

Hylan Versus Hyaluronic Acid for Osteoarthritis of the Knee: A Systematic Review and Meta-Analysis

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Objective. To compare the effectiveness and safety of intraarticular high-molecular hylan with standard preparations of hyaluronic acids in osteoarthritis of the knee.

Methods. We performed a systematic review and meta-analysis of randomized controlled trials comparing hylan with a hyaluronic acid in patients with knee osteoarthritis. Trials were identified by systematic searches of Central, Medline, EMBase, Cinahl, the Food and Drug Administration, and Science Citation Index supplemented by hand searches of conference proceedings and reference lists (last update November 2006). Literature screening and data extraction were performed in duplicate. Effect sizes were calculated from differences in means of pain-related outcomes between treatment and control groups at the end of the trial, divided by the pooled standard deviation. Trials were combined using random-effects meta-analysis.

Results. Thirteen trials with a pooled total of 2,085 patients contributed to the meta-analysis. The pooled effect size was -0.27 (95% confidence interval [95% CI] $-0.55, 0.01$), favoring hylan, but between-trial heterogeneity was high ($I^2 = 88\%$). Trials with blinded patients, adequate concealment of allocation, and an intent-to-treat analysis had pooled effect sizes near null. The meta-analyses on safety revealed an increased risk associated with hylan for any local adverse events (relative risk [RR] 1.91; 95% CI 1.04, 3.49; $I^2 = 28\%$) and for flares (RR 2.04; 95% CI 1.18, 3.53; $I^2 = 0\%$).

Conclusion. Given the likely lack of a superior effectiveness of hylan over hyaluronic acids and the increased risk of local adverse events associated with hylan, we discourage the use of intraarticular hylan in patients with knee osteoarthritis in clinical research or practice.

KEY WORDS. Knee; Osteoarthritis; Meta-analysis; Viscosupplementation.

INTRODUCTION

Injected hyaluronic acid is cleared from the osteoarthritic joint in less than a day (1). To increase average molecular

weight and half-life in the joint, hyaluronic acids have been modified to form hylan, chemically crosslinked hyaluronic acid molecules with average molecular weights up to 23×10^6 daltons, and resulting half-lives of 1.5–9 days (2). It has been suggested that higher viscosity and longer intraarticular half-life of hylan lead to better effectiveness (3,4). However, several authors have also reported local adverse reactions (hot, painful, swollen knee) typically occurring 24–72 hours after injection of hylan (5–8).

Six systematic reviews and meta-analyses (9–14) have been published on the effectiveness and safety of viscosupplementation. All of these studies compared hyaluronic acid and hylan with a sham intervention, but only one study (13) included trials comparing hylan with hyaluronic acids directly. Wang et al (11) and Lo et al (9) found indirect evidence that hylan might be more effective than hyaluronic acids, but heterogeneity of the studies limited conclusions. The most recent review (13), which also included direct comparisons of hylan and hyaluronic acids, did not pool results of included trials but concluded that effectiveness might differ between different preparations.

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The safety of hylan compared with conventional hyaluronic acids was rarely addressed. Two of the reviews indicated that intraarticular hyaluronic acid was associated with few adverse events, but sample sizes of included trials precluded any definitive conclusions (11,13). Only the review by Wang et al (11) acknowledged that crosslinked hylan might be associated with acute painful local reactions.

We performed a systematic review and meta-analysis of randomized controlled trials comparing hylan with standard hyaluronic acids to determine whether they differ in their effectiveness and safety. Previous claims that hylan has greater benefits compared with conventional preparations of hyaluronic acids were mainly based on implicit indirect comparisons from placebo-controlled trials. For example, Lo et al found a pooled effect size of -0.19 in trials comparing standard hyaluronic acids with placebo and a pooled effect size of -1.1 in trials comparing hylan with placebo (9). They concluded that hylan may be more efficacious in treating knee osteoarthritis compared with standard hyaluronic acids. We therefore performed an additional formal indirect comparison using results from trials included in previous meta-analyses that had compared hylan or hyaluronic acid with a sham intervention.

MATERIALS AND METHODS

Literature search. We searched the Cochrane Controlled Trials Register (Central), Medline, EMBase, and Cinahl from inception to November 2006 using truncated variations of preparation names including brand names combined with truncated variations of terms related to osteoarthritis all as text word. No methodologic filter for controlled clinical trials was applied (the exact search strategy is available from the authors). We entered relevant articles into Science Citation Index to retrieve reports that have cited these articles, manually searched conference proceedings and textbooks, screened reference lists of all obtained articles, and checked the proceedings of the US Food and Drug Administration advisory panel related to relevant approval applications. Finally, we asked authors and content experts for relevant references, and contacted manufacturers known to have conducted trials on viscosupplementation.

Trial selection. We included randomized or quasi-randomized controlled trials comparing intraarticular injections of hyaluronic acid with hylan in patients with osteoarthritis of the knee. Two reviewers (SR and EAK) independently evaluated reports for eligibility. Disagreements were resolved by consensus.

Quality assessment. Two of 4 reviewers (SR, SB, EAK, or AWSR) independently assessed concealment of treatment allocation, blinding, and analyses (15). Concealment of allocation was considered adequate if the investigators responsible for patient selection were unable to determine prior to allocation which treatment was next in line (central randomization; sealed, opaque, sequentially num-

bered assignment envelopes; coded drug packs, etc.). Patient blinding was considered adequate if patients were stated to be blind to the assigned treatment. Therapist blinding was considered adequate if preparations were explicitly described as indistinguishable or a double-dummy technique was used. The number of patients randomized per group and the number of patients analyzed per group were extracted to allow distinction between trials that had included all randomized patients in the analysis (considered as intent-to-treat analysis and therefore adequate) and trials that had not. Disagreements were resolved by consensus.

Outcome measures. The prespecified primary outcome of our meta-analysis was pain as currently recommended for osteoarthritis trials (16,17). If pain was assessed at more than 1 time point, we extracted the measurement at the end of the trial or at a maximum of 6 months after the last injection, whichever came first. If an article provided data on more than 1 pain scale, we extracted the outcome that was highest on a previously described hierarchy of pain-related outcomes (18). In this hierarchy, global pain takes precedence over pain on walking, the Western Ontario and McMaster Universities Osteoarthritis Index pain subscore, other measures of pain, function, and global treatment assessment. Secondary outcomes were the occurrence of flares (defined as a hot, painful, swollen knee typically within 24–72 hours after injection), effusions (defined as excessive joint fluid inside the treated knee occurring after an injection, typically diagnosed by clinical examination, ultrasound, or arthrocentesis), and any local adverse event (any definition as specified by the authors of individual trials).

Data collection. Data on publication status, trial design, patient characteristics, treatment regimens, pain, local adverse events, effusions, flares, quality assessment, and funding were extracted in duplicate (by SR, SB, EAK, or AWSR) using a standardized form. Any disagreements were resolved by discussion. If numerical data could not be extracted, we read means and measures of dispersion from figures in the report. In case of multiarm trials comparing hylan with different hyaluronic acids, we combined the groups with the different hyaluronic acids. In case of discrepancies between different reports of the same trial, we extracted data from the most recent relevant full-text journal article. For the meta-analyses of secondary outcomes on local adverse events, we considered only the first event if more than 1 event had occurred in the same patient. One trial (19) had a factorial design with participants randomly allocated to receive 1 of 3 different viscosupplementation preparations and allocated to receive either 1 treatment cycle during months 0–6 or 2 treatment cycles during months 0–6 and 7–12. Whereas the effectiveness was assessed after 1 cycle at 6 months, the occurrence of local adverse events was determined after either 1 or 2 cycles, depending on the number of cycles to which participants were allocated. Therefore, we treated patients allocated to 1 or 2 cycles as if they were from separate trials in the meta-analyses of local adverse events.

Statistical analysis. Whenever possible, we used results of an intent-to-treat analysis. Effect sizes were calculated by dividing the differences in mean values at the end of the trial across treatment groups by the pooled standard deviation corresponding to Cohen's *d* (20). If differences in end-of-trial values could not be calculated, we used differences in the mean changes from baseline to the end of the trial as a proxy measure. If some of the required data were unavailable we used approximations as described elsewhere (21). Negative effect sizes indicate superiority of hylan compared with conventional hyaluronic acids throughout. An effect size of -0.30 may be considered minimally clinically relevant. Based on a typical pooled standard deviation in trials assessing pain with a 10-cm visual analog scale (2.1 cm), this effect size corresponds to a 0.6-cm difference in pain scores between groups (21). For dichotomous outcomes we calculated relative risks.

We used a random-effects meta-analysis (22) to pool effect sizes and relative risks and calculated the I^2 statistic for each meta-analysis. This statistic describes the percentage of total variation across trials that is attributable to statistical heterogeneity rather than chance (23). I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high between-trial heterogeneity, respectively. We investigated the association between trial size and treatment effects in a funnel-plot by plotting effect sizes against their standard error (24). Asymmetry of the funnel-plot was assessed by the asymmetry coefficient: the difference in effect size per unit increase in standard error (24). We performed stratified meta-analyses to investigate potential sources of statistical heterogeneity. The following trial characteristics were considered for stratification: adequacy of concealment of allocation, blinding of patients, adequacy of the analysis, trial size, length of followup, funding, and preparation used in the control group. We used prespecified cutoffs of 200 randomized patients to distinguish between small- and large-scale trials and of 3 months to distinguish between trials with short and long followup. All stratification variables were prespecified in the protocol. Univariable random-effects meta-regression analysis was used to examine whether effect sizes were affected by these factors (25). In additional univariable random-effects meta-regression analyses, followup duration and molecular weight of standard hyaluronic acids were entered as continuous explanatory variables to explore whether these factors were associated with effect size. Finally, we performed post hoc sensitivity analyses excluding outlier studies from the main meta-analysis. Studies were considered as outliers if the confidence interval of the estimated effect size from these studies did not overlap with the pooled overall effect size. For these trials we determined the contribution to Cochran's heterogeneity *Q* statistic in the overall analysis as described by Baujat et al (26). All confidence intervals relate to the 95% limit and *P* values are 2-sided. Analyses were performed using Stata 9.2 (StataCorp, College Station, TX).

Indirect comparison of hylan and hyaluronic acids. Previous claims that hylan has greater benefits compared with conventional preparations of hyaluronic acids were mainly based on implicit indirect comparisons from pla-

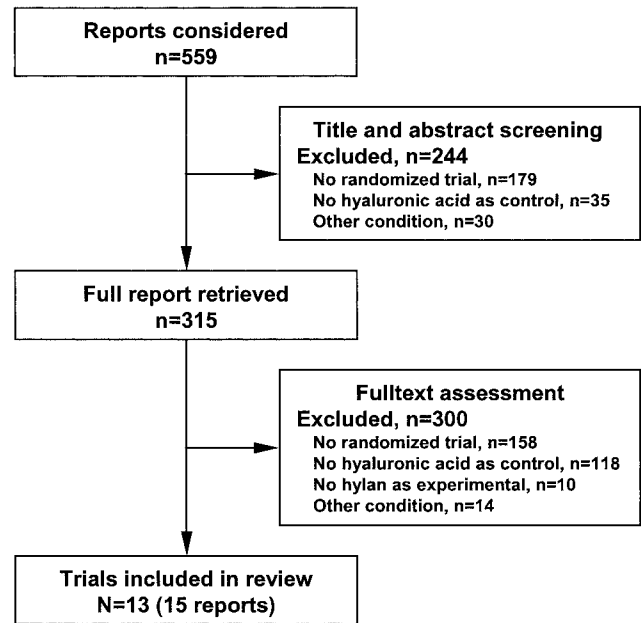


Figure 1. Flow diagram of articles evaluated for inclusion or exclusion.

cebo-controlled trials. We performed a formal indirect comparison using results from trials included in previous meta-analyses that compared hylan or hyaluronic acid with a sham intervention. We searched PubMed for systematic reviews and meta-analyses of placebo-controlled trials of hylan and conventional hyaluronic acids and extracted relevant data of component trials. Then we used univariable random-effects meta-regression to derive an indirect comparison of hylan and hyaluronic acid adjusted by the common sham intervention control group (27,28). The type of experimental intervention (hylan or hyaluronic acid) was used as the independent variable; the regression coefficient derived for this variable corresponds to the difference in effect sizes between trials of hylan and trials of hyaluronic acid as the experimental intervention and can be interpreted as the effect size indirectly comparing hylan and hyaluronic acid. We performed indirect comparisons based on all trials and stratified according to trial size using the cutoff described above.

RESULTS

We identified 559 references and considered 315 to be potentially eligible for the meta-analysis (Figure 1). Fifteen reports describing 13 trials met our inclusion criteria and were included in the meta-analysis. Eleven trials were published as full journal articles (19,29–38) and 2 trials were published as abstracts (39,40) (Table 1). Trial duration ranged from 3 weeks to 1 year (median 6 months) and only patients with osteoarthritis of the knee were recruited. Overall, the trials had allocated 2,085 patients to hylan or hyaluronic acid (median 62, range 31–660). The average age of patients ranged from 54 to 71 years (median 61 years) with an average duration of symptoms ranging from 4 to 7.7 years (median 5 years). Hyaluronic acid of

Table 1. Characteristics of identified randomized controlled trials*

Author, year (ref.)	Hyaluronic acid	Average molecular weight, kd	No. of patients hylan (HMW)†	No. of patients hyaluronic acid (LMW)†	Overall followup duration, weeks	Concealed allocation	Patient blinding	Therapist blinding	ITT	Supporting manufacturer	Outcome extracted
Wobig, 1999 (29)	Artzal/Healon	900/2,000	38	35/39	12	Unclear	Yes	Yes	Unclear	Genzyme/Biomatrix	Pain on activities (VAS)
Zhou, 2000 (30)	Unclear	1,000	20	20	26	Unclear	Unclear	No	Unclear	Unclear	Global pain (Likert)
Karlsson, 2002 (31)	Artzal	900	88	92	52	Unclear	Yes	No	No	Astra	Pain on walking (VAS)
Bayramoglu, 2003 (32)	Orthovisc	2,000	15	16	13	Unclear	Unclear	No	No	Unclear	Lequesne (Likert)
Garcia, 2004 (39)	Hyalgan	700	25	26	5	Unclear	No	No	Unclear	Wyeth and Sanofi	Pain overall (VAS)
Karatay, 2004 (33)	Orthovisc	2,000	20	20	3	Unclear	Unclear	No	Unclear	Unclear	WOMAC pain (Likert)
Karatosun, 2005 (34)	Orthovisc	2,000	46	46	52	Unclear	Yes	No	No	No	Pain on activities (Likert)
Rolf, 2005 (35)	Artzal	900	90	91	52	Unclear	Yes	No	No	Genzyme/Roche	Patient's global assessment (Likert)
Atamaz, 2006 (36)	Orthovisc	2,000	20	20	52	Unclear	Unclear	No	Unclear	Unclear	Global pain (VAS)
Jüni, 2007 (19)	Orthovisc/Ostenil	2,000/1,200	222	219/219	26	Yes	Yes	No	Yes	No	WOMAC pain (Likert)
Kirchner, 2006 (37)	Bio-Hyaluronan	3,000	161	160	12	Yes	Yes	No	No	Ferring	WOMAC pain (VAS)
Kotevoglu, 2006 (38)	Orthovisc	2,000	21	20	26	Unclear	Unclear	No	No	No	WOMAC pain (Likert)
Raman, 2006 (40)	Hyalgan	700	184	172	52	Unclear	No	No	Unclear	No	Pain overall (VAS)

* HMW = high molecular weight; LMW = low molecular weight; ITT = intent-to-treat analysis; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
 † Number of patients randomized and relevant for the meta-analysis.

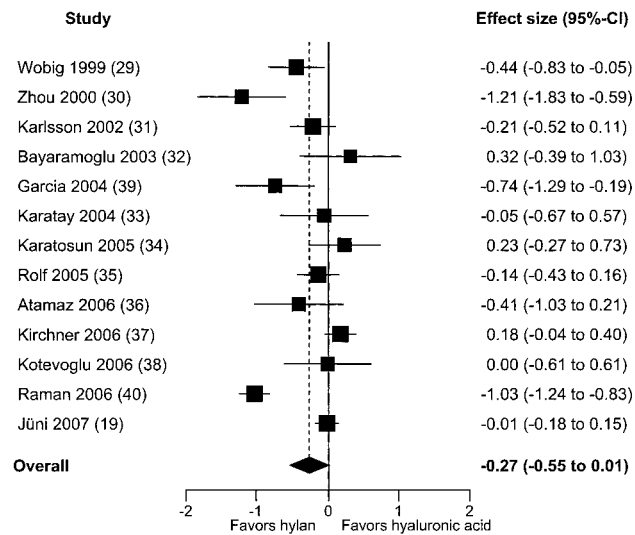


Figure 2. Forest plot of the meta-analysis of pain-related outcomes. The size of the boxes is proportional to the random-effects weights used in the meta-analysis. $I^2 = 88\%$ ($P < 0.001$). 95% CI = 95% confidence interval.

avian origin was used in 9 trials (31–36,38–40) and 1 trial used hyaluronic acid of bacterial origin as a control intervention (37). One trial used 2 different hyaluronic acids of avian origin (29) and a 3-arm trial used a hyaluronic acid of avian origin in 1 control group and a hyaluronic acid of bacterial origin in the other control group (19). For 1 trial (30), the origin of the hyaluronic acid was unclear.

Assessment of quality. All trials were reported as randomized. Concealment of allocation was judged to be adequate in only 2 trials (19,37). For all other trials, concealment of allocation remained unclear. Patients were blinded to the assigned intervention in 6 trials (19,29,31,34,35,37), explicitly aware of the assigned treat-

ment in 2 trials (39,40), blinding status of patients was unclear in the remaining 5 trials (30,32,33,36,38); only 1 trial was considered to have adequately blinded therapists (29). Only 1 trial (19) was considered to have performed an intent-to-treat analysis.

Pooled effect sizes. A total of 13 trials with 2,085 patients contributed to the meta-analysis of pain-related outcomes (Figure 2). The pooled effect size was -0.27 with a confidence interval overlapping the null (95% confidence interval [95% CI] $-0.55, 0.01$). An I^2 of 88% indicated a high degree of between-trial heterogeneity ($P < 0.001$ for heterogeneity) and the funnel-plot was symmetrical (asymmetry coefficient -0.02 ; 95% CI $-3.25, 3.20$).

The results from stratified analyses are presented in Table 2. Benefits of hylan were small in the 2 trials with adequate concealment of allocation (981 patients) (19, 37), the 6 patient-blind trials (1,486 patients) (19,29,31, 34,35,37), and the 1 trial analyzed according to the intent-to-treat principle (660 patients) (19), with effect sizes near the null effect and confidence intervals overlapping the null, excluding a minimally clinically relevant effect size of -0.30 . However, P values for interaction between these trial characteristics and treatment effect did not reach conventional levels of significance ($P = 0.19, 0.08, \text{ and } 0.55$). Between-trial heterogeneity was moderate in trials with adequate concealment of allocation (48%) and in trials with patient blinding (53%). Effect sizes varied somehow according to the preparation in the control group ($P = 0.09$ for interaction), with large effect sizes found in 2 trials (39,40) that used one particular preparation of avian origin as a control intervention (-1.00 ; 95% CI $-1.19, -0.80$). Both of these trials lacked blinding of patients. We found little evidence that effect sizes varied according to the type of origin of control preparations (avian versus bacterial; $P = 0.23$ for interaction). The meta-regression analyses using molecular weight and length of

Table 2. Results of the stratified meta-analyses—related methodologic characteristics*

	No. of trials	No. of patients randomized	Effect size (95% CI)	I^2 , %	P value for interaction†
All trials	13	2,085	$-0.27 (-0.55, 0.01)$	88	NA
Concealment of allocation					0.19
Adequate	2	981	$0.07 (-0.12, 0.25)$	48	
No or unclear	11	1,104	$-0.35 (-0.67, -0.04)$	83	
Blinding of patients					0.08
Yes	6	1,486	$-0.05 (-0.22, 0.11)$	53	
No or unclear	7	599	$-0.49 (-0.92, -0.05)$	80	
Intent-to-treat analysis					0.55
Yes	1	660	$0.01 (-0.18, 0.15)$	NA	
No or unclear	12	1,425	$-0.30 (-0.62, 0.02)$	87	
Number of patients randomized					0.94
>200	3	1,337	$-0.29 (-0.99, 0.41)$	97	
≤200	10	748	$-0.26 (-0.50, -0.03)$	58	
Length of followup					0.71
>3 months‡	5	789	$-0.33 (-0.83, 0.17)$	91	
≤3 months‡	8	1,296	$-0.22 (-0.50, 0.07)$	76	

* 95% CI = 95% confidence interval; NA = not applicable.

† P values for interaction are from meta-regression analysis.

‡ Results did not change when using 6 months as cutoff in a post-hoc analysis.

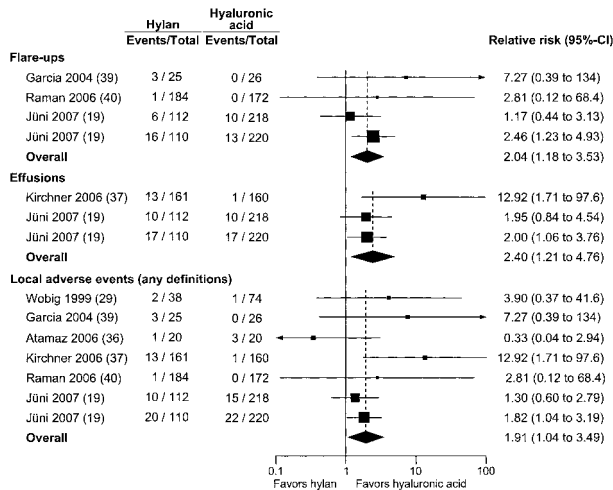


Figure 3. Forest plot of the meta-analyses of adverse effects. The size of the boxes is proportional to the random-effects weights used in the meta-analysis. Flare: $I^2 = 0\%$ ($P = 0.52$); effusions: $I^2 = 36\%$ ($P = 0.21$); local adverse events (any definition): $I^2 = 28\%$ ($P = 0.21$). 95% CI = 95% confidence interval.

followup as continuous explanatory variables showed no association between each of these factors and effect size (regression coefficient for molecular weight: 0.23 per 1000 kDa; 95% CI -0.34, 0.80 and for followup duration: 0.01 per month; 95% CI -0.08, 0.05).

Two trials (30,40) were found to be outliers. The study by Raman et al (40) contributed 55% to the overall heterogeneity of the meta-analysis. When this study was excluded from the analysis, the pooled effect size decreased to -0.17 (95% CI -0.37, 0.02) with an I^2 of 66%. The study by Zhou et al (30) contributed 9% to the overall heterogeneity of the meta-analysis. When this study was excluded from the analysis, the pooled effect size decreased to -0.21 (95% CI -0.49, 0.07) with an I^2 of 88%. Finally, when both studies were excluded the pooled effect size was -0.10 (95% CI -0.26, 0.06; $I^2 = 48\%$).

Adverse events. Six trials with 7 comparisons (1,540 patients) contributed to the meta-analysis of local adverse events (19,29,36,37,39,40). Definitions varied between trials and ranged from pain, swelling, or warming to severe inflammatory reactions of the treated knee. The meta-analysis showed a relative risk of 1.91 for hylan compared with hyaluronic acid (95% CI 1.04, 3.49) with low statistical heterogeneity ($I^2 = 28\%$; $P = 0.21$ for heterogeneity) (Figure 3).

Three trials with 4 comparisons (1,067 patients) contributed to the meta-analysis of flares (19,39,40), which yielded a pooled relative risk of 2.04 (95% CI 1.18, 3.53) and no between-trial heterogeneity ($I^2 = 0\%$; $P = 0.52$). Two trials with 3 comparisons (981 patients) contributed to the meta-analysis of joint effusions (19,37), which showed a pooled relative risk of 2.40 (95% CI 1.21, 4.76) for hylan, with moderate heterogeneity ($I^2 = 36\%$; $P = 0.21$).

Indirect comparisons. We identified 31 unique trials (3,983 patients), which were included in at least 1 of 3

meta-analyses (9,12,13) and contributed to the meta-regression analysis deriving indirect comparisons. Three trials with 443 patients evaluated hylan as an experimental intervention (4,31,41). Figure 4 (bottom) shows that the effect size indirectly comparing hylan and hyaluronic acid was -0.64 (95% CI -1.25, -0.02) with a high degree of statistical heterogeneity ($I^2 = 72\%$; $P < 0.001$). The effect size derived from the 9 large-scale trials (2,363 patients) was in favor of hyaluronic acid, with confidence intervals overlapping the null (0.23; 95% CI -0.31, 0.77), whereas the effect size derived from the 22 small trials (1,620 patients) was robustly in favor of hylan (-1.19; 95% CI -1.91, -0.46; $P = 0.006$ for interaction between effect size and trial size). Figure 4 (top) indicates that differences between large and small trials were not apparent for direct comparisons ($P = 0.85$ for interaction).

DISCUSSION

Our systematic review and meta-analysis of trials comparing hylan with hyaluronic acid found no robust evidence for a clinically relevant benefit of hylan compared with hyaluronic acid. Inclusion of all trials resulted in a small effect size of questionable relevance and a high degree of statistical heterogeneity, which made interpretation of results difficult. Pooling the 2 trials with adequate concealment of allocation resulted in the inclusion of 46% of patients, a decrease in statistical heterogeneity, and a clinically irrelevant pooled effect size near the null effect. Pooling the 6 patient-blind trials led to the inclusion of 72% of patients and again resulted in a decrease of heterogeneity and an effect size near the null. The only trial with an intent-to-treat analysis also had an adequate concealment of allocation and blinding of patients; this trial included 31% of patients and resulted in an effect size of -0.01 (19). This corresponds to a difference in pain between hylan and hyaluronic acid of 0.2 mm on a 10-cm visual analog scale. However, patients treated with hylan were approximately twice as likely as patients treated with hyaluronic acid to experience local adverse events, including effusions or flares.

Our review is based on an extensive literature search (42). Trial selection and data extraction including quality assessment were performed independently by 2 authors to minimize bias and transcription errors (43,44). As with any systematic review, our study is limited by the quality of included trials. The majority of trials had poor method-

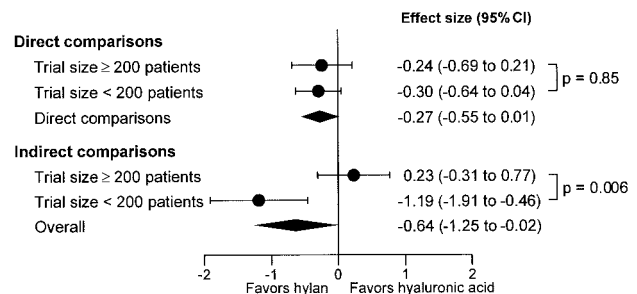


Figure 4. Comparison of meta-analyses of direct and indirect comparisons. 95% CI = 95% confidence interval.

ologic quality or inadequate reporting. For example, for almost all trials concealment of allocation was unclear and only 1 trial used blinding of therapists. All quality criteria used in this systematic review have been shown to be associated with bias in several studies (15,42,45–47). A major limitation relates to our inability to fully explain heterogeneity between trials: the decrease in heterogeneity was only modest in stratified analyses and *P* values for interaction between effect size and trial characteristics did not reach conventional levels of statistical significance. It should be noted that the relatively low number of trials included in our meta-analysis means that interaction tests only had limited power to detect relevant differences.

Another problem relates to insufficient standardization of safety outcomes: definitions and reporting of local adverse events differed considerably among the trials and the validity of our meta-analysis of local adverse events with variable definitions might therefore be low. However, relative risks rather than risk differences used in our meta-analysis minimize the impact of differences in the stringency of definitions of local adverse events. This notion is supported by the low heterogeneity between trials found for this analysis. For the more standardized definitions, flares and effusions, we could include only 3 and 2 trials, respectively. However, included trials were large and covered 50% and 46%, respectively, of all patients considered in the meta-analysis of effectiveness. The approximately 2-fold increase in the risk of local adverse events associated with hylan is clinically relevant. A risk increase was consistently found across trials and definitions, with a generally low degree of heterogeneity between trials. This robust evidence for an increased risk of local adverse events needs to be interpreted against the lack of evidence for a superiority of hylan over hyaluronic acid in terms of pain relief. Based on a control group rate of 77 local adverse events per 1,000 treated patients occurring over 1 year in the largest trial (19), the number needed to harm to induce 1 additional local adverse event would be 14 (95% CI 5, 324).

We are aware of 6 other meta-analyses (9–14) of the effectiveness of viscosupplementation. All except the Cochrane review by Bellamy et al (13) restricted their analysis to trials, which compared different hyaluronic acids or hylan with a sham intervention, but excluded direct head-to-head comparisons. Based on implicit indirect comparisons, some reviewers (9,11) discussed whether hylan might be more effective than conventional hyaluronic acids. Our meta-analysis is the first to directly compare hylan and conventional hyaluronic acids. The results contradict previous claims of greater benefits of hylan. Moreover, comparing these results with results from formal indirect comparisons, we demonstrated that previous, implicit indirect comparisons were misleading. The effect size from indirect comparisons was approximately 3 times higher than the pooled effect size of the direct comparisons. This was largely explained by an exaggerated benefit of hylan in small trials.

The most recent Cochrane review (13), updated in February 2006, considered 9 studies, which compared hylan and hyaluronic acids. We included 8 of these in our meta-analyses. One study (48,49), which was described as a

parallel-group randomized controlled trial by Bellamy et al (13), was an observational study in which the treatment decision was based on “the consultant to whom the patient was referred” (48). Given that this treatment decision might be related to the prognosis of patients (15), we excluded this study. Two other differences should be noted. First, we did not use a scale to assess the methodologic quality of trials because the type of scale used may affect methodologic judgments (50). Second, Bellamy et al (13) opted against combining data if different hyaluronic acids were used as control interventions or if pain was measured with different scales. To provide a meaningful synthesis of the evidence (51), we used effect sizes to standardize data from different pain scales and explored potential sources of heterogeneity in the entire body of data. Our analyses indicate that the heterogeneity between trials might be explained mainly by differences in methodologic quality rather than by differences in the type of hyaluronic acid used as a control intervention. Large effect sizes were found in 2 trials (39,40) that had used one particular preparation of avian origin as a control intervention, but both of these trials lacked blinding of patients.

In view of the likely lack of a superior effectiveness of hylan over hyaluronic acid and the increased risk of local adverse events associated with hylan, we discourage the use of intraarticular hylan in patients with osteoarthritis of the knee in clinical research or practice. No conclusions can be drawn from this meta-analysis regarding the effectiveness of viscosupplementation compared with sham interventions.

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AUTHOR CONTRIBUTIONS

Dr. Jüni had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Reichenbach, Dieppe, Jüni.

Acquisition of data. Reichenbach, Blank, Rutjes, Shang, King, Trelle.

Analysis and interpretation of data. Reichenbach, Blank, Dieppe, Jüni, Trelle.

Manuscript preparation. Reichenbach, Blank, Rutjes, Shang, King, Dieppe, Jüni, Trelle.

Statistical analysis. Reichenbach, Shang, Jüni, Trelle.

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