Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis
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CRD summary
The review assessed the effectiveness of intra-articular hyaluronic acid for the treatment of knee osteoarthritis. The authors concluded that the available evidence suggests that hyaluronic acid is not clinically effective and may be associated with increased risks of adverse events, and that further large, long-term trials are needed. The authors' cautious conclusion seems appropriate given the limited quality of the included studies.

Authors' objectives
To determine the effectiveness of intra-articular hyaluronic acid for the treatment of knee osteoarthritis.

Searching
MEDLINE, EMBASE, CINAHL, BIOSIS Previews and the Cochrane Controlled Trials Register were searched from inception to April 2004 for relevant articles published in English or German; the search terms were provided.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared intra-articular hyaluronic acid with a placebo were included in the review. Hyaluronic acid was used at dosages ranging from 16 to 40 mg (molecular weight 500 to 7,000 kDa).

Participants included in the review
Studies of participants with osteoarthritis were included in the review. The mean age of the participants ranged from 46 to 72 years.

Outcomes assessed in the review
Studies that reported pain at rest, pain during or immediately after movement, joint function and adverse events were eligible for inclusion. The time points at which these outcomes were assessed were categorised as follows: 2 to 6 weeks, 10 to 14 weeks, 22 to 30 weeks, and 44 to 60 weeks.

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

Assessment of study quality
Methodological quality was evaluated in terms of reported allocation concealment, degree of blinding, and whether an intention-to-treat analysis was reported. The authors did not state how the primary studies were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted the data from the primary studies, and any disagreements were resolved by discussion among three reviewers. Estimates of effect and its variance were extracted from the primary studies if these values were not explicitly reported in the tables.
Methods of synthesis
How were the studies combined?
The pooled weighted mean difference (WMD) and standardised mean difference (SMD) were calculated, along with 95% confidence intervals (CIs), for continuous outcomes, as appropriate, using a random-effects model. The pooled risk ratios (RRs) with 95% CIs were calculated for adverse events using a random-effects model. Regression methods were used to assess publication bias. Subgroup analyses for molecular weight were also performed.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic and the I-squared statistic. Planned sensitivity analyses included trial quality.

Results of the review
Twenty-two RCTs (n=2,902) were included in the meta-analyses.

The overall quality of the primary studies was considered unsatisfactory.

Pain at rest (8 RCTs).
A beneficial effect of hyaluronic acid compared with the control group was shown at 2 to 6 weeks, as assessed by a visual analogue scale (WMD -8.7 mm, 95% CI: -17.2, -0.2); due to a large degree of unexplained heterogeneity (94%), the summary estimate was not used. Individual study WMD estimates ranged from -29.00 to 8.30 mm. No statistically significant effect was found between hyaluronic acid and controls at 10 to 14 weeks, 22 to 30 weeks, or at 44 to 60 weeks in 2 high-quality trials. Poorer quality trials were shown to favour the intervention.

Pain during or immediately after exercise (9 RCTs).
No statistically significant difference between the treatment groups was shown at 2 to 6 weeks, as assessed by a visual analogue scale (WMD -3.8 mm, 95% CI: -9.1, 1.4); unexplained heterogeneity was high (81%). A statistically significant effect in favour of hyaluronic acid (WMD -4.2 mm, 95% CI: -7.5, -0.8) was shown with the removal of one trial with a significant interaction between treatment effect and severity of osteoarthritis. A statistically significant effect in favour of hyaluronic acid was also found at 10 to 14 weeks (WMD -4.3 mm, 95% CI: -7.6, -0.9) and at 22 to 30 weeks (WMD -7.1 mm, 95% CI: -11.8, -2.4); no unexplained heterogeneity was shown. Only one trial at 44 to 60 weeks was found; this showed no treatment effect. One trial of high quality was found; this was not found to influence the effect size at any point.

Joint function (9 RCTs).
No statistically significant differences between the groups were found at 2 to 6 weeks' follow-up (SMD 0.00, 95% CI: -0.23, 0.23), 10 to 14 weeks' follow-up (SMD -0.11, 95% CI: -0.31, 0.09), or at 22 to 30 weeks' follow-up (SMD -0.16, 95% CI: -0.45, 0.13); unexplained heterogeneity was found (66%, 59% and 62%, respectively). Two trials followed patients until 44 to 60 weeks, but no significant difference between the treatment groups was shown. No statistically significant between-group differences were found at 2 to 6 weeks' follow-up and 10 to 14 weeks' follow-up when only high-quality trials were considered. Poorer quality trials were shown to favour the intervention.

Adverse events (15 RCTs).
Adverse events occurred more frequently among individuals receiving hyaluronic acid, although this difference was not statistically significant (RR 1.08, 95% CI: 1.01, 1.15).

The funnel plot analysis indicated an over-selection or over-reporting of trials reporting adverse events in people treated with hyaluronic acid; this could be explained by lack of blinding.

The effect size did not appear to be associated with molecular mass.
Authors’ conclusions
The available evidence suggests that intra-articular hyaluronic acid is not clinically effective and may be associated with increased risks of adverse events. Further large, long-term trials are needed.

CRD commentary
The review question was supported by clear inclusion criteria relating to the outcome and study design. Several relevant sources were searched, but no attempt was made to locate any unpublished studies. Publication bias was assessed, though these analyses were reported only in relation to adverse events. Methods were used to minimise errors and bias in the extraction of data but, since the methods used to select studies were not described, it is not known whether any such efforts were made to reduce errors and bias in the selection process. Quality was assessed and the potential impact of aspects of study quality on the results was examined.

The analysis appeared appropriate and statistical heterogeneity was assessed. Loss to follow-up ranged from 0 to 50%; however, only six of the included trials analysed data on an intention-to-treat basis, and it is therefore possible that drop-outs might have influenced the results. In view of these considerations, the authors’ conclusion seems suitably cautious.

Implications of the review for practice and research
Practice: The authors suggested that intra-articular hyaluronic acid should not be used for the treatment of painful osteoarthritis.

Research: Further large, long-term trials with clinically relevant and uniform end points are needed. The use of predefined clinically important differences might assist in assessing the potential value of hyaluronic acid for knee osteoarthritis.

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