


Safety of Intra-Articular Hyaluronic Acid for Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized Trials Involving More than 8,000 Patients

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Abstract

Objective. The objective of this systematic review and meta-analysis was to report the safety of intra-articular hyaluronic acid (IAHA) in patients with symptomatic knee osteoarthritis (OA). **Methods.** We identified randomized controlled trials reporting the safety of IAHA versus IA saline in adults with symptomatic knee OA. Main safety outcomes were adverse events (AEs), local AEs, serious adverse events (SAEs), study withdrawals, and AE-related study withdrawals. **Results.** A total of 35 randomized controlled trials with 38 group comparisons comprising 8,078 unique patients (IAHA: 4,295, IA saline: 3,783) were included in the meta-analysis. Comparing IAHA with IA saline over a median of 6 months follow-up, there were no differences in the risk of AEs (42.4% vs. 39.7%, risk ratio [RR] = 1.01, 95% CI = 0.96-1.07, $P = 0.61$), SAEs (1.8% vs. 1.2%, RR = 1.44, 95% CI = 0.91-2.26, $P=0.12$), study withdrawals (12.3% vs. 12.7%, RR = 0.99, 95% CI = 0.87-1.12, $P = 0.83$), or AE-related study withdrawals (2.7% vs. 2.1%, RR = 1.37, 95% CI = 0.97-1.93, $P = 0.08$). Local AEs, all of which were nonserious, were more common with IAHA vs. IA saline (14.5% vs. 11.7%, RR = 1.21, 95% CI = 1.07-1.36, $P = 0.003$) and typically resolved within days. **Conclusion.** IAHA was shown to be safe for use in patients with symptomatic knee OA. Compared with IA saline, IAHA is associated with an increased risk of nonserious, transient local reactions. There was no evidence to suggest any additional safety risks of IAHA.

Keywords

hyaluronic acid, knee, meta-analysis, osteoarthritis, systematic review

Introduction

Knee osteoarthritis (OA) is the leading cause of disability in adults¹⁻³ and its prevalence is anticipated to rise exponentially over the next several decades. The pathogenesis of knee OA is multifactorial, but largely attributable to chronic overloading of the knee joint that promotes degradation of the articular cartilage.^{4,5} Hyaluronic acid (HA) is an integral component of synovial fluid. As part of its intra-articular function, it acts as a joint lubricant during shear stress and a shock absorber during compressive stress. The concentration and molecular weight of endogenous HA is often reduced in knee OA, leading to reduced viscoelastic properties of synovial fluid. Altered biodynamics with loss of other protective HA properties induce proinflammatory pathways.⁶ Intra-articular hyaluronic acid (IAHA) injections are intended to alleviate knee OA symptoms by reversing the OA-induced HA deficit.⁷ Numerous systematic reviews have evaluated the effectiveness of IAHA for knee OA, with varying conclusions.⁸⁻¹⁶ However, relatively less attention has been paid to the safety of IAHA. In 2012,

Rutjes and colleagues¹⁵ were among the first to report potential safety concerns with IAHA for knee OA. Since then, few studies have attempted to confirm the safety of IAHA and to further investigate the potential sources of heterogeneity among studies. The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to report on the safety of IAHA in patients with symptomatic knee OA.

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Methods

Data Sources and Searches

We developed and followed a review protocol that adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹⁷ We searched Medline, Embase, the Cochrane Database of Systematic Reviews, and the Directory of Open Access Journals, with no language restrictions, from inception to December 31, 2018 for RCTs of IAHA for symptomatic knee OA by using a combination of study design-, diagnosis-, and treatment-specific keywords (Supplemental Table 1). Additionally, reference lists of included papers and relevant meta-analyses were manually searched. We also included results from published and unpublished sources (e.g. abstracts, Food and Drug Administration website) to reduce the risk of publication bias.¹⁸ Manuscripts published in non-English language journals were translated to English by local-language medical translators.

Study Selection

Two independent researchers (LM, DF) reviewed titles and abstracts for possible inclusion. Primary inclusion criteria were RCTs of IAHA (IAHA group) versus IA saline (Saline group) for symptomatic knee OA; sample size at least 30 patients per group; identical treatment and follow-up conditions in each group; and at least one extractable safety outcome. The 30-patient minimum sample size criterion was included to minimize bias associated with small-study effects.¹⁹ Duplicate publications and studies that included concomitant surgical procedures were excluded.

Data Extraction

Data were independently extracted from eligible studies by 2 researchers (LM, DF). Data extraction discrepancies between the 2 researchers were resolved by discussion and consensus. The following variables were recorded in standardized data extraction forms: general manuscript information, patient characteristics (gender, age, body mass index), study characteristics (sample size, blinding assessment, industry funding, follow-up duration), HA characteristics (trade name, molecular weight, source, cross-linking, regulatory status), procedural details (number of injections), and safety outcomes. Safety outcomes included all-cause serious adverse events (SAEs), all-cause adverse events (AEs), local AEs, patient withdrawals, and AE-related patient withdrawals. Serious AE data were extracted based on investigator determination or report of any event that led to death, serious deterioration in health, life-threatening illness/injury, permanent impairment, hospitalization or prolongation of hospitalization, or medical/surgical intervention to prevent permanent impairment.

Treatment relatedness data were extracted based on investigator determination. We reviewed the article text, tables, and patient flow diagrams to determine the number of patient withdrawals in total as well as those occurring due to an AE. The Cochrane Collaboration tool was used to assess risk of bias.²⁰

Data Analysis

Safety outcomes in each group were compared using the risk ratio (RR) where an RR >1 indicated higher risk with IAHA and an RR <1 indicated lower risk with IAHA. When one group was compared to multiple groups within the same study, the sample size of the single group was adjusted to avoid double counting of patients.²¹ We used the I^2 statistic to estimate heterogeneity of outcomes among studies where a value of 0% represents no heterogeneity and larger values represent increasing heterogeneity.²² Substantial heterogeneity was defined by a Cochran Q test $P < 0.1$ or $I^2 > 50\%$. When substantial heterogeneity existed, a random effects model was planned; otherwise, a fixed-effect model was planned.²³ Publication bias was visually assessed with funnel plots and quantitatively assessed with Egger's regression test.²⁴ Predefined subgroup analyses were performed to explore the association of study-level factors on each safety outcome. We tested the stability of our estimates with two sensitivity analyses. The first sensitivity analysis was a one-study removed analysis in which we iteratively removed one study at a time to determine whether conclusions for each outcome were influenced by any single study. The second sensitivity analysis compared results of fixed-effect versus random effects models for each safety outcome. P -values were 2-sided with a significance level <0.05. Analyses were performed using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark).

Results

Study Selection

We screened 459 studies to determine eligibility for inclusion in this review. We excluded 424 studies, mostly due to a non-IA saline control group, inadequate sample size, or nonrandomized design. Ultimately, 35 RCTs with 38 group comparisons comprising 8,078 unique patients (IAHA: 4,295, Saline: 3,783) were included in this review. A flow diagram of study identification and selection is shown in **Figure 1**. A listing of excluded RCTs with reasons for exclusion is provided in Supplemental Table 2.

Patient and Study Characteristics

Baseline patient characteristics in the IAHA and Saline groups are reported in **Table 1**. Characteristics of patients in

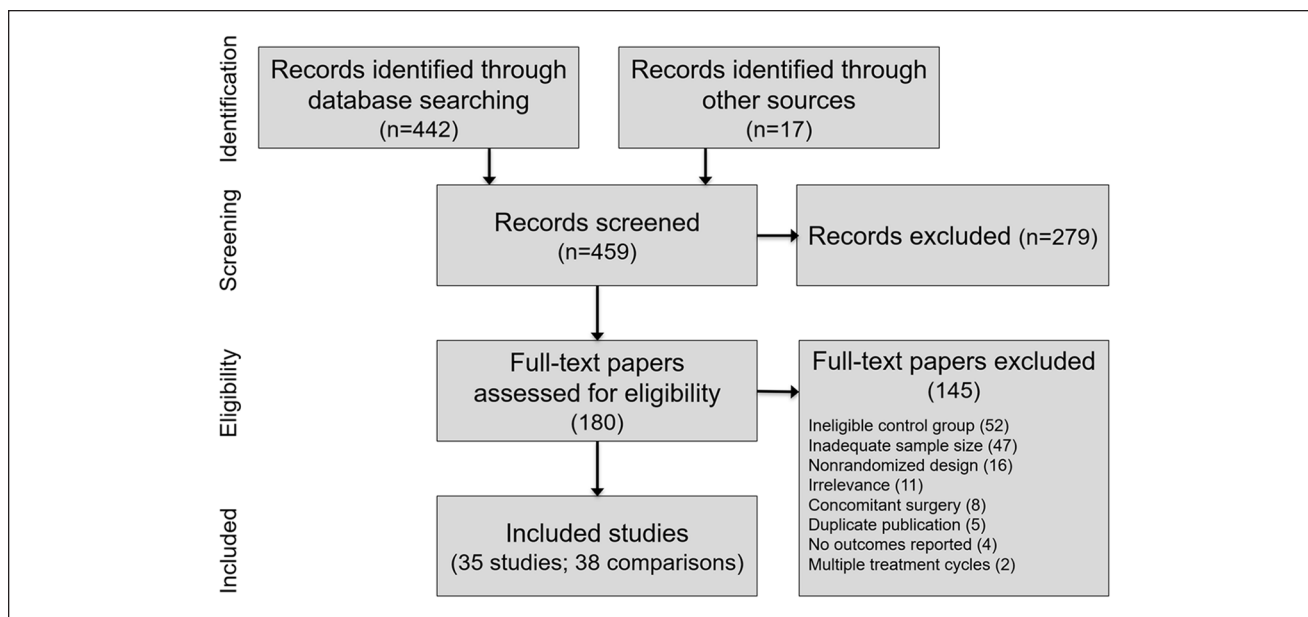


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

the IAHA and Saline groups were similar, with women comprising 60% of each group, a median age of 63 years in each group, and a median body mass index of 29 kg/m² in each group. Most studies utilized patient and outcome assessor blinding, but injector blinding was rarely specified. Most HA products were derived from avian sources. The total number of injections received in each series ranged from 1 to 5, except for one study that used 11 injections.²⁵ Median patient follow-up was 6 months (range: 5 weeks to 2 years) (Table 2). The most common potential sources of bias were lack of investigator blinding, industry funding, and incomplete outcome data (Figure 2).

Main Outcomes

Comparing IAHA with Saline groups, there were no differences in the risk of AEs (42.4% vs. 39.7%, RR = 1.01, 95% CI = 0.96-1.07, $P = 0.61$; Fig. 3), SAEs (1.8% vs. 1.2%, RR = 1.44, 95% CI = 0.91-2.26, $P = 0.12$; Fig. 4), study withdrawals (12.3% vs. 12.7%, RR = 0.99, 95% CI = 0.87-1.12, $P = 0.83$; Fig. 5), and AE-related study withdrawals (2.7% vs. 2.1%, RR = 1.37, 95% CI = 0.97-1.93, $P = 0.08$; Fig. 6). Local AEs, none of which were classified as serious, were more common with IAHA versus Saline (14.5% vs. 11.7%, RR = 1.21, 95% CI = 1.07-1.36, $P = 0.003$; Fig. 7). Significant heterogeneity or publication bias was not observed for any outcome, with the exception of publication bias for the risk of AEs (Egger's $P = 0.04$). Publication bias adjustment using the trim-and-fill method resulted in an almost identical nonsignificant difference in the risk of AEs (RR = 1.01, 95% CI = 0.96-1.06)

compared with the unadjusted values (RR = 1.01, 95% CI = 0.96-1.07).

Subgroup and Sensitivity Analyses

In subgroup analyses, no study-level factor influenced the risk of any safety outcome. The associations of these factors on the risk of local AEs are provided in Table 3. Subgroup analysis results of other safety outcomes were not reported since no heterogeneity was observed for the other safety outcomes (all $I^2 = 0\%$). In the first sensitivity analysis, study conclusions were upheld in most scenarios when the meta-analysis was recalculated after removing one study at a time. The only safety outcome in which conclusions were influenced by individual studies was AE-related withdrawals in which one-at-a-time removal of 20 (91%) studies did not alter conclusions, but removal of Brandt *et al.*²⁶ or Lohmander *et al.*²⁷ led to the conclusion of increased risk of AE-related withdrawal with IAHA injections (Supplemental Table 3). In the second sensitivity analysis, results of each safety outcome were largely identical when comparing fixed-effect and random effects meta-analysis models owing to low heterogeneity among studies (Supplemental Table 4).

Discussion

IAHA injections are generally perceived as safe for use in patients with symptomatic knee OA. This conclusion was corroborated in the current meta-analysis where we confirmed that IAHA was associated with an increase in local

Table I. Patient Characteristics in Randomized Controlled Trials Included in the Meta-Analysis.

Study	No. Randomized		Age (Years)		Female Patients (%)		BMI (kg/m ²)	
	HA	Saline	HA	Saline	HA	Saline	HA	Saline
Altman, 1998 ³⁴	164	168	62	65	61	53	32	30
Altman, 2004 ³⁵	173	174	63	63	46	64	30	30
Altman, 2009 ³⁶	293	295	63	61	63	63	32	33
Arden, 2014 ³⁷	108	110	65	61	55	46	27	28
Baltzer, 2009 ³⁸	135	107	57	60	55	64	a	a
Brandt, 2001 ²⁶	114	112	65	67	63	63	32	30
Chevalier, 2010 ³⁹	124	129	64	63	74	68	29	30
Day, 2004 ⁴⁰	116	124	62	62	56	61	30	29
Dickson, 2001 ⁴¹	53 ^b	57	65	64	57	56	29	29
Dixon, 1988 ²⁵	30	33	a	a	a	a	a	a
Dougados, 1993 ⁴²	55	55	67	69	76	65	a	a
Hangody, 2017 ⁴³	150	138	59	58	66	74	28	29
Henderson, 1994 ⁴⁴	45	46	69	64	67	72	a	a
Henrotin, 2017 ⁴⁵	40	41	67	63	63	76	29	31
Huang, 2011 ⁴⁶	100	100	66	64	74	78	26	25
Huskisson, 1999 ⁴⁷	50	50	66	65	76	58	a	a
Jorgensen, 2010 ⁴⁸	167	170	63	61	66	57	29	29
Karlsson, 2002a ⁴⁹	92	66 ^b	72	71	67	61	28	28
Karlsson, 2002b ⁴⁹	88	66 ^b	70	71	65	61	28	28
Kosuwon, 2012 ⁵⁰	30	30	61	61	100	100	27	26
Lohmander, 1996 ²⁷	120	120	59	58	56	56	28	27
Lundsgaard, 2008 ⁵¹	84	84	69	70	57	52	30	29
Neustadt, 2005 ⁵²	128	124	58	59	45	50	29	29
Petrella, 2002 ⁵³	30	30	67	63	36	43	30	33
Petrella, 2006 ⁵⁴	53	53	62	64	43	46	30	31
Petrella, 2008a ⁵⁵	50	50 ^b	69	71	54	60	27	27
Petrella, 2008b ⁵⁵	50	50 ^b	71	71	58	60	27	27
Petterson, 2018 ⁵⁶	184	185	60	59	59	57	30	30
Pham, 2004 ⁵⁷	131 ^b	85	65	65	71	69	29	29
Puhl, 1993 ⁵⁸	102	107	62	61	73	55	26	27
Rolf, 2005a ⁵⁹	90	91 ^b	55	53	44	38	27	28
Rolf, 2005b ⁵⁹	91	91 ^b	54	53	38	38	27	28
Saravanan, 2002 ⁶⁰	33	33	a	a	a	a	a	a
Seikagaku, 2001 ⁶¹	619	537	62	61	62	59	28	28
Shichikawa, 1983 ⁶²	52	55	a	a	a	a	a	a
Strand, 2012 ⁶³	251	128	61	60	60	60	28	29
Wobig, 1998 ⁶⁴	52	54	60	64	56	74	27	28
Wu, 1997 ⁶⁵	48 ^c	42 ^c	69	69	34	22	a	a

BMI = body mass index; HA = hyaluronic acid

^aValues not reported.

^bSample size of common comparator group within the same study adjusted to avoid double-counting in meta-analysis.

^cEstimated values.

nonserious AEs compared with saline injections (14.5% vs. 11.7%), but with no differences between treatment groups in the risk of AEs, SAEs, study withdrawals, and AE-related study withdrawals. These conclusions were robust in subgroup analyses and were not influenced by heterogeneity or publication bias.

Results of this meta-analysis confirmed that the risk of SAEs was comparable in patients receiving IAHA or saline. This finding agrees with a previous meta-analysis in which the risk of SAEs was no different with IAHA versus saline controls (RR = 1.24, $P = 0.32$).¹⁶ However, this is in contrast to the results of Rutjes *et al.*¹⁵ who concluded that

Table 2. Treatment Regimens of Randomized Controlled Trials Included in the Meta-Analysis.

Study	Blinding			Trade Name	HA Characteristics					
	Subjects	Injectors	Outcome Assessors		US Approved	Cross-Linked	Avian Origin	MW (kDa)	No. Injections	Follow-up (Days)
Altman, 1998 ³⁴	Yes	No	No	HYALGAN	Yes	No	Yes	730	5	182
Altman, 2004 ³⁵	Yes	No	Yes	DUROLANE	Yes	Yes	No	9000	1	182
Altman, 2009 ³⁶	Yes	No	Yes	EUFLEXXA	Yes	No	No	3600	3	182
Arden, 2014 ³⁷	Yes	No	Yes	DUROLANE	Yes	Yes	No	9000	1	42
Baltzer, 2009 ³⁸	Yes	No	Yes	HYA-JECT	No	No	No	1400	3	203
Brandt, 2001 ²⁶	Yes	No	Yes	ORTHOVISC	Yes	No	No	2900	3	189
Chevalier, 2010 ³⁹	Yes	No	Yes	SYNVISC	Yes	Yes	Yes	6000	1	182
Day, 2004 ⁴⁰	Yes	No	Yes	ARTZAL	Yes	No	Yes	1170	5	126
Dickson, 2001 ⁴¹	Yes	No	Yes	SYNVISC	Yes	Yes	Yes	6000	3	84
Dixon, 1988 ²⁵	Yes	No	Yes	HYALGAN	Yes	No	Yes	730	11	336
Dougados, 1993 ⁴²	No	No	No	HYALGAN	Yes	No	Yes	730	4	364
Hangody, 2017 ⁴³	Yes	Yes	Yes	MONOVISC	Yes	Yes	No	2900	1	182
Henderson, 1994 ⁴⁴	Yes	No	Yes	HYALGAN	Yes	No	Yes	730	5	35
Henrotin, 2017 ⁴⁵	Yes	Yes	Yes	KARTILAGE CROSS	No	No	No	^a	1	180
Huang, 2011 ⁴⁶	Yes	No	Yes	HYALGAN	Yes	No	Yes	730	5	175
Huskisson, 1999 ⁴⁷	Yes	No	Yes	HYALGAN	Yes	No	Yes	730	5	182
Jorgensen, 2010 ⁴⁸	Yes	No	Yes	HYALGAN	Yes	No	Yes	730	5	91
Karlsson, 2002a ⁴⁹	Yes	No	Yes	ARTZAL	Yes	No	Yes	1170	3	182
Karlsson, 2002b ⁴⁹	Yes	No	Yes	SYNVISC	Yes	Yes	Yes	6000	3	182
Kosuwon, 2012 ⁵⁰	Yes	No	Yes	GO-ON	No	No	No	1500	5	182
Lohmander, 1996 ²⁷	Yes	No	Yes	ARTZAL	Yes	No	Yes	1170	5	185
Lundsgaard, 2008 ⁵¹	Yes	No	Yes	HYALGAN	Yes	No	Yes	730	4	182
Neustadt, 2005 ⁵²	Yes	No	Yes	ORTHOVISC	Yes	No	No	2900	4	196
Petrella, 2002 ⁵³	Yes	Yes	Yes	SUPLASYN	No	Yes	No	1000	3	84
Petrella, 2006 ⁵⁴	Yes	No	Yes	SUPLASYN	No	Yes	No	1000	3	84
Petrella, 2008a ⁵⁵	Yes	No	No	HYALGAN	Yes	No	Yes	730	3	728
Petrella, 2008b ⁵⁵	Yes	No	No	SYNVISC	Yes	Yes	Yes	6000	3	728
Petterson, 2018 ⁵⁶	Yes	Yes	Yes	MONOVISC	Yes	Yes	No	2900	1	182
Pham, 2004 ⁵⁷	Yes	No	Yes	NRD101	No	^a	No	1900	3	365
Puhl, 1993 ⁵⁸	Yes	No	Yes	ARTZAL	Yes	No	Yes	1170	5	98
Rolf, 2005a ⁵⁹	Yes	No	Yes	SYNVISC	Yes	Yes	Yes	6000	3	364
Rolf, 2005b ⁵⁹	Yes	No	Yes	ARTZAL	Yes	No	Yes	1170	3	364
Saravanan, 2002 ⁶⁰	No	No	No	SYNVISC	Yes	Yes	Yes	6000	3	42
Seikagaku, 2001 ⁶¹	Yes	No	No	ARTZAL	Yes	No	Yes	1170	3	126
Shichikawa, 1983 ⁶²	Yes	No	No	NOT REPORTED	No	^a	^a	^a	5	35
Strand, 2012 ⁶³	Yes	No	Yes	GEL-ONE	Yes	Yes	Yes	^a	1	91
Wobig, 1998 ⁶⁴	Yes	Yes	Yes	SYNVISC	Yes	Yes	Yes	6000	3	182
Wu, 1997 ⁶⁵	Yes	No	No	ARTZAL	Yes	No	Yes	1170	5	182

HA = hyaluronic acid; MW = molecular weight; US = United States.

^aValues not reported.

IAHA increased the risk of SAEs (RR = 1.41, $P = 0.04$). In the current study, the risk of experiencing an SAE following IAHA was low, occurring in 1.8% of patients. Furthermore, as was shown in the meta-analysis of Rutjes *et al.*,¹⁵ none of the SAEs were related to IAHA but instead to unrelated conditions. Overall, it appears that SAEs following IAHA are rare, occur with a similar frequency as with IA saline, and are unrelated to the treatment itself.

We determined that IAHA increased the risk of nonserious, transient local reactions compared with IA saline. The most common local reactions were injection site pain, arthralgia, joint swelling, and joint effusion, which subsided within 2 to 3 days in most instances. Despite this increased risk in local reactions, IAHA was well tolerated with the percentage of patient withdrawals overall (12.3% vs. 12.7%) and withdrawals due to an AE (2.7% vs. 2.1%) comparably low in

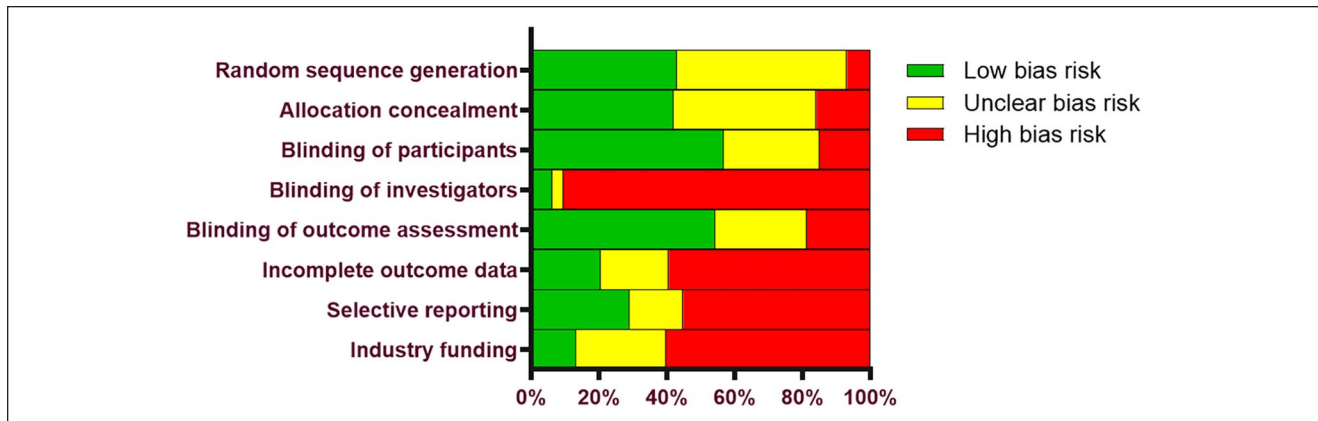


Figure 2. Risk of bias assessment with the Cochrane Collaboration Tool.

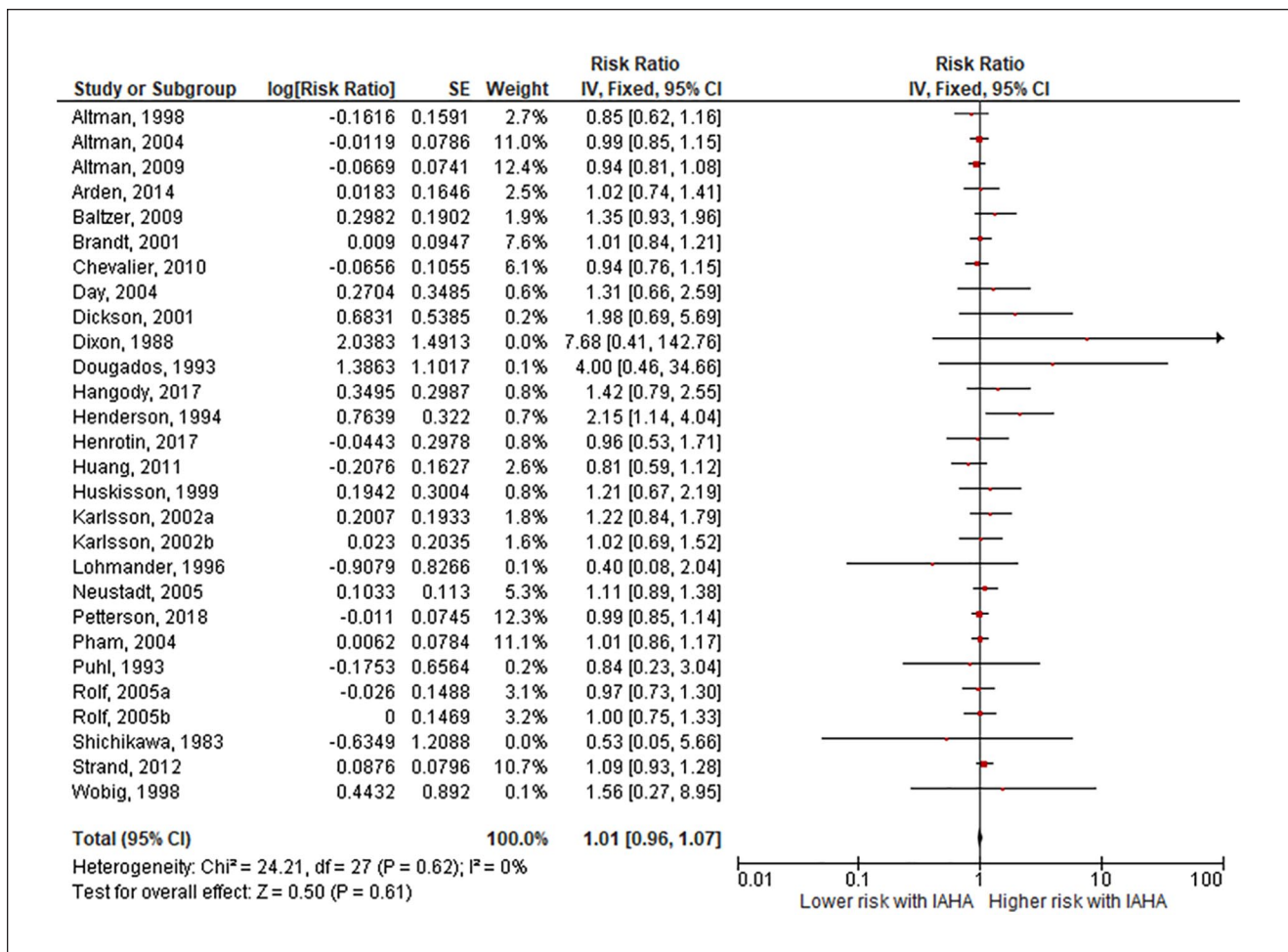


Figure 3. Forest plot of pooled risk ratio for adverse events with hyaluronic acid (HA) or saline injections. The risk ratio and 95% confidence interval are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with HA. A pooled risk ratio of less than 1 indicates lower risk with HA. Heterogeneity: $I^2 = 0\%$, $P = 0.62$. Publication bias: Egger's $P = 0.04$.

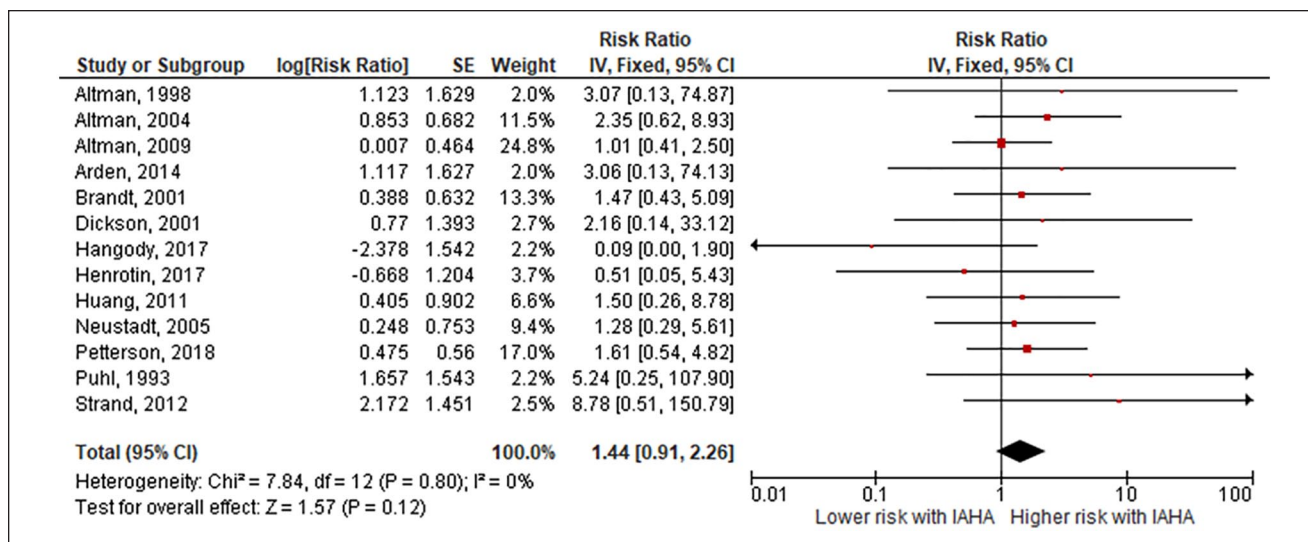


Figure 4. Forest plot of pooled risk ratio for serious adverse events with hyaluronic acid (HA) or saline injections. The risk ratio and 95% confidence interval are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with HA. A pooled risk ratio of less than 1 indicates lower risk with HA. Heterogeneity: $I^2 = 0\%$, $P = 0.80$. Publication bias: Egger's $P = 0.55$.

both IAHA and IA Saline groups. It was interesting that no factors related to study design or HA product characteristics influenced safety results, but this was not particularly surprising since there was little heterogeneity among studies.

Given this evidence supporting the safety of IAHA in relation to IA saline, it would be interesting for future studies to compare the safety of IAHA to active therapies recommended for treatment of symptomatic knee OA. In a clinical practice guideline for treatment of knee OA, nonsteroidal anti-inflammatory drugs (NSAIDs) were the only nonsurgical knee OA treatment recommended by the American Academy of Orthopaedic Surgeons (AAOS).²⁸ Yet, knee OA pain is chronic in nature and NSAIDs are not indicated for chronic use because of safety concerns. Furthermore, selective and nonselective oral NSAIDs increase the risk of serious cardiovascular events and should be used with caution in patients with high cardiovascular risk.²⁹ Finally, drug fact labels specify that "NSAIDs can increase the chance of a heart attack or stroke, either of which can lead to death."³⁰ Given that cardiovascular disease is highly prevalent in patients with OA,³¹ there appears to be a disconnect in societal guidelines regarding the safety profile of recommended therapies for knee OA. Rigorous safety evaluations of IAHA versus oral NSAIDs would help clarify the comparative risk profile of these therapies in patients with knee OA.

Strengths of this meta-analysis were inclusion of only RCTs utilizing saline controls and robust study conclusions

that were not influenced by heterogeneity among studies, publication bias, or analysis specifications. There were also several limitations of this meta-analysis that warrant additional discussion. First, patients treated with oral therapies or injection of active products were excluded from the control group. While safety comparisons to these other therapies are certainly warranted, inclusion of all potential therapies in a common control group would introduce significant biases that would complicate data interpretation. Second, in accordance with best evidence practices and following the methodology used by the AAOS in their systematic review of IAHA,³² we excluded studies with small sample sizes. While it is possible that important safety events may be missed using this methodology, exclusion of small studies reduces bias risk since they tend to report greater treatment benefits than large trials and often suffer from lower methodological quality.¹⁹ Finally, the effect of repeat IAHA cycles on safety outcomes could not be evaluated in this review, but has previously been reported to be safe with no reported SAEs in a previous review.³³

Conclusions

IAHA was shown to be safe for use in patients with symptomatic knee OA. Compared with IA saline, IAHA was associated with an increased risk of nonserious and transient local reactions. There was no evidence to suggest any additional safety risks of IAHA.

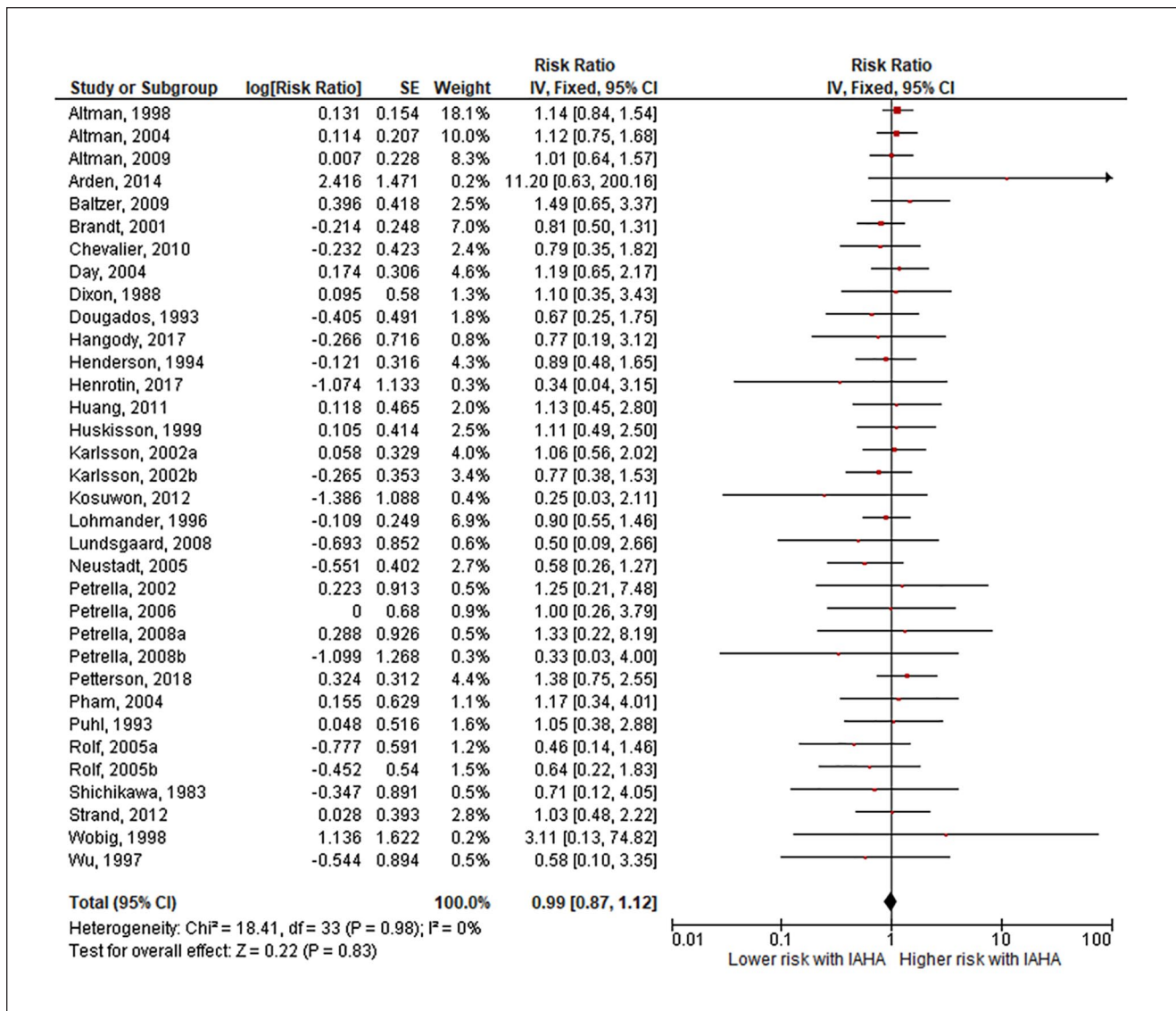


Figure 5. Forest plot of pooled risk ratio for study withdrawal with hyaluronic acid (HA) or saline injections. The risk ratio and 95% confidence interval are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with HA. A pooled risk ratio of less than 1 indicates lower risk with HA. Heterogeneity: $I^2 = 0\%$, $P = 0.98$. Publication bias: Egger's $P = 0.13$.

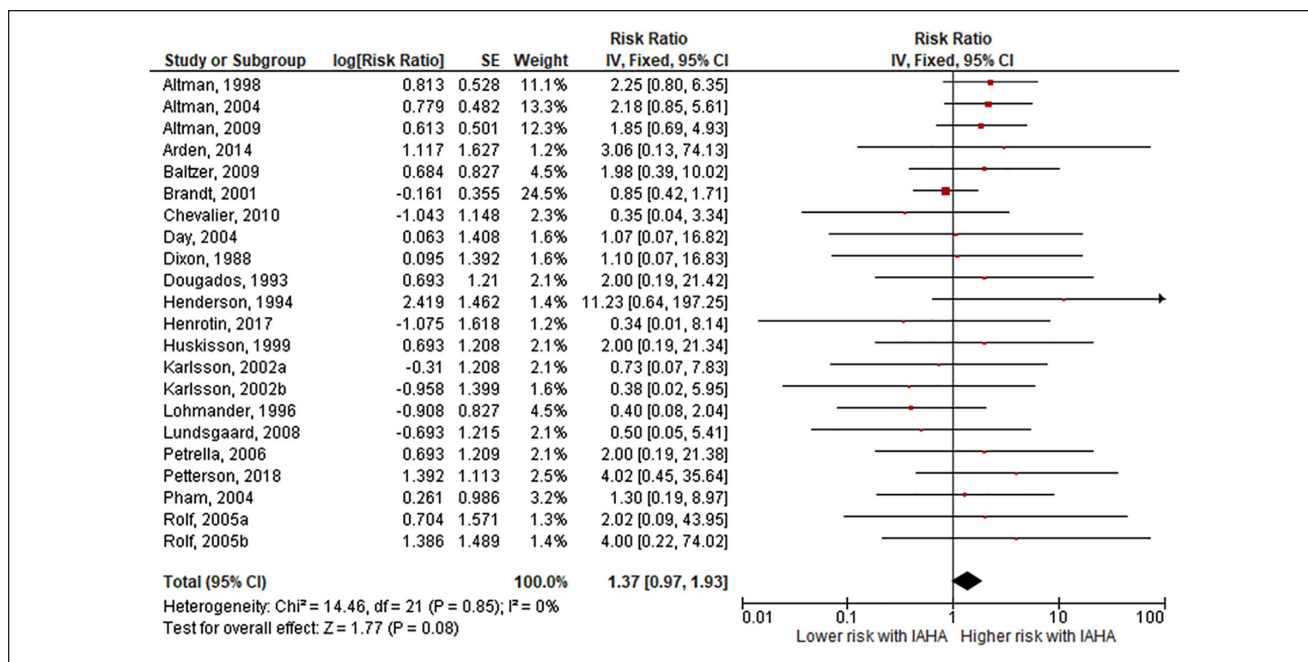


Figure 6. Forest plot of pooled risk ratio for adverse event-related study withdrawal with hyaluronic acid (HA) or saline injections. The risk ratio and 95% confidence interval are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with HA. A pooled risk ratio of less than 1 indicates lower risk with HA. Heterogeneity: $I^2 = 0\%$, $P = 0.85$. Publication bias: Egger's $P = 0.87$.

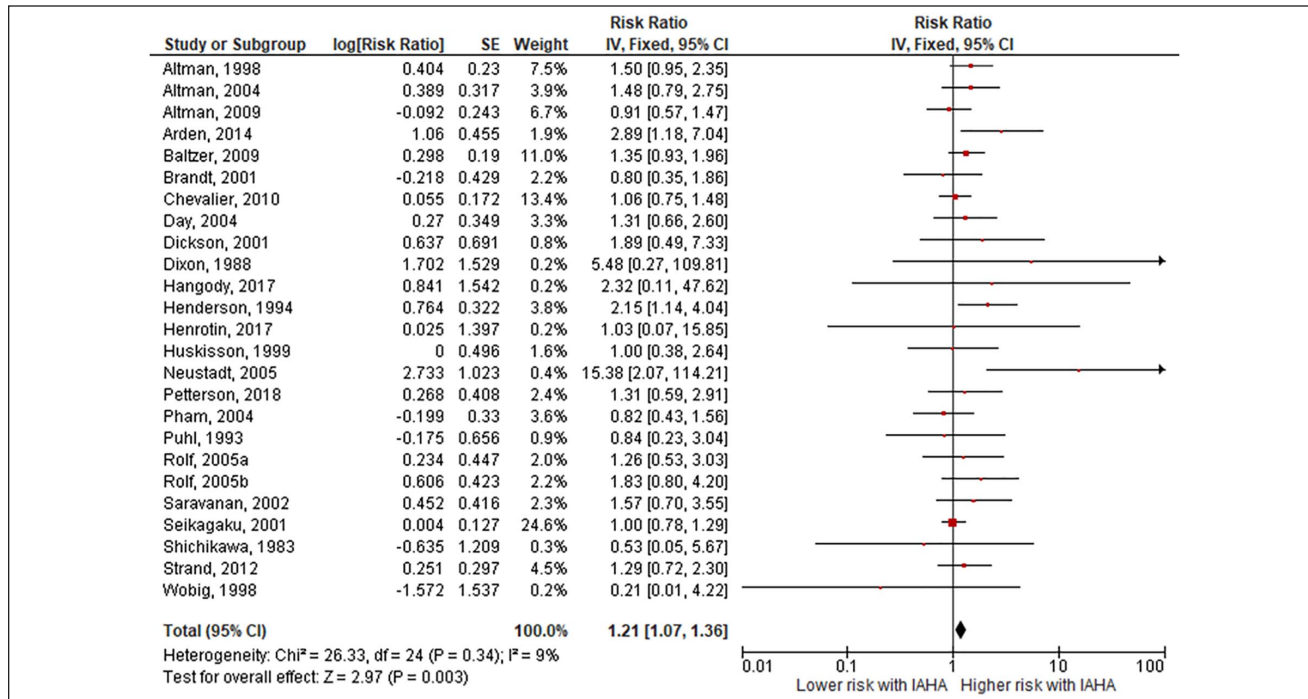


Figure 7. Forest plot of pooled risk ratio for local adverse events with hyaluronic acid (HA) or saline injections. The risk ratio and 95% confidence interval are plotted for each study. The size of the square is proportional to the sample size of the study. The pooled risk ratio is denoted by the diamond apex and 95% confidence interval denoted by the diamond width. A pooled risk ratio of more than 1 indicates higher risk with HA. A pooled risk ratio of less than 1 indicates lower risk with HA. Heterogeneity: $I^2 = 9\%$, $P = 0.34$. Publication bias: Egger's $P = 0.12$.

Table 3. Subgroup Analysis of Study-Level Factors on the Risk of Local Adverse Events.

Study-Level Factor	No. studies	RR	95% CI	P-value
No. injections				0.11
1-2	7	1.26	1.00-1.61	
3	10	1.09	0.92-1.28	
>3	8	1.55	1.16-2.07	
Follow-up duration				0.12
1-3 mo	7	1.65	1.20-2.28	
4-6 mo	14	1.14	0.99-1.31	
>6 mo	4	1.19	0.77-1.84	
Sample size				0.33
≥100 per group	13	1.17	1.02-1.34	
<100 per group	12	1.38	1.03-1.85	
Publication year				0.37
Before 2000	7	1.48	1.07-2.04	
2000-2009	12	1.14	0.98-1.34	
After 2009	6	1.23	0.95-1.60	
Outcome assessor blinding				0.41
No	4	1.12	0.91-1.39	
Yes	21	1.25	1.08-1.46	
Molecular weight (kDa)				0.43
≥6,000	7	1.28	1.00-1.64	
>1,500 to <6,000	6	1.00	0.73-1.37	
≤1,500	9	1.24	1.05-1.46	
Patient blinding				0.52
No	1	1.57	0.70-3.55	
Yes	24	1.20	1.06-1.36	
Cross-linked				0.60
Yes	10	1.29	1.03-1.60	
No	13	1.20	1.03-1.40	
Industry-funded study				0.66
No	5	1.30	0.91-1.87	
Yes	20	1.19	1.05-1.36	
HA origin				0.77
Bacterial	10	1.23	0.99-1.53	
Avian	14	1.20	1.03-1.39	
US approved HA				0.84
Yes	21	1.21	1.06-1.39	
No	4	1.17	0.85-1.61	
Injector blinding				0.98
No	21	1.21	1.06-1.37	
Yes	4	1.20	0.58-2.46	

HA = hyaluronic acid; RR = risk ratio; US = United States.

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References

- Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum.* 1987;30:914-8.
- van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis.* 1989;48:271-80.
- Peat G, McCauley R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis.* 2001;60:91-7.
- Arendt EA, Miller LE, Block JE. Early knee osteoarthritis management should first address mechanical joint overload. *Orthop Rev (Pavia).* 2014;6:5188.
- Crawford DC, Miller LE, Block JE. Conservative management of symptomatic knee osteoarthritis: a flawed strategy? *Orthop Rev (Pavia).* 2013;5:e2.
- Dahl LB, Dahl IM, Engström-Laurent A, Granath K. Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. *Ann Rheum Dis.* 1985;44:817-22.
- Smith MM, Ghosh P. The synthesis of hyaluronic acid by human synovial fibroblasts is influenced by the nature of the hyaluronate in the extracellular environment. *Rheumatol Int.* 1987;7:113-22.
- Sadabad HN, Behzadifar M, Arasteh F, Behzadifar M, Dehghan HR. Efficacy of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: a systematic review and meta-analysis. *Electron Physician.* 2016;8:2115-22.
- Wang F, He X. Intra-articular hyaluronic acid and corticosteroids in the treatment of knee osteoarthritis: a meta-analysis. *Exp Ther Med.* 2015;9:493-500.
- Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum.* 2014;43:593-9.
- Miller LE, Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. *Clin Med Insights Arthritis Musculoskelet Disord.* 2013;6:57-63.
- Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs.* 2012;26:257-68.
- Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis—meta-analysis. *Osteoarthritis Cartilage.* 2011;19:611-9.
- Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum.* 2009;61:1704-11.
- Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:180-91.
- Strand V, McIntyre LF, Beach WR, Miller LE, Block JE. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials. *J Pain Res.* 2015;8:217-28.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151:W65-W94.
- Cook DJ, Guyatt GH, Ryan G, Clifton J, Buckingham L, Willan A, et al. Should unpublished data be included in meta-analyses? Current convictions and controversies. *JAMA.* 1993;269:2749-53.
- Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ.* 2010;341:c3515.
- Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
- Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0. London, England: The Cochrane Collaboration; 2011.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-60.
- Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med.* 1997;127:820-6.
- Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-34.
- Dixon AS, Jacoby RK, Berry H, Hamilton EB. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. *Curr Med Res Opin.* 1988;11:205-13.
- Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. *Clin Orthop Relat Res.* 2001;(385):130-43.
- Lohmander LS, Dalen N, Englund G, Hämäläinen M, Jensen EM, Karlsson K, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. *Ann Rheum Dis.* 1996;55:424-31.
- American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee: evidence-based guideline. Available from: <https://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf>
- Coxib and Traditional NSAID Trialists' (CNT); Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet.* 2013;382:769-79.
- US Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause

- heart attacks or strokes. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory>
31. Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO. Association between osteoarthritis and cardiovascular disease: systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23:938-46.
 32. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for osteoarthritis of the knee: a systematic review of the evidence. *J Bone Joint Surg Am*. 2015;97:2047-60.
 33. Altman R, Hackel J, Niazi F, Shaw P, Nicholls M. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: a systematic review. *Semin Arthritis Rheum*. 2018;48:168-75.
 34. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. *J Rheumatol*. 1998;25:2203-12.
 35. Altman RD, Akermark C, Beaulieu AD, Schnitzer T; Durolane International Study Group. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2004;12:642-9.
 36. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). *Semin Arthritis Rheum*. 2009;39:1-9.
 37. Arden NK, Akermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. *Curr Med Res Opin*. 2014;30:279-86.
 38. Baltzer AW, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. *Osteoarthritis Cartilage*. 2009;17:152-60.
 39. Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, *et al*. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis*. 2010;69:113-9.
 40. Day R, Brooks P, Conaghan PG, Petersen M; Multicenter Trial Group. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intra-articular hyaluronan in osteoarthritis of the knee. *J Rheumatol*. 2004;31:775-82.
 41. Dickson DJ, Hosie G, English JR. A double-blind, placebo-controlled comparison of hylan G-F 20 against diclofenac in knee osteoarthritis. *J Clin Res*. 2001;4:41-52.
 42. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. *Osteoarthritis Cartilage*. 1993;1:97-103.
 43. Hangody L, Szody R, Lukasik P, Zgadzaj W, Lenart E, Dokoupilova E, *et al*. Intraarticular injection of a cross-linked sodium hyaluronate combined with triamcinolone hexacetonide (Cingal) to provide symptomatic relief of osteoarthritis of the knee: a randomized, double-blind, placebo-controlled multicenter clinical trial. *Cartilage*. 2018;9:276-83.
 44. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Ann Rheum Dis*. 1994;53:529-34.
 45. Henrotin Y, Berenbaum F, Chevalier X, Marty M, Richette P, Rannou F. Reduction of the serum levels of a specific biomarker of cartilage degradation (Coll2-1) by hyaluronic acid (KARTILAGE® CROSS) compared to placebo in painful knee osteoarthritis patients: the EPIKART study, a pilot prospective comparative randomized double blind trial. *BMC Musculoskelet Disord*. 2017;18:222.
 46. Huang TL, Chang CC, Lee CH, Chen SC, Lai CH, Tsai CL. Intra-articular injections of sodium hyaluronate (Hyalgan®) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the Asian population. *BMC Musculoskelet Disord*. 2011;12:221.
 47. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology (Oxford)*. 1999;38:602-7.
 48. Jørgensen A, Stengaard-Pedersen K, Simonsen O, Pfeiffer-Jensen M, Eriksen C, Bliddal H, *et al*. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. *Ann Rheum Dis*. 2010;69:1097-102.
 49. Karlsson J, Sjögren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford)*. 2002;41:1240-8.
 50. Kosuwon W, Sirichatiwapee W, Visanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Determination of cartilage volume using MRI in patients with knee osteoarthritis: efficacy study of 25 milligrams of sodium hyaluronate (2.5 ml) versus placebo. *J Clin Exp Pharmacol*. 2012;2:112.
 51. Lundsgaard C, Dufour N, Fallentin E, Winkel P, Gluud C. Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial. *Scand J Rheumatol*. 2008;37:142-50.
 52. Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. *J Rheumatol*. 2005;32:1928-36.
 53. Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med*. 2002;162:292-8.
 54. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol*. 2006;33:951-6.
 55. Petrella RJ, Cogliano A, Decaria J. Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Clin Rheumatol*. 2008;27:975-81.

56. Petterson SC, Plancher KD. Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: a multicenter, double-blind, randomized, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc.* 2019;27:1992-2002.
57. Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. *Ann Rheum Dis.* 2004;63:1611-7.
58. Puhl W, Bernau A, Greiling H, Köpcke W, Pforringer W, Steck KJ, *et al.* Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. *Osteoarthritis Cartilage.* 1993;1:233-41.
59. Rolf CG, Engstrom B, Ohrvik J, Valentin A, Lilja B, Levine DW. A comparative study of the efficacy and safety of hyaluronan viscosupplements and placebo in patients with symptomatic and arthroscopy-verified cartilage pathology. *J Clin Res.* 2005;8:15-32.
60. Saravanan V, Morgan T, Stobbs D, Daymond TJ. Inflammatory effusion after viscosupplementation with Hylan G-F 20. *Rheumatology (Oxford).* 2002;41:121.
61. US Food and Drug Administration. Summary of safety and effectiveness data: SUPARTZ 2001. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf8/P080020b.pdf
62. Shichikawa K, Igarashi M, Sugawara SIwasaka Y. Clinical evaluation of high molecular weight sodium hyaluronate (SPH) on osteoarthritis of the knee—multi-center well controlled comparative study [in Japanese]. *Jpn J Clin Pharmacol Ther.* 1983;4:545-58.
63. Strand V, Baraf HS, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2012;20:350-6.
64. WobigM, DickhutA, MaierR, VetterG. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther.* 1998;20:410-23.
65. Wu JJ, Shih LY, Hsu HC, Chen TH. The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. *Zhonghua Yi Xue Za Zhi (Taipei).* 1997;59:99-106.