Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis

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CRD summary
The authors concluded that corticosteroids appeared to be more effective than hyaluronic acid in the short term and hyaluronic acid appeared more effective in the longer term. This was a largely well-conducted review; the authors' conclusion is appropriately speculative and is likely to be reliable.

Authors' objectives
To evaluate the effects over time of intra articular hyaluronic acid compared with corticosteroids in patients with knee osteoarthritis.

Searching
MEDLINE, EMBASE, CINAHL, BIOSIS Previews and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to February 2009. Search terms were reported. Reference lists of retrieved articles were handsearched and conference proceedings of American College of Rheumatology, British Society for Rheumatology and Osteoarthritis Research Society were searched from January 1990 to February 2009. Unpublished data were sought from field experts, manufacturers and authors of studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that evaluated pain following use of intra articular hyaluronic acid compared with intra articular corticosteroids in patients with knee osteoarthritis were eligible for inclusion in the review. Trials had to include at least one of the following outcome measures using visual analogue or Likert methods: Western Ontario and McMaster Universities Osteoarthritis Index Pain Subscale; index joint pain when walking; index joint pain during activities other than walking; and spontaneous index joint pain. Drugs were administered in a variety of doses and regimens. Most trials included Hyalgan (Fidia farmaceutici S.p.A., Italy) as the hyaluronic intervention; others used Orthovisc (Anika Therapeutics, USA) and Synvisc (Genzyme, USA). Corticosteroid interventions were largely methylprednisolone administered over three weekly injections towards a total dose of 120mg. Most trials allowed use of concomitant analgesics. Mean age range of included patients was 49 to 72 years. A large proportion of participants were women (53% to 100%).

The authors did not state how many reviewers performed study selection.

Assessment of study quality
Methodological quality of included trials was assessed in terms of randomisation, allocation concealment, blinding, reporting of withdrawals and use of intention-to-treat analysis.

Two reviewers independently performed the quality assessment.

Data extraction
Data on means and standard deviations regarding change from baseline in pain score were extracted from the included trials. Some standard deviations were imputed (where necessary). Effect sizes and 95% confidence intervals (CI) were calculated using Hedges’ g statistic for separate time points as follows: two weeks (one to two weeks); four weeks (three to six weeks); eight weeks (seven to 10 weeks); 12 weeks (11 to 16 weeks); and 26 weeks (17 to 29 weeks). Sponsorship details were recorded. Authors were contacted for additional data, where necessary.

Two reviewers independently extracted data. Discrepancies were resolved by consensus.
Methods of synthesis
Effect sizes and 95% CIs were pooled in a random-effects meta-analysis (DerSimonian and Laird). Statistical heterogeneity was assessed using the $I^2$ statistic. Sensitivity analyses were carried out on trials that reported intention-to-treat analysis, method of blinding, those that compared Hyalgan with methylprednisolone and by removing one trial with a high withdrawal rate. Meta-regression analysis was performed on data adjusted for blinding and intention-to-treat status.

Results of the review
Seven RCTs (n=606 patients, 610 knees) were included in the meta-analysis. Overall, only two trials were considered to be higher quality. One trial was double-blinded, one reported allocation concealment and five used intention-to-treat analysis.

Statistically significant pooled effects were found in favour of corticosteroids at week two (-0.39, 95% CI -0.65 to -0.12). There was no statistically significant difference between the treatments at week four. At week eight, the trend was in favour of hyaluronic acid (0.22, 95% CI -0.05 to 0.49); this became statistically significant at week 12 (0.35, 95% CI 0.03 to 0.66) and week 26 (0.39, 95% CI 0.18 to 0.59). The results were consistent in sensitivity analysis and meta-regression showed no significant interactions.

There was moderate statistical heterogeneity in all analyses ($I^2$ range: 37% to 49%).

Authors' conclusions
Corticosteroids appeared to be more effective than hyaluronic acid in the short term (up to four weeks) and hyaluronic acid appeared more effective in the long term (four to 26 weeks).

CRD commentary
The review question was clear and supported by reproducible inclusion criteria in all aspects. The search strategy included several relevant sources of data. Attempts were made to minimise language bias and retrieve unpublished material. The review process was conducted with sufficient attempts to minimise error and bias, although the method of study selection was unclear. Appropriate criteria were used to assess the quality of included trials and the results of this were highlighted in the review findings. Of note was that more than half of the trials were industry-sponsored. Study details were clearly presented. The method of synthesis appeared to be suitable given the level of statistical heterogeneity. This was a largely well-conducted review; the authors' conclusion is appropriately speculative and is likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that clinicians will benefit from evidence of a response pattern when considering a treatment plan for patients with knee osteoarthritis.

Research: The authors stated that future studies should investigate the potential synergistic effect of hyaluronic acid and corticosteroids.

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