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Intra-Articular Hyaluronic Acid for Viscosupplementation in Osteoarthritis of the Knee: A Review of Clinical Effectiveness and Safety

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Authors: Khai Tran, Hannah Loshak

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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
CS	Corticosteroid
HA	Hyaluronic acid
HTA	Health technology assessment
IA	intra-articular
JBI	Joanna Briggs Institute
K-L	Kellgren-Lawrence
KSS	Knee Society score
MA	Meta-analysis
MCII	Minimal Clinically Important Improvement
MD	Mean difference
MW	Molecular weight
NAS-HA	Non-animal stabilized HA (naturally produced HA)
NR	Not reported
OA	Osteoarthritis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RR	Risk ratio
SMD	Standardized mean difference
SR	Systematic review
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] There are approximately five million Canadians living with OA (one in six), and the number is expected to rise to 10 million (one in four) by 2035.[1,2] The joints that are most commonly affected are knees, hips, hands, toes and spine.[1] Common joint symptoms include pain, stiffness and swelling that reduce mobility and physical function.[1]

As there is no cure for OA, treatments are aimed at reducing pain and improving physical function. [1] Common medications used in the management of knee OA include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), intraarticular injection of corticosteroids (IA-CS), and intraarticular injection of hyaluronic acid (IA-HA).[1] IA-CS can reduce pain for several weeks, while there is conflicting evidence for IA-HA injections in patients with knee OA.[1,3] Total joint replacement surgery is reserved for advanced OA when other treatments fail.[1]

The Kellgren-Lawrence (K-L) grade is the most commonly radiographic method used to assess the severity of knee OA using five grades, from 0 to 4, with grade 0 representing no presence of radiographic features of OA and grade 4 (late or severe OA) representing large osteophytes, marked joint space narrowing, severe sclerosis and definite bone deformity.[4] Most clinical trials included patients with early-to-moderate knee OA (K-L grade 1 to 3) and found greater clinical efficacy of IA-HA in those patients, while some studies found that IA-HA failed in patients with severe OA.[5,6]

Although IA-CS and IA-HA can provide a 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.[7,8] IA saline injection, often used as a placebo treatment in clinical trials, has been found to provide substantial pain relief in OA.[9] In fact, 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.[10]

Intraarticular drugs injected into the joint are rapidly cleared by the lymphatic drainage at a rate depending on the molecular weight (MW) of the molecules.[8] For instance, the half-life of IA-HA injected in the joint is about 26 hours, while half-life of NSAIDs and corticosteroids is only 1 to 4 hours. Other potential mechanism for rapid clearance of HA is its degradation by enzyme hyaluronidase present in the synovial fluid.[11] To shift away from degradation and enhance its long-term retention in the joint after injection, many products have been prepared and approved for commercial use, which differ in many characteristics including source or method of production (avian-derived HA versus HA produced from bacterial bio-fermentation), variation of MW (500 to 9,000 kDa), molecular structure (linear or cross-linked), method of cross-linking, and different injection regimens (concentration, volume and number of injection).[12] These factors together with the severity of disease may contribute to the current controversy surrounding the IA-HA treatments for knee OA.

The aim of this report is to review the clinical effectiveness and safety of IA-HA for patients with knee OA compared with placebo and IA-CS.

Research Question

1. What is the clinical effectiveness and safety of intra-articular hyaluronic acid for patients with osteoarthritis of the knee joint?

Key Findings

Evidence suggests that there may be differences in the efficacy of intraarticular hyaluronic acid for treatment of knee osteoarthritis with respect to hyaluronic acid products, numbers of injection regimen, and disease severity. Intraarticular hyaluronic acid was found to be more effective with high molecular weight and biological fermented products, with 2-to-4 injection regimens, and in patients with low-to-moderate osteoarthritis. However, studies with direct head-to-head comparison are needed to confirm these findings. Between intraarticular hyaluronic acid and intraarticular corticosteroid, evidence suggests that intraarticular corticosteroid is more effective in the shorter-term (up to 1 or 3 months), while intraarticular hyaluronic acid is more effective in the longer-term (up to 6 or 12 months) in reducing pain and functional improvement in patients with knee osteoarthritis.

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 (SRs), meta-analyses, or network meta-analyses, randomized controlled trials (RCTs), 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, requiring viscosupplementation of an osteoarthritic knee 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 their included studies were overlapped 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.[13] The critical appraisal checklists of the Joanna Briggs Institute were used to assess the quality of the included RCTs.[14] 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, 437 citations were excluded and 41 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 41 potentially relevant articles, 31 publications were excluded for various reasons, while 10 publications including 5 SRs and 5 RCTs met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart[15] of the study selection.

Summary of Study Characteristics

The characteristics of the identified SRs[16-20] (Table 2) and RCTs[21-25] (Table 3) are presented in Appendix 2.

Study Design

Four identified SRs[16,18-20] performed meta-analyses of RCTs examining the efficacy of IA-HA in knee OA regarding disease severity,[16] types of HA products,[20] treatment regimens,[18] and in comparison with IA-CS.[19] One SR[17] conducted a network meta-analysis (NMA) of long-term pharmacological intervention trials in knee OA.

Of the five identified RCTs, two[22,23] were double-blinded, one[25] was open-labeled, and two[21,24] were unclear about blinding.

Country of Origin and Publication Year

The SRs were conducted by authors from USA,[16,18,20] Italy[17] and China,[19] and were published in 2019,[16] 2018,[17] 2017[18,19] and 2016.[20] There were Canadian studies cited in the included SRs.

The additionally identified RCTs were conducted by authors from China,[21] USA,[22] Brazil,[23] India,[24] and Mexico,[25] and were published in 2019,[21] 2018,[22] 2017[23,24] and 2015.[25]

Population

In all identified SRs,[16-20] patients were adults with knee OA, mean age ranging from 49 to 76 years. Four SRs[16-19] included RCTs having patients with OA severity ranging from 1 to 4 on K-L grade, with lower grade representing greater joint space and less disease severity. One SR[20] did not report K-L grade.

Three identified RCTs[21,22,25] recruited adult patients with knee OA, mean age ranging from 39 to 60 years. Two RCTs[23,24] did not report the mean age of included patients. One RCT[21] had patients with K-L grade of 1 and 2, three RCTs[22,24,25] with K-L grade of 2 and 3, and one RCT[23] with K-L grade of 4.

Interventions and Comparators

There were four SRs[16-18,20] comparing IA-HA with placebo (saline injection), and one SR[19] compared IA-HA with IA-CS. Three of the SRs[16,18,20] comparing IA-HA with placebo conducted subgroup analyses with respect to disease severity (i.e., K-L of 1 to 3 versus K-L of 4),[16] treatment regimens (i.e., single versus multiple injection),[18] and types of HA products in terms of molecular weight (MW) (high MW, ≥ 3,000 kDa; moderate MW, < 3,000 and > 1,500 kDa; low MW, ≤ 1,500 kDa) or methods of production (Bio-HA [biologically fermented HA], AD-HA [avian-derived HA], NAS-HA [non-animal stabilized HA]).[20]

One identified RCT[22] compared lightly cross-linked HA (Monovisc, MW 1,000 to 2,900 kDa; single injection) with placebo. Four identified RCTs[21,23-25] compared IA-HA with IA-CS. The IA-HA products in those studies were sodium hyaluronate (MW 500 to 730 kDa; multiple injection),[21] Hylan GF 20 (Synvisc; MW ~6,000 kDa; single injection),[23,24] and Suprhyal (MW 9,000 kDa; multiple injection).[25] The IA-CS included triamcinolone[23,24] and betamethasone.[25]

Outcomes

The primary outcome evaluated in the included SRs[16-20] and RCTs[21,22,24,25] was pain, which was assessed by the pain subscale of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a preferred outcome measure. The WOMAC is a disease-specific questionnaire separately addressing the severity of pain (5 questions), stiffness (2 questions) and limitation on physical function (17 questions) for the activity of daily living during the past 48 hours.[26] Other pain measures included the visual analog scale (VAS) for pain during any activity, pain during walking or global measure of knee pain, pain during weight bearing, pain at rest, or other pain outcome assessments such as the Knee Injury and Osteoarthritis Score, Musculoskeletal Outcomes Data Evaluation and Management System, Index of Severity for Osteoarthritis for the Knee, and WOMAC total score.

Other outcomes investigated were treatment-related adverse events (AEs), discontinuation due to AEs, and functional assessment using WOMAC subscale, Lysholm score, Knee Society Score (KSS), patient success (defined as 50% improvement from baseline and ≥ 20 mm absolute improvement from baseline on WOMAC pain score), and percentage of patients achieving the Minimal Clinically Important Improvement (MCII). The authors defined MCII as *"15 of 100 for absolute improvement and 20% for relative improvement in clinical trials of rheumatic diseases, with pain, functional disability, patient global assessment, or physical global assessment used as the outcome criteria. To calculate the MCII, total scores were normalized to a 0 to 100 score."*[25] p.11

Follow-up period

Follow-up periods were generally 3 to 6 months in four SRs[16,18-20] and three RCTs.[22-24] The other SR[17] and RCTs[21,25] had follow-up periods up to 12 months.

Quality Appraisal Tools

Two SRs[17,18] used the Cochrane Collaboration risk of bias tool, and one SR[19] used the modified Jadad scale to assess the methodological quality of their cited RCTs. Two SRs[16,20] did not perform quality assessment of the included studies.

Data Analysis and Synthesis

The SRs quantitatively synthesized data from included RCTs using a meta-analysis[16,18-20] or network meta-analysis[17] approach. Pain data were analyzed and presented as the standardized mean difference (SMD). Dichotomous data such as the number of patients who experienced treatment-related AEs were presented as risk ratios (RR).

Two identified RCTs[22,25] analyzed data using the intention-to-treat (ITT) approach, while the others[21,23,24] did not. Sample size calculation was applied in two RCTs,[22,25] but not in the others.[21,23,24]

Funding

The work of four SRs[16-18,20] were funded by pharmaceutical companies. One SR[19] received public funding for its work.

Two RCTs[22,25] were funded by pharmaceutical companies and three RCTs[21,23,24] did not report the source of funding.

Summary of Critical Appraisal

The quality assessment of the SRs (Table 4) and RCTs (Table 5) are presented in Appendix 3.

All five identified SRs[16-20] provided appropriate research questions and explanations for the selection of the study designs for inclusion, used comprehensive literature search strategies, performed meta-analysis using appropriate methods, and reported the sources of conflict of interest and funding. None of the SRs[16-20] provided a list of excluded studies. Four SRs[16,18-20] did not provide an *a priori* protocol. In three SRs,[16,18,20] it was unclear whether study selection and data extraction were performed in duplicate. One SR[20] did not describe the included studies in adequate detail. Two SRs[16,20] did not use satisfactory techniques for assessing the risk of bias in individual studies included in the review. One SR[20] did not assess the potential impact of risk of bias in individual studies on the results of

the meta-analysis, and did not account for risk of bias in individual studies when interpreting or discussing the results. Two SRs[17,20] did not provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results. Four SRs[17-20] did not carried out appropriate investigation of publication bias. Overall, each SR had certain risk of bias in different areas including eligibility criteria, selection of included studies, data collection, study appraisal, and data synthesis and analysis.

Of the five identified RCTs, three[21-23] did not report the method of randomization, and four[21-24] did not report whether allocation to treatment groups concealed. Two RCTs[23,24] did not report patient characteristics, and one RCT[25] had an imbalance in body mass index between treatment groups at baseline. Blinding of participants and treatment physicians was applied in two RCTs,[22,23] unclear in two RCTs,[21,24] and not applied in one RCT (open-label).[25] In four RCTs, [21-24] it was unclear whether or not outcomes assessors were blinded to treatment assignment. In three RCTs,[21,23,24] it was unclear whether or not study groups were treated identically other than the intervention of interest. Two RCTs[23,24] did not adequately describe and analyze differences between groups in term of their follow up. In all RCTs, [21-25] outcomes were measured in the same way using reliable methods for treatment groups, appropriate statistical analyses were used, and trial design was appropriate for the topic. Overall, each of the identified RCTs had potential risk of selection, performance, detection and/or attrition biases, and their quality was considered as low.

Summary of Findings

The main findings and conclusions of the SRs[16-20] (Table 6) and RCTs[21-25] (Table 7) are presented in Appendix 4.

IA-HA compared with placebo (saline injection)

Four SRs[16-18,20] and one RCT[22] were identified for this comparison.

One SR and NMA[17] of long-term pharmacological intervention trials in knee OA found no statistically significant difference between IA-HA and saline injection (placebo) in long-term pain control (≥ 12 months). Similar results were observed after excluding trials at high risk of bias. The effect of IA-HA characteristics and OA severity on the clinical effectiveness of IA-HA was not explored in this SR and NMA.

One SR[16] performed subgroup analysis to compare the efficacy of IA-HA in patients with early-to-moderate OA (K-L grade 1 to 3) and patients with late OA (K-L grade 4). Pain was assessed at 4 to 13 weeks and 22 to 27 weeks of follow-up. At both follow-up periods, IA-HA showed statistically significant improvement in pain relief compared to placebo in patients with early-to-moderate OA, but not in patients with late OA. There was no statistically significant difference in treatment-related AEs between IA-HA and placebo in patients with early-to-moderate OA. In the late OA subgroup, IA-HA treatment was associated with significantly higher in treatment-related AEs compared to placebo. Treatment-related AEs were not specified. The tests for subgroups differences (early-to-moderate OA versus late OA) for pain relief at both follow-up periods and treatment-related AEs were statistically significant ($P < 0.05$). The authors suggested that IA-HA provides significant benefit in pain relief compared to placebo in patients with early-to-moderate knee OA, but not in patients with late OA.

One SR[18] performed a subgroup analysis to compare the efficacy of IA-HA administration as single injection or multiple injections in patients with knee OA, irrespective to the OA severity (K-L grade 1 to 4). Pain was assessed at 3 and 6 months. Two to 4 injections of IA-HA were associated with a statistically significant reduction in knee pain compared to placebo, while single injection was not, at both follow-up periods. Greater or equal to 5

injections of IA-HA versus placebo yielded a non-significant effect size estimate at 3 months, and a small but significant effect size estimate at 6 months follow-up. Test for subgroup differences between single versus multi-injection regimens at 3 months, but not at 6 months, was significant ($P < 0.0001$). There were no statistically significant differences between IA-HA (either 2 to 4 or ≥ 5 injections) and placebo with respect to treatment-related serious AEs. Studies with ≥ 5 injections of IA-HA were associated with statistically significant more treatment-related AEs compared to placebo. There were no statistically significant differences in treatment-related AEs between single injection and saline or between 2 to 4 injections and saline. Neither treatment-related serious AEs nor treatment-related AEs were specified. The authors suggested that 2-to-4 injection regimen of IA-HA provides maximum effect compared to placebo.

One SR[20] determined the efficacy of IA-HA for knee OA based on product MW and methods of production of HA. OA severity, injection regimen and follow-up period were not reported. Analysis of pain data revealed that the pooled effect sizes were highest for high MW when compared with moderate and low MW products. Test for subgroup differences was not conducted. For treatment-related AEs, subgroup analysis revealed that flare-up at injection site was significantly higher for high MW and low MW compared with moderate MW products. Subgroup analysis based on methods of production showed that AD-HA was associated with significantly higher flare-up at injection site compared with Bio-HA ($P < 0.05$). The authors suggested that IA-HA products with high MW (i.e., ≥ 3,000 kDa) and those produced by biological fermentation (Bio-HA) provide better efficacy and safety in treatment of knee OA.

One RCT[22] determined the efficacy of single IA injection of Monovisc, a lightly cross-linked HA with MW of 1,000 to 2,900 kDa. Enrolled participants had knee OA of moderate severity (K-L grade 2 or 3). Patient success rate (defined as 50% improvement from baseline and ≥ 20 mm absolute improvement from baseline on WOMAC pain score) was significantly higher than placebo at week 2 ($P < 0.001$) and week 4 ($P = 0.003$), but not at week 8 ($P = 0.090$), week 12 ($P = 0.333$), or week 20 ($P = 0.835$). There were no statistically significant differences between IA-HA and saline groups with respect to WOMAC physical function, patient global assessment VAS, evaluator global assessment VAS, and knee range of motion at all periods of follow-up from 2 to 26 weeks. There were also no statistically significant differences between IA-HA and saline groups in treatment-related AEs such as arthralgia, joint swelling and joint stiffness. The findings in this RCT were in line with those in the identified SRs[18,20] suggesting that relatively low MW and single injection regimen of HA is not more effective than placebo in pain relief and functional improvement in patients with knee OA.

IA-HA compared with IA-CS

One SR[19] and four RCTs[21,23-25] were identified for this comparison.

In the identified SR,[19] pooled-analysis of the pain outcome assessed by either VAS or WOMAC scores showed that IA-CS is more effective than IA-HA in short-term follow-up (up to 1 month). However, the treatment difference between groups was no longer statistically significant at 3 months. And by 6 months, IA-HA was more effective than IA-CS in pain relief in patients with knee OA (K-L grade 1 to 4). Treatment-related AEs, which were not specified, were significantly higher in the IA-HA group compared to IA-CS group ($P < 0.00001$). There were no significant differences between groups for proportion of rescue medical use, proportion of withdrawal for knee pain, and active range of knee flexion. The authors suggested that IA-CS is more effective than IA-HA in the short-term (up to 1

month), while IA-HA is more effective than IA-CS in the long-term (up to 6 months) in reducing pain associated with knee OA.

One RCT[25] comparing the clinical efficacy of IA-HA (Suprahyal; 9,000 kDa; multiple injection) and IA-CS (betamethasone; multiple injection) in patients with knee OA (K-L grade 2, 3) showed that IA-CS was more effective in pain relief than IA-HA up to 3 months of follow-up ($P < 0.0001$), while IA-HA was associated with significantly higher reduction in pain compared to IA-CS in 12 months. Functional improvement was significantly higher in IA-HA at every follow-up visit, from 3 to 12 months. Treatment-related AEs (e.g., pain, erythema, effusion) were rare and were not significantly different between groups.

Comparing the clinical efficacy of IA-HA (Synvisc; ~6,000 kDa; single injection) with triamcinolone in patients with knee OA (K-L grade 2, 3), one RCT[24] also showed that IA-HA treatment was associated with significant more reduction in pain than IA-CS at the later times of follow-up (i.e., 3 months ($P < 0.01$) and 6 months ($P = 0.03$) for VAS pain scores), while no statistically significant difference between groups was observed at early follow-up (1 to 4 weeks). KSS functional scores were significantly higher in IA-HA group at 3 and 6 months of follow-up, but not in 1 month, compared with IA-CS group.

One RCT[23] analyzed the functional improvement assessed by Lysholm and KSS scores between IA-HA (Synvisc; ~6,000 kDa; single injection) and triamcinolone in patients with late knee OA (K-L grade 4). The study found no statistically significant differences in functional improvement between groups at every time point of follow-up, although functional scores in both groups were significantly higher compared with baseline at 1 and 3 months ($P < 0.01$), but not at 6 months after injection.

One RCT[21] compared the efficacy of IA-HA (sodium hyaluronate; 500 to 730 kDa; multiple injection) versus IA-CS (product not reported) in patients with knee OA (K-L grade 1 and 2). The study found no significant differences between treatment groups at all times of follow-up (up to 12 months), although both treatments significantly reduced WOMAC pain and physical function scores ($P < 0.05$) and VAS pain scores ($P = 0.001$) compared to baseline. No treatment-related AEs were observed.

Limitations

The included SRs had several limitations. First, the majority of cited trials were funded by industry with moderate to high risk of bias, as assessed by the authors of the SRs. Second, there was substantial heterogeneity among trials in terms of eligibility criteria, product differences in IA-HA, injection regimens, outcome assessment, time of follow-up, and blinding. Third, there was limited number of studies specifically assessed the efficacy of IA-HA in patients with late knee OA, suggesting that this subgroup may not be the ideal candidates for IA-HA treatment. Fourth, different methods were used to assess knee pain, although WOMAC was the preferred measure (as ranked by the authors). There was even variability in scales used to measure WOMAC pain (e.g., VAS version [0 to100 mm or 0 to 500 mm], Likert version [0 to 20 or 5 to 25]). Fifth, although K-L grade was the most commonly used measure to assess knee OA severity by radiographic method, some studies used their own definitions and scoring systems. Sixth, there were no direct comparisons between different OA severities, HA products (e.g., MW, methods of production), and numbers of injections.

Limitations among identified RCTs included potential industry influence to the findings (two received industry funding, three did not report source of funding), lack of the determination of minimal clinically important difference between comparative groups, no assessment or

consideration of the effect of placebo effect in relation to IA-HA or IA-CS injections, and potential risk of biases as described in the Summary of Critical Appraisal section.

Conclusions and Implications for Decision or Policy Making

This review includes five SRs[16-20] and five additional RCTs.[21-25] Four SRs[16-18,20] and one RCT[22] were identified for the comparison between IA-HA and placebo, and one SR[19] and four RCTs[21,23-25] for comparison between IA-HA and IA-CS.

Evidence identified in this review suggests that HA products, injection regimens and disease severity may play a major role in optimizing the efficacy and safety of IA-HA, and thus, pooling of data from studies without considering the differences of HA and patient characteristics is inappropriate due to heterogeneity. Compared with placebo, IA-HA appears to provide significant benefit in pain relief in patients with early-to-moderate knee OA, but not in patients with late OA. Moreover, 2-to-4 injection regimens of IA-HA and IA-HA products with high MW as well as those produced by biological fermentation may provide better efficacy and safety in treatment of knee OA. Between IA-HA and IA-CS, evidence suggests that IA-CS injections are more effective in the short-term, while IA-HA injections are more effective in the long-term in pain relief and functional improvement, despite more observed IA-HA-associated topical AEs. As most cited RCTs in the SRs were conducted in Europe and North America including Canada, the overall findings in this review are likely to be generalizable to the Canadian context. Given the aforementioned limitations of the included studies, the findings should be interpreted with caution. Future head-to-head RCTs are warranted to directly compare different of regimens of IA-HA, different products of IA-HA, and different disease severity in the determination of IA-HA efficacy for the treatment of knee OA.

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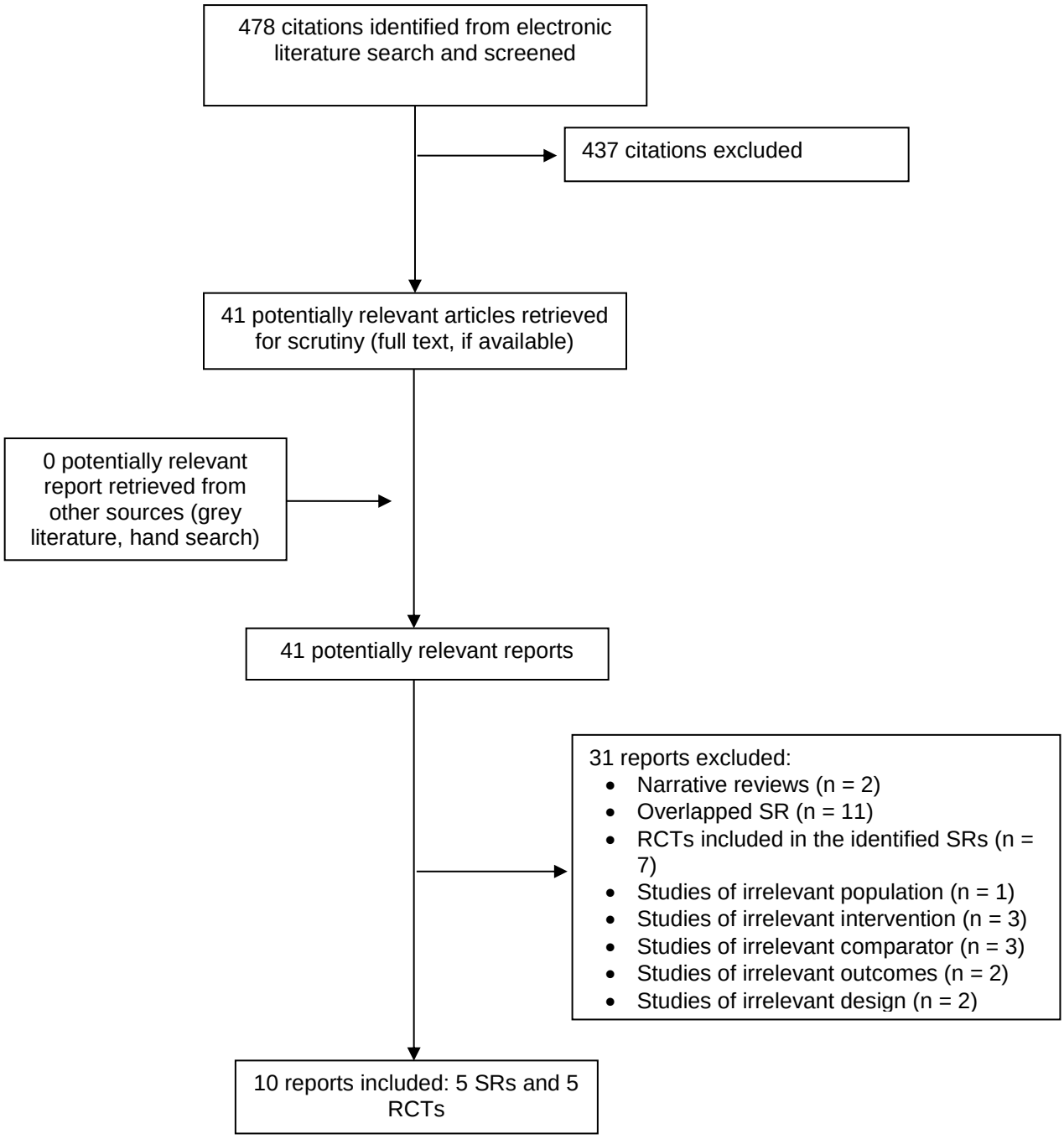
Appendix 1: Selection of Included Studies



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
Nicholls et al., 2019[16] USA Funding: Pharmaceuticals	Objectives: To compare the efficacy of IA-HA in patients with early-to-moderate knee OA and patients with late OA of the knee. 20 RCTs (n = 4,100) Risk of Bias tool for assessing the quality RCTs: No assessment done Databases: MEDLINE, EMBASE, and PubMed databases Search date: NR	Adults with knee OA Mean age (years): – IA-HA: 52.6 to 71.9 – Placebo: 56.2 to 67.0 % Male: – IA-HA: 0.0 to 56.9 – Placebo: 0.0 to 62.4 K-L grade:[a] – 1 to 3: 16 RCTs – 4: 4 RCTs	Interventions: – IA-HA of different products (Durolane, Euflexxa, Orthovisc, Synvisc, Hyalan, Monovisc, Adant, Suplasyn, Gel-ONE, Fermathron plus) – Placebo (saline) Dose: NR Number of injections: NR Follow-up: – 4 to 13 weeks – 22 to 27 weeks	– Pain (WOMAC[b], VAS) – Treatment-related AEs
Gregori et al., 2018[17] Italy Funding: Pharmaceuticals	Objectives: To determine the long-term (≥ 12 months) efficacy of pharmacological treatments in patients with knee OA. Total 47 RCTs, of which 12 RCTs (n = 1,051) compared HA with placebo Risk of Bias tool for assessing the quality RCTs: Cochrane Collaboration risk of bias Databases: MEDLINE (PubMed), Scopus, EMBASE, Web of Science, and the Cochrane Central Registered of Controlled Trials Search date: From inception to June 30, 2018	Adults with knee OA Mean age (years): 55 to 70 % Male: 30% K-L grade:[a] 1 to 4	Interventions: – IA-HA (products not specified) – Placebo (saline) Dose: varying in concentrations Number of injections: Multiple Follow-up: – ≥ 12 months	– Pain (WOMAC, VAS)
Concoff et al., 2017[18]	Objectives: To compare the efficacy of multiple versus single HA injections in patients with knee OA.	Adults with knee OA Mean age (years): 55 to 70	Interventions: – IA-HA from different production methods (Bio-	– Pain (WOMAC, VAS) – Treatment-related 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
USA Funding: Pharmaceuticals	30 RCTs (n = 5,848) Risk of Bias tool for assessing the quality RCTs: Cochrane Collaboration risk of bias Databases: MEDLINE, EMBASE, and PubMed databases Search date: NR	% Male: 30% K-L grade:[a] 1 to 4	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)	
He et al., 2017[19] China Funding: Public	Objectives: To compare the efficacy and safety of IA-HA and CS for knee OA 12 RCTs (n = 1,794) Risk of Bias tool for assessing the quality RCTs: Modified Jadad Scale Databases: EMBASE, PubMed, Web of Science, and the Cochrane library Search date: Since inception to August 2016	Adults with knee OA Mean age (years): – IA-HA: 49 to 75.9 – IA-CS: 50 to 75.3 % Male: 0 to 62% K-L grade:[a] 1 to 4	Interventions: – IA-HA of different products (Hyalgan, Orthovisc, NASHA, Ostenil, sodium hyaluronate, Hylastan SGL-80, hyaluronic acid, Synvisc) – CS of different products (Triamcinolone, methyl prednisone, decadron, corticosteroid) Dose: NR Number of injections: Single and multiple Follow-up: – 3 months – 6 months	– Pain (WOMAC, VAS) – Treatment-related 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
Altman et al., [20] USA Funding: Pharmaceuticals	Objectives: To determine whether there are differences in efficacy and safety with respect to intrinsic properties of available IA-HA injections for knee OA. 68 RCTs Risk of Bias tool for assessing the quality RCTs: No assessment done Databases: MEDLINE, EMBASE, and PubMed databases Search date: NR	Adults with knee OA Mean age (years): NR % Male: NR K-L grade:[a] NR	Interventions: – IA-HA of different MW (high, ≥ 3,000 kDa; moderate, < 3,000 and > 1,500 kDa; low, ≤ 1,500 kDa), and of different production methods (Bio-HA, AD-HA, NAS-HA) – Placebo (saline) Dose: NR Number of injections: NR Follow-up: up to 26 weeks (6 months)	– Pain (WOMAC, VAS) – Treatment-related AEs

AD-HA = Avian-derived hyaluronic acid; AEs = adverse events; Bio-HA = biologically fermented hyaluronic acid; CS = corticosteroid; HA = hyaluronic acid; IA = intra-articular; K-L = Kellgren-Lawrence; NAS-HA = non-animal stabilized HA (naturally produced HA); NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; VAS = Visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

[a] The Kellgren and Lawrence classification[4] 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.

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
Huang et al., 2019[21] China Funding: NR	Prospective, parallel, RCT (unclear about blinding) ITT: Unclear, but no lost to follow-up Sample size calculation: No	Adults with knee OA Mean age (years): – IA-HA: 54.8 – IA-CS: 54.3 % Male: – IA-HA: 15.8 – IA-CS: 17.5 K-L grade:[a] 1, 2	IA-HA (sodium hyaluronate, MW 500 to 730 kDa); 2 ml each week for 3 weeks (n = 40)	IA-CS (product and dosage: NR) (n = 40)	– Pain (WOMAC, VAS) – Treatment-related Aes Follow-up: 3, 6, 9, 12 months
Petterson et al., 2018[22] USA Funding: Pharmaceuticals	Multicenter, double-blind, placebo-RCT ITT: Yes Sample size calculation: Yes	Adults with idiopathic, symptomatic, knee OA Mean age (years) – IA-HA: 59.5 – Pla: 58.7 % Male: – IA-HA: 40.8 – Pla: 42.7 K-L grade:[a] 2, 3	IA-HA (Monovisc; lightly cross-linked; MW 1,000 to 2,900 kDa); single injection of 4 ml (88 mg) (n = 184)	Placebo (4 ml 0.9% saline) (n= 185)	Primary: – Patient success* (WOMAC, VAS) Secondary – WOMAC physical function subscore – Patient global assessment VAS – Evaluator global assessment VAS – Knee flexion and extension range of motion – Treatment-related Aes * Defined as 50% improvement from baseline and ≥ 20 mm absolute improvement from baseline on WOMAC VAS pain score Follow-up: 2, 4, 8, 12, 20, 24 weeks

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes and Follow-up
Campos et al., 2017[23] Brazil Funding: NR	Double-blind RCT ITT: No Sample size calculation: No	Adults with knee OA Mean age (years): NR % Male:26.7% K-L grade:[a] 4	IA-HA (hylan GF 20 (Synvisc); MW ~6,000 kDa; single injection 6 ml) (n = 50)	IA-CS (Triamcinolone; single injection 1 ml of 20 mg/ml) (n = 53)	Functional asessement: – Lysholm score – KSS score (physical, functional) Follow-up: 3, 6 months
Vaishya et al., 2017[24] India Funding: NR	RCT (unclear about blinding) ITT: NR Sample size calculation: No	Adults with knee OA Mean age (years): NR % Male: – IA-HA: 31 – IA-CS: 37.5 K-L grade:[a] 2, 3	IA-HA (Synvisc; MW ~6,000 kDa; single injection 48 mg) (n = 42)	IA-CS (Triamcinolone; single injection 40 mg) (n = 40)	– Pain (KSS, VAS) – Functional (KSS) Follow-up: 1, 4, 12, 24 weeks
Trueba Davalillo et al., 2015[25] Mexico Funding: Pharmaceuticals	Open-label RCT ITT: Yes Sample size calculation: Yes	Adults with knee OA Mean age (years): – IA-HA: 39.2 – IA-CS: 42.8 % Male: – IA-HA: 15.8 – IA-CS: 17.5 K-L grade:[a] 2, 3	IA-HA (Suprahyal; MW 9,000 kDa; 2.5 ml of 1% solution; one IA injection per week for 5 weeks) (n = 100)	IA-CS (betamethasone [1 ml of Diprospan Hypack]; two injections at day 0 and in the fourth week) (n = 100)	– Pain (WOMAC, VAS) – Functional (WOMAC) – Treatment-related Aes Follow-up: 3, 6, 9, 12 months

AEs = adverse events; CS = corticosteroid; HA = hyaluronic acid; IA = intra-articular; ITT: intention-to-treat; K-L = Kellgren-Lawrence; KSS = Knee Society Score; OA = osteoarthritis; RCT = randomized controlled trial; VAS = Visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

[a] The Kellgren and Lawrence classification[4] grades radiographic abnormalities at the tibiofemoral joint as: grade 0, 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.

Appendix 3: Quality Assessment of Included Studies

Table 4: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[13]	Nicholls et al., 2019[16]	Gregori et al., 2018[17]	Concoff et al., 2017[18]	He et al., 2017[19]	Altman et al., 2016[20]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	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	Yes	No	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Unclear	Yes	Unclear	Yes	Unclear
6. Did the review authors perform data extraction in duplicate?	Unclear	Yes	Unclear	Yes	Unclear
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	No
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?	No	Yes	Yes	Yes	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	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?	Yes	Yes	Yes	Yes	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	Yes	Yes	No
14. Did the review authors provide a satisfactory explanation for, and	Yes	No	Yes	Yes	No

AMSTAR 2 Checklist[13]	Nicholls et al., 2019[16]	Gregori et al., 2018[17]	Concoff et al., 2017[18]	He et al., 2017[19]	Altman et al., 2016[20]
discussion of, any heterogeneity observed in the results of the review?					
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	No	No	No	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; PICO = population, intervention, comparator, and outcomes; RoB = risk of bias

Table 5: Quality Assessment of Randomized Controlled Trials

JBI Critical Appraisal Checklist for RCT[14]	Huang et al., 2019[21]	Petterson et al., 2018[22]	Campos et al., 2017[23]	Vaishya et al., 2017[24]	Trueba Davalillo et al., 2015[25]
1. Was true randomization used for assignment of participants to treatment groups?	Unclear	Unclear	Unclear	Yes	Yes
2. Was allocation to treatment groups concealed?	Unclear	Unclear	Unclear	Unclear	Yes
3. Were treatment groups similar at the baseline?	Yes	Yes	Unclear	Unclear	No
4. Were participants blind to treatment assignment?	Unclear	Yes	Yes	Unclear	No
5. Were those delivering treatment blind to treatment assignment?	Unclear	Yes	Yes	Unclear	No
6. Were outcomes assessors blind to treatment assignment?	Unclear	Unclear	Unclear	Unclear	Yes
7. Were treatment groups treated identically other than the intervention of interest?	Unclear	Yes	Unclear	Unclear	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes	Yes	Unclear	Unclear	Yes
9. Were participants analyzed in the groups to which they were randomized?	Unclear	Yes	No	Unclear	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes	Yes	Yes	Yes	Yes

JBI Critical Appraisal Checklist for RCT[14]	Huang et al., 2019[21]	Petterson et al., 2018[22]	Campos et al., 2017[23]	Vaishya et al., 2017[24]	Trueba Davalillo et al., 2015[25]
11. Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes
12. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes
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	Yes	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
Nicholls et al., 2019[16]	
Knee OA of different severity (early-to-moderate [K-L: 1 to 3] or late OA [K-L: 4]): IA-HA (various products) versus placebo (saline) Pain at 4 to 13 weeks: • Total OA (20 RCTs [n = 3,485]; n = 1,866 for IA-HA, n = 1,619 for saline) SMD (95% CI) = -0.21 (-0.36 to -0.06); *P* < 0.0001; I^2 = 75% • Early-to-moderate OA (16 RCTs [n = 2,919]; n = 1,578 for IA-HA, n = 1,341 for saline) SMD (95% CI) = -0.30 (-0.44 to -0.15); *P* < 0.0001; I^2 = 68% • Late OA (4 RCTs [n = 566]; n = 288 for IA-HA, n = 278 for saline) SMD (95% CI) = -0.28 (-0.12 to 0.68); *P* = 0.17; I^2 = 72% • Statistically significant difference between subgroups (*P* = 0.008) • No evidence of publication bias Pain at 22 to 27 weeks: • Total OA (11 RCTs [n = 2,547]; n = 1,312 for IA-HA, n = 1,235 for saline) SMD (95% CI) = -0.22 (-0.35 to -0.10); *P* = 0.0005; I^2 = 56% • Early-to-moderate OA (9 RCTs [n = 2,039]; n = 1,058 for IA-HA, n = 981 for saline) SMD (95% CI) = -0.27 (-0.39 to -0.16); *P* < 0.00001; I^2 = 38% • Late OA (2 RCTs [n = 508]; n = 254 for IA-HA, n = 254 for saline) SMD (95% CI) = 0.03 (-0.14 to 0.21); *P* = 0.72; I^2 = 3% • Statistically significant difference between subgroups (*P* = 0.005) Sensitivity analysis (Removed three single-blinded and one non-blinded studies reporting early –to-moderate OA) • At 13 weeks: SMD (95% CI) = -0.16 (-0.32 to -0.01); *P* = 0.004 • At 26 weeks: SMD (95% CI) = -0.19 (-0.30 to -0.07); *P* = 0.001 Treatment-related AEs: • Total OA (12 RCTs [n = 2,870]; n = 1,534 for IA-HA, n = 1,336 for saline) RR (95% CI) = 1.14 (0.96 to 1.36); *P* = 0.14; I^2 = 47% • Early-to-moderate OA (9 RCTs [n = 2,440]; n = 1,304 for IA-HA, n = 1,104 for saline) RR (95% CI) = 1.03 (0.89 to 1.20); *P* = 0.68; I^2 = 36% • Late OA (3 RCTs [n = 462]; n = 230 for IA-HA, n = 232 for saline) RR (95% CI) = 1.76 (1.16 to 2.67); *P* = 0.008; I^2 = 0% • Statistically significant difference between subgroups (*P* = 0.02)	*"Treatment with IA-HA provides statistically significant pain relief compared to saline injections for patients with early-to-moderate knee OA, with no increase in the risk of treatment-related adverse effects, up to 6 months post-injection. IA-HA demonstrated no benefit over controls in the late OA subgroup and was associated with significantly greater treatment- related AEs."*[16] (p 158)
Gregori et al., 2018[17]	
Knee OA (K-L: 1 to 4): Long-term follow-up (≥ 12 months) of IA-HA (products not specified) versus placebo (saline) Pain at ≥ 12 months: • Total: 12 RCTs (n = 1,051); SMD (95% CI) = -1.97 (-5.56 to 1.53) • Excluded trials at high risk of bias: 5 RCTs (n = 605); SMD (95% CI) = -1.68 (-5.67 to 2.25)	*"In this systematic review and network meta-analysis of studies of patients with knee osteoarthritis and at least 12 months of follow-up, there was uncertainty around the estimates of effect size for change in pain for all comparisons with placebo. Large RCTs are needed to resolve the uncertainty around efficacy of medications for*

Main Study Findings	Author's Conclusions
	knee osteoarthritis."[17] (p 2564)
Concoff et al., 2017[18]	
Knee OA (K-L: 1 to 4): Single injection or multiple injections of IA-HA (of different production methods) versus placebo (saline) Pain at 13 weeks (3 months): • Single injection (2 RCTs; only one estimable study) SMD (95% CI) = -0.03 (-0.29 to 0.23) • 2 to 4 injections (6 RCTs) SMD (95% CI) = -0.76 (-0.98 to -0.53); $P < 0.00001$; $I^2 = 19\%$ • ≥ 5 injections (3 RCTs) SMD (95% CI) = -0.20 (-0.43 to 0.03); $P = 0.09$; $I^2 = 0\%$ • Total (9 RCTs of 2 to 4 and ≥ 5 injections) SMD (95% CI) = -0.57 (-0.83 to -0.32); $P < 0.0001$; $I^2 = 60\%$ • Statistically significant difference between subgroups ($P < 0.00001$) Pain at 26 weeks (6 months): • Single injection (2 RCTs) SMD (95% CI) = -0.04 (-0.20 to 0.13); $P = 0.67$; $I^2 = 0\%$ • 2 to 4 injections (10 RCTs) SMD (95% CI) = -0.36 (-0.63 to -0.09); $P = 0.008$; $I^2 = 82\%$ • ≥ 5 injections (6 RCTs) SMD (95% CI) = -0.18 (-0.35 to -0.01); $P = 0.04$; $I^2 = 45\%$ • Total (18 RCTs) SMD (95% CI) = -0.25 (-0.40 to -0.10); $P = 0.0009$; $I^2 = 74\%$ Treatment-related serious AEs: • 2 to 4 injections (2 RCTs) RR (95% CI) = 0.68 (0.39 to 1.20); $P = 0.19$; $I^2 = 0\%$ • ≥ 5 injections (2 RCTs) RR (95% CI) = 1.80 (0.59 to 5.48); $P = 0.30$; $I^2 = 0\%$ • Total (4 RCTs) RR (95% CI) = 0.83 (0.50 to 1.38); $P = 0.13$; $I^2 = 0\%$ • No statistically significant difference between subgroups Treatment-related AEs: • Single injection (4 RCTs) RR (95% CI) = 1.22 (0.85 to 1.75); $P = 0.28$; $I^2 = 64\%$ • 2 to 4 injections (4 RCTs) RR (95% CI) = 0.97 (0.86 to 1.08); $P = 0.57$; $I^2 = 0\%$ • ≥ 5 injections (5 RCTs) RR (95% CI) = 1.67 (1.09 to 2.56); $P = 0.02$; $I^2 = 0\%$ • Total (13 RCTs) RR (95% CI) = 1.13 (0.95 to 1.35); $P = 0.13$; $I^2 = 45\%$ • Statistically significant difference between subgroups ($P = 0.03$)	*"Overall, 2-4 and ≥5 injections regimens provided pain relief over IA-Saline, while single injection did not. Intra-articular injections of HA used in a 2-4 injection treatment regimen provided the greatest benefit when compared with IA-Saline with respect to pain improvement in patients with knee OA, and was generally deemed safe with few to no treatment-related AEs reported across studies. Future research is needed to directly compare these treatment regimens."*[18] (p 1)
He et al., 2017[19]	
Knee OA (K-L: 1 to 4): IA-HA versus IA-CS Pain (VAS score) • At 1 month (6 RCTs; n = 484) – Favors IA-CS MD (95% CI) = 0.67 (0.07 to 1.27); $P = 0.03$; $I^2 = 66\%$	*"Intraarticular CS is more effective on pain relief than intraarticular HA in short term (up to 1 month), while HA is more effective in the long term (up to 6 months). Two therapies benefit similarly for knee*

Main Study Findings	Author's Conclusions
• At 3 months (8 RCTs; n = 800) – No significant difference MD (95% CI) = -0.46 (-1.31 to 0.39); *P* = 0.29; I^2 = 85% • At 6 months (7 RCTs; n = 646) – Favors IA-HA MD (95% CI) = -0.73 (-1.25 to -0.21); *P* = 0.006; I^2 = 56% Pain (WOMAC score) • At 3 months (5 RCTs; n = 1,002) – No significant difference MD (95% CI) = -2.30 (-6.53 to 1.93); *P* = 0.29; I^2 = 77% • At 6 months (4 RCTs; n = 848) – Favors IA-HA MD (95% CI) = -5.15 (-8.77 to -1.54); *P* = 0.005; I^2 = 70% Proportion of rescue medical use • 3 RCTs (n = 389) – No significant difference RR (95% CI) = 1.04 (0.90 to 1.20); *P* = 0.58; I^2 = 0% Proportion of withdrawal for knee pain • 5 RCTs (n = 286) – No significant difference RR (95% CI) = 1.29 (0.57 to 2.92); *P* = 0.54; I^2 = 23% Active range of knee flexion • At 3 months (2 RCTs; n = 154) – No significant difference MD (95% CI) = 0.49 (-2.30 to 3.29); *P* = 0.73; I^2 = 27% • At 6 months (2 RCTs; n = 154) – No significant difference MD (95% CI) = 1.77 (-4.09 to 7.63); *P* = 0.55; I^2 = 74% Treatment-related AEs • 6 RCTs (n = 294) – Favors IA-CS RR (95% CI) = 1.66 (1.34 to 2.06); *P* < 0.00001; I^2 = 40%	*function improvement. Both two methods are relatively safe, but intraarticular HA causes more topical adverse effects compared with intraarticular CS."*[19] (p 95)
Altman et al., 2016[20]	
Knee OA (K-L: NR): IA-HA (different MW; different production methods) versus placebo (saline) Pain (WOMAC, VAS, or other measures) • High MW; ≥ 3,000 kDa (11 RCTs, n = 2,094) SMD (95% CI) = -0.52 (-0.56 to -0.48) • Moderate MW; <3,000 and > 1,500 kDa (4 RCTs; n = 621) SMD (95% CI) = -0.31 (-0.42 to -0.20) • Low MW; ≤ 1,500 kDa (15 RCTs; n = 2,639) SMD (95% CI) = -0.18 (-0.42 to -0.20) Treatment-related AEs • Flare-ups at the injection site stratified by production methods – Bio-HA or NAS-HA: 3.04% (54/1,776); 95% CI 2.34 to 3.95% – AD-HA: 13.19% (405/3,070); 95% CI 12.04 to 14.44% – Statistically significant difference between subgroups (*P* < 0.05) • Flare-ups at the injection site stratified by MW – High MW: 13.73%; 95% CI 12.33 to 15.27% – Moderate MW: 3.31%; 95% CI 2.04 to 5.30% – Low MW: 10.73%; 95% CI 9.27 to 12.39% – Statistically significant difference between high MW and moderate MW (*P* ≤ 0.001); between moderate MW and low MW (*P* ≤ 0.001); between high MW and low MW (*P* = 0.007) • Discontinuation of treatment due to treatment-related AEs stratified by MW	*"Despite similarities, IA-HA should not be treated as a group, as there are differences in IA-HA products that influence both efficacy and safety. In the available literature, IA-HA products with molecular weight ≥ 3,000 kDa and those derived from biological fermentation relate to superior efficacy and safety – factors that may influence selection an IA-HA product for OA of the knee."*[20] (p 2158)

Main Study Findings	Author's Conclusions
– High MW: 0.77%; 95% CI 0.48 to 1.21% – Moderate MW: 1.31%; 95% CI 0.40 to 2.16% – Low MW: 2.20%; 95% CI 1.70 to 2.84% – Statistically significant difference between high MW and low MW (*P* = 0.004) • Discontinuation of treatment due to treatment-related AEs stratified by production methods – Bio-HA or NAS-HA: 1.49%; 95% CI 1.05 to 2.12% – AD-HA: 1.00%; 95% CI 0.73 to 1.37% – No statistically significant difference between subgroups (*P* = 0.09)	

AD-HA = Avian-derived hyaluronic acid; AEs = adverse events; Bio-HA = biologically fermented hyaluronic acid; CI = confidence interval or credible interval; CS = corticosteroid; HA = hyaluronic acid; IA = intra-articular; K-L = Kellgren-Lawrence; MD = mean difference; MW = molecular weight; NAS-HA = non-animal stabilized HA (naturally produced HA); NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference; VAS = Visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table 7: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Huang et al., 2019[21]	
Knee OA (K-L: 1, 2): IA-HA (sodium hyaluronate; 500 to 730 kDa; multiple injection) versus IA-CS (product and dosage NR) Pain and physical function (WOMAC scores) • IA-HA (n = 40) – Baseline: 47.23 ± 5.37 – 3 months: 25.02 ± 4.98 – 6 months: 26.38 ± 5.20 – 9 months: 27.86 ± 4.34 – 12 months: 30.64 ± 8.36 • IA-CS (n = 40) – Baseline: 46.58 ± 5.74 – 3 months: 24.78 ± 4.55 – 6 months: 25.00 ± 4.65 – 9 months: 28.16 ± 5.12 – 12 months: 32.18 ± 6.88 • Both IA-HA and IA-CS treatments significantly reduced WOMAC scores at up to 12 months of follow-up compared to baseline ($P < 0.05$). No significant differences between treatment groups at all times of follow-up. Pain (VAS scores) • IA-HA (n = 40) – Baseline: 4.54 ± 0.60 – 12 months: 2.14 ± 1.52 – Difference: 2.40 ± 1.55; $P = 0.001$ • IA-CS (n = 40) – Baseline: 4.64 ± 0.54 – 12 months: 2.26 ± 1.71 – Difference: 2.38 ± 1.63; $P = 0.001$ • Both IA-HA and IA-CS treatments significantly reduced VAS scores at 12 months of follow-up compared to baseline ($P = 0.001$). No significant differences between treatment groups. Treatment-related AEs: No patients had deep venous thrombosis, low-grade fever or infections. Mild complications such as pain, nausea and dizziness were observed in 2 patients (1.7%) in the IA-HA group and 3 patients (2.5%) in the IA-CS group. These conditions were mild and were resolved after one or two days.	The authors found that both IA-HA and IA-CS treatments were equally effective in patients with early knee OA without any treatment-related AEs.
Petterson et al., 2018[22]	
Knee OA (K-L: 2, 3): IA-HA (Monovisc; lightly cross-linked; 1,000 to 2,900 kDa; single injection) versus placebo (saline) Patient success (defined as 50% improvement from baseline and ≥ 20 mm absolute improvement from baseline on WOMAC pain score) • Patient success was significantly higher in the IA-HA compared to saline at week 2 (44.38% versus 34.12%; $P < 0.001$) and week 4 (49.11% versus 45.29%; $P = 0.003$), but not at week 8 ($P = 0.009$), week 12 ($P = 0.333$) or week 20 ($P = 0.835$) after injection. • No statistically significant differences between IA-HA and saline groups with respect to WOMAC physical function, patient global assessment VAS, evaluator global	*"Monovisc, a single-injection intra-articular HA device, is a safe and effective treatment for providing a clinically meaningful reduction in knee pain within 2 weeks."*[22] (p 1992)

Main Study Findings	Author's Conclusions
assessment VAS, and knee range of motion. • No statistically significant differences between IA-HA and saline groups in treatment-related AEs such as arthralgia, joint swelling and joint stiffness.	
Campos et al., 2017[23]	
Knee OA (K-L: 4): IA-HA (Hylan GF 20 [Synvisc]; MW ~6,000 kDa; single injection) versus IA-CS (Triamcinolone) • Compared with baseline, functional assessments using Lysholm and KSS scores in both groups were significantly improved at 1 and 3 months ($P < 0.01$), but not at 6 months after injection. • No statistically significant differences between groups at each time point of follow-up.	*"Viscosuppplementation increased functional scores in patients with severe osteoarthritis of the knee, especially within three months on injection. However, it was not superior to the use of triamcinolone."*[23] (p 2273)
Vaishya et al., 2017[24]	
Knee OA (K-L: 2, 3): IA-HA (Synvisc; MW ~6,000 kDa; single injection) versus IA-CS (Triamcinolone) • KSS pain score – No statistically significant difference between groups at baseline ($P = 0.14$) and week 1 ($P = 0.47$) – Statistically significant improvement at week 4 (79.56 versus 75.35; $P = 0.01$), week 12 (80.24 versus 68.82; $P < 0.01$) and week 24 (76.80 versus 61.75; $P < 0.01$) in IA-HA group compared with IA-CS group. • KSS function score – No statistically significant difference between groups at baseline ($P = 0.12$), week 1 ($P = 0.16$) and week 4 ($P = 0.22$). – Statistically significant improvement at week 12 (73.90 versus 65.25; $P < 0.01$) and week 24 (70.60 versus 57.50; $P < 0.01$) in IA-HA group compared with IA-CS group. • VAS pain score No statistically significant difference between groups at baseline ($P = 0.09$), week 1 ($P = 0.34$) and week 4 ($P = 0.26$). Statistically significant improvement at week 12 (2.34 versus 2.80; $P < 0.01$) and week 24 (3.14 versus 3.60; $P = 0.03$) in IA-HA group compared with IA-CS group.	*"The present study demonstrated that both the triamcinolone and HA are safe and effective in relieving OA pain temporarily and are effective palliative agents and are not curative therapy. Steroid given IA can give pain relief for about 12 weeks while HA provides significant pain relief until six months after injection."*[24] (p 88)
Trueba Davalillo et al., 2015[25]	
Knee OA (K-L: 2, 3): IA-HA (Suprahyal; 9,000 kDa, multiple injection) versus IA-CS (betamethasone; multiple injection) Percent reduction in pain (Global, WOMAC) • At 3 months – IA-HA: 48.5%; 95% CI 45.8 to 51.3 – IA-CS: 66.3%; 95% CI 63.3 to 69.3 – Significantly higher in the IA-CS group compared to IA-HA group ($P < 0.0001$) • At 12 months – IA-HA: 33.6%; 95% CI 31.1 to 36.1 – IA-CS: 8.2%; 95% CI 5.2 to 11.1 – Significantly higher in the IA-HA group compared to IA-CS group ($P < 0.0001$) Functional improvement (WOMAC)	*"Both treatments effectively controlled OA symptoms. Betamethasone showed higher short-term effectiveness, while HA showed better long-term effectiveness, maintaining clinical efficacy in a large number of patients 1 year after administration."*[25] (p 9)

Main Study Findings	Author's Conclusions
• Higher in IA-HA group in every visit compared to IA-CS • At 12 months – IA-HA: 47.5%; 95% Ci 45.6 to 49.3 – IA-CS: 13.2%; 95% CI 11.4 to 14.9 – Significantly higher in the IA-HA group compared to IA-CS group (*P* < 0.0001) Percentage of patients achieving the MCII[a] • For a change of at least 15% for absolute change – At 9 months: IA-HA (81.4%) versus IA-CS (9.2%); *P* < 0.0001 – At 12 months: IA-HA (77.3%) versus IA-CS (6.1%); *P* < 0.0001 • For a change of at least 20% for relative improvement – At 9 months: IA-HA (87.6%) versus IA-CS (10.2%); *P* < 0.0001 – At 12 months: IA-HA (84.5%) versus IA-CS (5.1%); *P* < 0.0001 Treatment-related AEs • Rare and related to administration procedure. No significant differences between groups • Pain, erythema, effusion	

AEs = adverse events; Bio-HA = biologically fermented hyaluronic acid; CI = confidence interval or credible interval; CS = corticosteroid; HA = hyaluronic acid; IA = intra-articular; K-L = Kellgren-Lawrence; KSS = Knee Society score; MCII = Minimal Clinically Important Improvement; MW = molecular weight; NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; VAS = Visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

[a] "*MCII values were defined as 15 of 100 for absolute improvement and 20% for relative improvement in clinical trials of rheumatic diseases, with pain, functional disability, patient global assessment, or physical global assessment used as the outcome criteria. To calculate the MCII, total scores were normalized to a 0 to 100 score.*"[25] *(p 11)*