


Efficacy and Safety of Hylan G-F 20 Versus Intra-Articular Corticosteroids in People with Knee Osteoarthritis: A Systematic Review and Network Meta-Analysis

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ABSTRACT

BACKGROUND: Direct injection of corticosteroids into the joint is a standard treatment for knee osteoarthritis (OA). However, the treatment is somewhat controversial with regard to the benefit of both single and repeated injections; evidence that they are beneficial comes from small studies that show only modest improvements. The aim of this study was to estimate the short- and long-term clinical efficacy and safety of hylan G-F 20 versus intra-articular corticosteroids (IACS) for the treatment of pain in knee OA using Bayesian network meta-analysis.

METHODS: Based on a pre-specified protocol, MEDLINE, Embase, and CENTRAL were searched from inception to June 2018 to identify randomized controlled trials. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used to assess the included studies. Hylan G-F 20 and IACS were compared using Bayesian network meta-analysis. Efficacy was evaluated at 1, 3, and 6 months, and at the final follow-up for safety outcomes. A pain hierarchy was used to select 1 pain outcome per study.

RESULTS: Forty-two trials were included for analysis. The network meta-analysis of pain showed that hylan G-F 20 may be equivalent to IACS in the short-term, but by 6 months the benefit relative to IACS was statistically significant, standardized mean difference (95% credible interval): -0.13 (-0.26 , -0.01). There were no statistical differences in adverse events.

CONCLUSIONS: Hylan G-F 20 may perform better in relieving pain at 6 months post-injection compared to IACS. Both agents were relatively well tolerated, with no clear differences in safety.

KEYWORDS: Osteoarthritis, knee, hyaluronic acid, injections, intra-articular, molecular weight, network meta-analysis

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Background

Osteoarthritis (OA) is a leading cause of disability and the most common form of arthritis affecting around 250 million people worldwide,¹ and more than 27 million people in the United States.² Multiple factors play a role in development of OA, with elderly females, people with obesity, and African Americans being at greater risk of developing OA.³ Treatment for people with symptomatic OA of the knee starts with participation in self-management programs, neuromuscular education, and engagement in physical activity such as strengthening or low-impact aerobic exercises.⁴ In addition, pharmacological treatments are conditionally recommended in people who fail to obtain adequate pain relief with over-the-counter acetaminophen, non-steroidal anti-inflammatory drugs, or nutritional supplements.⁵

In the absence of effective disease-modifying medical interventions for knee OA, treatments are primarily symptomatic in nature, often including intra-articular (IA) injections of a corticosteroid (CS) for pain relief.⁶ IACS is a standard treatment for knee OA; however, clinical evidence for the effectiveness of this intervention is not robust.^{7–9} IACS injections have been linked with cartilage loss,⁷ radiographic worsening,⁸ and only short-term pain relief.⁹ In a systematic review of published literature on IACS injections (27 studies with 1767 participants), the quality of the evidence across outcomes was graded low due to inconsistent treatment effect estimates, great variation across trials, imprecise pooled estimates, and high or unclear risk of bias across most included trials.¹⁰ For these reasons, in the current study we took particular interest in change in efficacy estimates relative to time from injection.



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Hylan G-F 20 is an HA preparation consisting of hylan A, a 6000 kDa HA, and hylan B, a cross-linked derivative of natural HA.¹¹ There are 2 hylan G-F 20 formulations: a single-shot (wherein 6 mL is administered) and the once weekly \times 3 approach (wherein 2 mL is administered across multiple injections).^{12,13} An early Cochrane review found that hylan G-F 20 significantly improved pain and movement relative to placebo, significantly improved pain but not function relative to non-steroidal anti-inflammatory drugs, and significantly improved pain as well as function when added to standard of care.¹⁴ Despite mixed results from head-to-head trials comparing different HA formulations,¹⁵⁻¹⁷ many of the more recent meta-analyses have taken a broader focus by combining multiple HA formulations, and subsequently found lower efficacy estimates¹⁸ and higher rates of adverse events.¹⁹ Relative to agents that are low molecular weight and non-crosslinked, high molecular weight crosslinked agents are more effective.²⁰ Hylan G-F 20 is both crosslinked and has a high molecular weight, suggesting it may be more efficacious than other types of IAHA injections. For this reason, it is important to compare the efficacy of hylan G-F 20 to IACS injections in the treatment of knee OA, instead of comparing all IAHA agents as a group to IACS injections. Consequently, one reason for the imprecision and variation in findings from prior studies may be that they have not distinguished the intrinsic properties of HA injections, but have included all types of HA injections regardless of molecular weight or whether they are crosslinked.²¹

Consistent with these discrepancies in the published reviews, recommendations from multiple international guideline committees²²⁻²⁵ regarding the widespread use of HA to treat pain in knee OA are sometimes discordant.²⁶ A return to more focused meta-analyses will likely benefit this field. Therefore, the objective of this study was to evaluate the clinical efficacy and safety of hylan G-F 20 and IACS in people living with knee OA, 6 months post-treatment. A systematic literature review was conducted to identify relevant published literature, followed by a Bayesian network meta-analysis (NMA).

Methods

Eligibility criteria

Standard methods for conducting systematic reviews as per guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions were followed.²⁷ Eligibility criteria were developed using the Population, Intervention, Comparator, and Outcome (PICO) framework. RCTs evaluating efficacy and safety of treatments for adults with knee OA who were treated with IACS and HA were included.

Search methods

Relevant studies were identified by conducting searches in the following databases, from inception until 12 June 2018: MEDLINE (via PubMed), Embase (via Ovid), and the

Cochrane Central Register of Controlled Trials (via Wiley) (Supplemental Tables 1–3). As well, conference abstracts for the years 2016 to 2018 from the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), The Asian Pacific League of Associations for Rheumatology (APLAR), and Osteo-Arthritis Research Society International (OARSI) were searched. Hand-searching was also performed on the reference lists of previously published systematic literature reviews on the same topic and eligible articles screened through main database search to capture additional eligible studies that were missed during the main database search.

Study selection

Two investigators reviewed all abstracts identified in the systematic literature review. PICO criteria were applied, and abstracts deemed eligible for inclusion were advanced to full-text screening. Full-text articles were screened by 2 investigators. Articles deemed eligible after full-text screening were included in the systematic literature review. At each stage of the screening process, disagreements due to differences in interpretation between investigators were resolved by a third investigator in order to reach a consensus.

Data extraction

Data was extracted independently by 2 investigators, and if disagreements due to differences in interpretation could not be resolved, a third investigator was consulted to reach consensus. The Digital Outcome Conversion (DOC) Data version 2.0 software platform (Doctor Evidence, LLC, Santa Monica, CA, USA) was used to store and manage data. Extraction included trial characteristics, interventions, participant characteristics, as well as efficacy and safety outcomes. Characteristics of interest were age, gender, race/ethnicity, body mass index (BMI), and whether ACR criteria were used for the diagnosis of knee OA.

Pain scores at 1, 2, 3, and 6 months were the primary efficacy outcomes of interest for this review and analysis. A pain hierarchy was used to select 1 pain outcome from each study.³¹ Safety outcomes included overall adverse events, treatment-related adverse events, and serious adverse events.

Cochrane risk of bias tool

The Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used to assess the randomized trials.³⁰ This instrument is used to evaluate 7 domains of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias.

Statistical analysis

The primary outcome of interest was pain measured using a pain hierarchy.²⁸ Adverse events (overall, serious, treatment related) were also analyzed. Preliminary pairwise meta-analyses were performed using the DerSimonian-Laird method.²⁹ This was done to assess heterogeneity between studies and assess inconsistency across studies for potential exclusion from the network. For continuous variables, only change from baseline scores were analyzed using a random-effects model. If different studies reported different units for the same outcome, a standardized mean difference (SMD) was calculated. Comparative estimates for the continuous outcomes measured on the same scale were represented as mean difference (MD) with associated 95% confidence intervals (CI). We used these models to assess statistical heterogeneity by inspecting the forest plots, and the calculated I^2 using the R software package “metafor.”³⁰ Estimates based on direct and indirect evidence were compared to assess potential inconsistency.

The primary NMA was conducted using standard practice models described by the National Institute for Health and Care Excellence Decision Support Unit, Technical Support Documents (NICE DSU TSD) series.³¹ All analyses were performed in a Bayesian framework and involved a model with parameters, data, a likelihood distribution, and prior distributions. The NMA was performed for efficacy outcomes at 1, 3, and 6 (± 0.5) months; and the final follow-up time point for safety outcomes. The following characteristics were included in the baseline heterogeneity analysis: age, gender, BMI, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, VAS pain, WOMAC overall score. Inconsistency between direct and indirect evidence is more prevalent in the medical literature than previously supposed,³² and violates a basic assumption of NMA.³³ Consequently, consistency between direct and indirect evidence was evaluated for each path in our model.

For the NMA of continuous data, SMD and credible intervals (CrI) were used because the pain scales across the included studies were different. The SMD was calculated using a normal/identity link-likelihood model. For binary (eg, adverse) events, only intervention groups with at least 1 event were included to avoid divide by 0 errors for odds ratio (OR) and relative risk comparisons. This was done as an alternative to adding pseudo counts to the data. The binary data was analyzed as “OR” using the binomial/logit link-likelihood model. The R software package “gemtc” which utilizes jags was used to perform the calculations within a Bayesian framework using a random-effects model.³⁴ The model fit was evaluated via the deviance information criterion, which supported the use of a random-effects model over a fixed-effects model. A burn in of 5000 for 2 chains and 20 000 iterations were run with a thinning parameter of 10.

Results

Literature search findings

A total of 1114 publications were identified by the systematic review. After removing duplications, 804 unique publications were screened, and 659 were excluded (frequently for wrong study design, or not being an empirical study), leading to inclusion of 145 publications after title and abstract screening. After full-text screening and additional 61 studies were excluded (frequently for having the wrong intervention or lacking an outcome of interest) leaving 84 publications. Out of those 84 included publications, 42 were excluded from the statistical analysis (due to lack of actionable data). In the final analysis, 42 publications reporting on 42 distinct trials representing a total of 8047 adults were included in the NMA.^{7,16,35-75} The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies at each stage is presented in Figure 1.

Cochrane risk of bias tool

The studies tended towards low risk of bias, except for the random sequence generation and allocation concealment (selection bias) categories. Of the 41 studies, twenty had low risk of bias associated with random sequence generation (selection bias)^{7,36,38,41-43,45,46,48,51,55,58,60-62,64,68-71} and 21 had unclear risk due to the fact that although described as randomized, no description of the randomization procedure was presented.^{16,35,37,39,44,47,49,50,52,54,56,57,59,63,65-67,72-74} The second component of selection bias (allocation concealment) had 20 studies which described concealment methods and therefore had low risk^{7,16,36,41-43,45,46,48,49,51,54,55,58,60,61,64,65,70,71} and 21 studies with unclear risk as the concealment process was not described.^{35,37-40,44,47,50,52,56,57,59,62,63,66-69,72-74} In terms of performance bias, 26 studies blinded both participants and personnel and were judged to have low risk.^{7,16,35,36,40-43,45,46,48-51,54,55,58,60-62,65-67,69-71} Eight studies had unclear risk of performance bias due to either lack of information^{44,52,63,68,74} or participants but not investigators being blinded.^{37,47,56} Seven studies were considered at high risk of performance bias due to open-label study design.^{38,39,57,59,64,72,73} Studies generally had low risk of outcome assessment bias ($n = 31$).^{7,16,35,36,38-43,45-51,54,55,58,60-62,64-67,69-72} Six had an unclear risk of bias as there was no specification on the blinding methodology,^{44,52,63,68,73,74} and 4 studies had high risk of outcome assessment bias due to being unblinded,⁵⁷ or single blinded.^{37,56,59} Most studies ($n = 28$) were assessed to have low risk of attrition bias,^{7,16,35-38,41-44,46,48,49,51,54-56,58,59,61,62,64,66,68-72} though 7 studies were deemed “unclear” due to unspecified follow-up sample size ($n = 6$),^{52,57,63,67,73,74} and 5 were deemed high risk due to attrition rates greater than 20%.^{39,40,50,65} Almost all studies ($n = 39$) were assessed to have low risk of reporting bias,^{7,16,35-37,39-52,54-61,63,64,66-74} though 2

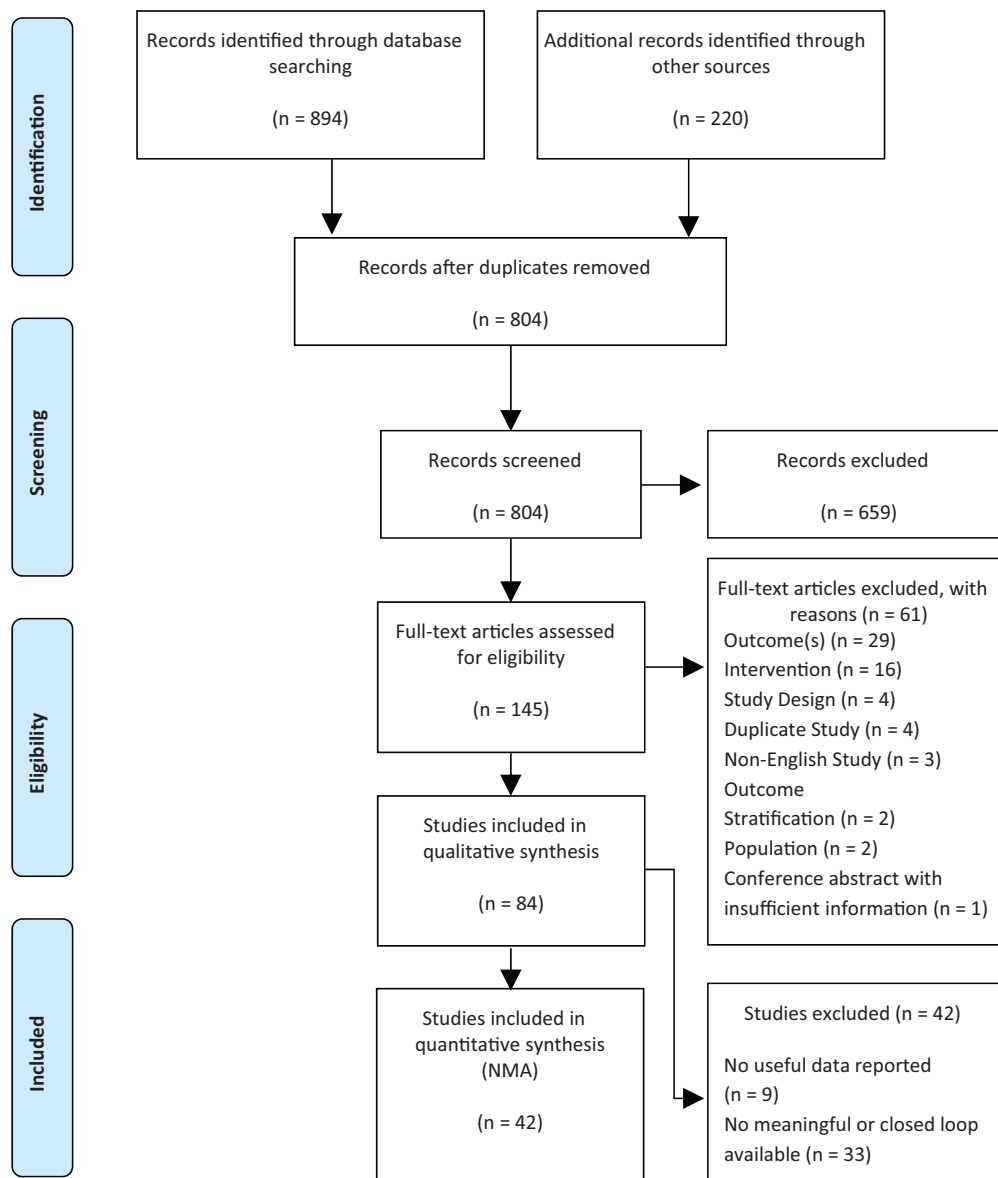


Figure 1. PRISMA flow diagram.

studies had a high risk of bias due to failing to report the use of paracetamol⁶² or the presence of knee effusion,⁶⁵ despite specifying that these would be investigated in the methods. Most studies had low risk of other sources of bias (n = 33).^{16,36,37,39,41,42,45,47-52,54-58,60-74} However, 8 studies were deemed to have unclear risk of additional bias^{7,35,38,40,43,44,46,59} (eg, baseline differences, power concerns, possible randomization failure, and different amounts of the active intervention and the saline-solution to be injected).

Network meta-analysis

The main network consisted of 4 nodes corresponding to 4 interventions: hylan G-F 20, IACS, HA other than hylan G-F 20, and placebo (administration route was intraarticular in 14 studies and oral in 1 study). Sensitivity analyses showed no significant difference between Synvisc® (hylan G-F 20, 2 ml

[16 mg], 3 weekly injections) and Synvisc-One® (hylan G-F 20, 6 ml [48 mg], 1 weekly injection), so they are combined in the primary models.

Trureba et al (2015) and Wobig et al (1998) were excluded from the NMA at 6 months because the magnitude of effects (4 and 1.4, respectively) were larger than all the other studies (effect size range: -0.81 to 0.63), which led to inconsistency in the network by skewing the direct effect point estimate. Karlsson et al (2002) was excluded due to being an outlier in the heterogeneity analysis of age. Iannitti et al was excluded due to being an outlier in the heterogeneity analysis of age and gender. After removal of these outliers, the evidence was consistent with no inconsistency between direct and indirect evidence.⁴⁹

Pain. Twenty-four studies reported pain score at 1 month, followed by 21 studies at 3 months, and 21 studies at 6 months (Figure 2 illustrates this network). In analyzing the results for

pain reduction at 1 month, all of the 3 treatments (hylan G-F 20, other HA formulations, IACS) were statistically superior to placebo, but not significantly different from each other (Figure 3).

However, at 6 months the pain reduction effect of hylan G-F 20 was significantly greater than IACS (SMD: -0.13, 95% CrI: -0.26, -0.01), as was the pain reduction of other HA formulations (SMD: -0.20, 95% CrI: -0.30, -0.09). Hylan G-F 20 and other HA formulations were statistically indistinguishable from one another (Supplemental Table 4). The pain reduction of IACS had attenuated but remained significantly greater than placebo (SMD: -0.16, 95% CrI: -0.26, -0.05).

Safety outcomes. Compared to participants treated with IACS, participants treated with hylan G-F 20 did not experience significantly different odds of adverse events (OR [95% CrI]: 1.32 [0.94, 1.93]), treatment-related adverse events (OR [95% CrI]: 2.72 [0.83, 9.75]), or serious adverse events (treatment-related or unrelated to treatment) (OR [95% CrI]: 0.53 [0.05, 2.53]) (Table 1).

Discussion

Using a Bayesian NMA approach, we found that a single or 3-injection course of hylan G-F 20 is likely to be superior to IACS at 6 months in terms of pain relief. This result is robust, and it is based on data from 21 published studies of generally low risk across the domains of bias in the Cochrane tool. Prior

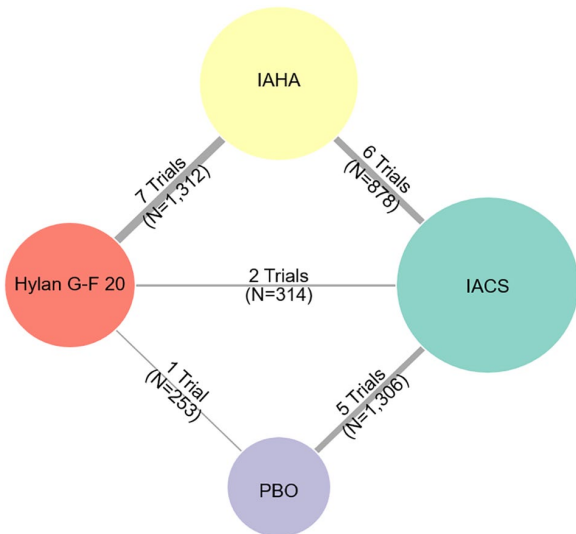


Figure 2. Network for change from baseline to 6months in pain scores. The numbers by the vertices indicate how many publications reported the respective comparison between the connected nodes (interventions). IACS, intra-articular corticosteroid; IAHA, intra-articular hyaluronic acid; PBO, placebo.

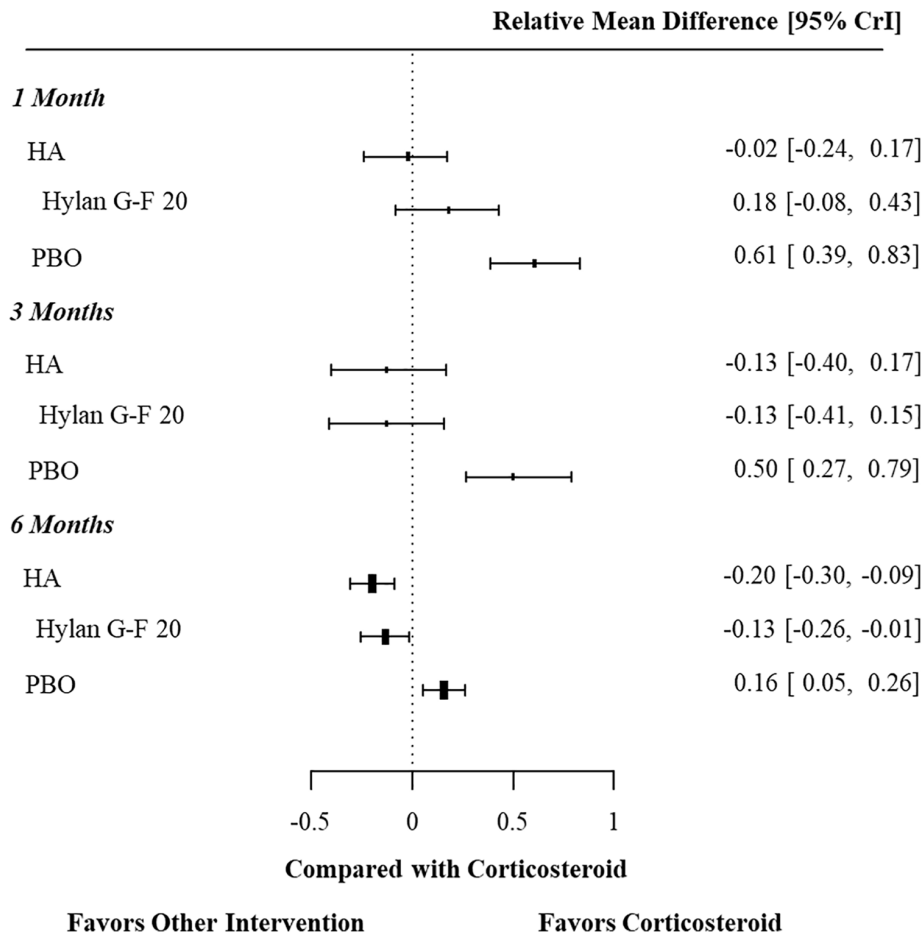


Figure 3. Pain score, results from the network meta-analysis. CrI, credible intervals; HA, intra-articular hyaluronic acid; PBO, placebo.

Table 1. Safety results of the network meta-analysis.

COMPARISON	ADVERSE EVENT	ADVERSE EVENT, SERIOUS	ADVERSE EVENT, TREATMENT-RELATED
Hylan G-F 20 vs IACS OR (95% CrI)	1.32 (0.94, 1.93)	0.53 (0.05, 2.53)	2.72 (0.83, 9.75)

CrI, credible interval; IACS, intra-articular corticosteroid; OR, odds ratio.

meta-analytic work has shown the SMD between IACS and placebo for the treatment of knee OA is 0.40 (calculated from a relative risk of 2.09, 95% CI: 1.20, 3.65).⁷⁵ Our findings show an SMD of 0.13 between hylan G-F 20 and IACS, suggesting a 33% improvement in absolute pain score with hylan G-F 20 over IACS for the treatment of knee OA. Additionally, based on this SMD, we can calculate the number needed to treat (NNT) as 14, using methods described by Furukawa et al 2011.⁷⁶ Hence, our meta-analysis suggests that when compared with IACS treatment, 14 adults would need to be treated with hylan G-F 20 in order to have 1 experience better pain relief.

Our results also show a time-dependent dynamic for the treatment effects of both IACS and HA. At early stages post-injection (1 month) IACS treatment seems to have a slight advantage. However, at 3 months the effect flips, and HA becomes more effective, with the difference reaching statistical significance at 6 months post-treatment. Our findings are similar to a previous smaller literature review and meta-analysis of 7 trials which found that IACS is more effective than HA in the short term (up to 4 weeks), whereas HA is more effective in the long term (4–26 weeks).⁶ This delayed effect of hylan G-F 20 has been commented on directly by authors in several of the included studies.^{36,39,57} It is consistent with the argument that the advantage of a high molecular weight agent, such as hylan G-F 20, may be due to a long-term increase in viscoelasticity of synovial fluid, but indirect actions of HA may be linked also to decreasing extra cellular matrix degradation and inflammation.^{77–79} The current findings cannot speak to the mechanism by which hylan G-F 20 and other HA formulations show improved efficacy over time, but they do demonstrate that the pattern of improvement continues through 6 months post-treatment.

The safety profiles of these interventions are similar. IACS showed, numerically, less overall adverse events and treatment-related adverse events, whereas hylan G-F 20 showed a smaller incidence of serious adverse events (treatment-related or unrelated to treatment) and injection side flare-ups. Although the overall adverse events were higher with hylan G-F 20, most of them were mild in nature. None of the safety outcome comparisons mentioned above reached statistical significance. However, there still remain safety concerns with IACS.⁸⁰ A recent review highlighted 4 main adverse joint events following IACS injections including accelerated OA progression, subchondral insufficiency fracture, and complications of osteonecrosis and rapid joint destruction (including bone loss). These findings suggest careful considerations of patient characteristics and needs before administering IACS.⁸⁰

A final consideration is the less obvious influence of sampling bias on the real-world overall benefit/risk ratio of these 2 treatments. Adults with uncontrolled hypertension, diabetes, immunocompromised status, and drepanocytes are more exposed to complications with IACS and are often excluded from these trials. This means that in addition to the support for the relative benefit of hylan G-F 20 quantified here, there is also an unquantifiable benefit due to these additional IACS-related adverse events which do not manifest in the trial data as those participants are often screened out.

Limitations

A primary limitation was the gap between the number of studies that officially met our PICO criteria and the number of those studies which provided sufficient data to be included in the network. Many studies did not report sufficient data to be included in the meta-analysis (eg, reporting baseline and endpoint data but not variance), and adverse events that had zero reported events in the arms of interest were not included in the analyses, which would have the effect of biasing upward the model-based estimates of adverse events. We attempted to calculate change from baseline scores (if not reported by study authors) using the baseline and endpoint scores. However, some studies did not report the associated variance and, therefore, we could not include these studies. In order to create a more robust network, this analysis used the assumption that, regardless of type, the effectiveness of all individual IAHA (other than hylan G-F 20) are the same. Similarly, all individual IACS were assumed to be the same. However, research indicates that there is some variation between individual IAHA and IACS, therefore a degree of imprecision was introduced into the network.²⁰ This is a limitation to the analysis that was conducted in this study. We removed from the network several studies that were outliers in the preliminary analysis, which, although allowing us to satisfy the consistency assumption necessary for NMA, also had the effect of omitting data.

Conclusion

Overall, the results of the NMA suggest that in people with knee OA, hylan G-F 20 is similar to IACS in improving symptoms in the short term but likely to be better in relieving pain at 6 months post-injection. This effect was also observed in other HA formulations. Both therapies were relatively well tolerated with no clear differences in safety.

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Authors' contributions

All authors contributed to the conception and design of the study, analysis and interpretation of the data, the drafting of the article, revision of the article for content, and final approval of the article.


Availability of data and materials

Not applicable. The data used for analysis was retrieved from openly published studies listed in our manuscript.

Ethics approval and consent to participate

Since our study is a systematic literature review and network meta-analysis, an Ethical Review Committee Statement is not applicable.

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Supplemental material

Supplemental material for this article is available online.

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