Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis

CRD summary
This review found that hylan appears unlikely to be more effective than hyaluronic acid for treating pain associated with osteoarthritis of the knee, and that it is associated with an increased risk of local adverse events. The review was well-conducted and the authors’ conclusions seem likely to be reliable.

Authors’ objectives
To evaluate the effectiveness and safety of intra-articular high-molecular hylan compared with standard preparations of hyaluronic acids for osteoarthritis of the knee.

Searching
The Cochrane CENTRAL Register, MEDLINE, EMBASE and CINAHL were searched to November 2006; the search strategy is available from the authors. Sources that cited relevant articles were sought using the Science Citation Index. Conference proceedings, textbooks and the reference lists of retrieved articles were handsearched, as were the proceedings of the U.S. Food and Drug Administration advisory panel that manages applications for approval in this area. Authors, content experts and manufacturers known to have conducted studies in the field were also contacted.

Study selection
Randomised controlled trials (RCTs) or quasi-RCTs of patients with osteoarthritis of the knee were eligible for inclusion. The participants in the review had a mean age of 61 years (range: 54 to 71) and their average symptom duration was 5 years (range: 4 to 7.7). Eligible studies compared hyaluronic acid with hylan, administered by intra-articular injection. Where stated, the hyaluronic acid used in the included studies was of either avian or bacterial origin. Two thirds of the studies were industry-funded or their source of funding was unclear. The primary outcome of the review was pain, assessed at the end of the study or at a maximum of 6 months after the last injection, whichever came first. Where more than one pain outcome was reported, the measure highest on a hierarchy of pain measures was used, with precedence given to global pain. The pain measures used in the primary studies included visual analogue and Likert scales. The secondary review outcomes were flares or effusions in the treated knee after the intervention, or any local adverse event (as reported in the primary study). Flare was defined as a hot, painful and swollen knee 24 to 72 hours after the intervention, and effusion was defined as excessive fluid in the treated joint, diagnosed by clinical examination, ultrasound or arthrocentesis. The median duration of follow-up in the primary studies was 6 months (range: 3 weeks to 1 year).

Two reviewers independently selected studies for inclusion, with any disagreements resolved by consensus.

Assessment of study quality
The following characteristics of validity were evaluated: allocation concealment, blinding of the patients and therapists, and intention-to-treat analysis (i.e. the inclusion of all randomised patients in the analysis).

Two reviewers independently assessed study validity, with any disagreements resolved by consensus.

Data extraction
For continuous outcomes, the effect size (Cohen's d) was estimated by comparing the mean end point pain scores in each group, divided by their pooled standard deviation. An effect size of -0.30 was deemed minimally clinically relevant. If differences between the groups at the end of the trial were not reported, mean changes from baseline were used. Where data were not available, they were imputed using methods described elsewhere (see Other Publications of Related Interest no.1). Relative risks (RRs) were calculated for binary data. For adverse events, the number-needed-to-harm (NNH; i.e. the number of patients who would need to be treated for an additional one to experience an adverse
event) was calculated. Where a participant experienced more than one local adverse event, only the first event was used in the analysis. Where multi-arm studies compared hylan with different types of hyaluronic acid, the hyaluronic acid groups were combined.

Two authors independently extracted the data using a standardised form, with any disagreements resolved by discussion.

**Methods of synthesis**

Effect sizes and RRs were pooled using a random-effects model and intention-to-treat analysis where possible. The $I^2$ and Cochran's Q statistics were used to assess statistical heterogeneity. For the $I^2$ statistic, values of 25%, 40% and 75% were taken to represent low, moderate and high levels of heterogeneity, respectively. The following potential sources of heterogeneity were investigated by pre-specified univariate random-effects meta-regression: allocation concealment, blinding, type of analysis, trial size (more or less than 200 participants), duration of follow-up (more or less than 3 months), funding source, type of control intervention and molecular weight of standard hyaluronic acid. Post hoc sensitivity analyses were undertaken to investigate the effect of excluding outlier studies (i.e. studies in which the confidence intervals (CIs) did not overlap with the pooled overall effect size of the meta-analysis). Publication bias was assessed using a funnel plot.

**Results of the review**

Thirteen RCTs (n=2,085) were included in the main analysis.

Most of the studies were poorly reported or were of a low methodological quality. Only 2 studies reported using adequate allocation concealment, and only one clearly performed an intention-to-treat analysis. Patients were clearly blinded in 6 studies and therapists in only one.

**Pain (13 RCTs).**

The meta-analysis showed a non significant trend favouring hylan over hyaluronic acid for pain outcomes (effect size -0.27, 95% CI: -0.55, 0.01; 13 RCTs). There was a high level of heterogeneity ($I^2=88\%; p<0.001$).

Stratified analyses showed no statistically significant benefit from hylan in trials with adequate allocation concealment (2 RCTs, n=981), patient blinding (6 RCTs, n=1,486), or use of intention-to-treat analysis (1 RCT, n=660), with effect sizes close to null and moderate between-trial heterogeneity (where relevant, $I^2=48$ to 53%).

When the results were stratified by study size and by duration of follow-up, the effect estimates did not change substantially and there was no significant association with treatment effect size. Stratification by the specific type of hyaluronic acid used in the control group showed large effect sizes, favouring hylan in the 2 studies (both unblinded) that used a specific type of avian hyaluronic acid (-1.00, 95% CI: -1.19, -0.80). However, there was no evidence of a statistically significant difference in effect size between hyaluronic acid of avian or bacterial origin, nor was there any significant association between molecular weight or duration of follow-up (using continuous measures) and effect size. Meta-regression did not indicate any statistically significant association between quality characteristics and treatment effect size (though statistical power was limited).

The post-hoc sensitivity analysis that excluded 2 outlying RCTs (n=396) yielded an effect size of -0.10 (95% CI, -0.26, 0.06; $I^2=48\%$).

The funnel plot for the main analysis was symmetrical (i.e. not suggestive of publication bias).

**Adverse events (6 RCTs).**

The meta-analysis indicated an increased risk in the hylan group of any local adverse event (RR 1.91, 95% CI: 1.04, 3.49; $I^2=28\%;$ 6 RCTs, n=1,540), flares (RR 2.04, 95% CI: 1.18, 3.53; $I^2=0\%;$ 3 RCTs, n=1,067) and joint effusion (RR 2.40, 95% CI: 1.21, 4.76; $I^2=36\%;$ 2 RCTs, n=981). The NNH to induce one additional local adverse event was 14 (95% CI: 5, 324).

The authors also reported additional results relating to indirect comparisons with placebo-controlled studies from...
previous meta-analyses (see Other Publications of Related Interest nos.2-4).

**Authors' conclusions**
Hylan appears unlikely to be more effective than hyaluronic acid for treating pain associated with osteoarthritis of the knee, and is associated with an increased risk of local adverse events.

**CRD commentary**
The review question and inclusion criteria were clear, the literature search covered an extensive range of relevant sources, and appropriate steps were taken to reduce the risk of error and bias in the review process (such as having more than one reviewer independently make decisions). Suitable methods appear to have been used for the meta-analysis of studies, for the assessment and investigation of potential sources of heterogeneity, and for indirect comparison using placebo-controlled studies. The review was well-conducted and the authors' conclusions seem likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that intra-articular hylan should not be used for patients with osteoarthritis of the knee.

Research: The authors stated that intra-articular hylan should not be used in clinical research on patients with osteoarthritis of the knee.

**Funding**
Swiss National Science Foundation, grant numbers 4053-40-104762/3, 3200-066378 and 3233-066377.

**Bibliographic details**

**PubMedID**
18050181

**DOI**
10.1002/art.23103

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adjuvants, Immunologic /administration & dosage /adverse effects /therapeutic use; Aged; Biocompatible Materials /administration & dosage /adverse effects /therapeutic use; Humans; Hyaluronic Acid /administration & dosage /adverse effects /analogs & derivatives /therapeutic use; Injections, Intra-Articular; Middle Aged; Osteoarthritis, Knee /drug therapy; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**
12008000243

**Date bibliographic record published**
01/09/2008

**Date abstract record published**
23/12/2008

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.