Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis – meta-analysis

Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE

CRD summary
The authors concluded that they demonstrated the therapeutic trajectory for intra-articular hyaluronic acid injection, for knee osteoarthritis pain, over six months after intervention. The effect was modest and clinically significant. Efforts were made to minimise bias in the review, but the diversity between the included trials and uncertainties in the evidence, suggest that these conclusions may not be reliable.

Authors' objectives
To compare the length of the treatment effect from intra-articular hyaluronic acid injection, with that from placebo, for the management of knee osteoarthritis.

Searching
Six databases, including MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), were searched up to March, 2010. No language or publication status restrictions were imposed; search terms were reported. Google Scholar was used to search the Internet. Reference lists of retrieved studies, and the proceedings of six conferences, were handsearched. Product inserts for viscosupplements (hyaluronic acid injections) were consulted, and experts, study or abstract authors, and manufacturers were contacted to obtain unpublished or unreported data.

Study selection
Randomised controlled trials of the therapeutic effects of intra-articular hyaluronic acid, compared with placebo, for the management of knee osteoarthritis, in humans, were eligible for inclusion. The primary outcome was pain reduction at seven pre-specified time points. Secondary outcomes were function, stiffness, or both at the first pre-specified endpoint out of eight weeks, 12 weeks, or the end of the trial.

The included trials were published between 1983 and 2009. The mean participant age ranged from 45 to 72 years, and the percentage of female participants ranged from 28 to 100. Other population characteristics, such as knee radiographic grade and baseline pain, were reported to vary across the trials.

Two reviewers independently selected trials for inclusion.

Assessment of study quality
Two reviewers independently assessed the risk of bias in the trials, from randomisation, allocation concealment, blinding, reporting of withdrawals, treatment of data, and the type and extent of sponsorship. High-quality trials were those that reported randomising more than 100 participants, an intention-to-treat analysis, adequate blinding, and allocation concealment.

Data extraction
The mean change, and standard deviation, for each outcome, were extracted or calculated to produce mean differences, and 95% confidence intervals, for treatment and placebo groups. Where possible, the data were extracted on an intention-to-treat basis. Where a study reported data on more than one pain scale, the authors used the one that was highest on their predefined hierarchy of outcome measures (given in paper). Where necessary, the mean and a measure of dispersion were estimated using published methods (referenced in paper).

Two reviewers independently extracted the data; any disagreements were resolved by consensus.

Methods of synthesis
Mean differences and 95% confidence intervals were pooled, using Bayesian random-effects models and Markov Chain Monte Carlo methods. The pooled effect estimates appeared to be standardised mean differences (estimated using the Hedge's g method). Statistical heterogeneity between studies was assessed using $I^2$; values of 25% or more indicated low
heterogeneity, 50% or more indicated moderate heterogeneity, and 75% or more indicated high heterogeneity.

Separate meta-analysis was performed for data at each time point, and a multivariate longitudinal regression model was used to adjust for correlation between the time points. Meta-regression was performed to examine how the factors of trial quality, treatment, and publication, individually modified the treatment effect, for overall pain.

**Results of the review**
Fifty-four randomised controlled trials were included in the review (7,545 participants; range 24 to 586). Sixteen trials met the criteria for high quality; details were provided for all trials. Drop-out rates ranged from zero to 50%, with 11 trials losing 20% of patients or more to follow-up. Follow-up ranged from four to 52 weeks.

Intra-articular hyaluronic acid was statistically significantly better than placebo, in treating pain at four weeks (SMD 0.31, 95% CI 0.17 to 0.45; 44 trials). This significant difference peaked at eight weeks (SMD 0.46, 95% CI 0.28 to 0.65; 26 trials), and reduced to a residual detectable effect at 24 weeks (SMD 0.21, 95% CI 0.10 to 0.31; 20 trials). Heterogeneity between trials was high at four weeks and eight weeks ($I^2=75\%$), and low at 24 weeks ($I^2=32\%$). The therapeutic trajectory was similar in the subset of high-quality trials, and in the multivariate analysis that adjusted for correlation between the assessment time points.

In the meta-regression, the most substantial changes in effect size for pain were observed for allocation concealment, double blinding, trial size, and the molecular weight of the hyaluronic acid preparation. All of the meta-regressions (except for the subset of unpublished trials) had moderate or high heterogeneity between trials. The therapeutic trajectory could not be assessed for secondary outcomes due to insufficient data at different time points, but the results for these outcomes were discussed.

**Authors' conclusions**
These findings showed the therapeutic trajectory of intra-articular hyaluronic acid, for knee osteoarthritis pain, over six months after intervention. The effect was modest and clinically significant.

**CRD commentary**
The review question and inclusion criteria were clearly defined. Extensive efforts were made to locate published and unpublished literature, with no publication status and language restrictions. Efforts were made to minimise any reviewer error or bias. Suitable quality assessment criteria were used, and the authors rated a small proportion (30%) of trials as high quality.

No individual trial details were presented, making it difficult to assess the details of the placebo arms, and if intervention participants were on other medications. The reasons for the high drop-out rates in some trials were unclear, and no side-effects from the medications were assessed. The heterogeneity between the trials was moderate or high in most meta-analyses (including the sensitivity analyses), suggesting that the quantitative methods of synthesis may not have been appropriate.

This was generally a well-conducted review and efforts were made to minimise bias in the review methods, but the diversity between the included trials and uncertainties in the evidence suggest that the authors' conclusions may not be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that intra-articular hyaluronic acid could be used in certain clinical situations or with other therapies.

**Research:** The authors stated that a re-evaluation of the overall cost-utility of intra-articular hyaluronic acid was needed.

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