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SUMMARY WITH CRITICAL APPRAISAL

Intra-Articular Hyaluronic Acid for Viscosupplementation in Osteoarthritis of the Hand, Shoulder, and Temporomandibular Joint: A Review of Clinical Effectiveness and Safety

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Abbreviations

AD-HA	Avian-derived hyaluronic acid
AEs	Adverse events
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
Bio-HA	Biologically fermented hyaluronic acid
CI	Confidence interval or credible interval
CMC	Carpometacarpal
CS	Corticosteroid
DASH	Disabilities of the Arm Shoulder and Hand
DFI	Dreiser's Functional Index
DHI	Duruöz Hand Index
FIHOA	Functional Index for Hand Osteoarthritis
GRADE	Grading of Recommendations Assessment, Development and Education
HA	Hyaluronic acid
HAQ-DI	Health Assessment Questionnaire Disability Index
HTA	Health technology assessment
IA	Intra-articular
ITT	Intention-to-treat
JBI	Joanna Briggs Institute
K-L	Kellgren-Lawrence
KSS	Knee Society Score
MA	Meta-analysis
MD	Mean difference
MINORS	Methodological Index for Non-Randomized Studies
MIO	Maximal interincisal opening
MMO	Maximum mouth opening
MW	Molecular weight
NAS-HA	Non-animal stabilized HA (naturally produced HA)
NR	Not reported
NRS	Numerical rating scale
OA	Osteoarthritis
OR	Odds ratio
PICO	Population, intervention, comparator, and outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RoB	Risk of bias
RR	Risk ratio
SAEs	Serious AEs
SMD	Standardized mean difference
SR	Systematic review
TMJ	Temporomandibular joint
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Context and Policy Issues

Osteoarthritis (OA), is the most common type of arthritis that causes damage to the articular cartilage and underlying bone.[1] It affects 9.6% of men and 18.0% of women over 60 years of age worldwide.[2] About five million Canadians living with OA (one in six), the number is expected to rise to 10 million (one in four) by 2035.[1,2] The joints that are affected by OA include knees, hips, hands, shoulder and temporomandibular joint (TMJ).[1] Common joint symptoms include pain, stiffness and swelling resulting in loss of function and disability.[1]

As there is no cure for OA, treatments aimed at reducing pain and improving functional outcomes.[1] Common nonoperative management of OA include nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular injection of corticosteroids (IA-CS).[1,3] Intra-articular injection of hyaluronic acid (IA-HA) has become accepted as an alternative treatment for the management of OA.[4]

Although IA-CS and IA-HA can provide clinically important improvement in pain and physical function, recent evidence suggests that the apparent clinical effectiveness of these treatments may be attributable by other factors including the placebo effect.[5,6] IA saline injection, often used in as placebo treatment in clinical trials, has been found to provide substantial pain relief in OA.[7] In fact, for knee OA, the effect size of the IA injection of saline was found to be statistically significant greater than no treatment on both short (≤ 3 months) and long-term (6 to 12 months) pain relief.[8]

In the process of updating the clinical effectiveness of IA-HA for treatment of OA of different joints, CADTH has undertaken to produce three consecutive reports covering the knee, hip and ankle, and hand, shoulder and TMJ. In the first recently published CADTH report, entitled “Intra-Articular Hyaluronic Acid for Viscosupplementation in Osteoarthritis of the Knee: A Review of Clinical Effectiveness and Safety”,[9] evidence suggests that there may be differences in the efficacy of IA-HA for treatment of knee osteoarthritis with respect to hyaluronic acid products, injection regimens, and OA disease severity. In the second companion report, entitled “Intra-Articular Hyaluronic Acid for Viscosupplementation in Osteoarthritis of the Hip or Ankle: A Review of Clinical Effectiveness”,[10] evidence suggests a lack of effect of IA-HA for treatment of hip OA, and a potential benefit of IA-HA for treatment of ankle OA.

The aim of this report is to review the clinical effectiveness of IA-HA for patients with OA of the hand, shoulder and TMJ compared with placebo and IA-CS.

Research Question

What is the clinical effectiveness and safety of intra-articular hyaluronic acid for patients with osteoarthritis of the hand, shoulder and temporomandibular joint?

Key Findings

For shoulder osteoarthritis, there were no significant differences between intra-articular hyaluronic acid and placebo or between intra-articular hyaluronic acid and intra-articular corticosteroid with respect to pain reduction and functional outcomes. Adverse events were considered unrelated to the study products.

For temporomandibular joint osteoarthritis, there were no significant differences between intra-articular hyaluronic acid and intra-articular corticosteroid, or between intra-articular

hyaluronic acid and no injection during arthrocentesis with respect to pain reduction and functional outcomes. There was no significant difference in adverse events between intra-articular hyaluronic acid and intra-articular corticosteroid.

For hand osteoarthritis, evidence was mixed for the comparison between intra-articular hyaluronic acid and intra-articular corticosteroid with respect to pain reduction and functional outcomes. There was no significant difference in pain reduction or functional outcomes between intra-articular hyaluronic acid and placebo. Adverse events were local and considered unrelated to study products.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline via OVID the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were hyaluronic acid and joints or joint disorders. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials, controlled clinical trials, or any other type of clinical trial. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and May 28, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients, in any setting, with osteoarthritic hand (including wrist), shoulder, or temporomandibular joint
Intervention	Intra-articular injection of hyaluronic acid (any products) for viscosupplementation
Comparator	• Placebo • Intra-articular injection of corticosteroids
Outcomes	Clinical effectiveness (e.g., changes to disease severity scale; changes in pain, joint mobility, functioning, functioning without aids; frequency of treatment injection, decrease use of opioid and non-opioid analgesics); and safety (e.g., side effects, adverse events, injection site reaction)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), and randomized controlled trials (RCTs).

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2014. Systematic reviews, in which the included studies were overlapped

completely with another SR published at a later date, were excluded. Primary studies were excluded if they had been included in the identified SRs.

Critical Appraisal of Individual Studies

The AMSTAR-2 checklist was used to assess the quality of SRs.[11] The critical appraisal checklists of the Joanna Briggs Institute were used to assess the quality of the included RCTs.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 478 citations were identified in the literature search. Following screening of titles and abstracts, 465 citations were excluded and 13 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of the 13 potentially relevant articles, eight publications were excluded for various reasons, while five publications including three SRs and two RCTs met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart[13] of the study selection.

Summary of Study Characteristics

The characteristics of the identified SRs[14-16] (Table 2) and RCTs[17,18] (Table 3) are presented in Appendix 2.

Study Design

One SR[14] included 15 studies (five RCTs, six prospective cohorts, one retrospective cohort, and three case series) that assessed the efficacy of IA-HA injections for shoulder (glenohumoral) OA. One SR[15] included eight RCTs of low risk of bias in meta-analysis to determine the effects of IA-CS on TMJ OA compared with placebo (4 RCTs) and IA-HA (4 RCTs). One SR[16] included 13 RCTs in assessing the efficacy and safety of intra-articular therapies, including IA-HA, IA-CS and other pharmacological injections, in the treatment of hand (carpometacarpal and interphalangeal) OA.

Two additionally identified studies[17,18] were prospective, parallel RCT. One[17] was double-blinded and the other[18] was unclear about blinding. Both RCTs determined the efficacy (one on long-term[17] and one on short-term[18]) of arthrocentesis with and without IA-HA injection for treatment of TMJ OA.

Country of Origin and Publication Year

The SRs were conducted by authors from Canada,[14] China[15] and the Netherlands,[16] and were published in 2019,[14] 2018[15] and 2016.[16]

The additionally identified RCTs were conducted by authors from Norway[17] and India,[18] and were published in 2019[17] and 2017.[18]

Population

For the SR involving shoulder OA,[14] participants were adults (> 18 years), with mean age and disease severity not reported. Percentage of males in the studies ranged from 27% to

76%. For the SR involving TMJ OA,[15] participants were adults with a mean age ranging from 27 to 53 years, and percentage of male participants ranging from 12% to 22%. Disease severity was not reported. For the SR involving hand OA,[16] participants were adults (> 18 years), with mean age and sex not reported. Patients with varying disease severity were included (Kellgren-Lawrence grade 1 to 4, or Eaton stage ≥ 2).

Both identified RCTs[17,18] included adults with TMJ OA. Mean age was reported in one RCT (51 years),[17] but not in the other.[18] Disease severity was not reported in either RCT. Sample sizes were relatively small; n = 37 in one RCT,[17] n= 20 in the other.[18]

Interventions and Comparators

One SR[14] evaluating the efficacy of IA-HA injections for shoulder OA compared IA-HA (of different products) with IA-CS, placebo, or no treatment. One SR[15] determined the effects of IA-CS on TMJ OA compared with placebo or IA-HA. Only the comparison between IA-CS and IA-HA, but not IA-CS versus placebo, was relevant for the current review and presented here. One SR[16] various IA therapies, including IA-HA and IA-CS, with placebo in the treatment of hand OA. The comparisons of IA-HA versus placebo, IA-HA versus IA-CS, and comparisons of different frequencies of injection or different forms of IA-HA with each other were presented in this review.

Both additionally identified RCTs[17,18] compared TMJ arthrocentesis/lavage alone with arthrocentesis/lavage plus IA-HA, which was Synvisc[17] or sodium hyaluronate.[18]

Outcomes

The primary outcome evaluated in the included SRs[14-16] and RCTs[17,18] was pain, which was assessed by the 10 cm or 100 mm visual analog scale (VAS).

Functional outcomes of the shoulder were assessed using various instruments such as Constant-Murley Shoulder score, Short-Form Health Survey questionnaire, Western Ontario Rotator Cuff Index score, Simple Shoulder Test, Western Ontario and McMaster Universities Osteoarthritis Index, Western Ontario Osteoarthritis of the Shoulder, and University of California, Los Angeles Shoulder Rating Scale.[14] Functional outcomes for the TMJ were assessed by evaluating jaw movement (e.g., maximum mouth opening, lateral and contralateral excursion, and protrusion of the lower jaw), and joint sounds (clicking and crepitation).[15,17,18] Functional outcomes for the hand were assessed using various instruments such as Duruöz Hand Index, Dreiser's Functional Index, Disabilities of the Arm Shoulder and Hand, Health Assessment Questionnaire Disability Index, and Functional Index for Hand Osteoarthritis.[16]

Adverse events (AEs) were reported in all three SRs,[14-16] and they were localized and minor.

Follow-up period

In the SRs, the follow-up periods were 3 and 6 months for shoulder OA,[14] 3 to 4 weeks and 6 months for TMJ OA,[15] and 3 and 6 months for hand OA.[16] One RCT[17] assessing the long-term efficacy of IA-HA in TMJ OA had a mean duration of follow-up of 47 months, ranging from 25 to 79 months. The other RCT[18] had maximum follow-up of 12 weeks.

Quality Appraisal Tools

All three SRs,[14-16] used the Cochrane Collaboration risk of bias tool to assess the methodological quality of their cited RCTs. However, only one SR[16] incorporated the risk of bias of its cited studies in the results.

Data Analysis and Synthesis

Two SRs[14,15] quantitatively synthesized data from included RCTs using a meta-analysis. Pain data were analyzed and presented as mean difference (MD) of scores on VAS. One SR[16] also used meta-analysis to pooled data for the comparison between IA-CS and placebo, but narratively described the findings of its cited studies for the comparisons of IA-HA versus placebo and IA-HA versus IA-CS.

None of the identified RCTs[17,18] analyzed data using the intention-to-treat (ITT) approach or applied a sample size calculation in the recruitment of participants.

Funding

Two SRs[14,15] and one RCT[17] did not report the source of funding, while one SR[16] and one RCT[18] reported that they did not receive any financial support for their works.

Summary of Critical Appraisal

The quality assessment of the SRs[14-16] (Table 4) and RCTs[17,18] (Table 5) are presented in Appendix 3.

All three SRs[14-16] provided appropriate research questions and explanations for selection of the study designs for the inclusion, used comprehensive literature search strategies, performed study selection and data extraction in duplicate, described the included studies in adequate detail, used satisfactory techniques for assessing the risk of bias in individual studies included in the review, performed meta-analysis using appropriate methods, and provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results. None of the SRs provided a list of excluded studies, and they did not assess the potential impact of risk of bias in individual studies on the results of the meta-analysis (i.e. there was no subgroup analysis based on risk of bias). One SR[16] reported on the sources of funding for the studies included in the review, while the other two[14,15] did not. Investigation of publication bias was applied by one SR,[14] and was not applicable in the other two due to small number of studies.[15,16] Conflict of interest and sources of funding were reported in one SR,[16] but not in the other two.[14,15] Overall, the SRs were explicit in terms of eligibility criteria, selection of studies and data collection, but might have some risk of bias in study appraisal, and data synthesis and analysis.

In both identified RCTs,[17,18] the method of randomization was adequately reported, the outcomes were measured in the same way for treatment groups using reliable methods, and the trial design was appropriate. However, unlike the Norwegian study,[17] the study from India[18] had potential biases in selection, performance, detection, attrition and reporting, as nine of 13 items in the critical appraisal checklist were marked “unclear”. Thus, one RCT[18] had unclear risk of bias, and the other[17] had low risk of bias.

Summary of Findings

The main findings and conclusions of the SRs[14-16] (Table 6) and RCTs[17,18] (Table 7) are presented in Appendix 4.

Shoulder (glenohumeral) OA

One SR[14] was identified that studied the effectiveness of IA-HA to reduce pain and improve function in shoulder OA compared with baseline, placebo, and IA-CS.

Pain

Pooled analysis of studies of different design including retrospective cohort, prospective cohort, and RCTs demonstrated that IA-HA significantly improved pain at three months and six months compared to baseline. However, pain improvements were also observed in control groups including IA-CS or placebo (saline). Between IA-HA and placebo, there was no significant difference in pain reduction. One retrospective study cited in the SR[14] found that IA-HA reduced pain for up to six months while IA-CS reduced pain up to one month only. The other cited RCT found no significant difference in pain reduction between IA-HA and IA-CS.

Functional outcome

IA-HA showed significant improvement in function and decrease in disability at six months compared to baseline. Compared with placebo, IA-HA had statistically significant, but clinically insignificant increase in range of motion, and there was no significant difference between IA-HA and placebo for improvement in function. There was also no significant difference between IA-HA and IA-CS for improvement in function.

AEs

IA-HA injections were associated with common AEs (pooled event rate of 33.92%), including musculoskeletal pain, headache, pain at injection site, abscess, chest pain, diarrhea and flu symptoms. Some serious AEs (pooled event rate of 5.35%) were observed such as severe musculoskeletal pain, abscess, chest pain, and cancer. The authors stated that all of these events were considered unrelated to the study products. Injections of IA-CS or placebo were also associated with common AEs (pooled event rate of 48.88%), including rash, local effusion, pain at injection site, and musculoskeletal pain.

Temporomandibular Joint OA

One SR[15] and two RCTs[17,18] were identified that studied the effect of IA-HA to reduce pain and improve function compared with placebo and IA-CS.

Pain

Pooled analysis of VAS scores for pain in the SR[15] showed that there were no significant differences between IA-HA and IA-CS injections with or without arthrocentesis at short-term (one or two weeks) or at long-term (six months) follow-up. One RCT[17] (risk of bias: low) found no significant difference in VAS scores for pain between arthrocentesis with IA-HA injection and arthrocentesis alone at long-term follow-up (six months and up to four years). One RCT[18] (risk of bias: high) found that both arthrocentesis with and without IA-HA improved pain at week 12 compared to baseline, and the difference between groups was statistically significant in favor of arthrocentesis with IA-HA.

Function

Pooled analysis of maximum mouth opening (MMO) measurement in the SR[15] revealed no significant differences between IA-HA and IA-CS injections with or without arthrocentesis at short-term (one or two weeks) or at long-term (six months) of follow-up. One RCT[17] (risk of

bias: low) found no significant difference between arthrocentesis with IA-HA injection and arthrocentesis alone at long-term follow-up (up to four years) with respect to MMO, lateral and contralateral excursion, protrusion, and joint sounds (clicking and crepitation). One RCT[18] (risk of bias: high) found that both arthrocentesis with and without IA-HA increased MMO at week 12 compared to baseline, and the difference between groups was statistically significant, favoring HA. Lateral and protrusion movement was improved in both groups at week 12, but the difference between groups was not statistically significant.

AEs

Three cited RCTs in the SR[15] reported that there was no significant difference between IA-HA and IA-CS in terms of TMJ pain after injections, ear pressure, generalized rashes, and chewing dysfunction. The identified RCTs[17,18] did not report AEs.

Hand OA

One SR[16] was identified that investigated the effect of intra-articular therapies including IA-HA and IA-CS for hand OA. The efficacy and safety of IA-HA compared with placebo, with IA-CS, and with different frequencies or different forms of HA were presented in this review.

Pain

Three RCTs (one with high risk of bias and two with unclear risk of bias) cited in the SR[16] reported that pain on VAS was reduced in both IA-HA and placebo compared to baseline, but there were no between-group differences up to 24 weeks.

For the comparison between IA-HA and IA-CS, four cited RCTs (two with high risk of bias, and two with unclear risk of bias) found no significant difference between groups in pain on VAS up to 26 weeks. One cited RCT with high risk of bias found IA-CS was better and faster in pain relief up to three weeks, while IA-HA was non-inferior to IA-CS afterward. Another cited RCT with high risk of bias found that IA-CS was transitory better than IA-HA at one and six months.

For comparison between IA-HA injection regimens, one cited RCT with high risk of bias reported that pain on VAS was improved only in groups with two or three injections, but not in single injection group.

For comparison between IA-HA products, one RCT with unclear risk of bias found that both low molecular weight (MW) and high MW IA-HA improved pain on VAS compared to pre-treatment. However, no between-group differences were observed at 12 weeks.

Function

The SR[16] found that there were no significant differences between IA-HA and placebo groups in term of function (three RCTs), grip strength (one RCT), pinch strength (two RCTs), and range of motion of the thumb (one RCT).

Evidence on the comparative effect of IA-HA versus IA-CS on hand function was mixed. Among the RCTs cited in the SR,[16] three RCTs (one with high risk of bias and two with unclear risk of bias) found no significant difference between IA-HA and IA-CS groups in self-reported function after 26 weeks of injection. Similarly, no significant differences between IA-HA and IA-CS groups were observed in other efficacy outcomes including grip strength (one RCT), pinch strength (one RCT), and range of motion of the thumb (one RCT), quality of life (one RCT), and joint crepitation (one RCT). One cited RCT with high risk of bias reported more improvement in function in the IA-CS group at 12 months. More

improvement in grip strength at one month (one RCT) and better relief of joint swelling (one RCT) were also observed in the IA-CS group. In contrast, single studies reported that IA-HA was associated with better in pinch strength after 12 weeks (one RCT) and 24 weeks (one RCT), range of motion of thumb (one RCT), and relief in joint warmth (one RCT).

Functional outcomes were not reported in the comparisons between IA-HA injection regimens or IA-HA products.

AEs

In both IA-HA and placebo groups, no treatment-related AEs were observed in two cited RCTs of the SR.[16] One cited RCT reported AEs observed in the IA-HA group (three local AEs and two cases of surgery unrelated to HA use) and in the placebo group (two local AEs and one case of surgery unrelated to placebo).

In both the IA-HA and IA-CS groups, three cited RCTs reported that the incidence of AEs was relatively low in both groups and no between-group difference was observed. These AEs were local side effects such as pain, swelling following the injection, skin and nail abnormalities, and a few cases of surgery that were not treatment-related. The other three cited RCTs found no AEs in either group.

Between IA-HA injection regimens of IA-HA products, minor AEs were observed, including local pain, swelling and redness at the injection site.

Limitations

The included SRs had several limitations. First, there was heterogeneity in terms of type of HA administered, the number of injections, dosage, and technique of injection (ultrasound-guided or fluoroscopy technique versus blind technique). Second, baseline demographics of patients with respect to disease severity was not reported in two SRs[14,15] and varied among cited studies in one SR.[16] Third, each SR included a limited number of relevant studies with relatively small sample sizes. Fourth, the level of evidence from cited studies in the SRs was mixed owing to differences in study design and methodological quality.

The two identified RCTs[17,18] had relatively small sample sizes and had no placebo control (i.e., saline injection). In those studies, the intervention group was arthrocentesis of the TMJ with injection of IA-HA, while the control group had arthrocentesis alone. One RCT[18] had poor methodological quality and was assessed as having high risk of bias.

Conclusions and Implications for Decision or Policy Making

This review includes three SRs[14-16] and two RCTs.[17,18]

For shoulder OA, there were no significant differences between IA-HA and placebo or between IA-HA and IA-CS with respect to pain reduction and functional outcomes. Adverse events were considered unrelated to the study products.

For TMJ OA, there were no significant differences between IA-HA and IA-CS, or between IA-HA and no injection during arthrocentesis with respect to pain reduction and functional outcomes. There was no significant difference in AEs between IA-HA and IA-CS.

For hand OA, evidence was mixed for the comparison between IA-HA and IA-CS with respect to pain reduction and functional outcomes. There was no significant difference in pain reduction or functional outcomes between IA-HA and placebo. The efficacy of injection

regimen or different products of IA-HA remains to be determined. AEs were local and considered unrelated to study products.

Based on the current review, there is insufficient evidence to establish the potential benefit of IA-HA for reducing pain and improving functional outcomes in shoulder OA, TMJ OA or hand OA. Further research, with larger well-designed trials, is warranted to determine the efficacy of IA-HA with respect to HA products, injection regimens, and OA disease severity of the hand, shoulder and TMJ.

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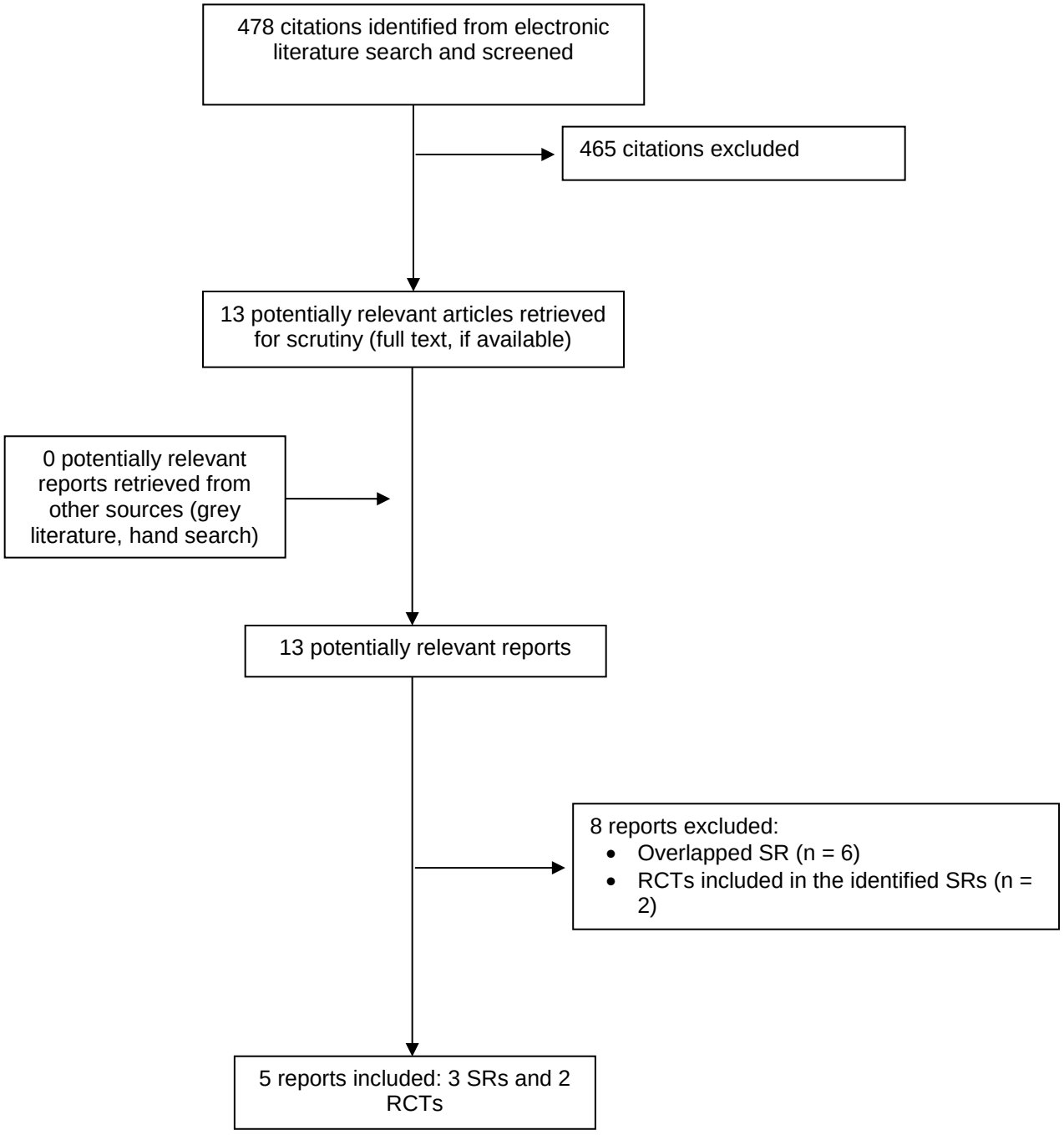
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions, Dose, Number of injections, Follow-up Period	Outcomes
Zhang et al., 2019[14] Canada Funding: NR	Objectives: To evaluate the efficacy of HA to reduce pain in patients with glenohumeral (shoulder) OA. 15 studies, including 5 RCTs, 6 prospective cohorts, 1 retrospective cohort, and 3 case series (n = 1,595) Risk of Bias tool for assessing the quality of studies: Cochrane risk of bias for RCTs, MINORS for non-randomized studies Assessment of quality of evidence: GRADE approach Databases: MEDLINE, CENTRAL, EMBASE, and PubMed databases Search date: from inception to January 16, 2018	Adults with glenohumeral OA Mean age (years): NR % Male: 27 to 76% Disease severity: NR	Interventions: – IA-HA of different products (Orthovisc, sodium hyaluronate, hylan G-F 20, Euflexxa) – Corticosteroids – Placebo (saline) – No treatment HA administration Dose: 2 to 8 mL Injection technique: image-guided, blind or combination of both MW: high (620 to 3200 kDa); low (500 to 730 kDa) Structure: single chain, branched Number of injections: single, multiple (2 to 5) Follow-up: – 3 months – 6 months	– Pain (VAS) – Function (Constant-Murley Shoulder score, Short-Form Health Survey questionnaire, Western Ontario Rotator Cuff Index score, Simple Shoulder Test, WOMAC[b] Index, Western Ontario Osteoarthritis of the Shoulder, and University of California, Los Angeles Shoulder Rating Scale) – AEs
Liu et al, 2018[15] China Funding: NR	Objectives: To determine the effects of IA-CS on TMJ OA compared with placebo or IA-HA. Total 16 studies: 8 studies were included for meta-analysis, while 8 studies were excluded due to low quality (high risk of bias) with or without sufficient data Risk of Bias tool for assessing the quality RCTs: Cochrane Collaboration risk of bias Databases: MEDLINE, EMBASE, SCI (ISI) Web of Knowledge, PubMed, the Cochrane	Adults with TMJ OA Mean age (years): 27 to 53 % Male: 12.1 to 21.7% Disease severity: NR	Interventions: – IA-HA (products not specified) – IA-CS (products not specified) – Placebo (saline) Dose: varying in concentrations Number of injections: Not specified	– Pain (VAS) – MIO – AEs

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions, Dose, Number of injections, Follow-up Period	Outcomes
	Library, the Chinese Biomedical Database, the China National Knowledge Infrastructure, and the Wangfang Database Search date: From January 1, 1980 to June 30, 2016		Follow-up: – Short-term: 3 to 4 weeks – Long-term: 6 months	
Kroon et al., 2016[16] The Netherlands Funding: None	Objectives: To assess the benefits and harms of intra-articular therapies in the treatment of hand OA. 13 RCTs (n = 4,119) Risk of Bias tool for assessing the quality RCTs: Cochrane Collaboration risk of bias Databases: Pubmed, EMBASE, CENTRAL, CINAHL, Academic Search Premier and ScienceDirect. Also, ClinicalTrials.gov, WHO ICTRP search portal and ISRCTN registry. Search date: Since inception to May 2015	Adults with hand OA (thumb-base, interphalangeal, erosive) Mean age (years): NR % Male: NR Disease severity K-L grade:[a] 1 to 4 Eaton stage:[c] ≥ II	Interventions: – IA-HA from different production methods (Bio-HA, AD-HA); low MW (47%); high MW (43%); moderate MW (10%) – Placebo (saline) Dose: varying in concentrations Number of injections: Single and multiple Follow-up: – 13 weeks (3 months) – 26 weeks (6 months)	– Pain (VAS or NRS) – Function (DHI, DFI, DASH, HAQ-DI, FIHOA) – Grip strength – Pinch strength – Range of motion of the thumb – Joint pain on pressure – Quality of life – Joint crepitation – AEs

AD-HA = Avian-derived hyaluronic acid; AEs = adverse events; Bio-HA = biologically fermented hyaluronic acid; CS = corticosteroid; DASH = Disabilities of the Arm Shoulder and Hand; DFI = Dreiser's Functional Index; DHI = Duruöz Hand Index; FIHOA = Functional Index for Hand Osteoarthritis; GRADE = Grading of Recommendations Assessment, Development and Education; HA = hyaluronic acid; HAQ-DI = Health Assessment Questionnaire Disability Index; IA = intra-articular; K-L = Kellgren-Lawrence; MINORS = Methodological Index for Non-Randomized Studies; MIO = maximal interincisal opening; NAS-HA = non-animal stabilized HA (naturally produced HA); NR = not reported; NRS = numerical rating scale; OA = osteoarthritis; RCT = randomized controlled trial; TMJ = temporomandibular joint; VAS = Visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

[a] The Kellgren and Lawrence classification[19] grades radiographic abnormalities at the tibiofemoral joint as: grade), no radiographic abnormalities; grade 1, doubtful joint space narrowing with possible osteophyte formation; grade 2, possible joint space narrowing with definite osteophyte formation; grade 3, definite joint space narrowing, moderate osteophyte formation, some sclerosis, and possible deformity of bone ends; grade 4, severe joint space narrowing, large osteophyte formation, marked sclerosis, and definite deformity of bone ends.

[b] The WOMAC is a disease-specific questionnaire separately addressing the severity of pain (5 questions) and any limitation on physical function (17 questions) for the activity of daily living during the past 48 hours.

[c] The Eaton and Littler Classification of Basilar Thumb Arthritis:[20] Stage I, subtle carpometacarpal joint space widening; stage II, slight carpometacarpal joint space narrowing, sclerosis, and cystic changes with osteophytes or loose bodies < 2 mm; stage III, advanced carpometacarpal joint space narrowing, sclerosis, and cystic changes with osteophytes or loose bodies > 2 mm; stage IV, arthritic changes in the carpometacarpal joint as in stage III with scaphotrapezial arthritis

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes and Follow-up
Bergstrand et al., 2019[17] Norway Funding: NR	Prospective, parallel, double-blinded RCT ITT: No Sample size calculation: No	Adults with TMJ OA Mean age (years): – With IA-HA: 47 – Control: 55 % Male: – IA-HA: 5 – Control: 30 Mean duration of TMJ symptoms (months) – IA-HA: 64.2 – Control: 63.5 Mean VAS score (0 to 100) – IA-HA: 63 – Control: 64 Mean MIO (mm) – IA-HA: 34 – Control: 37	Arthrocentesis with lavage and IA-HA injection (Synvisc, MW ~6,000 kDa); 1 mL (n = 20; finish = 20)	Arthrocentesis with lavage (n = 20; finish = 17)	– Pain (VAS) – Jaw movement (MIO, lateral and contralateral excursion, protrusion of the lower jaw) – Joint sounds Follow-up: mean duration of follow-up, 47 months (range, 25 to 79 months)
Gurung et al., 2017[18] India Funding: None	Prospective, parallel, RCT (unclear about blinding) ITT: No Sample size calculation: No	Adults with TMJ OA Mean age (years): NR % Male: – IA-HA: 80 – Control: 60 Disease severity: NR	Arthrocentesis with lavage and IA-HA injection (sodium hyaluronate; injection of 0.5 mL of 20 mg/ml) (n = 10)	Arthrocentesis with lavage (n = 10)	– Pain (VAS) – Jaw movement (MMO) Follow-up: day 1, day 5, day 7, week 4, week 6, week 12

AEs = adverse events; CS = corticosteroid; HA = hyaluronic acid; IA = intra-articular; ITT: intention-to-treat; K-L = Kellgren-Lawrence; KSS = Knee Society Score; MIO = maximum interincisal opening; MMO = maximum mouth opening; OA = osteoarthritis; Pla = placebo (saline); RCT = randomized controlled trial; VAS = Visual analog scale

Appendix 3: Quality Assessment of Included Studies

Table 4: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[11]	Zhang et al., 2019[14]	Liu et al., 2018[15]	Kroon et al., 2016[16]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	No	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	NA	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	No	Yes

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; NA = not applicable; PICO = population, intervention, comparator, and outcomes; RoB = risk of bias

Table 5: Quality Assessment of Randomized Controlled Trials

JBI Critical Appraisal Checklist for RCT[12]	Bergstrand et al., 2019[17]	Gurung et al., 2017[18]
1. Was true randomization used for assignment of participants to treatment groups?	Yes	Yes
2. Was allocation to treatment groups concealed?	Yes	Unclear
3. Were treatment groups similar at the baseline?	Yes	Unclear
4. Were participants blind to treatment assignment?	Yes	Unclear
5. Were those delivering treatment blind to treatment assignment?	Yes	Unclear
6. Were outcomes assessors blind to treatment assignment?	Yes	Unclear
7. Were treatment groups treated identically other than the intervention of interest?	Yes	Unclear
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	No 3 patients lost to follow-up in the control group	Unclear
9. Were participants analyzed in the groups to which they were randomized?	No	Unclear
10. Were outcomes measured in the same way for treatment groups?	Yes	Yes
11. Were outcomes measured in a reliable way?	Yes	Yes
12. Was appropriate statistical analysis used?	Yes	Unclear
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes	Yes

JBI = Joanna Briggs Institute; RCT = randomized controlled trial

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Zhang et al., 2019[14]	
Shoulder (glenohumeral) OA **VAS Pain** IA-HA versus baseline (Pooled analysis of studies of all designs including retrospective cohort, prospective cohort and RCTs – At 3 months: MD (95% CI) = 26.3 mm (22.0 to 30.3) – At 6 months: MD (95% CI) = 29.5 mm (25.5 to 33.4) IA-HA versus placebo (saline) – One RCT: MD = 2.8 mm in favor of HA group, but did not reach statistical significance (*P* = 0.112) – One RCT: MD = -1.2 ± 3.4 mm; no significant difference between groups (*P* = 0.720) IA-HA versus IA-CS at 6 months • One retrospective cohort: IA-HA reduced pain for up to 6 months while IA-CS reduced pain up to 1 month only. At 6 months: 36.0 ± 7.4 mm versus 68.0 ± 12.7 mm • One RCT: 28.92 ± 2.23 mm versus 30.39 ± 3.04 mm; not significant Subgroup analysis for types of control at 3 months • CS: MD (95% CI) = 27.0 mm (21.2 to 32.8) • Saline: MD (95% CI) = 24.7 mm (21.3 to 28.1) • No control: MD (95% CI) = 28.0 mm (15.3 to 40.7) **Functional outcome** IA-HA versus baseline – Improvement in function (4 studies): Statistically significant at 6 months – Decrease in disability (3 studies): Statistically significant at 6 months IA-HA versus placebo – Range of motion (1 RCT): Statistically significant, but clinically insignificant increase in range of motion in favor of IA-HA. – Improvement in function (1 RCT): No significant difference between groups IA-HA versus IA-CS • Improvement in function (1 RCT, 1 prospective case series): No significant difference between groups **AEs** AEs after IA-HA • Common AEs (33.92%): Musculoskeletal pain, headache, pain at injection site, abscess, chest pain, diarrhea and flu symptoms • SAEs (5.35%): Severe musculoskeletal pain, abscess, chest pain, and cancer • All of these events were not related to the study products. AEs after control (IA-CS or saline) injection – Common AEs (48.88%): Rash, local effusion, pain at injection site, and musculoskeletal pain – SAEs (2.24%): Not reported	*"Intra-articular HA injection is safe and improves pain for patients with glenohumeral OA. Pain improvements also reported in the control group suggest that a significant placebo effect may be present with respect to intra-articular shoulder injection. Further randomized controlled trials are necessary to evaluate the efficacy of HA and identify optimal dosing and route of administration."*[14] (*p*604)

Main Study Findings	Author's Conclusions
Liu et al., 2018[15]	
Temporomandibular Joint (TMJ) OA **IA-HA versus IA-CS** (some patients did not undergo arthrocentesis and received only IA injections of CS or HA) **VAS Pain** – Short-term (1, 2 weeks; 2 RCTs; n = 103) MD (95% CI) = 0.36 (-0.72 to 1.43); I^2 = 0; P = 0.52 – Long-term (6 months; 1 RCT; n = 40) MD (95% CI) = 1.40 (-0.49 to 3.29) **MIO** – Short-term (1, 2 weeks; 2 RCTs; n = 103) MD (95% CI) = -1.40 (-6.28 to 3.48); I^2 = 0; *P* = 0.57 – Long-term (6 months; 1 RCT; n = 40) MD (95% CI) = -3.30 (-10.87 to 4.27) **Success rate** (No definition provided) – Short-term (1, 2, 4 weeks; 3 RCTs; n = 107) OR (95% CI) = 0.41 0.17 to 1.00); I^2 = 0; *P* = 0.05; in favor of HA – Long-term (1 to 2 years; 1 RCT; n = 24) OR (95% CI) = 2.00 (0.38 to 10.41) **AEs (3 RCTs)** – No significant difference between IA-HA and IA-CS in terms of TMJ pain after injections, ear pressure, generalized rashes, and chewing dysfunction.	*"Corticosteroid and hyaluronate have marked effectiveness on TMJ OA; however, hyaluronate might be better alternative to some extent." (p. 505)*
Kroon et al., 2016[16]	
Hand (carpometacarpal) OA • **IA-HA versus placebo** (3 RCTs; n = 196; 1 RCT with high risk of bias and 2 RCTs with unclear risk of bias) Pain – Pain on VAS was reduced in both groups, with no significant between-group differences up to 24 weeks in 2 studies. One study did not perform test for group differences. Function – No between-group differences were observed for other efficacy outcomes such as function (3 RCTs), grip strength (1 RCT), pinch strength (2 RCTs) and range of motion of the thumb (1 RCT) AEs – No treatment-related AEs were observed in both groups in 2 RCTs. One RCT reported AEs in both groups (IA-HA: three local AES and two cases of surgery unrelated to HA; placebo: two local AEs and one case of surgery unrelated to placebo) • **IA-HA versus IA-CS** (6 RCTs; n = 405) Pain – No significant difference between groups in pain on VAS up to 26 weeks (4 RCTs; 2 with high risk of bias and 2 with unclear risk of bias). – IA-CS was transitory superior to IA-HA at 1 and 6 months (1 RCT with high risk of bias). – IA-CS had a better and faster pain relief initially up to 3 weeks, while IA-HA was non-inferior to IA-CS thereafter (1 RCT with high risk of bias). Function	*"Despite a beneficial short-term safety profile, IA corticosteroids or HA do not appear more effective than placebo in CMC OA."[16]* (p119)

Main Study Findings	Author's Conclusions
– No significant difference between groups in self-reported function after 26 weeks (3 RCTs; one with high risk of bias and 2 with unclear risk of bias). – One RCT with high risk of bias reported more improvement in function in IA-CS group at 12 months. – No significant difference between groups in other efficacy outcomes including grip strength (1 RCT), pinch strength (1 RCT), range of motion of the thumb (1 RCT), joint pain on pressure (1 RCT), quality of life (1 RCT) and joint crepitation (1 RCT). – More improvement in grip strength in the IA-CS group at 1 month (1 RCT), and better relief of joint swelling in the IA-CS group (1 RCT) – IA-HA was associated with better in pinch strength after 12 weeks (1 RCT) and 24 weeks (1 RCT), range of motion of thumb (1 RCT), and relief in joint warmth (1 RCT). AEs – Incidence of AEs were relatively low in both IA-HA and IA-CS groups and no between-group difference was observed (3 RCTs). These AEs were local side effects such as pain, swelling following the injection, skin and nail abnormalities, and few cases of surgery that was not treatment-related. – No AEs were observed in other 3 RCTs. • **IA-HA injection regimens** (1 RCT, n = 42, high risk of bias) Pain – Pain on VAS improved only in groups with 2 or 3 injections, but not in single injection group. – At 12 weeks, there were no between-group differences on 100-mm VAS of 43.1 ± 22.8, 39.5 ± 28.6, 29.8 ± 21.9 for one, two or three injection respectively. AEs – Minor AEs were observed in 30% of each group, including local pain, swelling, heat and/or redness, which subsided within days. • **IA-HA products** (1 RCT, n = 80, unclear risk of bias) Pain – Pain on VAS improved in both low MW and high MW IA-HA groups. However, no between-group differences were observed at 12 weeks on 10-cm VAS of 4.23 ± 2.90, 4.03 ± 2.56 for low and high MW IA-HA products, respectively. AEs – Minor AEs were observed in both groups, including mild pain, and/or ecchymosis in the injection site.	

AEs = adverse events; CI = confidence interval; CMC = carpometacarpal; CS = corticosteroids; HA = hyaluronic acid; IA = intra-articular; MD = mean difference; MIO = maximal interincisal opening; MW = molecular weight; OR = odds ratio; RCT = randomized controlled trial; SAEs = serious AEs; TMJ = temporomandibular joint; VAS = visual analog scale

Table 7: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Bergstrand et al., 2019[17]	
Arthrocentesis with lavage + IA-HA (Synvisc) (n = 20) versus arthrocentesis with lavage alone (n = 17) for treatment of TMJ OA • Pain by VAS Lavage + IA-HA – Baseline: 63 mm ± 16.6 – At 6 months: 40 mm ± 14.5	*"Both methods resulted in significant long-term improvements in pain and jaw function"*[17] (*p*82)

Main Study Findings	Author's Conclusions
– At final follow-up (~ 4 years): 25 mm ± 27.7 (*P* < 0.001 compared to baseline) Lavage alone – Baseline: 64 mm ± 24.8 – At 6 months: 29 mm ± 32.2 – At final follow-up (~ 4 years): 16 mm ± 20.5 (*P* < 0.001 compared to baseline) No between-group difference in change of VAS scores was observed (*P* = 0.276) • Maximum incisor opening Lavage + IA-HA – Baseline: 34 mm ± 10 – At final follow-up (~ 4 years): 39 mm ± 8 (*P* = 0.0009 compared to baseline) Lavage alone – Baseline: 37 mm ± 10 – At final follow-up (~ 4 years): 43 mm ± 8 (*P* = 0.007 compared to baseline) Difference between groups was not statistically significant (*P* = 0.223) • Lateral excursion to affected side Lavage + IA-HA – Baseline: 7.6 mm ± 3.3 – At final follow-up (~ 4 years): 9.0 mm ± 2.5 (*NS* compared to baseline) Lavage alone – Baseline: 7.5 mm ± 3.5 – At final follow-up (~ 4 years): 9.3 mm ± 2.9 (*NS* compared to baseline) Difference between groups was not statistically significant • Contralateral excursion Lavage + IA-HA – Baseline: 7.2 mm ± 2.7 – At final follow-up (~ 4 years): 8.7 mm ± 3.0 (*NS* compared to baseline) Lavage alone – Baseline: 6.7 mm ± 2.7 – At final follow-up (~ 4 years): 8.4 mm ± 3.2 (*NS* compared to baseline) Difference between groups was not statistically significant • Protrusion Lavage + IA-HA – Baseline: 6.0 mm ± 1.5 – At final follow-up (≥ 2 years): 6.1 mm ± 2.8 (*NS* compared to baseline) Lavage alone – Baseline: 6.1 mm ± 1.7 – At final follow-up (~ 4 years): 5.8 mm ± 2.4 (*NS* compared to baseline) Difference between groups was not statistically significant • Joint sounds (clicking and crepitation) There was no significant difference in joint sounds between baseline and final follow-up (IA-HA, *P* = 0.0236; placebo, *P* = 0.495) or between groups (*P* = 0.084)	
Gurung et al., 2017[18]	
Arthrocentesis with lavage + IA-HA (sodium hyaluronate) (n = 10) versus arthrocentesis with lavage alone (n = 10) for treatment of TMJ OA • Pain by VAS Lavage + IA-HA – Baseline: 5.90 cm ± 0.73	*"Combination of arthrocentesis with HA injection showed much better outcome than arthrocentesis alone"*[18] (*p*42)

Main Study Findings	Author's Conclusions
– At week 12: 1.30 cm ± 0.48 (*P* < 0.05 compared to baseline) Lavage alone – Baseline: 5.40 cm ± 0.94 – At week 12: 2.40 cm ± 1.07 (*P* < 0.05 compared to baseline) Difference between groups was statistically significant (*P* = 0.007) • Maximum mouth opening Lavage + IA-HA – Baseline: 35.80 mm ± 1.61 – At week 12: 45.60 mm ± 1.83 (*P* < 0.05 compared to baseline) Lavage alone – Baseline: 37.20 mm ± 2.09 – At week 12: 42.50 mm ± 2.36 (*P* < 0.05 compared to baseline) Difference between groups was statistically significant (*P* = 0.004) • Lateral and protrusive movement was improved in both groups at week 12 compared to baseline. Difference between groups was statistically significant (*P* = 0.13)	

HA = hyaluronic acid; IA = intra-articular; NS = not statistically significant; VAS = visual analog scale