

Hyaluronic Acid Injections or Oral Nonsteroidal Anti-inflammatory Drugs for Knee Osteoarthritis

Systematic Review and Meta-analysis of Randomized Trials

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Background: Intra-articular hyaluronic acid (HA) injections and oral nonsteroidal anti-inflammatory drugs (NSAIDs) are common treatments for symptomatic knee osteoarthritis (OA). However, the comparative effects of these treatments are unclear.

Purpose: To compare the efficacy and safety of intra-articular HA injections compared with oral NSAIDs for the treatment of knee OA.

Study Design: Systematic review; Level of evidence, 1.

Methods: We systematically searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for randomized trials of knee OA treatment with HA injections compared with oral NSAIDs. The main outcomes were knee pain, knee function, adverse events (AEs), serious AEs, study withdrawals, and study withdrawals because of AEs. Pooled effect sizes were reported at the final follow-up with standardized mean difference (SMD) for efficacy outcomes and risk ratio (RR) for safety outcomes.

Results: In 6 randomized trials of 831 patients (414 HA, 417 NSAIDs), with follow-up ranging from 5 to 26 weeks, HA injections were associated with small, statistically significant improvements in knee pain (SMD, 0.15; $P = .04$) and knee function (SMD, 0.23; $P = .01$) compared with oral NSAIDs. The risk of AEs was lower with HA compared with NSAIDs (19.8% vs 29.0%; RR, 0.74; $P = .01$). The risk of a serious AE (RR, 1.37; $P = .71$), study withdrawal (RR, 1.05; $P = .68$), or study withdrawal because of an AE (RR, 0.65; $P = .22$) was comparable between groups. Gastrointestinal concerns were the most frequent AE reported, occurring more often with NSAIDs (23.4% vs 14.1%; $P = .001$). AEs reported more frequently with HA injections were injection site pain (11.7% vs 4.7%; $P < .001$), headache (8.4% vs 4.4%; $P = .03$), and arthralgia (8.1% vs 2.9%; $P = .001$). Significant heterogeneity or publication bias was not observed for any outcome.

Conclusion: Comparing short-term outcomes of HA injections with oral NSAIDs for treatment of knee OA, HA injections provided statistically significant but not clinically important improvements in knee pain and function, along with a lower overall risk of AEs.

Keywords: knee function; knee pain; nonsteroidal anti-inflammatory drug; safety; viscosupplementation

Osteoarthritis (OA) is a degenerative disease of the synovial joints that is characterized by progressive articular destruction and manifests clinically as joint pain and dysfunction. Knee OA is the leading cause of disability in older adults,¹¹ and the prevalence of this disease is anticipated to increase in the coming decades.³² More than 1 in 3 Americans over 60 years of age have radiographic evidence of knee OA, with 35%-40% of affected patients reporting bothersome symptoms.¹⁷

Numerous pharmacologic and nonpharmacologic treatment options are available to individuals with symptomatic knee OA. In the clinical practice guidelines for knee OA

treatment released by the American Academy of Orthopaedic Surgeons,⁴ the only recommended nonsurgical treatment appropriate for all patients was nonsteroidal anti-inflammatory drugs (NSAIDs). Oral NSAIDs are prescribed to approximately 65% of patients with knee OA¹⁹ despite significant limitations and health risks. Most patients who chronically consume NSAIDs continue to report persistent pain and disability, and over half will discontinue use within 1 year of receiving a prescription.³⁶ Compared with placebo, ibuprofen increases the risk of stroke by over 3-fold.³⁹ Diclofenac, which is the most effective NSAID available for OA treatment,¹⁴ increases the risks of stroke by 3-fold, cardiovascular death by 4-fold, and all-cause death by 2-fold.³⁹ Further, NSAIDs as a class increase the risk of gastrointestinal complications with long-term use.³⁶ For these reasons, oral NSAIDs are

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generally recommended for intermittent or cyclic use. Yet, this recommendation poses a dilemma to individuals with knee OA—continue with a therapy that may provide partial symptom relief at the expense of systemic complication risks or utilize an intermittent or cyclic medication regimen but with insufficient symptom control during periods of NSAID abstinence. In the typically older patient population with knee OA, an ideal nonsurgical treatment would provide clinically important improvements in OA-related symptoms without systemic complication risks.

Intra-articular injection of hyaluronic acid (HA) is intended to alleviate knee symptoms by improving the viscoelastic properties of synovial fluid and reversing OA-induced proinflammatory pathways.¹⁵ HA injections have been demonstrated to be safe for the treatment of knee OA,³⁷ but efficacy results have been mixed.^{5-7,13,31,34,35,37,40} Because HA injections and oral NSAIDs are among the most commonly utilized nonoperative knee OA treatments,¹⁰ evaluation of their comparative efficacy and safety is warranted. Bannuru et al⁷ performed the only known direct-evidence meta-analysis of randomized trials comparing HA injections with oral NSAIDs for knee OA. The review included randomized trials published through 2013 and evaluated efficacy outcomes through 12-week follow-up. Yet, HA injections may provide symptom relief for longer periods,³⁷ and oral NSAID use over longer durations is prevalent.²¹ Therefore, the objective of the current study was to extend these findings by performing a contemporary systematic review and meta-analysis comparing the efficacy and safety of HA injections and oral NSAIDs for treating knee OA through 26-week follow-up.

METHODS

The methodology, analysis, and reporting of this systematic review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²⁸ The review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) public database (CRD42019128797; <http://www.crd.york.ac.uk/PROSPERO>).

Eligibility Criteria and Search Strategy

Eligible studies were randomized trials comparing HA injections with oral NSAIDs for treatment of knee OA. We systematically searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for

potentially eligible studies, with supplemental searches conducted in the Directory of Open Access Journals and Google Scholar. Manual searches of the reference lists of included papers and relevant meta-analyses were performed. No date, language, or sample size restrictions were applied to the searches. The search strategy included a combination of study design-, diagnosis-, and treatment-specific keywords (see Appendix Table A1). Two researchers (L.M.), both with expertise in systematic review searching, independently screened titles and abstracts for eligibility. Full-text manuscripts were obtained for all eligible studies and for those where eligibility was uncertain. Disagreements related to study eligibility were resolved by discussion. The final searches were performed on March 31, 2019.

Data Extraction

Data were extracted independently from eligible studies by 2 researchers (L.M.) using standardized data collection forms developed a priori. Data extraction discrepancies between the 2 researchers were resolved by discussion. Data items included metadata, patient characteristics, study characteristics, treatment regimens, efficacy outcomes, and safety outcomes. Efficacy outcomes included knee pain and knee function, which were extracted from papers in a nonbiased manner using the knee OA outcome meta-analysis hierarchy of Juhl et al.²⁵ We extracted efficacy data at 3 distinct intervals— 4 ± 1 weeks, 12 ± 1 weeks, and 26 ± 1 weeks—which align with typical reporting standards in the HA injection literature. The 26-week follow-up duration was chosen to approximate the 6-month stated duration of the effect on product labeling of HA products. Safety outcomes included adverse events (AEs), serious AEs, study withdrawals, and study withdrawals because of AEs. We also extracted and analyzed individual AEs reported in each study. Safety data were reported through the final follow-up in each trial. The frequency of AEs was categorized as very common ($\geq 10\%$), common (1% to 10%), or uncommon (0.1% to 1%).³⁸ We used the Cochrane Collaboration tool to assess the risk of bias in individual studies.²² Industry funding was considered as high risk of bias under the “other sources of bias” domain.

Data Analysis

Pooled efficacy outcomes were reported using the standardized mean difference (SMD) statistic. The SMD is used as a summary statistic when studies assess the same outcome

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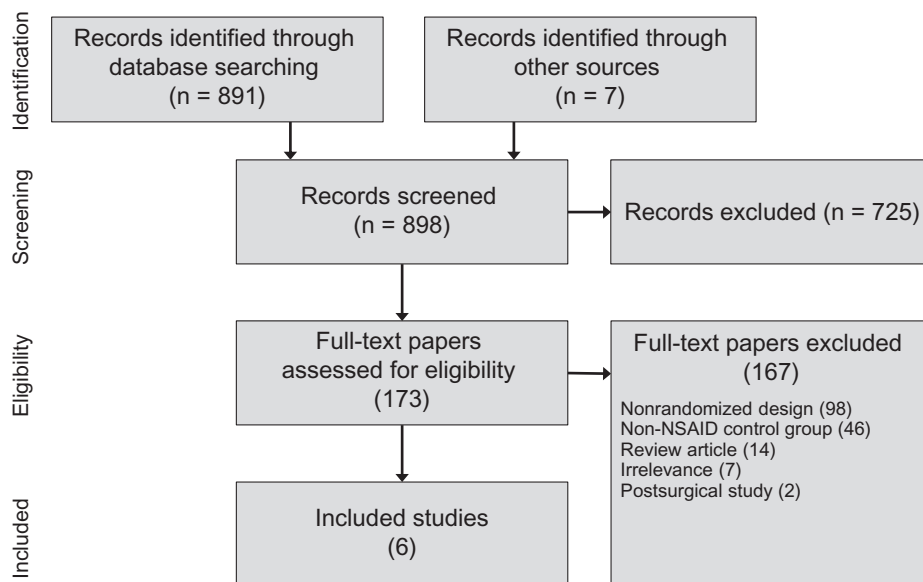


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram. NSAID, nonsteroidal anti-inflammatory drug.

using different scales, and, therefore, it is necessary to standardize the results to a uniform scale for analysis purposes. The SMD expresses the size of the treatment effect relative to the variability observed. For reference, SMD values of 0.2, 0.5, 0.8, and 1.0 are defined as small, medium, large, and very large effect sizes, respectively.¹² Positive SMD values favored the HA group and negative values favored the NSAID group. The primary efficacy analysis was performed at the final follow-up in each trial, with temporal trends at each interval evaluated in a sensitivity analysis. Pooled safety outcomes were reported using the risk ratio (RR); an RR < 1 indicated lower risk with HA injections, and an RR > 1 indicated higher risk with HA injections. For each outcome, the effect size and 95% CI were calculated for each study, and the overall pooled results were visually displayed using forest plots. We used the I^2 statistic to estimate the heterogeneity of outcomes among studies, where a value of 0% represented no heterogeneity and larger values represented increasing heterogeneity.²³ Significant heterogeneity was defined by a Cochran Q test ($P < .1$ or $I^2 > 50\%$). When significant heterogeneity existed, a random-effects model was planned; otherwise, a fixed-effects model was planned.²⁷ Publication bias was assessed by visual inspection of funnel plots and with Egger regression test.¹⁸ In accordance with Cochrane Collaboration recommendations, we planned to perform a meta-regression on the association of study-level factors with any efficacy or safety outcome reported in at least 10 studies; otherwise, these associations would be reported descriptively only. We analyzed the frequency of individual AEs in each group using counts and frequencies and compared the groups using the Fisher exact test. P values were 2-sided with a significance level < .05. Analyses were performed using Stata v 14.2 (StataCorp) and Review Manager v 5.3 (The Cochrane Collaboration).

RESULTS

Study Selection

Among 898 records identified in our searches, we reviewed the full text of 173 potentially relevant papers. After review, 167 papers were excluded from further consideration, most commonly because of nonrandomized controlled study design or use of a non-NSAID control group. Ultimately, 6 randomized controlled trials comprising 831 patients (414 HA, 417 NSAIDs) were included in this review. A PRISMA flow diagram depicting the study identification and selection process is provided in Figure 1.

Patient and Study Characteristics

Baseline patient and study characteristics in each group are reported in Table 1. The mean patient age in each study ranged from 57 to 69 years, and there was a slight female predominance in most studies. Studies generally enrolled patients with mild-to-moderate radiographic evidence of knee OA; no study enrolled patients with a Kellgren-Lawrence grade 4 diagnosis. The total sample size in each trial ranged from 60 to 327, and follow-up durations ranged from 5 to 26 weeks. The study of Buendía-López et al⁸ included follow-up data through 52 weeks, but only outcomes through 26 weeks were extracted for meta-analysis. HA injections and oral NSAID treatment protocols varied among studies. HA injection treatment regimens included a single course of 1- (1 study), 3- (3 studies), or 5- (2 studies) weekly injections, and 3 studies facilitated patient blinding via use of oral placebos. The oral NSAID group consumed diclofenac in 2 studies and loxoprofen, etoricoxib, naproxen, or unspecified NSAIDs in 1 study each. Patient blinding in

TABLE 1
Patient and Study Characteristics in Randomized Controlled Trials Included in the Meta-analysis^a

Study	No. Randomized (HA, NSAID)	Age, y (HA, NSAID)	Female, % (HA, NSAID)	BMI, kg/m ² (HA, NSAID)	Symptom Duration, y (HA, NSAID)	K-L Grade	Treatment Regimen	Effectiveness Outcomes	Follow-up, wk
Adams, 1995 ¹	31, 34	61, 63	68, 68	27, 24	5, 8	1-3	HA: 3-weekly Synvisc injections NSAID: Usual NSAIDs and 3-weekly arthrocentesis	Pain: Pain with motion VAS Function: Restriction of activity VAS	26
Altman, 1998 ²	164, 163	62, 63	61, 57	32, 32	≥1, ≥1	2-3	HA: 5-weekly Hyalgan injections and oral placebo bid NSAID: Naproxen 500 mg bid and 5-weekly sham injections	Pain: Pain on 50-foot walk VAS Function: Not reported	26
Dickson, 2001 ¹⁶	53, 55	65, 64	57, 55	29, 29	—	—	HA: 3-weekly Synvisc injections and oral placebo qd NSAID: Diclofenac 100 mg qd and 3-weekly arthrocentesis	Pain: WOMAC Pain Function: WOMAC Function	12
Petrella, 2002 ³³	30, 30	67, 66	36, 42	30, 29	—	1-3	HA: 3-weekly Suplasyn injections and oral placebo bid NSAID: Diclofenac 75 mg bid and 3-weekly saline injections	Pain: WOMAC Pain Function: WOMAC Function	12
Ishijima, 2014 ²⁴	100, 100	68, 69	72, 71	24, 24	—	1-3	HA: 5-weekly Suvenyl injections NSAID: Loxoprofen 60 mg tid	Pain: Pain VAS Function: JKOM	5
Buendía-López, 2018 ⁵	36, 35	57, 57	53, 52	25, 25	—	1-2	HA: 1 Durolane injection NSAID: Etoricoxib 60 mg qd	Pain: WOMAC Pain Function: WOMAC Function	26 ^b

^abid, twice a day; BMI, body mass index; HA, hyaluronic acid; JKOM, Japanese Knee Osteoarthritis Measure; K-L, Kellgren-Lawrence; NSAID, nonsteroidal anti-inflammatory drug; qd, four times a day; tid, three times a day; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^bStudy follow-up was through 52 wk, but data for meta-analysis were extracted through 26 wk only.

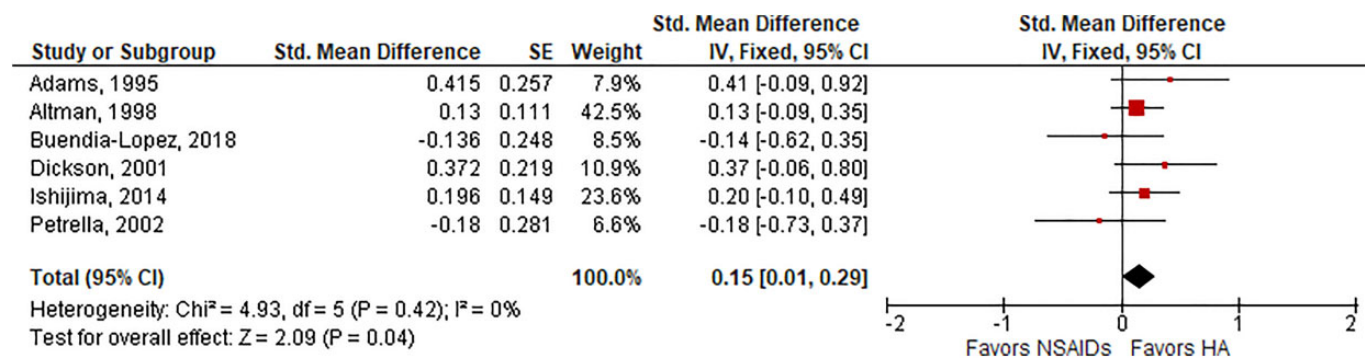


Figure 2. Standardized mean difference (SMD) for knee pain with hyaluronic acid (HA) injection vs oral nonsteroidal anti-inflammatory drugs (NSAIDs). SMD = 0.15 ($P = .04$), favoring HA injections, in fixed-effects model. Heterogeneity: $I^2 = 0\%$, $P = .42$. Publication bias: Egger P value = .84. IV, inverse variance; SE, standard error.

the oral NSAID group was conducted using additional arthrocentesis or saline injections in 4 studies. The most common potential sources of bias were lack of reports specifying investigator or participant blinding, industry bias, and incomplete outcome data (Appendix Table A2, Figure A1).

Efficacy Outcomes

Among 6 trials with follow-up ranging from 5 to 26 weeks, HA injections were associated with a small, statistically significant improvement in knee pain compared with oral NSAIDs (SMD, 0.15; $P = .04$) (Figure 2). Heterogeneity

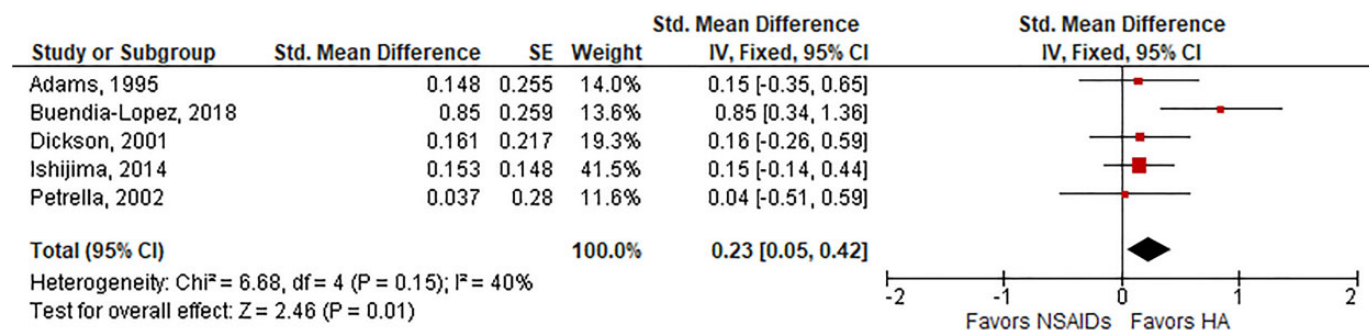


Figure 3. Standardized mean difference (SMD) for knee function with hyaluronic acid (HA) injection vs oral nonsteroidal anti-inflammatory drugs (NSAIDs). SMD = 0.23 (P = .01), favoring HA injections, in fixed-effects model. Heterogeneity: I² = 40%, P = .15. Publication bias: Egger P value = .62. IV, inverse variance; SE, standard error.

TABLE 2
 Sensitivity Analysis of Temporal Trends in Efficacy Outcomes With Hyaluronic Acid Injection vs Oral Nonsteroidal Anti-Inflammatory Drugs^a

Follow-Up	Knee Pain	Knee Function
4-5 wk	SMD = 0.00, P = .99 (3 studies)	SMD = 0.13, P = .33 (2 studies)
12 wk	SMD = -0.03, P = .78 (3 studies)	SMD = 0.01, P = .97 (2 studies)
26 wk	SMD = 0.17, P = .07 (3 studies)	SMD = 0.49, P < .01 (2 studies)
Final (≥4 wk) ^b	SMD = 0.15, P = .04 (6 studies)	SMD = 0.23, P = .01 (5 studies)
Final (≥12 wk) ^c	SMD = 0.17, P = .05 (4 studies)	SMD = 0.36, P = .01 (3 studies)

^aSMD, standardized mean difference.

^bFinal follow-up interval in each study between 4 and 26 wk used for analysis.

^cFinal follow-up interval in each study between 12 and 26 wk used for analysis.

TABLE 3
 Summary of Safety Outcomes With HA Injection vs Oral NSAIDs^a

Outcome	No. Studies	Frequency, %		Meta-analysis Results				Publication Bias (Egger P Value)
		HA	NSAID	Model	Risk Ratio (95% CI) ^b	P	Heterogeneity (I ²)	
AE	5	19.8	29.0	Fixed	0.74 (0.59, 0.94)	.01	45%, P = .12	.58
Serious AE	5	1.2	0.9	Fixed	1.37 (0.26, 7.14)	.71	0%, P = .58	.83
Study withdrawals	6	22.5	21.6	Fixed	1.05 (0.82, 1.36)	.68	39%, P = .14	.88
AE-related study withdrawals	4	3.9	7.0	Fixed	0.65 (0.33, 1.30)	.22	36%, P = .20	.70

^aAE, adverse event; HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug.

^bRisk ratio values <1 indicate lower risk and values >1 indicate higher risk for hyaluronic acid injections.

among studies was low (I² = 0%; P = .42), and publication bias was not observed (Egger P = .84). Similar results were observed for knee function, in which a small effect size favoring HA injections was observed in 5 trials (SMD, 0.23; P = .01) (Figure 3), with low-to-moderate heterogeneity (I² = 40%; P = .15) and no evidence of publication bias (Egger P = .62). In a sensitivity analysis of temporal trends, there were no statistically significant differences between groups for knee pain or knee function at 4-week or 12-week follow-up. At 26-week follow-up, HA injections were associated with small but not statistically significant improvements in knee pain (SMD, 0.17; P = .07) and

moderate improvements in knee function (SMD, 0.49; P < .01) relative to oral NSAIDs (Table 2).

Safety Outcomes

A summary of safety outcomes is provided in Table 3. The risk of AEs was lower with HA injections than oral NSAIDs (19.8% vs 29.0%; RR, 0.74; P = .01) (Appendix Figure A2). The risk of a serious AE (RR, 1.37; P = .71) (Appendix Figure A3), study withdrawal (RR, 1.05; P = .68) (Appendix Figure A4), or study withdrawal because of an AE (RR, 0.65; P = .22) (Appendix Figure A5) was comparable

TABLE 4
Frequency of Individual AEs With HA Injection
vs Oral NSAIDs^a

AE ^b	HA (n = 383)	NSAID (n = 385)	P
Very common			
Gastrointestinal	54 (14.1)	90 (23.4)	.001
Injection site pain	45 (11.7)	18 (4.7)	<.001
Common			
Headache	32 (8.4)	17 (4.4)	.03
Arthralgia	31 (8.1)	11 (2.9)	.001
Local skin reaction	23 (6.0)	29 (7.5)	.47
Pruritis	12 (3.1)	7 (1.8)	.26
Uncommon			
Drug allergy/intolerance	0	4 (1.0)	.12
Lower leg effusion	1 (0.3)	2 (0.5)	>.99
Unspecified	2 (0.5)	2 (0.5)	>.99
Cardiac	1 (0.3)	0	.50

^aData are reported as count (%). AE, adverse event; HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug.

^bFrequency of adverse events categorized according to guidelines set forth by the Council for International Organizations of Medical Sciences Working Group.³⁸

between groups. Significant heterogeneity or publication bias was not observed for any safety outcome. While the overall risk of AEs was lower with HA injections, analysis of individual AEs revealed distinct risks associated with each treatment. Gastrointestinal concerns were the most frequent AE reported, occurring more often in patients treated with NSAIDs (23.4% vs 14.1%; $P = .001$). AEs reported more often in the HA group included injection site pain (11.7% vs 4.7%; $P < .001$), headache (8.4% vs 4.4%; $P = .03$), and arthralgia (8.1% vs 2.9%; $P = .001$) (Table 4).

Post-Hoc Meta-Regression Results

Because <10 trials were included in this meta-analysis, meta-regression results were reported descriptively only. For each efficacy and safety outcome, we evaluated the influence of double blinding, industry funding, sample size, number of HA injections, and oral NSAID type. The most consistent finding of this analysis was related to the risk of AEs among influential confounders. Specifically, the overall risk of AEs remained lower with HA injections than oral NSAIDs among double-blind trials (RR, 0.75; 95% CI, 0.60, 0.95), trials without industry funding (RR, 0.75; 95% CI, 0.60, 0.95), and trials with sample sizes of at least 100 per group (RR, 0.67; 95% CI, 0.50, 0.91) (Appendix Table A3).

DISCUSSION

HA injections and oral NSAIDs are common treatments for knee OA, yet there is a paucity of high-quality evidence directly comparing these treatments. In this systematic review and meta-analysis of randomized trials comparing HA injections with oral NSAIDs, we identified several main findings. Regarding efficacy, statistically significant improvements in knee pain and knee function were observed with HA injections relative to oral NSAIDs, but

the differences were not clinically important. Regarding safety, the overall risk of AEs was lower with HA injections, yet each treatment was associated with a distinct risk profile where oral NSAIDs increased the risk of gastrointestinal concerns and HA injections increased the risk of local reactions and headache. Finally, because only 6 trials were included in this review with only 3 providing follow-up results through 26 weeks, additional studies are warranted to provide more stable effect size estimates and to facilitate more robust analyses regarding potential sources of heterogeneity.

That HA injections yielded statistically significant improvements in knee OA symptoms relative to oral NSAIDs was a novel finding and warrants further discussion. The only previous systematic review and meta-analysis directly comparing HA injections with oral NSAIDs for knee OA was performed by Bannuru et al,⁷ who reported no differences between groups for knee pain. Our results were nearly identical to those of Bannuru et al for knee pain at 4 weeks (SMD, 0.00 vs SMD, 0.01) and 12 weeks (SMD, -0.03 vs SMD, -0.05). However, our study additionally evaluated pain at 26-week follow-up, whereas Bannuru et al's study utilized 12 weeks of follow-up. Our study showed that the efficacy benefits of HA injections were mainly realized with longer follow-up duration, which explains the discrepant conclusions between the 2 meta-analyses. Collectively, the results of these meta-analyses suggest that the efficacy of HA injections and oral NSAIDs is generally comparable through 12 weeks, with slightly greater symptomatic relief with HA injections through 26 weeks. However, the magnitude of the treatment effect was small, and, therefore, the group differences observed in efficacy outcomes were not clinically important.

The efficacy data presented here should be balanced against treatment safety considerations, particularly because patients with knee OA are often elderly with polypharmacy.⁹ Oral NSAIDs increased the risk of gastrointestinal concerns, whereas HA injections were associated with higher risk for local events and headache. Gastrointestinal complications associated with NSAID use can be mitigated by using Cox-selective NSAIDs, with further risk reductions with the addition of a proton-pump inhibitor.³ Strategies to prevent local events with HA injections are less clear, but it appears that younger age, longer time since diagnosis, and previous HA injections increase these risks.²⁶ Serious AEs were rare, occurring in approximately 1% of patients, and none were related to treatment. Unfortunately, we were unable to determine long-term risks with either treatment, which would have more relevance to the typical patient with knee OA who attempts nonsurgical treatments over a period of years.²⁹ For example, the increased cardiac risks associated with NSAIDs may not be detectable for at least 12 to 18 months,²⁰ a duration that greatly exceeds the follow-up duration of studies in the current review. Ultimately, the results of this meta-analysis suggest that the risk-to-benefit profile may slightly favor HA injections over oral NSAIDs in the short term, but longer term data are needed to better replicate real-world conditions and are encouraged to provide higher quality evidence to assist in clinical decision making.

An important consideration that was not formally assessed in this meta-analysis, yet strongly influences treatment selection, is the cost of therapy. The cost of a 6-month course of oral NSAIDs is highly variable, ranging from \$130 for over-the-counter naproxen, to \$440 for generic celecoxib, to \$1750 for brand name celecoxib (Celebrex),³⁰ while a course of HA injections that is anticipated to provide 6 months of symptom relief costs approximately \$1100.⁴¹ In previous studies, cost-effectiveness appears to have been comparable with HA injections and nonselective oral NSAIDs (each approximately \$15,000 per quality-adjusted life year).²⁹ Cox-selective NSAIDs, on the other hand, were not cost-effective for treatment of knee OA.^{29,30} Because HA injections resulted in slightly better clinical outcomes than oral NSAIDs in the current study, but likely at a higher cost, contemporary cost-effectiveness analyses that compare these 2 treatments are warranted.

Strengths of this meta-analysis included reporting of knee pain, knee function, and detailed safety data through 26-week follow-up, none of which have been compared previously with these treatments. There were also several limitations pertaining to the quality and quantity of the underlying studies included in this review. First, only 6 trials comparing HA injections with oral NSAIDs for knee OA treatment have been conducted, with only 3 providing follow-up results through 26 weeks. This limited number of studies provided low statistical power to detect publication bias and temporal trends in efficacy and hindered adequate exploration of sources of heterogeneity, such as HA type, oral NSAID type, blinding techniques, and industry funding. Second, none of the trials enrolled patients with severe knee OA, and, therefore, the comparative efficacy of HA injections and oral NSAIDs in this patient population remains unclear. Third, patient-reported efficacy outcomes were susceptible to bias because patients were aware of their treatment assignment in 3 of 6 studies. Fourth, while some studies used sham injections to reduce bias in patient-reported outcomes, the AEs reported in this study may differ from real-world practice because events, such as injection site pain and local skin reaction, would not apply to patients taking oral NSAIDs only. Finally, because few patients with knee OA ultimately receive knee arthroplasty²⁹ and must resort to chronic use of nonoperative treatments, the short-term outcomes of this meta-analysis may not be reflective of the results associated with longer term HA and oral NSAID use.

CONCLUSION

Comparing short-term outcomes of HA injections and oral NSAIDs for treatment of knee OA, HA injections provided statistically significant but not clinically important improvements in knee pain and function, along with a lower overall risk of AEs.

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APPENDIX

TABLE A1
Medline Search Strategy^a

Study design
1. clinical trial.pt
2. clinical trial, phase I.pt
3. clinical trial, phase II.pt
4. clinical trial, phase III.pt
5. clinical trial, phase IV.pt
6. controlled clinical trial.pt
7. randomized controlled trial.pt
8. random*
General diagnosis
9. arthriti**, ti, ab
10. arthro**, ti, ab
11. gonarthriti**, ti, ab
12. gonarthro**, ti, ab
13. osteoarthritis*, ti, ab

(continued)

Table A1 (continued)

General diagnosis
14. osteoarthritis, majr
15. osteoarthro**, ti, ab
Diagnosis location
16. knee, mp
Hyaluronic acid
17. adant, mp
18. arthrum, mp
19. artz*, mp
20. biohy, mp
21. durolane, mp
22. euflexxa, mp
23. gel-one, mp
24. gelsyn*, mp
25. healon, mp

(continued)

Table A1 (continued)

Hyaluronic acid
26. hya-ject, mp
27. hyalectin, mp
28. hyalgan, mp
29. hyaluron*, mp
30. hylan, mp
31. hymovis, mp
32. monovisc, mp
33. nrd101, mp
34. nuflexxa, mp
35. orthovisc, mp
36. ostenil, mp
37. supartz, mp
38. suplasyn, mp
39. synjoint, mp
40. synvisc*, mp
41. trivisc, mp
42. viscosupplement*, mp
43. visco-3, mp
Nonsteroidal anti-inflammatory drugs
44. aspirin
45. celebrex
46. celecoxib
47. cox-2
48. diclofenac

(continued)

Table A1 (continued)

Nonsteroidal anti-inflammatory drugs
49. diflunisal
50. etodolac
51. fenoprofen
52. ibuprofen
53. indomethacin
54. ketoprofen
55. meclufenamate
56. mefanamic
57. meloxicam
58. nabumetone
59. naproxen
60. nonsteroidal anti-inflammatory drug
61. NSAID
62. oxaprozin
63. piroxicam
64. sulindac
65. tolmetin
Combination terms
66. or/1-8
67. or/9-15
68. or/16
69. or/17-43
70. or/44-65
71. and/66-70

^aAn asterisk represents wildcard end-truncation.

TABLE A2
Cochrane Risk of Bias Assessment Among Individual Studies

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Adams, 1995 ¹	■	■	■	■	■	■	■	■
Altman, 1998 ²	■	■	■	■	■	■	■	■
Dickson, 2001 ¹⁶	■	■	■	■	■	■	■	■
Petrella, 2002 ³³	■	■	■	■	■	■	■	■
Ishijima, 2014 ²⁴	■	■	■	■	■	■	■	■
Buendía-López, 2018 ⁸	■	■	■	■	■	■	■	■

■ low bias risk; ■ uncertain bias risk; ■ high bias risk.

TABLE A3
Post Hoc Subgroup Analysis of the Association of Study-Level Factors With Treatment Effects With HA Injection vs Oral NSAIDs^a

Variable	SMD (95% CI) ^b		Risk Ratio (95% CI) ^c			
	Knee Pain	Knee Function	AE	Serious AE	Study Withdrawal	Study Withdrawal Because of AE
Double-blinding						
Yes	0.14 (-0.04, 0.32)	0.11 (-0.22, 0.45)	0.75 (0.60, 0.95)	1.31 (0.29, 5.97)	1.11 (0.85, 1.47)	0.66 (0.32, 1.36)
No	0.17 (-0.06, 0.39)	0.29 (0.06, 0.51)	0.34 (0.06, 1.84)	0.99 (0.06, 15.6)	0.80 (0.43, 1.48)	0.61 (0.08, 4.90)

(continued)

Table A3 (continued)

Variable	SMD (95% CI) ^b		Risk Ratio (95% CI) ^c			
	Knee Pain	Knee Function	AE	Serious AE	Study Withdrawal	Study Withdrawal Because of AE
Industry funding						
Yes	0.17 (0.00, 0.34)	0.13 (-0.15, 0.40)	0.34 (0.06, 1.84)	0.99 (0.06, 15.6)	0.60 (0.31, 1.19)	0.61 (0.08, 4.90)
No	0.11 (-0.14, 0.36)	0.32 (0.07, 0.58)	0.75 (0.60, 0.95)	1.31 (0.29, 5.97)	1.15 (0.88, 1.51)	0.66 (0.32, 1.36)
Sample size						
≥100/group	0.15 (-0.02, 0.33)	0.15 (-0.14, 0.44)	0.67 (0.50, 0.91)	1.93 (0.16, 22.8)	1.03 (0.77, 1.37)	0.64 (0.31, 1.32)
<100/group	0.15 (-0.10, 0.39)	0.29 (0.05, 0.54)	0.86 (0.60, 1.25)	1.02 (0.21, 4.94)	1.16 (0.67, 2.00)	0.80 (0.10, 6.45)
No. of HA injections						
1	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>
3	0.24 (-0.04, 0.52)	0.13 (-0.15, 0.40)	0.84 (0.58, 1.22)	1.03 (0.18, 5.78)	1.09 (0.61, 1.94)	0.14 (0.01, 2.65)
5	0.15 (-0.02, 0.33)	0.15 (-0.14, 0.44)	0.67 (0.50, 0.91)	1.93 (0.16, 22.8)	1.03 (0.77, 1.37)	0.64 (0.31, 1.32)
Oral NSAID type						
Cox-selective	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>
Nonselective ^b	0.18 (0.03, 0.33)	0.14 (-0.06, 0.34)	0.73 (0.58, 0.93)	1.26 (0.31, 5.20)	1.04 (0.80, 1.34)	0.59 (0.29, 1.18)

^aAE, adverse event; HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; SMD, standardized mean difference.

^bBolded values indicate a statistically significant difference between groups because the 95% CI of the SMD does not include 0.

^cBolded values indicate a statistically significant difference between groups because the 95% CI of the risk ratio does not include 1.

^dData reported in a single trial; therefore, pooled estimates are not available.

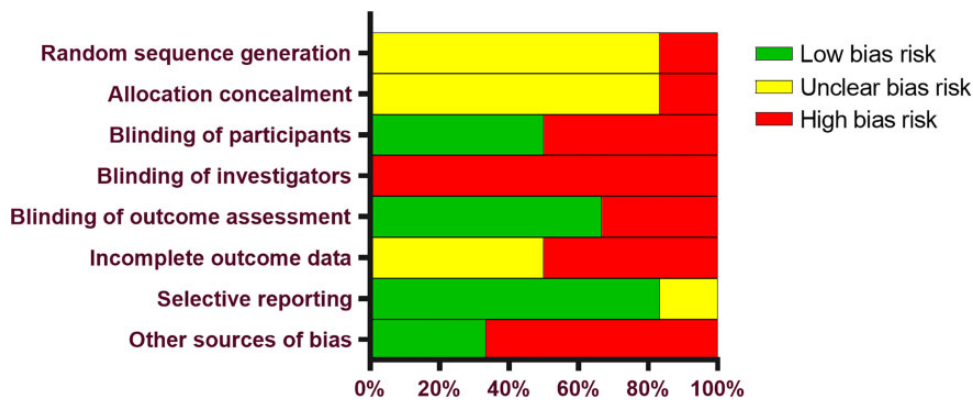


Figure A1. Cochrane risk of bias assessment among possible sources of bias.

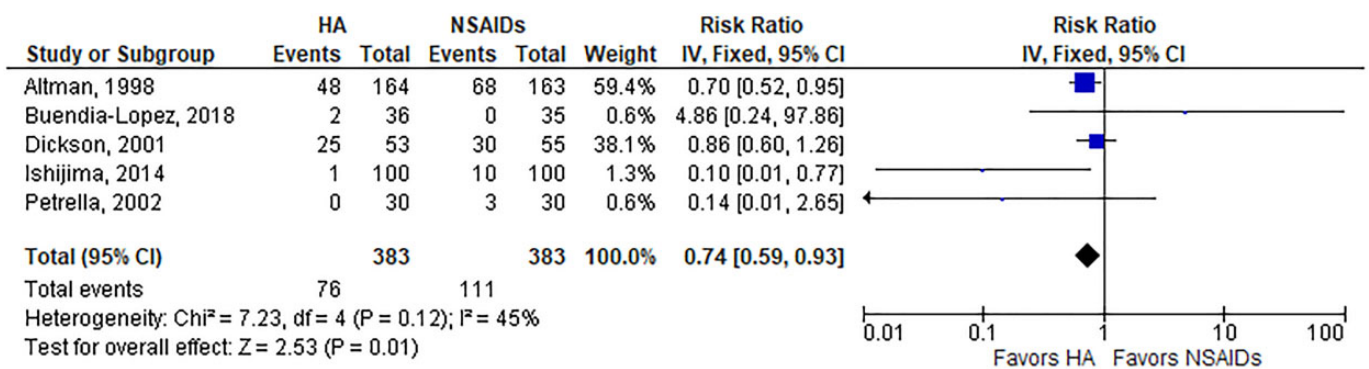


Figure A2. Risk of adverse event with hyaluronic acid (HA) injection vs oral nonsteroidal anti-inflammatory drugs (NSAIDs). Risk ratio = 0.74 (P = .01), favoring hyaluronic acid injections, in fixed-effects model. Heterogeneity: I² = 45%, P = .12. Publication bias: Egger P value = .58. IV, inverse variance.

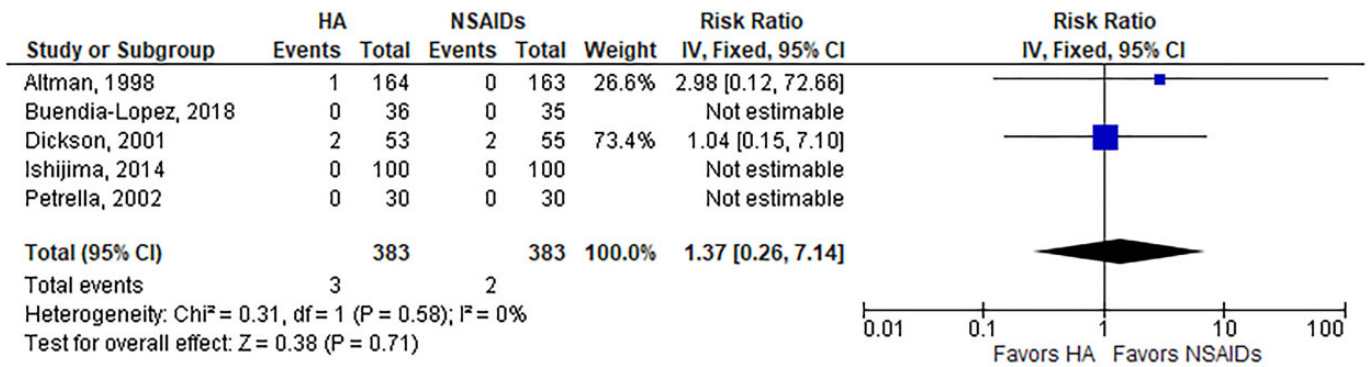


Figure A3. Risk of serious adverse event with hyaluronic acid (HA) injection vs oral nonsteroidal anti-inflammatory drugs (NSAIDs). Risk ratio = 1.37 ($P = .71$), indicating no group differences, in fixed-effects model. Heterogeneity: $I^2 = 0\%$, $P = .58$. Publication bias: Egger P value = .83. IV, inverse variance.

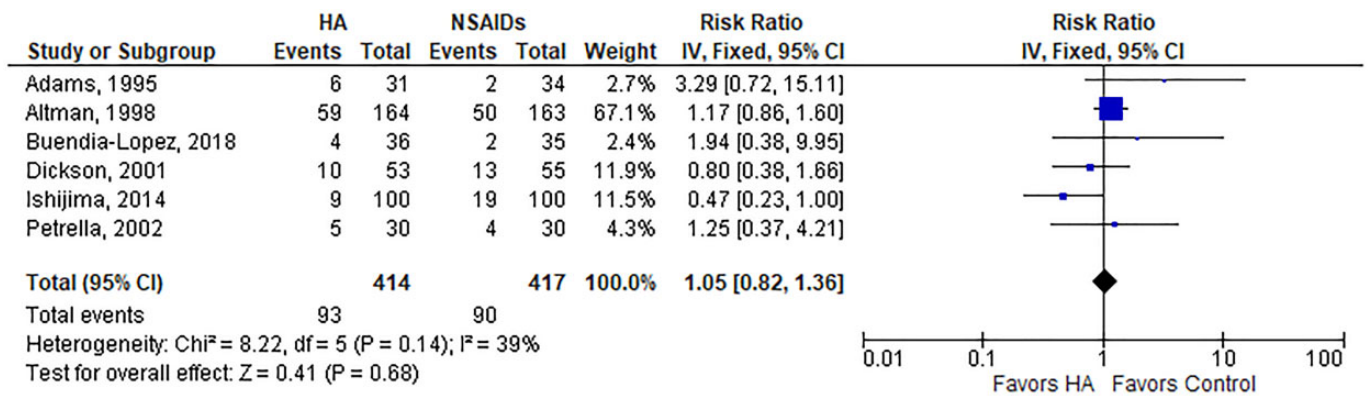


Figure A4. Risk of study withdrawal with hyaluronic acid (HA) injection vs oral nonsteroidal anti-inflammatory drugs (NSAIDs). Risk ratio = 1.05 ($P = .68$), indicating no group differences, in fixed-effects model. Heterogeneity: $I^2 = 39\%$, $P = .14$. Publication bias: Egger P value = .88. IV, inverse variance.

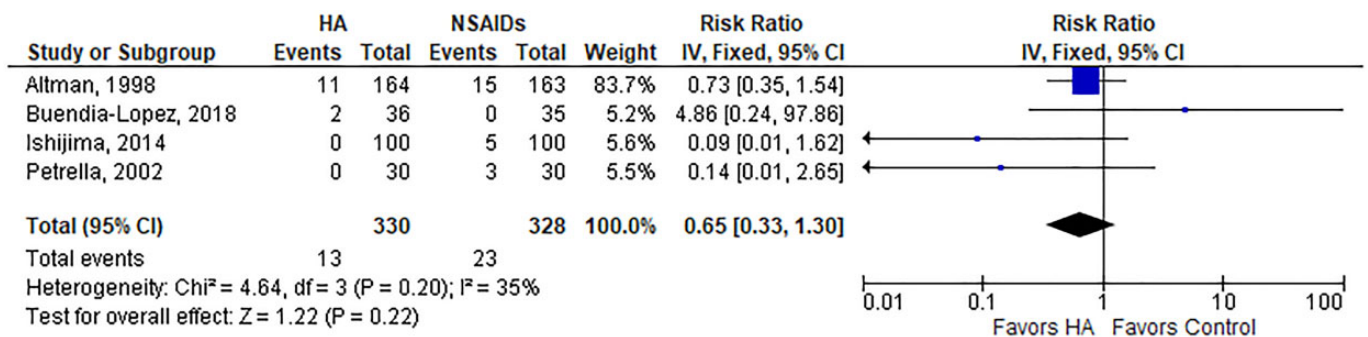


Figure A5. Risk of study withdrawal because of adverse event with hyaluronic acid (HA) injection vs oral nonsteroidal anti-inflammatory drugs (NSAIDs). Risk ratio = 0.65 ($P = .22$), indicating no group differences, in fixed-effects model. Heterogeneity: $I^2 = 35\%$, $P = .20$. Publication bias: Egger P value = .70. IV, inverse variance.