Hyaluronic acid injections relieve knee pain
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CRD summary
This review assessed intra-articular hyaluronic acid for treating pain from knee osteoarthritis. The authors concluded that intra-articular hyaluronic acid has a modest early effect on pain but not at 15 to 22 weeks. The authors' conclusions appear to reflect the evidence presented, but differences between the studies and other review limitations mean that the reliability of these conclusions is unclear.

Authors' objectives
To evaluate the efficacy of intra-articular hyaluronic acid injections for the treatment of pain in patients with osteoarthritis of the knee.

Searching
MEDLINE was searched from 1965 to August 2004 using the reported terms. The reference lists of included articles and reviews were screened. The Cochrane Library and websites of the Agency for Healthcare Research and Quality were also searched. Only studies reported in the English language were included.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion. Reviews, meta-analyses and comparison trials were excluded. All of the included trials were placebo-controlled.

Specific interventions included in the review
Studies that compared intra-articular hyaluronic acid (hyaluronan or hylan GF-20) viscosupplementation injections with placebo were eligible for inclusion. Most of the included studies evaluated hyaluronan (hyaluronic acid, hyaluronan or hyaluronate); 2 studies used GF-20. Injections were generally given weekly for between 3 and 5 weeks. Control intra-articular injections were mostly saline. Some studies allowed concomitant treatment with acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), rescue treatment and exercise, either alone or in combination.

Participants included in the review
Studies of patients with osteoarthritis of the knee were eligible for inclusion. The mean age of the participants in the included studies was 63 years (range: 58 to 70). The participants had unilateral or bilateral osteoarthritis diagnosed clinically or radiologically (details were reported).

Outcomes assessed in the review
Studies that evaluated pain using a visual analogue scale (VAS) were eligible for inclusion. Studies that reported VAS as part of the Western Ontario McMaster Universities Index scale were excluded. The review evaluated knee pain on activity or rest using a VAS of 100 mm over four time intervals: 1 week, 5 to 7 weeks, 8 to 12 weeks, and 15 to 22 weeks after the last hyaluronic acid injection.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the following criteria described by Chalmers: recruitment of participants; rejection log; definition of treatments; randomisation; blinding; prior estimates of numbers; compliance; statistical inference; statistical analysis; handling of withdrawals and side-effects; start and end dates; and timing and tabulation of events. Studies scoring more than 0.75 for validity were classified as good quality.
Two reviewers independently assessed and scored study validity.

**Data extraction**
Two reviewers independently extracted the data and resolved any disagreements through consensus.

Authors of potentially eligible studies were contacted for additional data. For each study, mean differences between hyaluronic acid and placebo in the change in VAS from baseline were reported; standard errors were calculated where required. One study that involved two subgroups of pain severity was treated as two separate trials. One study that compared two different hyaluronic acid-containing treatments (one with and one without NSAIDs) was also treated as 2 separate trials.

**Methods of synthesis**

How were the studies combined?
Pooled mean differences between hyaluronic acid and placebo were calculated using the random-effects model of DerSimonian and Laird. Publication bias was assessed using Egger's regression model.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic and examined using Galbraith plots. Meta-analyses were also undertaken after excluding poor-quality studies. Meta-regression was used to examine the influence of type of pain (activity or rest), form of hyaluronic acid used and study quality (good or poor).

**Results of the review**

Nine double-blind RCTs (at least 1,000 patients) were included. The 9 studies considered 11 separate trials.

Five studies were classified as good quality. Only 2 studies reported an intention-to-treat analysis.

At 1 week, hyaluronic acid was associated with a significant improvement in pain compared with placebo; the mean difference was 4.4 (95% confidence interval, CI: 1.1, 7.2) and significant heterogeneity was found (p<0.001). After restricting the analysis to good-quality RCTs, there was no significant difference between treatments but the significant heterogeneity persisted (p<0.001).

At 5 to 7 weeks, hyaluronic acid was associated with a significant improvement in pain compared with placebo for all studies (mean difference 17.6, 95% CI: 7.5, 28.0); significant heterogeneity was found (p<0.001). It was also associated with a significant improvement in pain for good-quality studies (mean difference 7.2, 95% CI: 2.4, 12.0; based on 2 studies); no significant heterogeneity was found (p=0.688).

At 8 to 12 weeks, hyaluronic acid was associated with a significant improvement in pain compared with placebo for all studies (mean difference 18.1, 95% CI: 6.3, 29.9); significant heterogeneity was found (p<0.001). It was also associated with a significant improvement in pain for good-quality studies (mean difference 7.1, 95% CI: 3.0, 11.3; based on 3 studies); no significant heterogeneity was found (p=0.332).

At 15 to 22 weeks, there was no significant difference in pain between hyaluronic acid and placebo for all studies (3 good-quality studies); significant heterogeneity was found (p<0.001).

Egger's test suggested the absence of publication bias (p=0.096).

The meta-regression showed no significant association between outcome and type of pain. Studies using hylan GF-20 showed significantly better outcomes than studies using hyaluronon at 5 to 7 and 8 to 12 weeks. Poorer quality studies showed larger treatment effects than good-quality studies, but the difference was only significant at 1 week.

**Cost information**
The authors stated that one injection of hyaluronic acid costs approximately $230, indicating that a 3- to 5-week course
of treatment (including other pharmacy, hospital and clinic charges) may cost more than $1,000 per knee.

**Authors' conclusions**
Hyaluronic acid has a modest effect on pain from osteoarthritis of the knee at 5 to 7 weeks and at 8 to 10 weeks after the last injection, but not at 15 to 22 weeks.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design; the inclusion criteria for study design and outcomes were strict. Several relevant sources were searched but the restriction to English language studies might have resulted in the omission of some relevant data. No specific attempts to locate unpublished studies were reported, but a formal assessment of publication bias suggested that this was not present in the review. Methods were used to minimise reviewer errors and bias in the validity assessment and data extraction, but it was unclear whether similar steps were taken at the study selection stage. Only double-blind RCTs were included. Validity was assessed using specified criteria but the results were only partially reported.

The finding of significant heterogeneity suggested that pooling may not have been appropriate. However, subgroup analysis and regression analysis were used to examine potential sources of heterogeneity. The studies appeared to use different units of analysis (some used knees and others patients), but no assessment of the likely impact of this on the results was reported. The authors' conclusions appear to reflect the evidence presented but, given the limitations highlighted, the reliability of these conclusions is unclear.

**Implications of the review for practice and research**
Practice: The authors stated that the decision to give three to five injections of hyaluronic acid should only be made after patients have had a trial of conservative treatment for at least 3 months, or if patients cannot tolerate NSAIDs. Patients receiving hyaluronic acid injections should be advised that benefits may not be felt until 5 to 10 weeks after the last injection. The cost-benefit of using hyaluronic acid injections must be compared with alternative treatments.

Research: The authors did not state any implications for further research.

**Bibliographic details**

**PubMedID**
16144589

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adjuvants, Immunologic /administration & dosage /economics; Cost-Benefit Analysis; Humans; Hyaluronic Acid /administration & dosage /economics; Injections, Intra-Articular /economics; Osteoarthritis, Knee /drug therapy; Randomized Controlled Trials as Topic; Regression Analysis; Time Factors; Treatment Outcome

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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.