated data.

2.5. Data extraction

A data extraction form was done independently by two randomly reviewers (E. A and L. W) to ensure similarity in extraction. The extraction form was revised later on. Any disputes were determined by discussion. The extracted data contained the characteristics of the RCTs and participants such as authors, study design, subgroups diagnosis/criteria used, age of patients, male–female ratio, treatment groups (number), duration of treatments/frequency and outcome measures.

2.6. Assessment of risk of bias

The risk of bias of RCTs was investigated independently by two authors (E. A and L. W), using the modified version of Cochrane's tool for assessing the risk of bias (Higgins et al., 2019; Guyatt et al., 2008). In a surgical procedure, neither the surgeon nor the patient could be effectively masked. Thus, blinding of patients and operator (performance bias) was eliminated.

2.7. Data synthesis

Network geometry was presented by drawing a network plot to study if the included RCTs on the different treatments were connected (Salanti et al., 2008).

Post-treatment value of the outcomes of interest was used to calculate the standardized mean difference (SMD). Results from the NMA were presented as a summary of relative effect sizes for each possible pair of treatments. The statistical unit was the number of patients/joints.

All statstics were conducted by frequentist NMAs using random effect model in STATA (StataCorp. 2011. Stata Statistical Software: Release 14. College Station, TX,USA) using the mvmeta command (White, 2015). To identify the presence of local inconsistency, the loop-specific approach was performed separately in each closed loop of the network. The difference between direct and indirect estimates for a defined comparison in the loop (inconsistency factor) was analysed. Then, the amount of the inconsistency factors and their 95% CIs were used to infer the detection of inconsistency in each loop. Additionally, a common heterogeneity estimate within each loop was assumed (Higgins et al., 2012). The results of this approach were presented in a forest plot using the ifplot command in STATA (Chaimani et al., 2013). To check the assumption of consistency in the entire network, the 'design-by treatment' model using STATA and the mvmeta command, as described by Higgins and colleagues, was done (Higgins et al., 2012; White, 2015; Salanti et al., 2011). The ranking probabilities for all treatments at each possible rank for each intervention were estimated. Then, the treatment hierarchy was analysed using the surface under the cumulative ranking (SUCRA) curve and mean ranks (Salanti et al., 2011; Veroniki et al., 2016). SUCRA can also be presented as a percentage of treatment that can be ranked first without uncertainty. A rank–heat plot was drawn to show and present the treatment hierarchy across the multiple outcomes of interest (Veroniki et al., 2016). To assess whether the duration of follow-up influenced the outcomes of interest and type of arthrogenous TMDs subdivisions, meta-regression analysis of the posttreatment pain intenisty and follow-up time was considered. RCTs with a high risk of bias were excluded and repeat the analysis to assess the robustness of results. A comparison-adjusted funnel plot was conducted to assess network-wide publication bias and small study effect for outcomes with at least 10 RCTs in the network (Macaskill et al., 2001).

2.8. Certainty of the evidence

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach of meta-analysis (Guyatt et al., 2008; Chaimani et al., 2013) was implemented to identify the certainty of meta-analysis effect estimates for all outcomes of interest. There are four levels of quality of evidence including (1) High quality of evidence (the real effect close to that of the estimated effect). (2) Moderate quality evidence (the actual effect is likely to be near to the estimated effect, but there is a possibility it is substantially different). (3) Low-quality evidence (the real effect may be significantly different from the estimated effect). (4) Very low-quality evidence (the real effect is likely to be significantly different from the estimate of the effect). In the GRADE system, RCTs begin as high-quality evidence but may be rated down due to limitations in the study design (risk of bias), inconsistency, imprecision, indirectness, and publication bias. Summary of confidence for the present evidence was estimated using RevMan.

3. Results

3.1. Study selection

3.1.1. Literature search outcome

From 1200 articles from all databases, a total of 36 RCTs met the inclusion criteria and were accepted for the NMA (Fridrich et al., 1996; Goudot et al., 2000; Carmeli et al., 2001; Holmlund, 2001; Minakuchi et al., 2001; Shi et al., 2002; Venancio et al., 2005; Bjørnland et al., 2007; Ismail, 2007; Politi et al., 2007; Schiffman et al., 2007; Haketa et al., 2010; Antônio et al., 2012; Craane et al., 2012; Huddleston Slater et al., 2012; Manfredini et al., 2012; de Carli et al., 2013; Gencer et al., 2014; Tabrizi et al., 2014; Cömert Kiliç et al., 2015; Hanc et al., 2015; Hegab et al., 2015; Cömert Kiliç, 2016; Fernández Sanromán et al., 2016; Korkmaz et al., 2016; Patel and Idrees, 2016; Bouloux et al., 2017; Fernández-Ferro et al., 2017; Gorrela et al., 2017; Gurung et al., 2017; Ozdamar et al., 2017; Tatli et al., 2017; Yapıcı-Yavuz et al., 2018; Isacsson et al., 2019; Bergstrand et al., 2019; Ohrnell Malekzadeh et al., 2019). Fig. 1 shows the details of searching and retrieving RCTs.

3.1.2. Presentation of network geometry

Thirty-six RCTs, in the overall follow-up period (ranged from one week to 4 years), twenty-seven RCTs in the short term (≤5

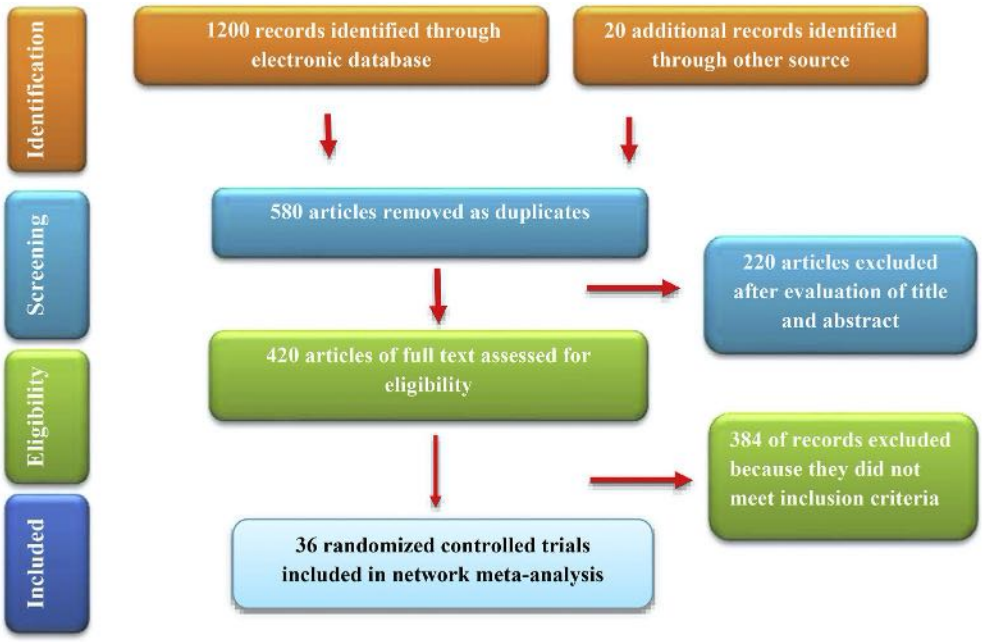

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

months) and nineteen RCTs in the intermediate term (≥6 months) reported on posttreatment pain intensity after treatment of patients with arthrogenous TMDs using twelve interventions versus control/placebo. The twelve interventions were conservative treatments, IAI-HA, IAI-CS, Arthrocentesis-PRP, Arthrocentesis-HA, Arthrocentesis-CS, Arthrocentesis-alone, Arthroscopy-alone, Arthroscopy-PRP, Arthroscopy-HA, open TMJ surgery and physical therapy. Twenty-nine RCTs in the overall follow-up period (ranged from one week to 4 years), twenty-three RCTs in the short term (≤5 months) and seventeen RCTs in intermediate-term (≥6 months) reported on posttreatment improved mouth opening after treatment of patients with arthrogenous TMDs using eleven interventions versus control/placebo. The eleven interventions were conservative treatments, IAI-HA, IAI-CS Arthrocentesis-PRP, Arthrocentesis-HA, Arthrocentesis-CS, Arthrocentesis-alone, Arthroscopy-alone, Arthroscopy-PRP, Arthroscopy-HA, and physical therapy (Fig. 2).

3.1.3. Study characteristics

The characteristics of the RCTs are summarised in (Online version 3).

3.1.4. Risk of bias within included studies

Fifteen RCTs showed an unclear risk of bias, twelve RCTs a low risk of bias and nine RCTs a high risk of bias (Online version 4).

3.1.5. Results of individual studies

Individual data for overall follow up time and at the short and intermediate-term for all outcomes of posttreatment pain reduction and MMO was tabulated in (Online version 5 and Online version 6, respectively). Also, individual data for ID and TMJ OA groups were clarified in (Online version 7). Intervention group with reported posttreatment values of pain and improved mouth opening, standard deviation and number of patients were tabulated and presented.

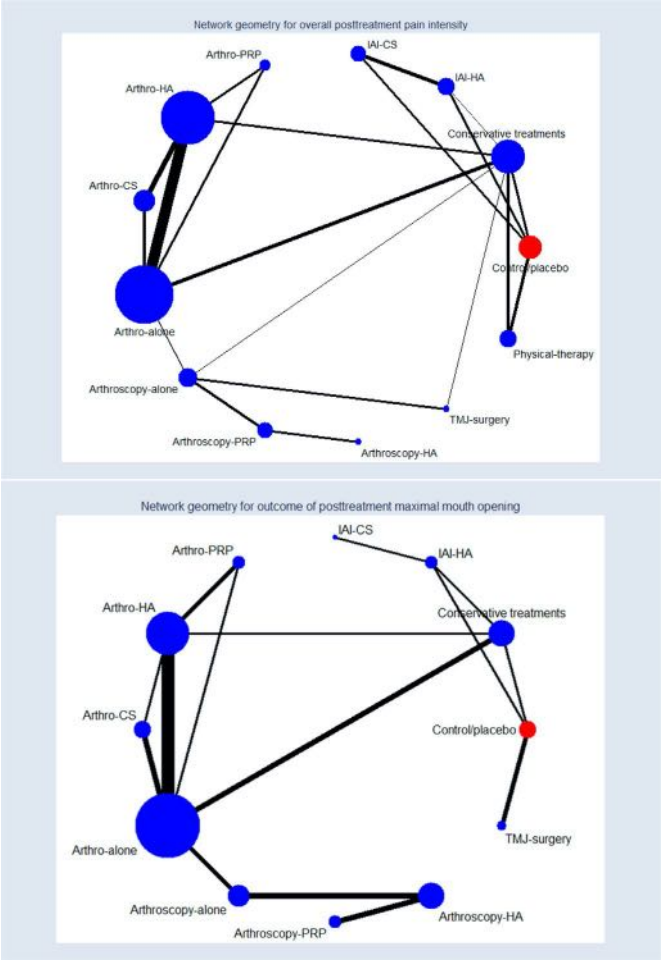

Fig. 2. Network geometry for the outcomes of overall posttreatment pain intensity and maximal mouth opening; IAI-intraarticular injection, Arthro: arthrocentesis, PRP: platelet-rich plasma, HA: hyaluronic acid, CS: corticosteroid, TMJ: temporomandibular joint.

3.2. Synthesis of results

3.2.1. Results of the outcome variables

3.2.1.1. Overall posttreatment pain intensity

a. Overall posttreatment pain intensity, control/placebo vs other treatments, SMD

There was significant pain reduction after IAI-CS (very low-quality evidence), IAI-HA (very low-quality evidence), Arthroscopy-PRP (very low-quality evidence), Arthrocentesis-PRP (very low-quality evidence), open TMJ surgery (very low-quality evidence), Arthrocentesis-HA (moderate-quality evidence), and Arthrocentesis-CS (moderate-quality evidence), when compared to control/placebo. The follow-up time ranged from one month to 4 years posttreatment (Fig. 3).

b. Overall posttreatment MMO, control/placebo vs other treatments, SMD

There was a significant improvement in MMO after Arthroscopy-PRP (very low-quality evidence), Arthroscopy-HA (very low-quality evidence), Arthroscopy-alone (low-quality evidence), and IAI-CS (very low-quality evidence) when compared to control/placebo. The follow-up time ranged from one month to 4 years posttreatment (Fig. 4).

3.2.2. Subgroup analysis based on the duration of follow-up time

3.2.2.1. Posttreatment pain intensity

a. Overall posttreatment pain intensity at short-term (≤5 months), control/placebo vs other treatments, SMD

There was a significant pain reduction following IAI-HA (very low-quality evidence) and IAI-CS (very low-quality evidence) when compared to control/placebo and conservative treatments (Fig. 5).

b. Overall posttreatment pain intensity at intermediate-term (≥6 months), control/placebo vs other treatments, SMD

There was a significant decrease in posttreatment pain intensity after Arthroscopy-PRP (very low-quality evidence), Arthrocentesis-PRP (very low-quality evidence), Arthroscopy-HA (very low-quality evidence), open TMJ surgery (very low-quality evidence), IAI-CS (very low-quality evidence), Arthroscopy-alone (low-quality evidence) and Arthrocentesis-HA (moderate-quality evidence) and when compared to the control/placebo groups (Fig. 6).

3.2.2.2. Posttreatment MMO

a. Posttreatment MMO at short-term (≤5 months), control/placebo vs other treatments, SMD

There was a significant improvement in MMO after Arthroscopy-alone (low-quality evidence), Arthroscopy-PRP (very low-quality evidence) and Arthroscopy-HA (very low-quality evidence) when compared to control/placebo (Fig. 7).

b. Posttreatment MMO at intermediate-term (≥6 months), control/placebo vs other treatments, SMD

There was a significant improvement in MMO after Arthroscopy-PRP (very low-quality evidence), Arthroscopy-HA (very low-quality evidence), Arthroscopy-alone (low-quality evidence), IAI-HA (very low-quality evidence), IAI-CS (very low-quality evidence), Arthrocentesis-PRP (very low-quality evidence) and Arthrocentesis-HA (moderate-quality evidence), Arthrocentesis-CS (very low-quality evidence) and Arthrocentesis-alone (very low-quality evidence), when compared to control and placebo (Fig. 8).

3.2.3. Exploration for inconsistency

For the outcome of overall posttreatment pain intenisty, loop-specific tests to assess local inconsistency did not detect any

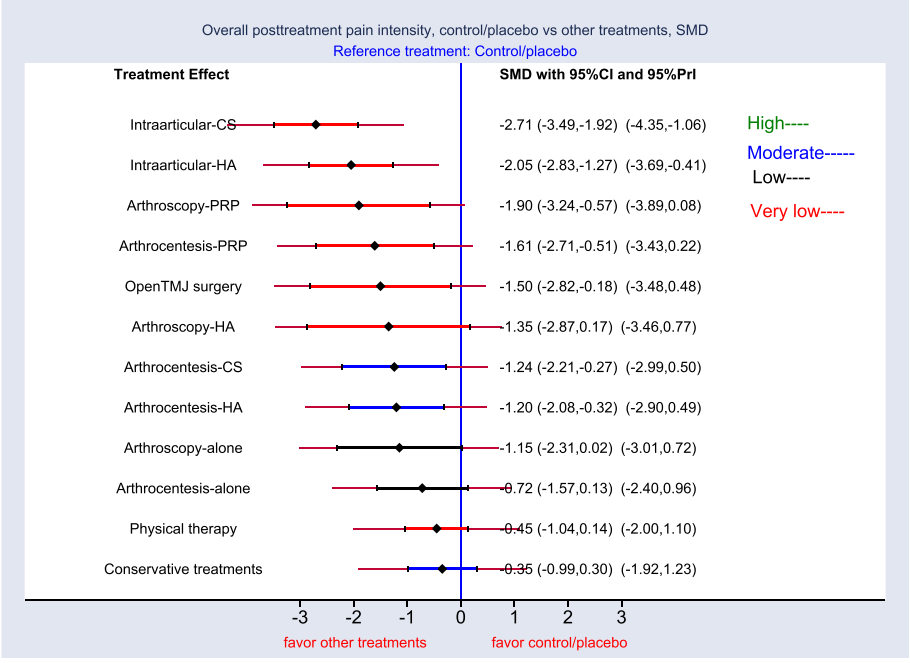

Fig. 3. Forest plot of network meta-analysis for overall post-treatment pain intensity, arthrogenous TMDs. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval. PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid.

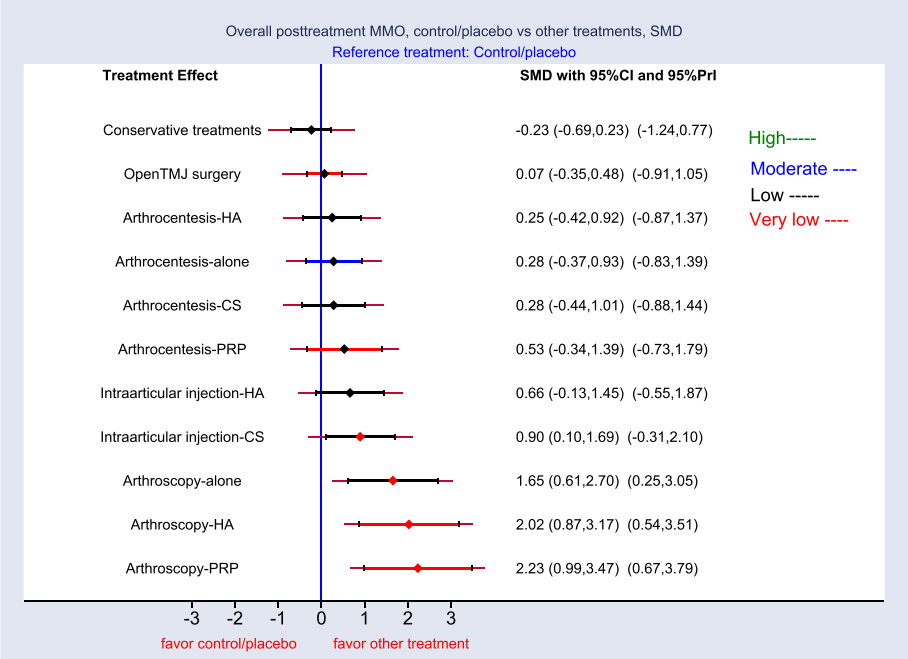

Fig. 4. Forest plot of network meta-analysis for overall post-treatment MMO, arthrogenous TMDs. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval, PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid. MMO = maximal mouth opening.

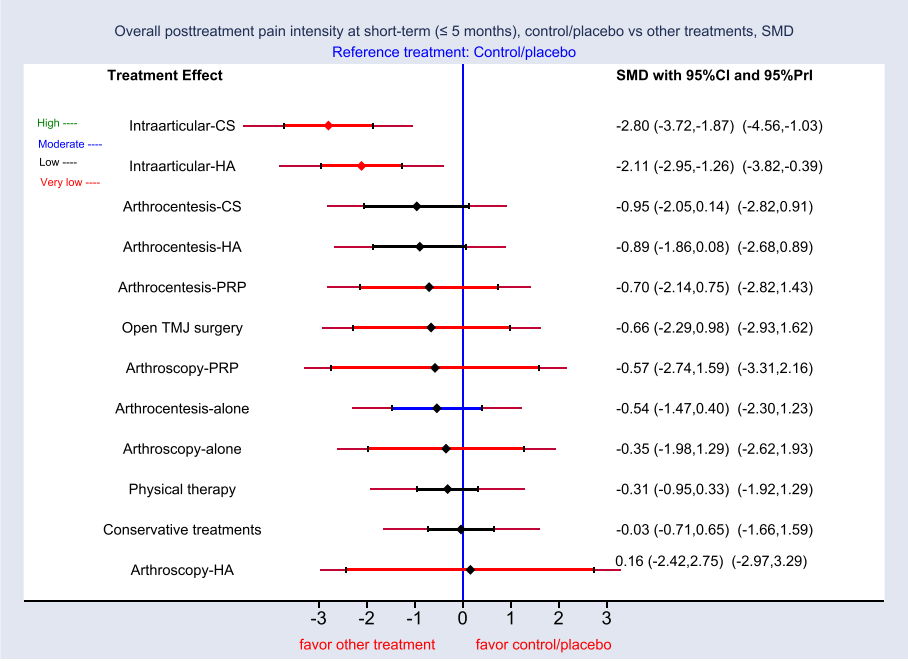

Fig. 5. Forest plot of network meta-analysis for post-treatment pain intensity in the short term, arthrogenous TMDs. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval. PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid.

statistical inconsistency between direct and indirect evidence. All confidence intervals were truncated from zero. There were small inconsistencies (but they did not reach statistical significance) in control/placebo–splint–manual therapy, control/placebo–conservative–manual therapy and conservative–arthroscopy–manual therapy loops. These inconsistencies were due to variation of follow up time and subgroups of arthrogenous TMD. Thus, after subgroup groupings, there was not any inconsistency based on loop specific tests. Based on design-by-treatment interaction model to test a global inconsistency in the network, no significant inconsistency was identified within the evidence network as a whole ($P = 0.96$). Therefore, both inconsistency and consistency models were fitted. For sensitivity analyses based on the type of arthrogenous TMDs, substantial elimination was observed in several formed loops which showed insignificant inconsistency for all analyses. As well as, a global test revealed statistically insignificant ($P > 0.05$). The IF plots for all outcomes and subgroups analysis are presented in (Online version 8).

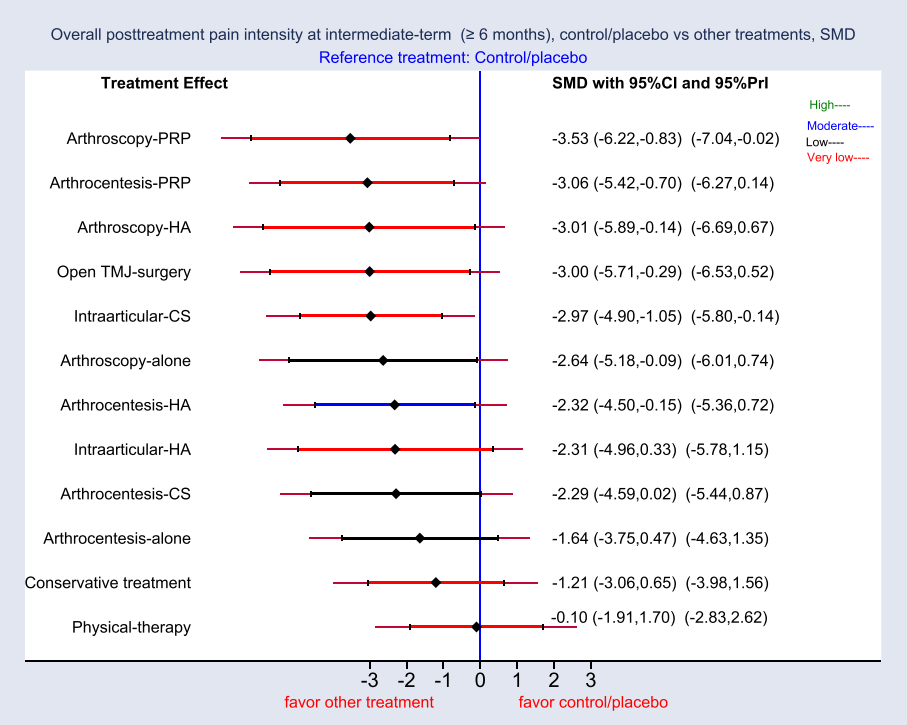

Fig. 6. Forest plot of network meta-analysis for post-treatment pain intensity in the intermediate term, arthrogenous TMDs. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval. PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid.

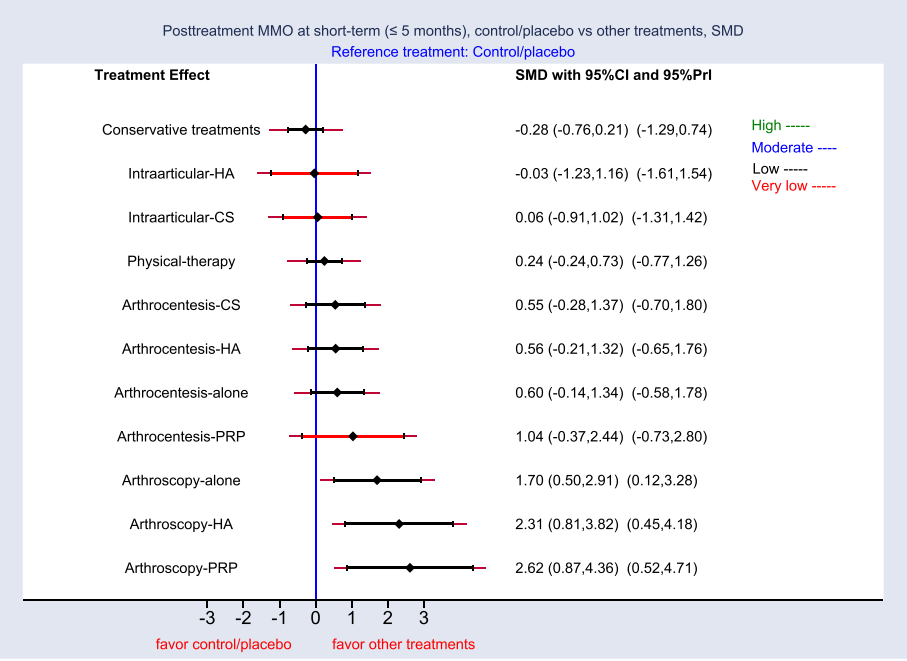

Fig. 7. Forest plot of network meta-analysis for post-treatment MMO in the short term, arthrogenous TMDs. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval. PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid, MMO = maximal mouth opening.

3.2.4. Treatment ranking

3.2.4.1. Posttreatment pain intensity

a. Overall posttreatment pain intensity (1 week–4 years)

The most effective treatment to reduce arthrogenous post-treatment pain intensity at the follow-up time ranged from one week to 4 years was IAI-CS (very low-quality evidence), followed by IAI-HA (very low-quality evidence), Arthroscopy-PRP, (very low-quality evidence), Arthrocentesis-PRP (moderate-quality evidence), open TMJ-surgery (very low-quality evidence), Arthroscopy-HA (very low-quality evidence), Arthrocentesis-HA very low-quality evidence), Arthrocentesis-CS (low-quality evidence), Arthroscopy-alone (low-quality evidence), Arthrocentesis-alone (moderate-quality evidence), physical therapy (moderate-quality evidence), conservative treatment (very low-quality

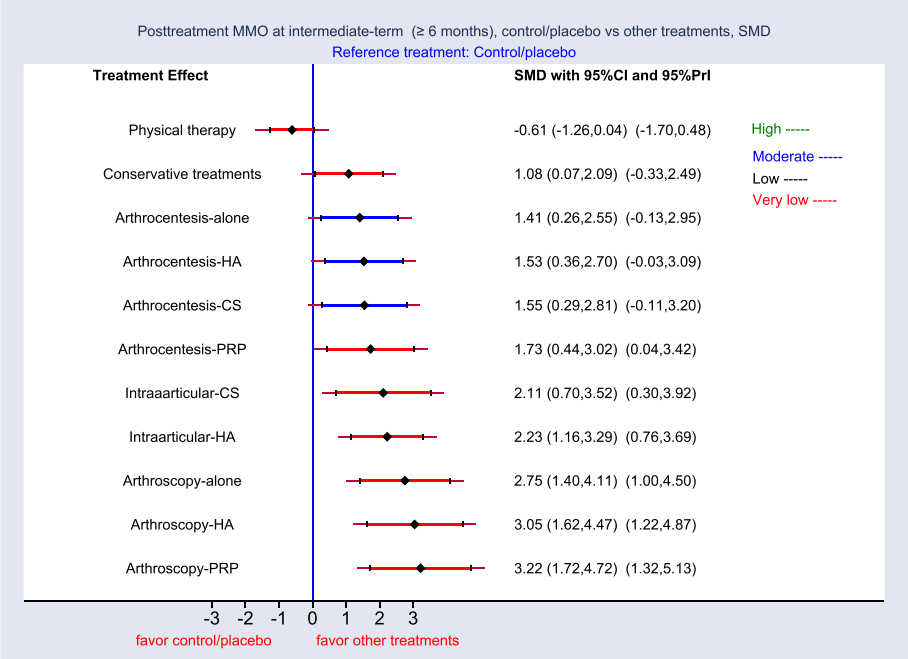

Fig. 8. Forest plot of network meta-analysis for post-treatment MMO in the intermediate term, arthrogenous TMDs. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval. PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid. MMO = maximal mouth opening.

evidence) and control/placebo (very low-quality evidence) (Fig. 9, and Online version 9).

a. Posttreatment pain intensity at short term follows up (≤5 months).

The most effective treatment to reduce pain in the short-term follow-up of arthrogenous TMD patients was IAI-HA (very low-quality evidence), followed by IAI-CS (very low-quality evidence), Arthrocentesis-HA (moderate-quality evidence), Arthrocentesis-CS (low-quality evidence), Arthrocentesis-PRP (very low-quality

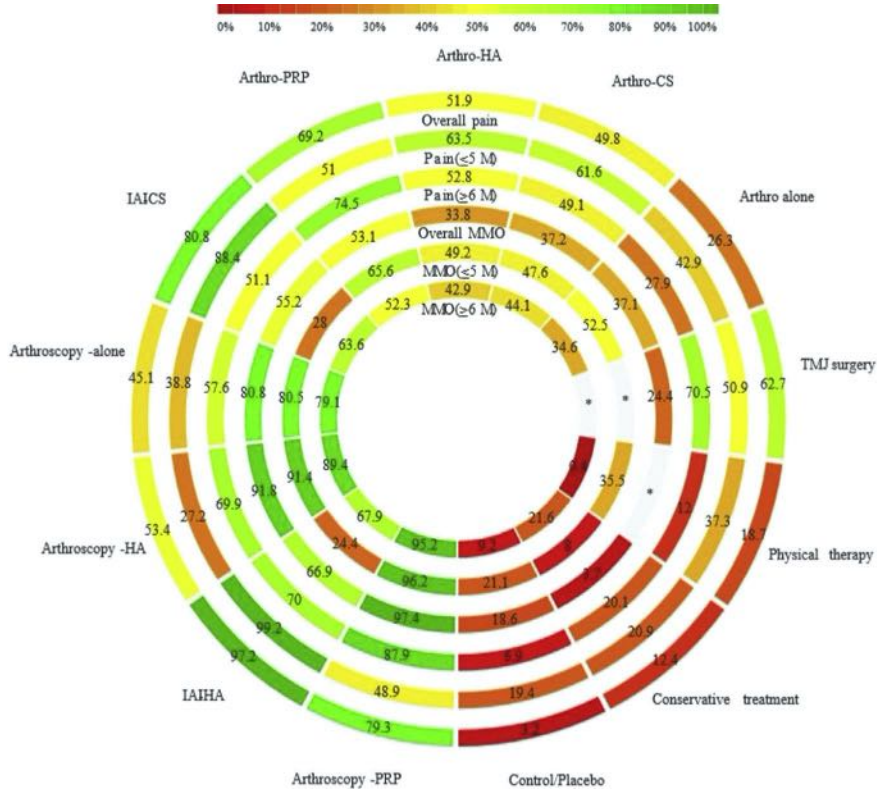

Fig. 9. Rank–heat plot identifying the hierarchy of multiple treatments for post-treatment pain intensity and MMO at the subgroup follow-up time. IAI = intraarticular injection, CS = corticosteroid, PRP = platelet-rich plasma, Arthro= Arthrocentesis, HA = hyaluronic acid, MMO = maximal mouth opening, M = month, TMJ = temporomandibular joint.

evidence), open TMJ-surgery (very low-quality evidence), Arthroscopy-PRP, (very low-quality evidence), Arthrocentesis-alone (moderate-quality evidence), Arthroscopy-alone (low-quality evidence), physical therapy (moderate-quality evidence), Arthroscopy-HA (very low-quality evidence), conservative treatment (very low-quality evidence), and control/placebo (very low-quality evidence) (Fig. 9, and Online version 9).

b. Posttreatment pain intensity at intermediate-term follow-up (≥6 months)

The most effective treatment to reduce pain intensity in the intermediate-term follow-up group of arthrogenous TMD patients was Arthroscopy-PRP (very low-quality evidence), followed, by Arthrocentesis-PRP (very low-quality evidence), TMJ surgery (very low-quality evidence), IAI-HA (very low-quality evidence), Arthroscopy-HA (very low-quality evidence), Arthroscopy-alone (low-quality evidence), Arthrocentesis-HA (moderate-quality evidence), IAI-CS (very low-quality evidence), Arthrocentesis-CS (low-quality evidence), Arthrocentesis-alone (moderate-quality evidence), conservative treatments (very low-quality evidence), physical therapy (very low-quality evidence), and control/placebo (7.1 %) (Fig. 9, and Online version 9).

3.2.4.2. Posttreatment MMO

a. Overall posttreatment MMO (1 week—4 years)

The most effective treatments that increased the MMO in arthrogenous TMD patients at the follow-up time ranged from 1 month to 4 years posttreatment was Arthroscopy-PRP (very low-quality evidence), followed by Arthroscopy-HA (very low-quality evidence), Arthroscopy-alone (low-quality evidence), IAI-CS (very low-quality evidence), IAI-HA (very low-quality evidence), Arthrocentesis-PRP (very low-quality evidence), arthrocentesis-CS (low-quality evidence), Arthrocentesis-HA (moderate-quality evidence), physical therapy (low-quality evidence), control/placebo (very low-quality evidence) and conservative treatments (moderate-quality evidence) (Fig. 9, and Online version 9).

b. Posttreatment MMO at short-term (≤5 months).

The most effective treatments that increased the MMO in arthrogenous TMD patients in the short-term follow-up was Arthroscopy-PRP (very low-quality evidence), followed by Arthroscopy-HA (very low-quality evidence), Arthroscopy-alone (low-quality evidence), Arthrocentesis-PRP (very low-quality evidence), Arthrocentesis-alone (very low-quality evidence), Arthrocentesis-HA (moderate-quality evidence), arthrocentesis-CS (low-quality evidence), physical therapy (low-quality evidence), IAI-CS (very low-quality evidence), IAI-HA (very low-quality evidence, control/placebo (very low-quality evidence) and conservative treatments (very low-quality evidence) (Fig. 9, and Online version 9).

c. Posttreatment MMO at intermediate-term (≥6 months)

The most effective treatments that increased the MMO in the long-term follow-up of arthrogenous TMD patients was Arthroscopy-PRP (very low-quality evidence), followed by Arthroscopy-HA (very low-quality evidence), Arthroscopy-alone (low-quality evidence), IAI-HA (very low-quality evidence), IAI-CS (very low-quality evidence), Arthrocentesis-PRP (very low-quality evidence), Arthrocentesis-CS (low-quality evidence), Arthrocentesis-HA (moderate-quality evidence), Arthrocentesis-alone (moderate-quality evidence), conservative treatments (moderate-quality evidence), control/placebo (very low-quality evidence) and physical therapy (very low-quality evidence) (Fig. 9, and Online version 9).

3.2.5. Sensitivity analyses

NMA was done based on the type of arthrogenous TMDs, either internal derangement which include those patients with disc displacement with and without reduction and closed lock and TMJ osteoarthritis/osteoarthrosis/arthralgia. Those RCTs which involved patients with internal derangement and TMJ OA were excluded.

a. Internal derangement (articular disc displacement with/without reduction and closed lock)

Nineteen RCTs (800 patients) reported on posttreatment pain intensity, and seventeen RCTs (697 patients) reported on the posttreatment improvement of mouth opening after treatment of patients with anterior disc displacement (ADD) with/without reduction and closed lock using nine treatment methods. Interventions were occlusal splint therapy, conservative treatments, arthrocentesis-PRP, arthrocentesis-HA, arthrocentesis-CS, Arthrocentesis-alone, Arthroscopy-alone and TMJ surgery. The comparator was control. The follow-up times ranged from 1 month to 12 months post-treatment. Physical therapy, Arthroscopy-PRP, Arthroscopy-HA, IAI-CS, and IAI-HA did not report on posttreatment pain reduction. Therefore, these groups were dropped from these network analyses.

1. Posttreatment pain intensity, control vs other treatments, internal derangement, SMD

There was a significant pain reduction following Arthrocentesis-PRP (very low-quality evidence), Arthrocentesis-CS (low-quality evidence), Arthrocentesis-HA (moderate-quality evidence) and Arthrocentesis-alone (moderate-quality evidence) when compared to control (Fig. 10).

Of the 9 treatment methods used for this ADD subgroup, the most effective treatment in reducing pain intensity for patients with ADD with reduction and closed lock was Arthrocentesis-PRP (very low-quality evidence), followed by Arthrocentesis-CS (low-quality evidence), Arthrocentesis-HA (moderate-quality evidence), open TMJ surgery (very low-quality evidence), Arthrocentesis-alone (moderate-quality evidence), conservative treatments (low-quality evidence), Arthroscopy-alone (very low-quality evidence), occlusal splint therapy (low-quality evidence), and control (very low-quality evidence) (Fig. 11).

a. Posttreatment MMO, control vs other treatments, Internal derangement, SMD

There was a significant increase in MMO after Arthroscopy-alone (very low-quality evidence), Arthrocentesis-HA (very low-quality evidence), Arthrocentesis-CS (low-quality evidence), Arthrocentesis-alone (moderate-quality evidence), Arthrocentesis-PRP (moderate-quality evidence) when compared to control group. There was no statistically significant difference between conservative treatments, low-quality evidence) and occlusal splint therapy (low-quality evidence) when compared to control (Fig 11).

The most effective treatments in increasing MMO in patients with ID was Arthroscopy-alone (98.1%), followed by Arthrocentesis-PRP (very low-quality evidence), Arthrocentesis-CS (low-quality evidence), —Arthrocentesis-alone (moderate-quality evidence), HA (moderate-quality evidence), control (very low-quality evidence), conservative treatments (low-quality evidence) and occlusal splints therapy (low-quality evidence) (Fig. 12).

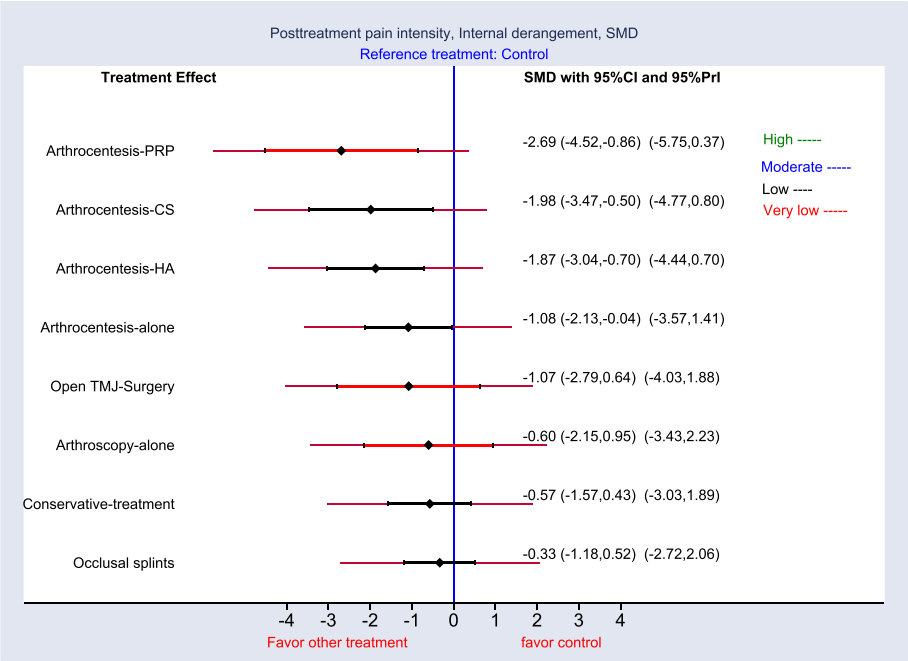

Fig. 10. Forest plot of network meta-analysis for post-treatment pain intensity, internal derangement. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval. PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid.

b. TMJ Osteoarthritis/osteoarthrosis/arthralgia

Eight RCTs (379 patients) reported on pain intensity and eight RCTs (359 patients) on improved mouth opening after treatment of patients with TMJ osteoarthritis/osteoarthrosis using seven treatment methods. Interventions were Arthrocentesis-PRP, Arthrocentesis-HA, Arthrocentesis-CS, Arthroscopy-alone Arthroscopy-PRP and Arthroscopy-HA. The comparator was Arthrocentesis-alone. The follow-up times ranged from 1.5 months to 4 years post-treatment. Conservative treatments, occlusal splint therapy, physical therapy, IAI-HA, IAI-CS, open joint surgery, and control/placebo did not report on the outcome of improved mouth opening. Thus, these groups were dropped from these network meta-analyses.

a. Posttreatment pain intensity, TMJ osteoarthritis, Arthrocentesis-alone vs other treatments, SMD

There was significant pain reduction following Arthroscopy-alone, Arthroscopy-PRF and Arthroscopy-HA when compared to

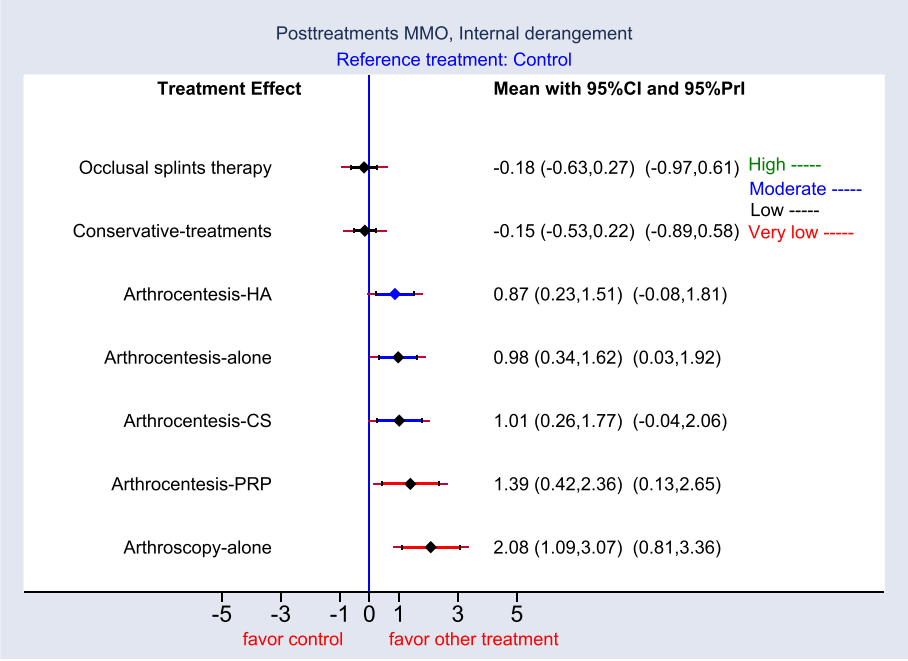

Fig. 11. Forest plot, network meta-analysis for post-treatment MMO, internal derangement. SMD = standardized mean difference, CI= confidence interval, PrI: predictive interval. PRP = platelet-rich plasma, HA= hyaluronic acid, CS = corticosteroid, MMO = maximal mouth opening.

Arthrocentesis-alone. There was no statistically significant difference after Arthrocentesis-HA, Arthrocentesis-CS, and Arthrocentesis-PRP when compared to Arthrocentesis alone (Fig. 13).

Of the 7 treatment methods included in the TMJ osteoarthritis/osteoarthrosis subgroup, the most effective treatment in reducing pain intensity was Arthroscopy-PRP (very low-quality evidence), then followed by Arthroscopy-HA (very low-quality evidence), Arthroscopy-alone (very low-quality evidence), Arthrocentesis-PRP (very low-quality evidence), Arthrocentesis-alone (low-quality evidence), Arthrocentesis-HA (low-quality), Arthrocentesis-CS (very low-quality) (Fig. 11).

b. Posttreatment MMO, TMJ osteoarthritis, Arthrocentesis-alone vs other treatments, SMD

There was a significant improvement in MMO after Arthroscopy-PRP (very low-quality evidence), Arthroscopy-HA (very low-quality evidence) and Arthroscopy-alone (very low-quality evidence) when compared to Arthrocentesis alone. There was no statistically significant difference between Arthrocentesis-PRP, Arthrocentesis-HA and Arthrocentesis-CS when compared to Arthrocentesis-alone (all very low-quality evidence) (Fig. 14).

The most effective treatment in increasing MMO in patients with TMJ OA was Arthroscopy-PRP (very low-quality evidence), followed by Arthroscopy-HA (very low-quality evidence), Arthroscopy alone (very low-quality evidence), Arthrocentesis-PRP (very low-quality evidence), Arthrocentesis-CS (very low quality evidence), Arthrocentesis-HA (very low-quality evidence) and Arthrocentesis-alone (low-quality evidence) (Fig. 11).

3.2.6. Additional analysis

a. Meta-regression analysis between follow-up time and pain intensity

There was an insignificant positive association between reduction of pain intensity and followed-up times which reported in the various RCTs ($r = 0.050$, $P = 0.251$).

b. Meta-regression, the association between type of arthrogenous TMDs and pain intensity

There was an insignificant negative association between pain intensity scores and different diagnosis of arthrogenous TMDs (articular disc displacement, osteoarthritis, osteoarthrosis or arthralgia) ($r = -0.253$, $P = 0.969$).

c. Associations between blinding assessors and posttreatment pain reduction

Blinded assessors performed twenty-three RCTs; eleven RCTs did not report sufficient information whether an assessor was blinded or unblinded and two RCTs were unblinded. Posttreatment reduction of pain values throughout all the follow-up times of included RCTs was 3.2 ± 1.8, 2.1 ± 1.3, and 2.9 ± 2.5 for those RCTs with unblinded, unclear and blinded assessors respectively. So, these results showed that not performing blinding assessment would be resulting in either underestimation or overestimation of the size of the effect (Online version 10).

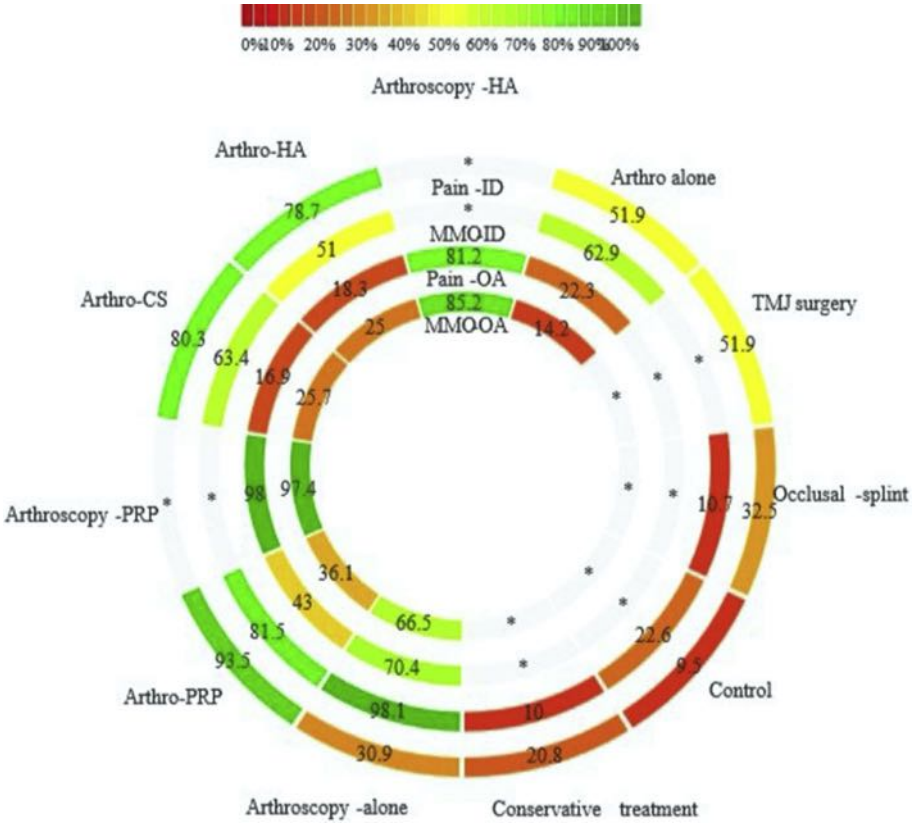

Fig. 12. Rank-heat plot identifying the hierarchy of multiple treatments for post-treatment pain intensity and MMO based on the type of arthrogenous TMDs. IAI = intraarticular injection, CS = corticosteroid, PRP = platelet-rich plasma, Arthro = Arthrocentesis, HA = hyaluronic acid, MMO = maximal mouth opening, M = month, TMJ = temporomandibular joint, ID = internal derangement, OA = osteoarthritis.

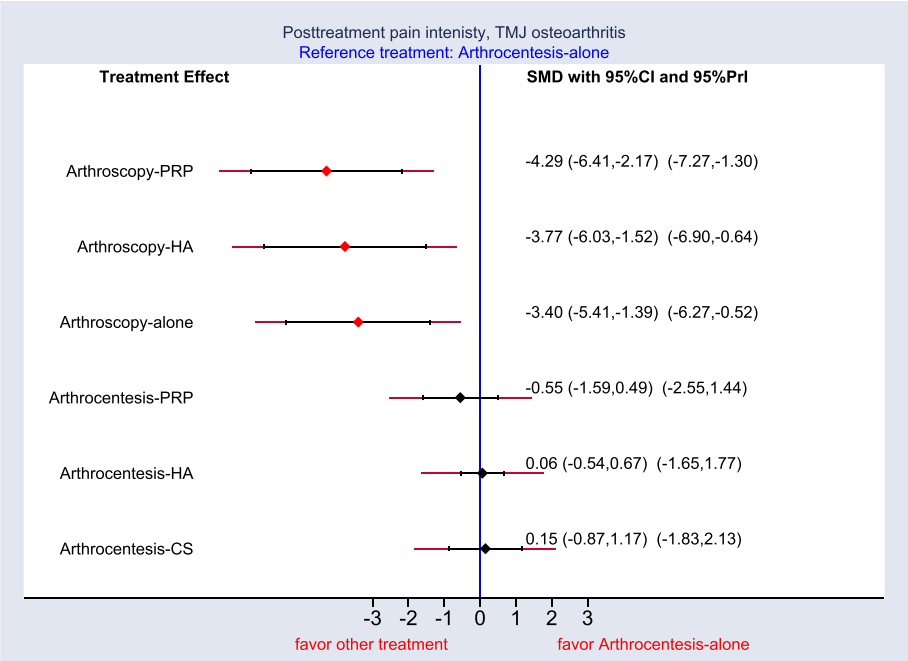

Fig. 13. Forest plot of network meta-analysis for post-treatment pain, intensity TMJ Osteoarthritis. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval, PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid.

d. Association between the number of IAI's of adjuvant pharmacological agents such as PRP, HA or CS and posttreatment pain intensity

There was no critical difference between posttreatment pain intensity after RCTs that used a single injection (2.8 ± 1.9) versus those RCTs that performed double or multiple IAI of PRP, HA or CS.

3.2.7. *Funnel plot and publication bias*

Funnel plot for the primary outcome of pain intensity showed a relative symmetrical funnel shape which denotes that there was no publications bias (Online version 11).

3.2.8. *Confidence of evidence*

For all outcomes (overall posttreatment pain and MMO), the quality of evidence of direct, indirect and NMA estimates for all

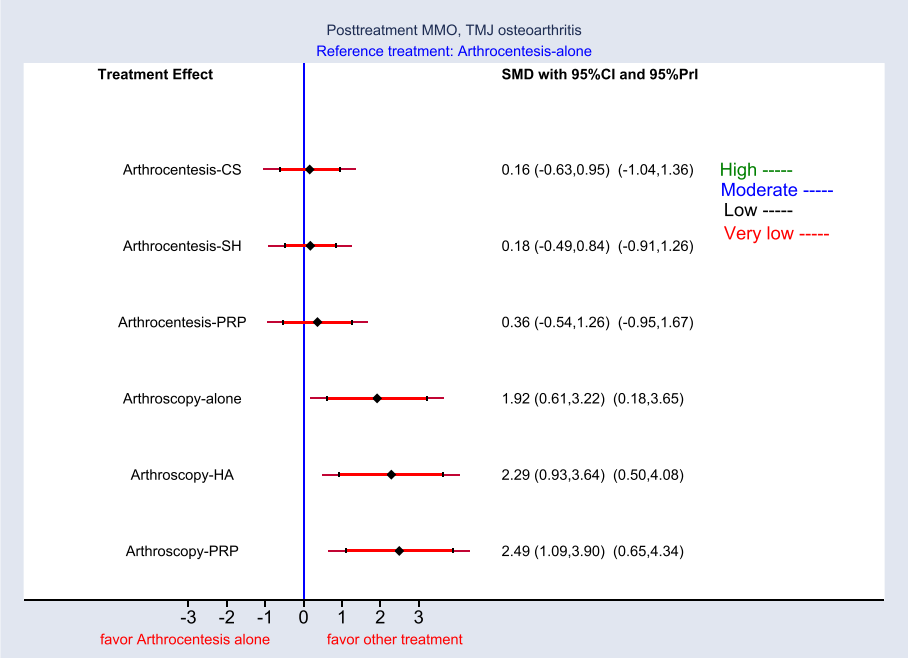

Fig. 14. Forest plot of network meta-analysis for post-treatment MMO, TMJ Osteoarthritis. SMD = standardized mean difference, CI = confidence interval, PrI = predictive interval. PRP = platelet-rich plasma, HA = hyaluronic acid, CS = corticosteroid.

comparisons ranged from moderate to very low. At various comparisons, the evidence was downgraded because of study limitations, imprecision or incoherence. More details about the quality of evidence for all outcomes based on the GRADE system are summarized in (Online version 12).

4. Discussion

The literature comparing the different invasive, minimally invasive and non-invasive therapies in the treatment of arthrogenous TMD is rather controversial and to some extent, contradictory. To date, it has been very difficult to give clear therapeutic recommendations. Thus, the results of the present NMA are able to help close this confusing gap of knowledge for the treatment of arthrogenous TMDs by showing a clear superiority of the minimally invasive procedures (IAIs, Arthroscopy and Arthrocentesis, each in combination with PRP, HA or CS) over the non-invasive procedures both in the short and intermediate-term periods for reducing pain and increasing MMO in patients with osteoarthritis and/or internal derangement.

Regarding open surgery, there are not enough data available to draw meaningful conclusions as to the efficacy of open surgery versus minimally invasive procedures, as open surgery should be reserved for progressive stages of arthrogenous diseases. Developing clinically relevant RCTs to study the efficacy of open joint surgery will be difficult to perform except for answering very concise questions, such as discopexy.

The positive effect of HA in arthrocentesis and/or arthroscopy may surpass the effect of merely preventing intraarticular bleeds, which may promote intraarticular scarring (Machon et al., 2018). PRP may not only prevent intra-articular bleeding but may also have an anti-inflammatory response that may give it an edge over HA. Further high-quality studies are advisable to compare the efficacy of HA viscosupplementation versus PRP or even combinations of both for the different arthrogenous indications. The same precaution is appropriate when rating IAIs with arthrocentesis and arthroscopy.

Our results showed surprisingly good effects of IAIs of HA and CS compared to the established more invasive procedures such as arthrocentesis and arthroscopy. This effect can be explained by repetitive IAIs of HA and CS in included RCTs compared to RCTs that used single IAIs of HA or PRP in combination with arthrocentesis or arthroscopy, as both arthrocentesis and arthroscopy in combination with PRP, HA, and CS were evaluated and showed partially less favourable results than merely intraarticular injections. This would imply that lavage will not add or could even worsen the effect of the pharmacological instillations, which goes against generally acknowledged clinical experience. A superiority of IAIs of CS and HA in the short-term may be explained by the respective arthrogenous TMD indications, where IAIs with CS and HA are applied in lower Wilkes stages as compared to arthroscopy, which is usually performed in higher Wilkes stages (IV and V) where IAIs will experience a reduced success rate regarding reduction of pain and improvement of MMO. According to the present NMA, both IAIs with CS and HA should have their place in short-term minimally invasive pain reduction and subsequent improvement of mobility.

Meanwhile, adjuvant benefits of PRP in combination with arthrocentesis and arthroscopy showed promising outcomes for pain reduction and improved mouth opening for arthrogenous TMDs, although the evidence was at very low-level of quality. When looking for these results from the methodological point of view, the performance of intervention/treatments under blinding conditions either for patients or operator/investigators for the stage of surgical procedures or postoperative assessment are essential steps for a well-designed RCT. However, for interventions such as occlusal splint therapy, IAI, arthrocentesis, arthroscopy or TMJ surgery, blinding for participant and researchers is not possible. However, assessor blinding could be achieved and should be performed for all RCTs. In the current study, twenty-three RCTs were performed by blinded assessors; eleven RCTs did not report sufficient information whether an assessor was blinded or unblinded and two RCTs were not blinded. It is worthy to note that five of six RCTs that assessed arthrocentesis and arthroscopy in combination with IAI of PRP were not performed by blinded assessment or did not clearly report any information, so we assume they did not have blind assessments. Thus, those RCTs may have underestimated posttreatment pain reduction when compared to RCTs, which have assessed their outcomes by blinded assessors. Therefore, these studies were downgraded for risk of bias (mainly due to performance bias) creating a decreased number of RCTs and a smaller sample size. Therefore, future RCTs with larger sample size and blinded assessors are needed to assess a real effect of PRP either with arthrocentesis or arthroscopy before final conclusions can be drawn.

There are multiple limitations which should be considered when interpreting our results: (1) Included RCTs did not sufficiently mention the stage of arthrogenous TMDs based on the Wilkes classification. Thus, the present NMA included different stages of arthrogenous TMDs, which may affect the results. (2) There was heterogeneity in dosage, several sessions/injections and concentration of HA, PRP or CS medications used in cases of IAIs with or without arthrocentesis and arthroscopy, which could be a confounding factor. For instance, some RCTs used multiple IAIs of PRP (Cömert Kiliç et al., 2015; Hegab et al., 2015), HA or CS (Shi et al., 2002; Bjørnland et al., 2007; Korkmaz et al., 2016). Although most of the included RCTs applied RDC/TMD or DC/TMD, other RCTs used other criteria or clinical and radiographic examination. So, selection bias may have been introduced during patient recruitment and selection (3) Because all included RCTs used different criteria in the recruitment of patients with respect to the severity and chronicity of TMD signs and symptoms at baseline, selection bias may be present in the original RCTs. Thus, a minimum of 3 months of TMD signs and symptoms was used in the present study as a bar to include those patients.

The present study has the following strengths: (1) To avoid under and over estimation of the effect size measure with subsequent flaw conclusion, the certainty of the evidence for all outcomes was assessed using the GRADE system. (2) To identify the impact of effect modifiers such as follow-up time and type of different diagnosis of arthrogenous TMDs, subgroup analyses were performed according to the duration of follow-up (short-term and intermediate-term) and type of arthrogenous TMDs (displaced articular discs and TMJ osteoarthritis/arthralgia). Additionally, meta-regression analyses were performed between the primary outcome of posttreatment pain intensity and these confounding factors. (3) Presence of transitivity and absence of incoherence were checked using global, local and node split statistical tests, which all indicate insignificant inconsistencies. Thus, all evidence and analyses were derived from consistency assumptions. Insignificant correlation between the follow-up times and subgroup diagnoses of arthrogenous TMDs and changes in post-treatment pain intensity proved again that transitivity and consistency assumptions had been upheld in the current study.

5. Conclusions

In arthrogenous TMDs, minimally invasive procedures were shown to be significantly more effective than conservative treatment for both pain reduction and improvement of MMO, on a

short- (up to 5 months) and intermediate-term level (6 months–4 years). According to available data, IAI-HA can be considered as the most effective among the minimally invasive procedures for short-term pain reduction, whereas there were no significant differences between IAI-HA, arthrocentesis and/or arthroscopy for intermediate-term pain reduction. Improvement of mouth opening, however, is the clear domain of arthroscopy (with or without pharmacological instillations), being significantly superior to IAIs and arthrocentesis (including pharmacological instillations). Effectiveness of both arthroscopy and arthrocentesis can be boosted by pharmacological instillations (PRP, HA), with PRP possibly showing advantages over HA. Though CS showed good results according to the NMA, CS should be used with caution due to recent warnings regarding mandibular growth inhibition in children, heterotopic ossification/calcification, condylar erosion and resorption, especially if applied repeatedly and in higher doses. Last but not least, the present NMA supports the challenge for a paradigm shift in arthrogenous TMDs towards minimally invasive procedures as first-line therapy for the short-term improvement in pain and MMO. Thus, in contrast to traditional concepts mandating exhaustion of conservative treatment options, minimally invasive procedures deserve to be implemented as an efficient first-line treatment (e.g. IAIs and/or arthrocentesis) or should be considered rather early, i.e. as soon as patients do not show a clear benefit from an initial conservative treatment.

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Declaration of Competing Interest

There is no conflict of interest to declare.

Ethical approval

Not required.

Patient consent

Not required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.10.004.

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