Effectiveness of intra-articular hyaluronic acid for ankle osteoarthritis treatment: a systematic review and meta-analysis

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CRD summary
This review concluded that intra-articular hyaluronic acid could significantly reduce pain in ankle osteoarthritis compared to before treatment. It was likely to have been superior to reference therapy. The authors' conclusions are limited by the small number and limited quality of the available studies and results based on subjective reporting of pain.

Authors' objectives
To evaluate the effectiveness of hyaluronic acid injection for the treatment of ankle osteoarthritis.

Searching
PubMed, Scopus (both from January 1995 to June 2012) and several Cochrane databases were searched without language restriction. Search terms were reported. ClinicalTrials.gov, bibliographies of included trials and reference lists from relevant meta-analysis were searched for additional studies.

Study selection
Randomised controlled trials (RCTs) or prospective cohort studies that used intra-articular hyaluronic acid to treat ankle osteoarthritis in adult patients were eligible. Ankle osteoarthritis had to be confirmed by clinical and radiologic assessment and symptoms had to have lasted for more than six months. Studies that did not assess function or pain scores and studies which used hyaluronic acid injection for the treatment of ankle osteochondral lesions were excluded.

About half the studies had a comparator treatment which included arthroscopic debridement, exercise or saline solution. Mean age ranged from 45 to 60 years and 54.8% of participants were men. Average body mass index (BMI) varied between 22.7 and 31.7 kg/m². Most trials recruited patients with ankle osteoarthritis severity of Kellgren-Lawrence scale grade ≥2. Injection volume per dose ranged from 1ml to 2.5ml; total injection dose ranged between one and five.

Two reviewers independently evaluated studies for inclusion.

Assessment of study quality
The study quality was assessed using the Jadad scale for randomised controlled trials (ranged from 0 to 5 points) and the Newcastle-Ottawa Scale for the prospective studies (maximum scores to be achieved was 9 points). Total scores of less than 3 points for RCTs and scores of less than 4 points for prospective studies were considered low methodological quality.

Two reviewers independently assessed study quality; any discrepancies were resolved through discussion and consensus.

Data extraction
Data were extracted to calculate mean differences and their 95% confidence intervals between the baseline and status after therapy; and between intra-articular hyaluronic acid injections and other reference treatments. Effect sizes were estimated from the average pain scores from the ankle osteoarthritis scale. If the outcomes were not evaluated by the ankle osteoarthritis scales, data were extracted from the visual analogue scale to calculate the corresponding value. Only data provided in the third month after the initial treatment was used. If such data were not available, the latest records close to the third month after the treatment were used.

It appeared that more than one reviewer was involved in data extraction.

Methods of synthesis
Pooled standardised mean differences and their corresponding 95% confidence intervals were calculated using fixed-
effect meta-analysis (where there was no evidence of heterogeneity) or a random-effects model was used. Heterogeneity was assessed using $I^2$ and Cochran Q test. Univariate meta-regression was used to assess the influence of variables such as total active ingredients administered, injection volume per dose and total number of injection doses. Publication bias was assessed with funnel plot and the Egger test.

**Results of the review**

Nine studies (Four RCTs and five prospective studies) were included in the review (354 participants). The quality of the studies ranged from 1 to 5 points for RCTs and 4 to 6 points for prospective studies. Follow-up duration ranged from three to 18 months. Most studies used the ankle osteoarthritis score. The overall effect size of improvement scores from baseline was 2.01 (95% CI 1.27 to 2.75; $I^2$=92%). There was no significant difference in effect size when compared hyaluronic acid with reference treatments such as saline (three RCTs), exercise (one study) and arthroscopy (one study). When studies with the saline control group were pooled separately (three RCTs) to calculate the mean differences from baseline, the results showed the placebo effect of the treatment; which accounted for 87% of the observed efficacy.

Subgroup and meta-regression analyses were reported.

Fifteen percent of participants who underwent the administration of intra-articular hyaluronic acid experienced adverse effects. The reported adverse effects were transient post-injection pain (28 participants), ankle effusion (one participant), inguinal lymph node enlargement (one participant) and local pruritus (one participant). All adverse reactions resolved spontaneously without specific treatment.

Evidence of publication bias was reported.

**Authors’ conclusions**

Intra-articular hyaluronic acid administration could significantly reduce pain in ankle osteoarthritis compared with the condition before treatment, and it was likely to be superior to reference therapy.

**CRD commentary**

The review question and inclusion/exclusion criteria were clearly defined. Relevant sources were searched without language restriction which reduced language bias. The authors searched ClinicalTrials.gov for unpublished studies, but the funnel plot suggested evidence of publication bias. Appropriate review methods to reduce reviewer error and bias were used. Appropriate criteria were used to assess the study quality, but the full results were not reported. Appropriate methods were used to pool data and assess heterogeneity by using subgroup analyses and meta-regression.

Some sources of heterogeneity were investigated, but the role of variables other than drug regimen did not appear to have been investigated. Results were based on subjective reporting of pain with patients in most studies being aware of their treatment status.

The authors’ conclusions reflect the available evidence, but they were limited by the small number and limited quality of available studies.

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

**Practice:** The authors recommended using multiple doses with an appropriate injection volume to achieve maximum effectiveness. The authors also stated that injection volumes for ankle osteoarthritis treatments should be limited to 2ml per dose.

**Research:** The authors stated that injections of extremely high molecular weight hyaluronic acid were likely to associate with early post-injection pain, guidance by imaging tool to reduce the possibility of extra-articular administration was highly recommended.

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