Is there evidence in support of the use of intra-articular hyaluronate in treating rheumatoid arthritis of the knee: a meta-analysis of the published literature

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CRD summary
The authors concluded that intra-articular hyaluronate was an effective and safe alternative therapy for the rheumatoid knee. The evidence appeared to support the authors’ conclusions, but it should be borne in mind that the small number of included trials only reported short-term outcomes and their findings may not be applicable to other non-Japanese populations.

Authors' objectives
To evaluate the effectiveness of intra-articular hyaluronate injection for the treatment of the rheumatoid knee.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), UpToDate, Clinical Evidence, Web of Knowledge, HighWire Press and Japana Centra Revuo Medicina databases were searched from 1980 through December 2008. Search terms were reported. Reference lists of included studies were also screened. Studies were eligible if they were published in English or Japanese.

Study selection
Randomised controlled trials (RCTs) and quasi-randomised trials were eligible if they compared the efficacy and safety of different types of intra-articular hyaluronate products with placebo (saline or active placebo) for treatment of the rheumatoid knee in patients (with rheumatoid arthritis stated by the trial authors or diagnosed using criteria of the American College of Rheumatology). Eligible trials had to list all articular hyaluronate products and measure the degree of change in pain and inflammation.

The primary review outcome was the intensity of global pain (pain at rest and on movement) measured one week after the end of the trial using a Likert scale (options on the Likert scale were marked, moderate, reasonable or no improvement). Secondary outcomes were signs of global inflammation measured on similar Likert scales, overall effectiveness of articular hyaluronate (with treatment considered effective when scored as moderate or marked improvement) and safety (adverse events). Patients with missing follow-up data were classified as unsuccessful treatment.

All of the included trials had been published in Japanese. All trials used articular hyaluronate of bacterial origin (NRD-101 or Sevenyl). In all but one trial, the dose was five injections per week; in one trial, articular hyaluronate was given five to seven times per week. All but one trial used an active control (0.01% or 0.6% articular hyaluronate added to saline); one trial used a saline only control. Treatment duration was not reported.

Two reviewers independently conducted the searches; disagreements on inclusions were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed validity using the Jadad criteria (randomisation, blinding and withdrawals). Trials scoring more than 2 out of the maximum of 5 points were considered to be good-quality.

Data extraction
Outcome data were extracted as relative risks (RRs) with 95% confidence intervals (CI).

The authors did not state how data were extracted for the review.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using a fixed-effect model, with a random-effects model used in the presence of heterogeneity. Heterogeneity was assessed using the Q statistic and the I² statistic (I² >= 50% was taken as indicating substantial heterogeneity).

Sensitivity analyses were performed after excluding outlying studies from analyses.

The possibility of publication bias was explored using funnel plots and Egger's regression test.

**Results of the review**

Five RCTs were included (n=720 patients). Sample size ranged from 20 to 286. Four RCTs scored the maximum 5 points on the Jadad scale; the fifth RCT scored 4 points. Drop-out rates ranged from 0 to 14.3%.

Results for treatment effects one week after the last treatment were reported.

**Global pain** (pain at rest and on movement): Intra-articular hyaluronate was associated with a statistically significant reduction in pain compared with control treatments (RR 1.64, 95% CI 1.14 to 2.35). Significant heterogeneity was found (I²=78%). After excluding one trial, the remaining four trials were homogeneous (I²=0%), with no significant change in the treatment effect. Some asymmetry was noted in the funnel plot, but Egger's test was non significant.

Intra-articular hyaluronate was associated with a statistically significant reduction in global inflammation (RR 1.61, 95% CI 1.34 to 1.92; I²=0%; four RCTs; n=484 patients) and overall effectiveness (RR 1.50, 95% CI 1.14 to 1.97; I²=79%; five RCTs; n=720 patients). One trial was responsible for the heterogeneity in the effectiveness analysis. The funnel plot showed a small degree of asymmetry, but Egger's test for publication bias was not significant.

There was no statistically significant difference between articular hyaluronate and control treatments in adverse effects of ‘minor clinical relevance’, such as transient pain at injection site (four RCTs; n=676 patients; I² 0%). Egger's test showed evidence of publication bias (p=0.06).

**Authors’ conclusions**

Intra-articular hyaluronate was an effective and safe alternative therapy for the rheumatoid knee.

**CRD commentary**

The review question was clearly stated and inclusion criteria appropriately defined. Multiple sources were searched, but no specific attempts were made to minimise publication bias; the potential for publication bias was assessed, but was of limited usefulness given the small number of included trials. There was also the potential for language bias. Methods were used to minimise reviewer errors and bias in study selection and validity assessment, but it was not clear whether similar steps were taken in data extraction.

Only RCTs were included; their validity was assessed and, although only scores were reported, trials appeared to be of high-quality. No information was provided about treatment duration or co-interventions. Data were pooled using meta-analyses and heterogeneity was assessed. Individual trials responsible for heterogeneity were identified, but there was no discussion as to why outcomes from these trials might differ from the others. The evidence appeared to support the authors' conclusions, but it should be borne in mind that the small number of included trials reported short-term outcomes and findings may not generalise to other non-Japanese populations.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors state that there is a need for more studies to evaluate articular hyaluronate injections in patients with rheumatoid arthritis and to develop guidelines for this treatment.

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