Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis

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Abstract

Background: Osteoarthritis of the knee affects up to 10% of the elderly population. The condition is frequently treated by intra-articular injection of hyaluronic acid. We performed a systematic review and meta-analysis of randomized controlled trials to assess the effectiveness of this treatment.

Methods: We searched MEDLINE, EMBASE, CINAHL, BIOSIS and the Cochrane Controlled Trial Register from inception until April 2004 using a combination of search terms for knee osteoarthritis and hyaluronic acid and a filter for randomized controlled trials. We extracted data on pain at rest, pain during or immediately after movement, joint function and adverse events.

Results: Twenty-two trials that reported usable quantitative information on any of the predefined end points were identified and included in the systematic review. Even though pain at rest may be improved by hyaluronic acid, the data available from these studies did not allow an appropriate assessment of this end point. Patients who received the intervention experienced a reduction in pain during movement: the mean difference on a 100-mm visual analogue scale was –3.8 mm (95% confidence interval [CI] –9.1 to 1.4 mm) after 2–6 weeks, –4.3 mm (95% CI –7.6 to –0.9 mm) after 10–14 weeks and –7.1 mm (95% CI –11.8 to –2.4 mm) after 22–30 weeks. However, this effect was not compatible with a clinically meaningful difference (expected to be about 15 mm on the visual analogue scale). Furthermore, the effect was exaggerated by trials not reporting an intention-to-treat analysis. No improvement in knee function was observed at any time point. Even so, the effect of hyaluronic acid on knee function was more favourable when allocation was not concealed. Adverse events occurred slightly more often among patients who received the intervention (relative risk 1.08, 95% CI 1.01 to 1.15). Only 4 trials explicitly reported allocation concealment, had blinded outcome assessment and presented intention-to-treat data.

Interpretation: According to the currently available evidence, intra-articular hyaluronic acid has not been proven clinically effective and may be associated with a greater risk of adverse events. Large trials with clinically relevant and uniform end points are necessary to clarify the benefit–risk ratio.

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Osteoarthritis affects about 10% of the population over 55 years of age. Of those, one-quarter are severely disabled.[1] The condition is characterized by degeneration of the articular cartilage and subsequent subchondral bone changes. The underlying mechanisms remain unknown, but the glycosaminoglycan–proteoglycan matrix may play a major role.[2]

Hyaluronic acid, a glycosaminoglycan, is widely used for the treatment of osteoarthritis of the knee. A survey of 2 general practices in the United Kingdom showed that about 15% of patients with osteoarthritis received intra-articular treatment with glucosamine sulfates.[3] The costs of such treatment are significant. At present, 1 syringe of hyaluronic acid costs at least Can$130 (US$110). The treatment of knee osteoarthritis is covered by the US Medicare program but not by provincial formularies in Canada. In Austria (which has 8 million inhabitants) more than 10 million euros (approximately US$12 million or Can$15 million) is spent by social insurance programs annually for hyaluronic acid preparations (excluding the cost of application).

Hyaluronic acid has beneficial effects in vitro.[4] Because of its viscoelastic quality, it may replace synovial fluid. Furthermore, it may reduce the perception of pain. Beneficial molecular and cellular effects have also been reported.[2,4] Hyaluronic acid is frequently applied by intra-articular injection, but the evidence concerning its clinical relevance is conflicting. The European League against Rheumatism (EULAR) recommends the intra-articular application of hyaluronic acid as "category 2" evidence (at least 1 controlled study without randomization).[5] The American College of Rheumatology recommends intra-articular hyaluron therapy for patients with no response to nonpharmacologic therapy and simple analgesics.[6] In contrast, other specialists have concluded that "hyaluronate sodium is not efficacious" in the treatment of osteoarthritis.[7] The first state-of-the-art systematic review and meta-analysis was published recently,[8] and its authors concluded "that intra-articular hyaluronic acid, at best, has a small effect."

We performed a systematic review and meta-analysis of

the effect of intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee. In contrast to 2 previous meta-analyses on this subject,[8,9] we used a different approach to data synthesis and interpretation: instead of analyzing a composite effect size over time, we allocated trial data, when possible, to 3 outcome groups that we assumed would be relevant for patients with osteoarthritis. We specifically looked at pain at rest, pain during exercise and joint function as distinct outcomes, measured repeatedly over time. In addition, we assessed adverse events and the impact of both trial quality and molecular mass of the product. This analysis allows us to provide important additional insight into the effects of intra-articular administration of hyaluronic acid for the treatment of osteoarthritis of the knee.

Methods

We identified all randomized controlled trials comparing various preparations of hyaluronic acid with placebo in patients with osteoarthritis. We searched MEDLINE, EMBASE, CINAHL, BIOSIS and the Cochrane Controlled Trial Register from inception until April 2004. The search string was [(osteoarthritis) or (degenerative arthritis) or (gonarthrosis) or (knee near arthralgia) or (knee near pain) or (patella near pain) or (patellofemoral near pain) or (patello near femoral pain) or (retropatellar near pain) or (femoropatellar near pain) or (femoro-patellar near pain)] and [(hyaluronan) or (hyaluronate) or (viscosupplementation) or (visco near supplementation) or (hyaluronic acid)]. For the MEDLINE and EMBASE searches we used validated search terms to identify randomized controlled trials (see Appendix 1).[10,11] We predefined a variety of clinical outcomes: pain at rest, pain during or immediately after movement, joint function and adverse events. We also predefined time points of assessment in broad categories: 2–6 weeks, 10–14 weeks, 22–30 weeks and 44–60 weeks.

Two reviewers (J.A. and P.M.) independently abstracted data from each trial and entered the data on a predefined form. We compared the results and resolved disagreement by discussion among 3 reviewers (J.A., P.M., M.M.).

We determined whether concealment of allocation to treatment was reported, the degree of blinding (doctor blinded to the intervention, patient blinded to the intervention, assessor of the end point blinded to the intervention) and whether an intention-to-treat analysis was reported.

We extracted estimates of the effect of the intervention and its variance from the figures in the article, if these values were not explicitly reported in the text or tables. If a trial did not report measures of variability, we calculated them from p values or confidence intervals. For one trial[12] we took the median to be representative of the mean and converted the interquartile range into a standard deviation by dividing it by 1.35.[13] With one exception, all trials with data that could be extracted for quantitative analysis reported on loss to follow-up.

We used random-effects models to pool the data. Continuous outcomes were combined by either weighted mean differences or standardized mean differences, as appropriate.[13] We used summary risk ratios to combine adverse events. We calculated 95% confidence intervals (CIs) for all point estimates.

We used Cochrane's Q for heterogeneity, together with the resulting degrees of freedom (df), to calculate the proportion of variation due to unexplained heterogeneity: $I^2 = (Q - \text{df})/Q$.[14] A value of less than 20% is consistent with little variability between studies, and 20% to 50% can be considered to represent a moderately large degree of variation. Regression methods were used to assess the presence of publication bias.[15]

We used multivariate meta-regression analysis to assess whether an effect had been influenced by allocation concealment (blinding of randomization, yes versus no or unclear), blinded outcome assessment (blinded treating physician, patient and outcome assessor, explicitly reported versus not explicitly reported or unclear) and intention-to-treat analysis (explicitly reported versus not explicitly reported or unclear). We repeated the analyses for only those trials that fulfilled all 3 criteria.

We assessed the impact of the molecular mass of the hyaluronic acid on efficacy. We used molecular mass as an ordinal category and then collapsed categories of molecular mass into 2 categories (≤ 900 kDa and > 900 kDa) and repeated the analysis.

Results

The electronic search of databases resulted in 1159 hits, and we retrieved 42 publications for closer inspection (Fig. 1). Of these, 24 studies were potentially eligible.[12,16–38] The clinical and methodologic characteristics of the trials that reported at least one of the end points of interest are presented in Table 1 and Table 2.

Trial quality

Overall, the quality of the reported trials was unsatisfactory. Only 4 trials reported concealment of allocation and blinding of the outcome observer, and presented data from an intention-to-treat analysis.[12,22,31,33] Seven trials reported allocation concealment.[12,22,29,31–34] Eight trials reported an intention-to-treat analysis, but only 6 of these presented data that could be extracted from the intention-to-treat analysis.[12,16,28,30,31,37] Sixteen trials reported that the outcome observer was blinded to the intervention.[12,16,18,20,22,23,26–33,35,37]

Two trials did not present any usable quantitative information.[30,35] Therefore, only 22 trials were included in the analysis of at least 1 of the predefined efficacy end points (Fig. 1).

Pain at rest

Eight trials (with a total of 10 comparisons) reported reduction of pain at rest for the treatment group (n = 231) relative to the control group (n = 237) at 2–6 weeks.[12,17,20,21,24–26,31] Unexplained statistical heterogeneity was excessive (I^2 = 94%), and we could not identify a particular trial causing this excess variability (Fig. 2). Pooling in the face of such a high degree of heterogeneity of unknown cause is not advisable. If the data were pooled, the mean difference in the visual analogue scale was in favour of hyaluronic acid (–8.7 mm, 95% CI –17.2 to –0.2 mm, p = 0.046) (Table 3). For trials in which allocation concealment was unclear or there was no intention-to-treat analysis, the effect was overestimated by

15.6 mm (95% CI –3.2 to 34.4, $p = 0.11$). For trials in which outcome assessment was not blinded, the effect was also overestimated, by 13.6 mm (95% CI –0.6 to 27.7, $p = 0.06$).

Two high-quality trials[12,33] assessed pain at rest at 10–14 and 22–30 weeks, and 2 trials (1 of which was of high quality)[12,24] at 44–60 weeks; there were no significant effects at these time points (Table 3).

Pain during or immediately after exercise

Nine trials (with a total of 10 comparisons) reported pain reduction in the treatment group ($n = 559$) relative to the control group ($n = 582$) at 2–6 weeks.[16,19–21,24,26–28,31] The weighted mean difference was –3.8 mm on the visual analogue scale (95% CI –9.1 to 1.4 mm, $p = 0.15$) (Table 3). Again, there was an excessive degree of unexplained statistical heterogeneity ($I^2 = 81\%$). One trial had a qualitative interaction: among patients with less severe osteoarthritis (Kellgren and Lawrence grades I and II[39]), those who received hyaluronic acid had better pain reduction than those who received placebo; however, among patients with more advanced disease (grades III and IV), pain increased with hyaluronic acid.[26] When this trial was excluded, the effect remained largely unchanged (weighted mean difference –4.2 mm), although the precision was higher (95% CI –7.5 to –0.8 mm, $p = 0.015$), and heterogeneity was acceptable ($I^2 = 20\%$).

At 10–14 weeks, 5 comparisons were available (435 intervention patients, 442 control patients).[16,19,27,28,33] The weighted mean difference between the treatment and control groups was –4.3 mm (95% CI –7.6 to –0.9 mm, $p = 0.013$) (Fig. 3A). There was no unexplained heterogeneity ($I^2 = 0\%$).

At 22–30 weeks, 4 comparisons were available (227 intervention patients, 236 control patients).[16,19,27,33] The weighted mean difference between the treatment and control groups was –7.1 mm (95% CI –11.8 to –2.4 mm, $p = 0.003$) (Fig. 3B). There was no unexplained heterogeneity ($I^2 = 0\%$).

Only one trial followed patients until 44–60 weeks (47 intervention patients, 48 control patients),[24] and it showed no effect (Table 3).

Trial quality had no undue influence on the effect size at any point, but only one trial[33] was of high quality.

Joint function

Nine trials reported a measure of joint function at 2–6 weeks (489 intervention patients, 505 control patients).[12,18,20–22,24,27,31,32] Because different measurement systems were used in these trials, we calculated standardized effects. The standardized weighted mean difference between the groups at 2–6 weeks was 0.00 (95% CI –0.23 to 0.23, $p = 0.99$) (Fig. 4A). There was a high degree of unexplained statistical heterogeneity ($I^2 = 66\%$). Even though there was no statistically significant pooled effect, unclear or absent allocation concealment led to considerable inflation of the effect (by 2.6 points on the z score, 95% CI 1.2 to 3.9, $p < 0.001$). Other measures of quality did not influence the effect size.

Six trials (with a total of 7 comparisons) reported data on function at 10–14 weeks (533 intervention patients, 490 control patients).[12,18,22,27,29,32] The standardized weighted mean difference between the groups was –0.11 (95% CI –0.31 to 0.09, $p = 0.28$) (Fig. 4B). Heterogeneity was considerable ($I^2 = 59\%$), but there were no obvious differences in study or patient characteristics that would explain this high degree of heterogeneity. Unclear or absent allocation concealment led to considerable inflation of the summary effect (by 3.0 points on the z score, 95% CI 1.1 to 4.9, $p < 0.001$). Other measures of quality did not influence the effect size.

Data from 22–30 weeks were available for 4 trials (with a total of 5 comparisons) (295 intervention patients, 247

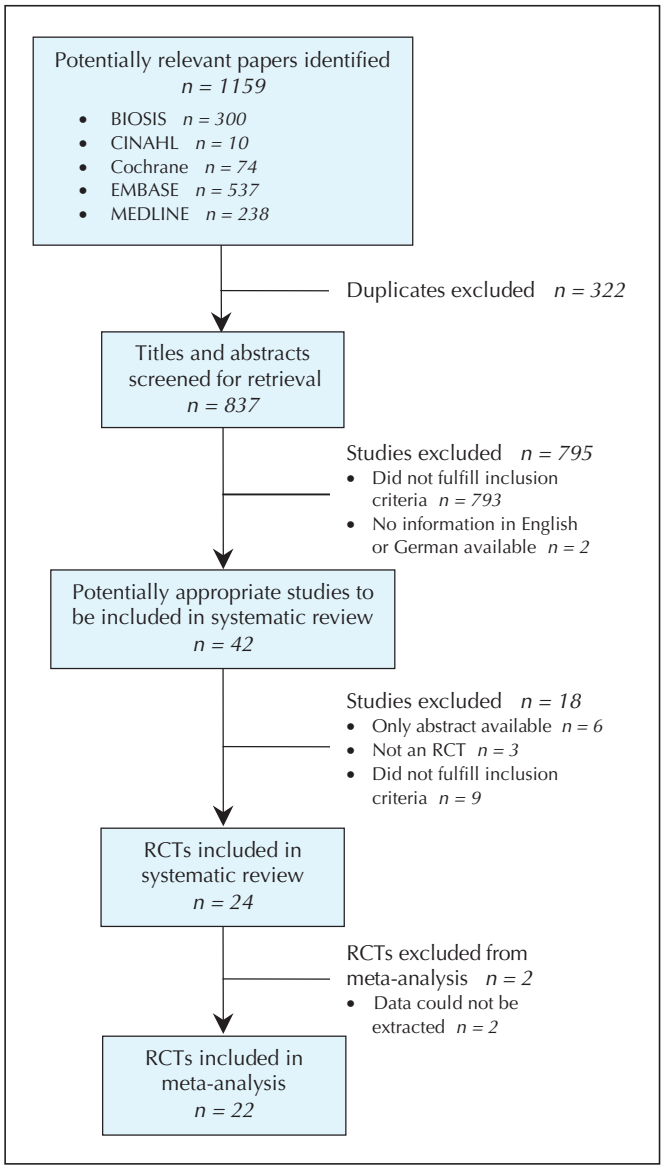

Fig. 1: Flow of articles through the systematic review. RCT = randomized controlled trial.

Table 1: Characteristics of studies included in the meta-analysis

Author	Intervention	End points	Reporting quality*
Altman and Moskowitz 1998[16]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: NR Pain on movement: VAS for pain during 50-ft walk Joint function: Data could not be used for analysis Adverse events: Data could not be used for analysis	AC: No or unclear ITT: Yes Blinding: Yes
Bragantini et al 1987[17]	Hyalgan (Fidia Pharm. Corp, Italy): 20 mg or 40 mg HA, 500–730 kDa v. 2 mL saline vehicle; total of 3 injections, 1 injection per wk	Pain at rest: VAS for spontaneous pain intensity Pain on movement: Walking pain, 1–5 point scale (binary†) Joint function: NR Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: No or unclear
Brandt et al 2001[18]	ORTHOVISC (Anika Therapeutics, USA): 2 mL (30 mg HA), 1000–2900 kDa v. 2 mL saline vehicle; total of 3 injections, 1 injection per wk	Pain at rest: NR Pain on movement: Data could not be used for analysis Joint function: WOMAC function score Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: Yes
Bunyaratavej et al 2001[19]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 4 injections, 1 injection per wk	Pain at rest: NR Pain on movement: VAS for pain on active movement Joint function: NR Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: No or unclear
Carrabba et al 1995[20] — HA-5 trial	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL buffered saline solution; total of 5 injections, 1 injection per wk	Pain at rest: VAS for pain at rest Pain on movement: VAS for pain on movement Joint function: Lesquesne index of severity for OA of the knee Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: Yes
Corrado et al 1995[21]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: VAS for pain at rest Pain on movement: VAS for pain on movement Joint function: Joint mobility on flexion (in degrees) Adverse events: NR	AC: No or unclear ITT: No or unclear Blinding: No or unclear
Dahlberg et al 1994[12]	Sodium hyaluronate (Seikagaku Corp, Japan): 2.5 mL (25 mg HA), 600–1200 kDa v. 2.5 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: VAS for pain in the knee Pain on movement: NR Joint function: VAS for subjective rating of total knee function Adverse events: Data could not be used for analysis	AC: Yes ITT: Yes Blinding: Yes
Day et al 2004[22]	ARTZ (Seikagaku Corp, Japan): 2.5 mL (25 mg HA), 600–1200 kDa v. 2.5 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: NR Pain on movement: NR Joint function: WOMAC function score Adverse events: NR	AC: Yes ITT: Yes Blinding: Yes
Dixon et al 1988[23]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL placebo (0.2 mg HA); total of 11 injections, at days 0, 7, 14, 21, 35, 49, 63, 77, 105, 133, 161	Pain at rest: Data could not be used for analysis Pain on movement: Data could not be used for analysis Joint function: Data could not be used for analysis Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: Yes
Dougados et al 1993[24]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 4 injections, 1 injection per wk	Pain at rest: VAS for pain at rest during the past 2 d Pain on movement: VAS for pain after exercise during the past 2 d Joint function: Lesquesne Functional Index Adverse events: Data could not be used for analysis	AC: No or unclear ITT: No or unclear Blinding: No or unclear
Grecomoro et al 1987[25]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 3 injections, 1 injection per wk	Pain at rest: VAS for spontaneous pain intensity Pain on movement: Data could not be used for analysis Joint function: NR Adverse events: NR	AC: No or unclear ITT: No or unclear Blinding: No or unclear
Henderson et al 1994[26]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: VAS for pain at rest Pain on movement: VAS for pain on active movement Joint function: NR Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: Yes
Huskisson and Donnelly 1999[27]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: Data could not be used for analysis Pain on movement: VAS for knee pain on walking Joint function: Lesquesne Functional Index Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: Yes

Table 1 continued

Author	Intervention	End points	Reporting quality*
Jubb et al 2003[28]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 3 injections, 1 injection per wk	Pain at rest: NR Pain on movement: VAS for knee pain on walking Joint function: Data could not be used for analysis Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: Yes Blinding: Yes
Karlsson et al 2002[29]	Artzal (Astra Läkemedel, Sweden): 2.5 mL (25 mg HA), ~1000 kDa v. 3 mL saline solution; Synvisc (Roche, Sweden): 2.0 mL (16 mg HA), ~7000 kDa v. 3 mL saline solution; total of 3 injections, 1 injection per wk	Pain at rest: Data could not be used for analysis Pain on movement: NR Joint function: WOMAC function score Adverse events: No. of patients with or without adverse events (binary)	AC: Yes ITT: No or unclear Blinding: Yes
Lohmander et al 1996[30]	Artzal (Astra Läkemedel, Sweden): 2.5 mL (25 mg HA), ~1000 kDa v. 3 mL saline solution; total of 5 injections, 1 injection per wk	Pain at rest: NR Pain on movement: NR Joint function: Data could not be used for analysis Adverse events: Data could not be used for analysis	AC: No or unclear ITT: Yes Blinding: Yes
Petrella et al 2002[31] — group 1 v. group 4	Suplasyn (Bioniche Life Sciences Inc, Canada): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline solution; total of 3 injections, 1 injection per wk	Pain at rest: VAS for pain at rest Pain on movement: VAS for self-paced walking pain Joint function: Time needed for self-paced walking of a 40-m distance Adverse events: NR	AC: Yes ITT: Yes Blinding: Yes
Puhl et al 1993[32]	ARTZ (Seikagaku Corp, Japan): 2.5 mL (25 mg HA), 600–1200 kDa v. 2.5 mL saline vehicle (0.25 mg HA); total of 5 injections, 1 injection per wk	Pain at rest: Data could not be used for analysis Pain on movement: Data could not be used for analysis Joint function: Lesquesne Functional Index Adverse events: No. of patients with or without adverse events (binary)	AC: Yes ITT: No or unclear Blinding: Yes
Russell et al 1992[33]	Sodium hyaluronate (Pharmacia Orthopedic, Inc): 2 mL 1% sodium hyaluronate (HA), 1000 kDa v. 2 mL saline; total of 3 injections, 1 injection per wk	Pain at rest: VAS for pain at rest Pain on movement: VAS for pain with activity Joint function: NR Adverse events: No. of patients with or without adverse events (binary) up to wk 4	AC: Yes ITT: Yes Blinding: Yes
Sala and De Miguel 1995[34]	Hyalgan (Fidia Pharm. Corp, Italy): 2 mL (20 mg HA), 500–730 kDa v. 2 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: Data could not be used for analysis Pain on movement: Data could not be used for analysis Joint function: NR Adverse events: No. of patients with or without adverse events (binary)	AC: Yes ITT: No or unclear Blinding: No or unclear
Scale et al 1994[35]	Synvisc (Biomatrix Inc, USA): 2 mL (16 mg HA) ,~7000 kDa v. 2 mL saline solution; total of 2 injections on days 0 and 14 (2-INJ group) and total of 3 injections, 1 injection per wk (3-INJ group)	Pain at rest: Data (night pain) could not be used for analysis Pain on movement: NR Joint function: Data could not be used for analysis Adverse events: Data could not be used for analysis	AC: No or unclear ITT: No or unclear Blinding: Yes
Tamir et al 2001[36]	BioHy: 2 mL (20 mg HA), 2400–3600 kDa v. 2 mL saline solution; total of 5 injections, 1 injection per wk	Pain at rest: Data could not be used for analysis Pain on movement: Data could not be used for analysis Joint function: NR Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: No or unclear
Wobig et al 1998[37]	Synvisc (Biomatrix Inc, USA): 2 mL (16 mg HA), ~7000 kDa v. 2 mL saline solution; total of 3 injections, 1 injection per wk	Pain at rest: Data could not be used for analysis Pain on movement: Data could not be used for analysis Joint function: NR Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: Yes Blinding: Yes
Wu et al 1997[38]	ARTZ (Seikagaku Corp, Japan): 2.5 mL (25 mg HA), 600–1200 kDa v. 2.5 mL saline vehicle; total of 5 injections, 1 injection per wk	Pain at rest: Data could not be used for analysis Pain on movement: Data could not be used for analysis Joint function: Data could not be used for analysis Adverse events: No. of patients with or without adverse events (binary)	AC: No or unclear ITT: No or unclear Blinding: No or unclear

Note: HA = hyaluronic acid, NR = not reported, VAS = visual analogue scale, AC = allocation concealment, ITT = intention to treat, WOMAC = Western Ontario and MacMaster universities, OA = osteoarthritis.
*"Blinding" indicates that the outcome assessor was blinded to the intervention.
†Binary data other than from adverse events could not be used for analysis.

Table 2: Characteristics of the patients included in the studies of the meta-analysis

	All patients			Treatment group					Placebo group				
Study	Patients, no.	Withdrawals, %	Female, %	Patients, no.	Female, %	Age, yr*	Weight, kg*	OA duration, mo*	Patients, no.	Female, %	Age, yr*	Weight, kg*	OA duration, mo*
Altman and Moskowitz[16]	330	33	57	163	61	62 (10)	89 (18)	–	167	53	65 (10)	86 (18)	–
Bragantini et al[17]													
HA 40 mg group	38	5	75	20	–	57 (1.7)†	–	–	18	–	57 (1.7)†	–	–
HA 20 mg group	37	5	75	19	–	57 (1.7)†	–	–	18	–	57 (1.7)†	–	–
Brandt et al[18]	226	23	63	114	63	65 (8.4)	–	–	112	63	67 (8.4)	–	–
Bunyaratavej et al[19]	49	None	–	24	–	59 (10)	66 (12)	30 (37)	25	–	61 (9)	65 (12)	36 (41)
Carrabba et al[20] — HA-5 trail	40	None	72	20	65	60.6 (7.9)	70.5 (4.4)	34.8 (15.6)	20	80	60 (7)	69.9 (3.5)	32.4 (16.8)
Corrado et al[21]	40	13	77	21	67	61.3 (12.5)	–	26.4 (30.3)	19	89	61.2 (9.8)	–	44 (63.6)
Dahlberg et al[12]	52	8	–	28	–	46 (8)	81 (13)	–	24	–	44 (9)	84 (18)	–
Day et al[22]	240	7	41	116	56	62 (39–79)‡	84 (44–122)‡	§	124	61	62 (33–75)‡	80 (52–120)‡	§
Dixon et al[23] ¶	63	16	54	30	–	68.5 (43–85)‡	75.3 (42–105)‡	–	33	–	–	–	–
Dougados et al[24]	110	14	71	55	76	67.0 (9.7)	68.0 (12.6)	60 (42.4)	55	65	69.0 (10.6)	72.0 (16.8)	77 (75.5)
Grecomoro et al[25] ¶	40	5	56	20	–	64.9 (10.9)	–	–	20	–	–	–	–
Henderson et al[26]													
Severity group 1	40	None	63	20	50	63.9 (1.9)	–	–	20	75	60 (1.9)	–	–
Severity group 2	51	14	75	25	80	72.1 (1.7)	–	–	26	69	67 (1.7)	–	–
Huskisson and Donnelly[27]	100	19	67	50	76	65.8 (8.8)	–	§	50	58	64.8 (9.3)	–	§
Jubb et al[28]	408	22	68	208	73	63.5 (9.5)	–	94.8 (85.2)	200	64	65.0 (9.1)	–	102 (90)
Karlsson et al[29]													
Artzal group	158	6	67	92	67	72 (7)	81(13)	–	66	61	71 (6)	81 (16)	–
Synvisc group	154	2	65	88	65	70 (7)	79 (13)	–	66	61	71 (6)	81 (16)	–
Lohmander et al[30]	240	21	56	120	56	58.5 (8.4)	80.6 (12.9)	–	120	56	58.0 (8.4)	78.5 (14.1)	–
Petrella et al[31] — group 1 v. group 4	53	9	40	25	36	67.3 (8.9)	–	–	28	43	62.6 (9.5)	–	–
Puhl et al[32]	209	7	64	102	63	62.1 (41–75)‡	73.7 (45–108)‡	§	107	55	60.8 (40–74)‡	76.2 (40–101)‡	§
Russell et al[33]	142	18	56	71	56	61.3 (40–75)‡	–	–	71	60	64.1 (46–75)‡	–	–
Sala and De Miguel[34]	40	None	72	20	65	63 (8)	81 (2)	25.2 (55.2)	20	80	61 (9)	70 (4)	9.6 (21.6)
Scale et al[35]													
Study 1	50	NR	59	25	68	61.5 (15.2)	73.7 (11.6)	63.3 (54)	25	50	58.6 (12.9)	79.7 (9)	70.8 (78)
Study 2	30	NR	38	15	27	58.3 (9.0)	79.3 (11.7)	30 (28.2)	15	50	58.6 (12.9)	79.7 (9)	70.8 (78)
Tamir et al[36]	49	14	73	25	76	71	–	–	24	71	70	–	–
Wobig et al[37]	117	2	65	57	56	60 (2)†	76 (2)†	72 (10.8)†	60	74	64 (2)†	76 (2)†	72 (7.2)†
Wu et al[38]	116	50	28	62	34	68.9 (9.4)	–	16.4 (3.1)	54	23	69.2 (8.1)	–	20.7 (6.6)

*Continuous data are given as mean (standard deviation) except where indicated.
†Continuous data are given as mean (standard error).
‡Continuous data are given as mean (range).
§Data not presented as mean (standard deviation), mean (standard error), or mean (range).
¶ No detailed data available for treatment and control groups.

control patients).[12,18,27,29] The standardized weighted mean difference did not differ between treatment and control groups (p = 0.27) (Table 3 and Fig. 4C). Heterogeneity was considerable (I^2 = 62%).

Two trials followed patients until 44–60 weeks (73 intervention patients, 70 control patients),[12,24] and there were no differences in the end points of interest (p = 0.30) (Table 3).

Adverse events

Fifteen trials (with a total of 17 comparisons; 1033 intervention patients, 986 control patients) reported on adverse events in a way that allowed data extraction.[17–20,23,26–29,32–34,36–38] The degree of detail and accuracy varied among these trials. Adverse events, mostly of minor clinical relevance (such as transient pain at the injection site), occurred more frequently among patients who received the intervention (summary relative risk 1.08, 95% CI 1.01 to 1.15, p = 0.021). There was no unexplained heterogeneity (I^2 = 0%). Bias in the funnel plot analysis (mean bias 0.6, 95% CI 0.2 to 1.1, p = 0.01) could not be explained by lack of blinding in the meta-regression (ratio of risk ratios 0.77, 95% CI 0.49 to 1.21, p = 0.27), which suggests selective over-reporting or over-publication of trials reporting adverse events in patients treated with hyaluronic acid.

Impact of molecular mass

The effect size is ordered in Fig. 2, Fig. 3 and Fig. 4 according to molecular mass, but no clear association is evident. This lack of association was confirmed by the meta-regression analyses.

Sensitivity analysis

We repeated the analyses for pain at rest, pain after movement and joint function at 2–6 weeks and 10–14 weeks for only those trials that reported allocation concealment, blinded outcome assessment and intention-to-treat analysis. There was no significant effect in favour of the intervention (Table 4).

Interpretation

The methodologic quality of most of the trials was poor. Treatment with intra-articular hyaluronic acid did not have a proven beneficial effect on osteoarthritis pain at rest. Pain during or after movement was slightly lower relative to placebo, but this effect is of borderline clinical relevance at best. Moreover, the effect appears to have been inflated by trials of low methodologic quality. Intra-articular hyaluronic acid did not lead to improvement in joint function but may have been associated with a higher rate of side effects than placebo.

Patients with chronic rheumatoid arthritis rated pain as "somewhat better" at a mean difference of 8 mm on a visual analogue scale and as "much better" at a 15-mm difference.[40] The summary estimates obtained in this meta-analysis fell short of being the difference defined as "somewhat better," and the confidence intervals sometimes

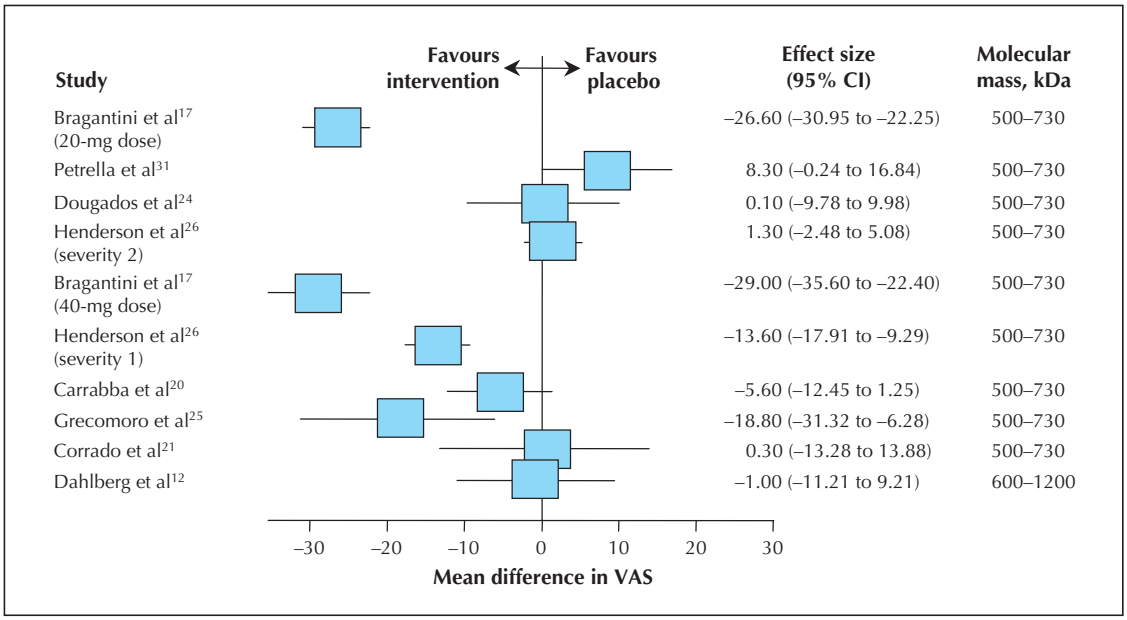

Fig. 2: Effectiveness of hyaluronic acid compared with placebo for pain at rest at 2–6 weeks. Data are presented as the study means (boxes) and 95% confidence intervals (CIs, horizontal lines). There is no summary effect, and the data are not weighted (because of excessive heterogeneity). Bragantini and associates[17] reported on 2 strata separately (20-mg and 40-mg doses), as did Henderson and colleagues[26] (severity groups 1 and 2). The trials are ranked according to the molecular mass of the hyaluronic acid preparation. VAS = visual analogue scale.

included the range defined as "much better"; however, the latter were also compatible with increased pain. This finding was augmented by the sensitivity analyses, where the confidence intervals barely exceeded 15 mm (Table 4).

In several instances, only a few trials were available for a given end point at a particular time. A more significant problem, however, was the low methodologic reporting quality of the trials. Low-quality trials, particularly those

Table 3: Mean difference in pain and function between treatment with hyaluronic acid and treatment with placebo at 4 time points

End point	2–6 wk	10–14 wk	22–30 wk	44–60 wk
Pain at rest, mm VAS (95% CI)	–8.7 (–17.2 to –0.2)*	–5.2 (–13.3 to 2.9)	–6.0 (–22.3 to 10.3)	–0.75 (–9.6 to 8.1)
Pain during or after exercise, mm VAS (95% CI)	–3.8 (–9.1 to 1.4)*	–4.3 (–7.6 to –0.9)	–7.1 (–11.8 to –2.4)	–0.5 (–12.5 to 11.5)
Function, z value (95% CI)	–0.00 (–0.23 to 0.23)	–0.11 (–0.31 to 0.09)	–0.16 (–0.45 to 0.13)	–0.17 (–0.50 to 0.16)

Note: A minus indicates superiority of hyaluronic acid (a reduction of pain or functional impairment). CI = confidence interval.
*Pooling is questionable because of a high degree of unexplained statistical heterogeneity.

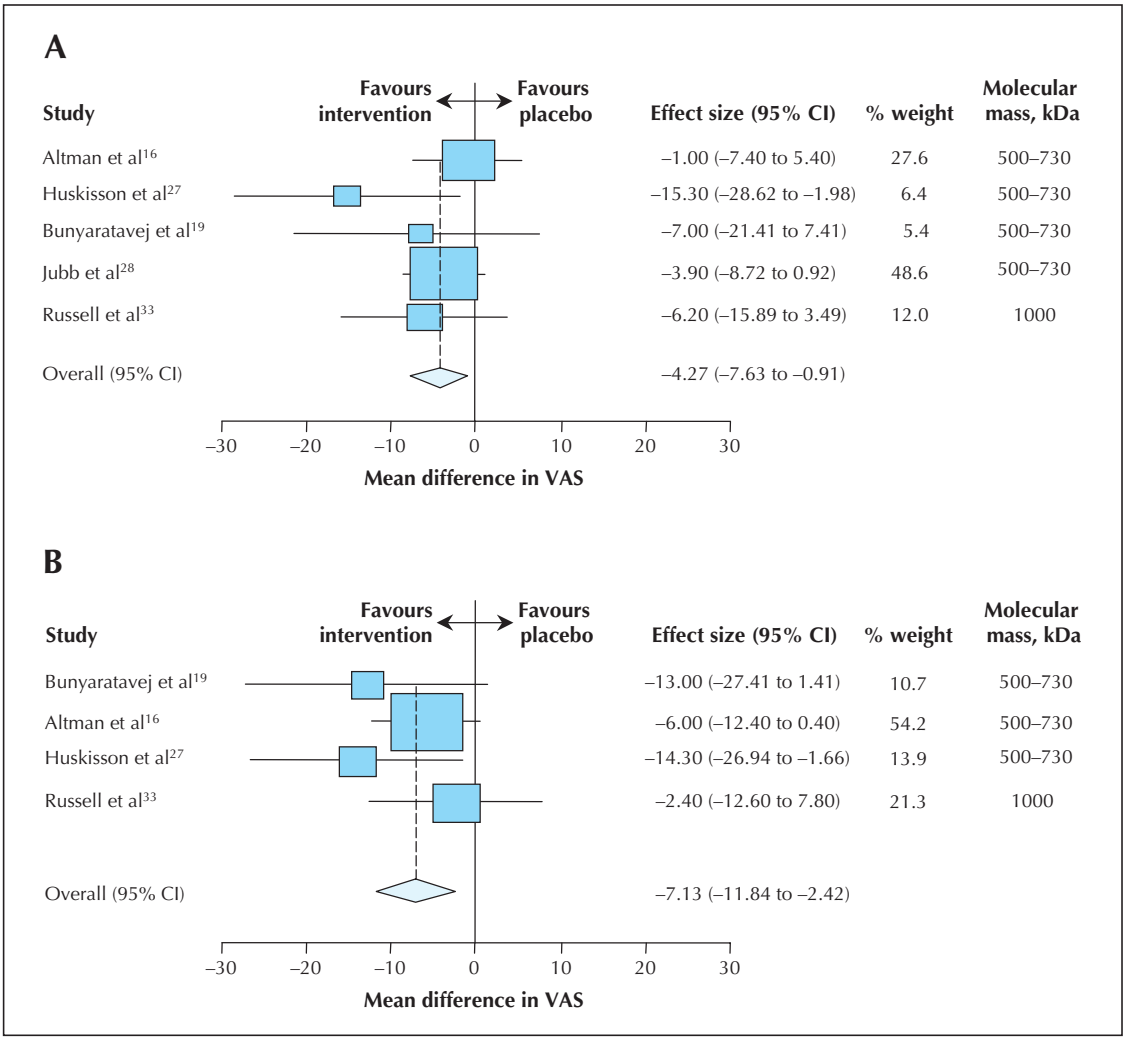

Fig. 3: Effectiveness of hyaluronic acid compared with placebo for pain after exercise. A: At 10–14 weeks. B: At 22–30 weeks. Data are presented as weighted mean difference for each study (boxes), 95% CIs (horizontal lines) and summary weighted mean difference with 95% CI (diamond). The trials are ranked according to the molecular mass of the hyaluronic acid preparation.

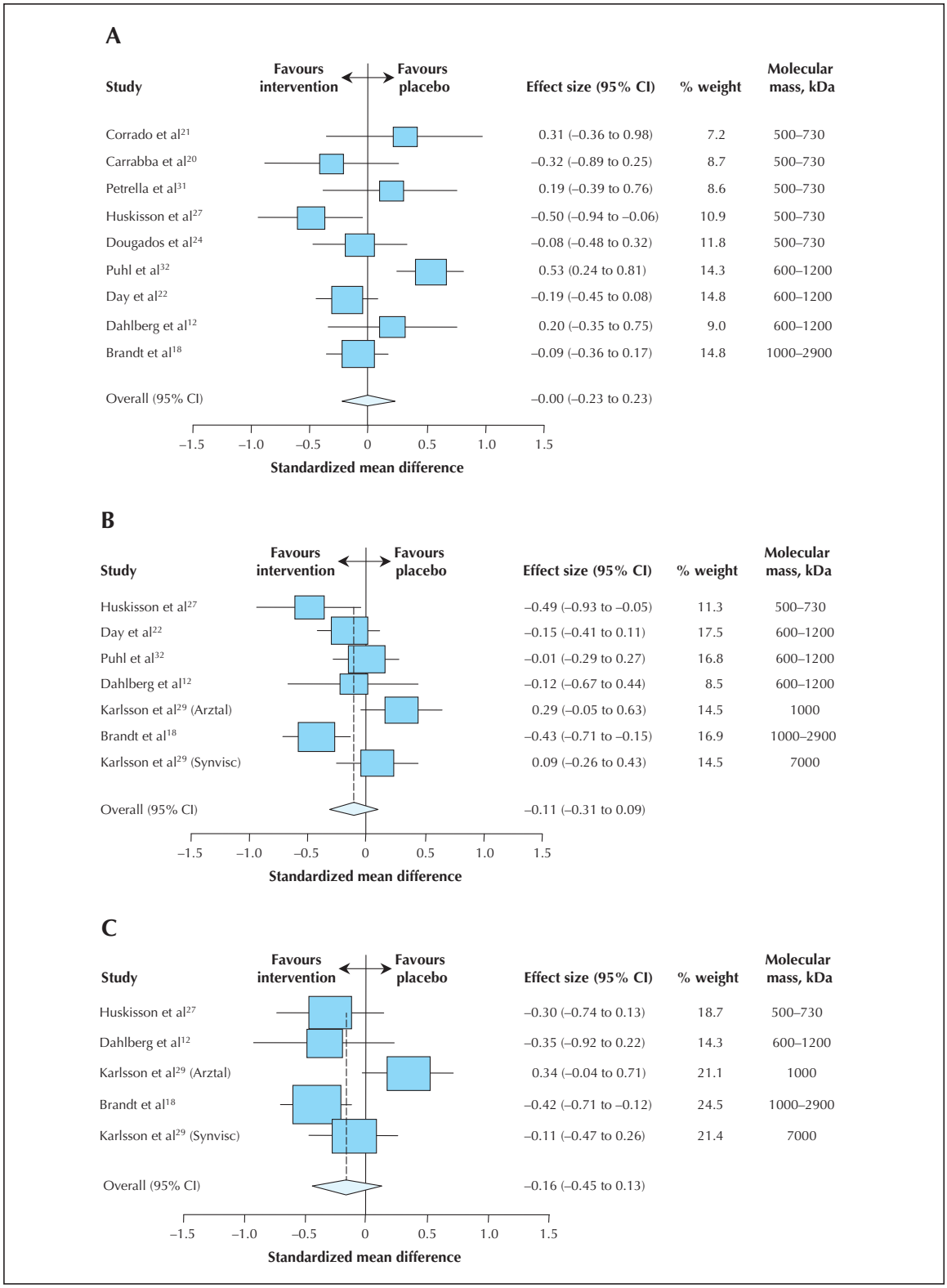

Fig. 4: Effectiveness of hyaluronic acid compared with placebo for joint function. A: At 2–6 weeks. B: At 10–14 weeks. C: At 22–30 weeks. Data are presented as standardized, weighted study mean differences (boxes), 95% CIs (horizontal lines) and summary standardized, weighted mean difference with 95% CI (diamond). Karlsson and collaborators[29] reported on 2 strata separately (by brand of hyaluronic acid preparation: Arztal and Synvisc). The trials are ranked according to the molecular mass of the hyaluronic acid preparation.

not reporting allocation concealment and those not reporting blinding, are known to favour interventions.[15,41–44] Our data are compatible with these findings.

Another problem is the wide range of reported end points. We tried to compose clinically useful and comparable outcome categories for the trials. Within our selection algorithm we planned to categorize all reported end points (a total of 125) into 12 categories and to discard end points that could not be allocated. We analyzed only 4 of these 12 categories (the most relevant from a clinical perspective). The remaining 8 categories were global pain, pain on touch, joint effusion, joint stiffness, quality of life, pain medication, overall assessment by patient and overall assessment by observer.

Only 2 papers were excluded because there was no abstract available in English or German. From their titles, it was doubtful that these were randomized controlled trials, but we could not confirm study type. Including non-English studies and unpublished studies in a meta-analysis may even introduce bias.[43,45] It is difficult to determine the trade-off between detecting all of the available evidence and introducing bias through inclusion of inferior studies identified by a comprehensive search.[45]

We applied multiple statistical tests, and a type 1 error — detecting an effect where none existed — is possible. This possibility should be borne in mind when interpreting the data.

Finally, there were only a limited number of trials for each end point and time point, which led to wide confidence intervals. Even so, the limits did not exceed a clinically meaningful difference in many instances. We could not detect publication bias (data not shown) except perhaps with regard to adverse event reporting. This does not necessarily exclude the possibility of such bias, but if there was any selection or publication bias, it would probably have exaggerated the effect.

We are aware of 3 relevant systematic reviews.[8,9,46] One of these was an update of the EULAR recommendations for management of knee osteoarthritis.[46] The literature search for that review was systematic, but it covered only 2 databases (MEDLINE and EMBASE). A summary quality score was used, and the median score was 20 out of 28. This high score is surprising, considering that the standard of reporting for the 3 most important items was poor.[41] Perhaps the high scores were the result of summing individual items. The use of such scores, however, is not advisable.[47] The task force that prepared the EULAR update[46] did not perform a quantitative summary but counted the number of positive trials, an approach that may be misleading.[48] The authors' conclusion that "there is evidence to support the efficacy of HA [hyaluronic acid]" is not, in our opinion, well supported by the information presented.

The second systematic review and meta-analysis[8] covered the same search period as ours. Lo and associates[8] chose a hierarchy of relevant end points and selected the highest-ranking end point in each trial. The time of assessment was 2–3 months, but if data for this time point were not available, data were extracted on pain at 1–4 months after the first intra-articular injection. This creative approach may lump together end points that are only weakly related. The authors also extracted data on change from baseline, choosing not to rely on the assumption that the groups were comparable before treatment began. Indeed, for 2 trials[24,26] the groups were not comparable at baseline. Nevertheless, trials are usually designed for simple between-group comparisons. Using such a change score might reduce the power or precision of an individual study.[49]

The trials included in the analysis of Lo and associates[8] differed slightly from those in our analysis: we identified and included 4 published studies[17,19,25,38] not used by Lo and associates, whereas those authors included 3 studies that we did not (2 published only as abstracts[50,51] and 1 in which the patient's other knee served as the control [i.e., observations may not be independent][52]). Lo and associates concluded that at best there is a small effect. Unsurprisingly, their findings were similar to the results of our meta-analysis.

The third systematic review and meta-analysis[9] was published recently, but the search included only studies published up to 2001. Wang and colleagues[9] used 3 end points to calculate "efficacy scores," standardizing for different pain measures and summing efficacy scores over time. This approach transforms scores to a palatable size but makes clinical inferences very difficult. It is questionable if combining data from trials of highly variable length is reasonable. We found 7 additional studies,[12,19,22,28,29,31,33] including 2 published before 2002 and 1 published before 2001. Wang and colleagues stated that hyaluronic acid led to significant improvements in pain and functional outcomes with few

Table 4: Mean difference in pain and function between treatment with hyaluronic acid and treatment with placebo at 2 time points in high-quality trials*

	2–6 wk		10–14 wk	
End point	Mean difference (95% CI)	No. of trials	Mean difference (95% CI)	No. of trials
Pain at rest, mm VAS	4.1 (–5.0 to 13.2)	2[12,31]	–5.2 (–13.3 to 2.9)	2[12,33]
Pain during or after exercise, mm VAS	–6.7 (–16.7 to 3.3)	1[31]	–6.2 (–15.9 to 3.5)	1[33]
Function, z value	–0.04 (–0.30 to 0.22)	3[12,22,31]	–0.14 (–0.38 to 0.09)	2[12,22]

Note: A minus indicates superiority of hyaluronic acid (a reduction of pain or functional impairment).
*All trials reported blinding, allocation concealment and intention-to-treat analysis.

adverse events. Even though some of their reported results were of statistical significance, they were certainly not of clinical relevance.

Experimental studies and animal studies suggest that the molecular mass of hyaluronic acid may affect pain and the underlying inflammatory mechanisms in osteoarthritis.[2,53] Lo and associates[8] observed that studies using the highest-molecular-weight hyaluronic acid had much greater effect sizes but also exhibited crucial heterogeneity, but another trial found no significant difference in clinical efficacy between 2 hyaluronic acid preparations.[29] We observed no association between molecular mass and effect of hyaluronic acid by informal methods (ranking the effects) or formal methods for indirect comparisons (meta-regression analysis).

The currently available evidence suggests that intra-articular hyaluronic acid is not clinically effective and may be associated with increased risk of adverse events. Therefore, this type of therapy should not be used for the treatment of painful osteoarthritis (except in clinical trials) until a large long-term trial with clinically relevant and uniform end points has clarified the benefit–risk ratio. Using predefined clinically important differences could further help in the assessment of its value for patients with knee osteoarthritis. Such an approach is of particular importance when considering the public health impact of the disease and its treatment.

This article has been peer reviewed.

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Appendix 1: Search terms

MEDLINE	
Condition	(osteoarthritis) or (degenerative arthritis) or (gonarthrosis) or (knee near arthralgia) or (knee near pain) or (patella near pain) or (patellofemoral near pain) or (patello near femoral pain) or (retropatellar near pain) or (femoropatellar near pain) or (femoro-patellar near pain)
Intervention	(hyaluronan) or (hyaluronate) or (viscosupplementation) or (visco near supplementation) or (hyaluronic acid) or ('Hyaluronic-Acid' / therapeutic-use in MIME,MJME)
RCT filter	(((((RANDOMIZED-CONTROLLED-TRIAL in PT) or (CONTROLLED-CLINICAL-TRIAL in PT) or (RANDOMIZED-CONTROLLED-TRIALS) or (RANDOM-ALLOCATION) or (DOUBLE-BLIND-METHOD) or (SINGLE-BLIND-METHOD)) not (TG=ANIMAL not (TG=HUMAN and TG=ANIMAL))) or (((((CLINICAL-TRIAL in PT) or (explode CLINICAL-TRIALS) or ((clin* near trial*) in TI) or ((clin* near trial*) in AB) or ((((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in TI) or (((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in AB)) or (PLACEBOS) or (placebo* in TI) or (placebo* in AB) or (random* in TI) or (random* in AB) or (RESEARCH-DESIGN)) not (TG=ANIMAL not (TG=HUMAN and TG=ANIMAL))) not (((RANDOMIZED-CONTROLLED-TRIAL in PT) or (CONTROLLED-CLINICAL-TRIAL in PT) or (RANDOMIZED-CONTROLLED-TRIALS) or (RANDOM-ALLOCATION) or (DOUBLE-BLIND-METHOD) or (SINGLE-BLIND-METHOD)) not (TG=ANIMAL not (TG=HUMAN and TG=ANIMAL)))) or ((((TG=COMPARATIVE-STUDY) or (explode EVALUATION-STUDIES) or (FOLLOW-UP-STUDIES) or (PROSPECTIVE-STUDIES) or (((control* or prospectiv* or volunteer*) in TI) or ((control* or prospectiv* or volunteer*) in AB))) not (TG=ANIMAL not (TG=HUMAN and TG=ANIMAL))) not (((((RANDOMIZED-CONTROLLED-TRIAL in PT) or (CONTROLLED-CLINICAL-TRIAL in PT) or (RANDOMIZED-CONTROLLED-TRIALS) or (RANDOM-ALLOCATION) or (DOUBLE-BLIND-METHOD) or (SINGLE-BLIND-METHOD)) not (TG=ANIMAL not (TG=HUMAN and TG=ANIMAL))) or (((((CLINICAL-TRIAL in PT) or (explode CLINICAL-TRIALS) or ((clin* near trial*) in TI) or ((clin* near trial*) in AB) or ((((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in TI) or (((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in AB)) or (PLACEBOS) or (placebo* in TI) or (placebo* in AB) or (random* in TI) or (random* in AB) or (RESEARCH-DESIGN)) not (TG=ANIMAL not (TG=HUMAN and TG=ANIMAL))) not (((RANDOMIZED-CONTROLLED-TRIAL in PT) or (CONTROLLED-CLINICAL-TRIAL in PT) or (RANDOMIZED-CONTROLLED-TRIALS) or (RANDOM-ALLOCATION) or (DOUBLE-BLIND-METHOD) or (SINGLE-BLIND-METHOD)) not (TG=ANIMAL not (TG=HUMAN and TG=ANIMAL)))))))
EMBASE	
Condition	(osteoarthritis) or (degenerative arthritis) or (gonarthrosis) or (knee near arthralgia) or (knee near pain) or (patella near pain) or (patellofemoral near pain) or (patello near femoral pain) or (retropatellar near pain) or (femoropatellar near pain) or (femoro-patellar near pain)
Intervention	(hyaluronan) or (hyaluronate) or (viscosupplementation) or (hyaluronic acid) or ('hyaluronic-acid' / all subheadings in DEM,DER,DRM,DRR)
RCT filter	((Random*) or (explode 'major-clinical-study' / all subheadings) or (explode 'controlled-study' / all subheadings) or (trial* or control* or study or compar*) or (explode 'clinical-article' / all subheadings) or (Placebo* or blind* or doubl*))
Cochrane	
Condition	(osteoarthritis) or (degenerative arthritis) or (gonarthrosis) or (knee near arthralgia) or (knee near pain) or (patella near pain) or (patellofemoral near pain) or (patello near femoral pain) or (retropatellar near pain) or (femoropatellar near pain) or (femoro-patellar near pain)
Intervention	(hyaluronan) or (hyaluronate) or (viscosupplementation) or (visco near supplementation) or (hyaluronic acid)
CINAHL	
Condition	(osteoarthritis) or (degenerative arthritis) or (gonarthrosis) or (knee near arthralgia) or (knee near pain) or (patella near pain) or (patellofemoral near pain) or (patello near femoral pain) or (retropatellar near pain) or (femoropatellar near pain) or (femoro-patellar near pain)
Intervention	(hyaluronan) or (hyaluronate) or (viscosupplementation) or (hyaluronic acid) or ('Hyaluronic-Acid' / all topical subheadings / all age subheadings in DE)
RCT filter	(explode 'Clinical-Trials' / all topical subheadings / all age subheadings in DE)
BIOSIS	
Condition	(osteoarthritis) or (degenerative arthritis) or (gonarthrosis) or (knee near arthralgia) or (knee near pain) or (patella near pain) or (patellofemoral near pain) or (patello near femoral pain) or (retropatellar near pain) or (femoropatellar near pain) or (femoro-patellar near pain)
Intervention	(hyaluronan) or (hyaluronate) or (viscosupplementation) or (visco near supplementation) or (hyaluronic acid)