Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis

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CRD summary
This review assessed the effectiveness of intra-articular hyaluronic acid for knee osteoarthritis. The authors concluded that intra-articular hyaluronic acid had a small effect on pain compared with intra-articular placebo, but publication bias may have overestimated the effect. No firm conclusions could be drawn about the highest molecular weight hyaluronic acid. The authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the effectiveness of intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee.

Searching
MEDLINE (1966 to February 2003) and the Cochrane Controlled Trials Register were searched; the search terms were stated. The reference lists of included studies were also checked. Selected journals of rheumatic diseases (Arthritis and Rheumatism, Osteoarthritis and Cartilage and the Journal of Rheumatology) and abstracts from scientific meetings (American College of Rheumatology Annual Scientific Meeting and the Osteoarthritis Research Society International Meeting) were handsearched from 1986 through 2002. The authors of the included studies were contacted for details of unpublished studies.

Study selection
Study designs of evaluations included in the review
Single- or double-blinded randomised controlled trials (RCTs) were eligible for inclusion if the follow-up was for at least 2 months and the drop out-rate was less than 50%.

Specific interventions included in the review
Studies that compared intra-articular hyaluronic acid (given at least every week for 3 weeks) with intra-articular placebo injection were eligible for inclusion.

Participants included in the review
Studies of participants with osteoarthritis of the knee were eligible for inclusion.

Outcomes assessed in the review
Studies that presented data for pain measured on one of the measures recommended by the Osteoarthritis Research Society were eligible for inclusion. In order of preference these measures were: global knee pain score (visual analogue or Likert scale); knee pain on walking (visual analogue or Likert scale); Western Ontario and McMaster Universities Osteoarthritis Index; Lequesne index; and knee pain during activities other than walking (visual analogue or Likert scale).

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
Studies were assessed for losses to follow-up and intention-to-treat analysis (described as such by authors, or attempts to analyse data from all randomised patients or no drop-outs). The authors did not state who performed the validity assessment.

Data extraction
Two reviewers independently extracted the data using standardised forms. Any discrepancies were discussed until consensus was reached. Authors were contacted for details of missing or ambiguous data. For each study, the numbers of patients randomised and evaluated, and the change in pain from baseline (or failing that the pain at the time of interest), were extracted.

The standardised mean difference was calculated at preferably 2 to 3 months after the first injection (or if not reported, at 1 to 4 months) and used as the effect size (ES). Means and measures of dispersion were estimated from figures when not reported, while standard deviations were estimated using median coefficients of variance from similar studies. Where studies reported more than one measure of pain, the one highest in the pain outcome hierarchy was selected. An ES of 0.2 to 0.5 was considered small, where a large ES was 1.0 or more. One study with two hyaluronic acid treatment arms was treated as two separate studies and the number of controls used in each comparison was halved.

**Methods of synthesis**

How were the studies combined?

Pooled ES and 95% confidence intervals (CIs) were calculated using a random-effects meta-analysis. Publication bias was assessed using a funnel plot, the Egger test, and by separate pooling of published and unpublished studies.

How were differences between studies investigated?

Statistical heterogeneity was tested using the Cochran Q statistic and was examined using forest plots. Published and unpublished (entirely unpublished or insufficient information to calculate an ES) studies and studies using the highest molecular weight formulation of hyaluronic acid were analysed separately.

**Results of the review**

Twenty-two studies (n=2,949) were included.

The mean drop-out rate, where reported, was 12.4%. Seventeen studies were sponsored by industry. The sample size ranged from 24 to 408. Seven RCTs provided data on an intention-to-treat basis.

The forest plot showed two outlier studies with an ES greater than 1.5. Both used the highest molecular weight hyaluronic acid. The other study using this formulation showed a non statistically significant ES.

Statistically significant heterogeneity was detected (P<0.001) for the meta-analysis of all studies. The meta-analysis of the 3 RCTs (n=252) using the highest molecular weight hyaluronic acid showed statistically significant heterogeneity (P<0.001). After removing these 3 RCTs, heterogeneity was no longer statistically significant (P=0.58).

Overall, the studies found a small effect for hyaluronic acid compared with placebo (ES 0.32, 95% CI: 0.17, 0.47, P<0.001). After removal of the 3 RCTs using the highest molecular weight hyaluronic acid, the effect decreased (ES 0.19, 95% CI: 0.10, 0.27, P<0.001).

There was evidence of publication bias (asymmetrical funnel plot and Egger test P=0.07).

Unpublished studies showed a non significant ES for hyaluronic acid compared with placebo (ES 0.07, 95% CI: -0.15, 0.28).

**Authors’ conclusions**

Intra-articular hyaluronic acid had a small effect on pain in comparison with intra-articular placebo, but there were concerns that publication bias may have overestimated the effect. The highest molecular weight hyaluronic acid may be of greater benefit than the lower molecular weight compound, but the results differed among studies and no firm conclusions could be drawn.

**CRD commentary**
The review question was clear in terms of the study design, participants, intervention and outcomes. Relevant sources were searched and attempts were made to locate unpublished studies, thus minimising the potential for publication bias. The possibility of publication bias was assessed. Non-English studies were eligible and this reduced the possibility of language bias. The methods used to select the studies and assess validity were not described, so it is not known whether any efforts were made to reduce errors and bias. Methods were used to minimise bias in the data extraction process. Validity was assessed, although there were some limitations of the criteria used.

Statistical heterogeneity was assessed and differences between the studies were discussed prior to the meta-analysis. In addition, the influence of various factors on the results was explored. The authors' conclusions took account of the variability among studies and the possibility of publication bias. Their conclusions are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that the controversy surrounding the efficacy of intra-articular hyaluronic acid was justified and findings from the review did not support its efficacy.

Research: The authors stated that further independent trials are required that use intention-to-treat analysis to examine the effect of higher molecular weight hyaluronic acid, and attempt to define sub-groups (if any) that respond better to this treatment.

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