

---

## Therapeutic effects of hyaluronate injections in patients with chronic painful shoulder: a meta-analysis of randomized controlled trials

Saito S, Furuya T, Kotake S

---

### CRD summary

The authors concluded that hyaluronate injections were effective in relieving pain and safe for the treatment of patients with chronic painful shoulder; further research was needed. Limitations of the evidence and potential for bias in the review mean that the findings should be interpreted with caution, but the authors' conclusion on the need for further research seems appropriate.

### Authors' objectives

To assess the efficacy and safety of hyaluronate injections for the treatment of chronic painful shoulder.

### Searching

PubMed, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), UpToDate, Clinical Evidence, Web of Knowledge and Japana Centra Revuo Medicina were searched from 1980 to December 2008 for relevant articles in English and Japanese. Search terms were reported. Reference lists were searched manually.

### Study selection

Randomised controlled trials (RCTs) that assessed the efficacy and safety of hyaluronate injections versus placebo, non-steroidal anti-inflammatory drugs (NSAIDs) or physiotherapy in the treatment of chronic painful shoulder were eligible for inclusion. The outcomes of interest were pain reduction, shoulder range of movement, total functional score and adverse events.

The included studies were conducted between 1988 and 2008 and were of patients with periarthritis scapulohumeralis, frozen shoulder, adhesive capsulitis, rotator cuff tear, persistent shoulder pain, supraspinatus tendinosis and shoulder impingement syndrome. Comparators included other hyaluronates and steroid injections. Where reported, treatment schedules in most studies involved five weekly injections. Pain was measured using the Likert scale or a 100mm visual analogue scale (VAS). Shoulder range of movement and total functional score were assessed using total Constant-Murley score, Japanese Orthopaedic Association shoulder score, University of California at Los Angeles shoulder score and American Shoulder and Elbow Surgeons Standardised Shoulder Assessment Form.

The authors did not state how many reviewers screened studies for inclusion.

### Assessment of study quality

Three reviewers independently assessed study quality using criteria adapted from the Jadad scale (no further details provided). Studies received a score between 1 and 5.

### Data extraction

Dichotomous outcome data were extracted to calculate odds ratios (ORs) or risk ratios (RRs) and their 95% confidence intervals (CIs). Continuous data were extracted to calculate mean differences and 95% CIs. Where insufficient data were presented on continuous outcomes, treatment effects and variances (standard deviations) were estimated from figures presented in the primary articles. Where necessary, primary authors were contacted for further information.

The authors did not state how many reviewers extracted data.

### Methods of synthesis

A fixed-effect model where there was no evidence of statistical heterogeneity or random effects model where there was evidence of statistical heterogeneity were used to combine odds ratios or risk ratios and mean differences, with 95%

CI. Where both dichotomous and continuous data were reported for the same outcome, data were combined to calculate odds ratios and standardised mean differences (SMDs).

Statistical heterogeneity was assessed using Cochran's Q and  $I^2$ . Sensitivity analysis was performed by excluding statistically heterogeneous studies. Subgroup analyses were undertaken for type of shoulder range of movement (extension movements, abduction, external rotation, internal rotation).

Publication bias was assessed using Egger's test.

### Results of the review

Nineteen RCTs (n=2,120 participants, range 20 to 660) were included in the review. Follow-up ranged from immediately after the last injection to 26 weeks. The mean quality score was 3.3 (range 1 to 5); only one trial used intention-to-treat analysis, six adequately described patient selection and outcome and six used concealed random allocation.

**Pain:** Hyaluronate injections were statistically significantly more effective than placebo in reducing pain (RR 1.41, 95% CI 1.17 to 1.70; five RCTs and SMD 0.40, 95% CI 0.22 to 0.59; five RCTs). There was no evidence of statistical heterogeneity ( $I^2=33.9%$  and  $I^2=0%$ ).

Hyaluronate injections versus other hyaluronates showed no statistically significant difference in pain intensity (five RCTs). There was evidence of significant statistical heterogeneity ( $I^2=72.2%$ ). Hyaluronate injections were significantly more effective in reducing pain intensity versus steroid injections (SMD 0.39, 95% CI 0.07 to 0.71,  $I^2=0%$ ; five RCTs).

**Shoulder movement (seven RCTs):** Hyaluronate injections statistically significantly improved the range of movement compared to placebo (SMD 0.17, 95% CI 0.05 to 0.28). Subgroup analyses showed that hyaluronate injections modestly improved abduction (SMD 0.29, 95% CI 0.12 to 0.46), but did not significantly affect external rotation (data not reported).

**Total functional scores:** Hyaluronate injections statistically significantly improved total functional scores compared to placebo (SMD 0.36, 95% CI 0.01 to 0.71; four RCTs). There was no evidence of statistical heterogeneity.

There were no statistically significant differences between hyaluronate injections and placebo in the number of adverse events (13 RCTs,  $I^2=0%$ ).

There was no evidence of publication bias.

### Authors' conclusions

Hyaluronate injections were effective in relieving pain and were safe for the treatment of patients with chronic painful shoulder, but further research was needed.

### CRD commentary

The review question was stated, but the inclusion criteria lacked clarity. Several electronic databases were searched. No specific searches for unpublished data were reported and language restrictions were applied, so potentially relevant data may have been missed. Publication bias was formally assessed and there no evidence of it was found. The authors assessed study quality using a modified version of previously published criteria. However, as few details on the criteria assessed and only overall scores were reported, the quality of the studies was unclear. Quality assessment was performed in duplicate. It was unclear whether study selection and data extraction were performed in duplicate, so reviewer error and bias may have been introduced.

The authors acknowledged clinical and methodological heterogeneity among trials and potential for bias due to conversion of outcome measures to standardised measures. The authors acknowledged the low methodological quality of some trials and the short duration of most trials.

Given the limitations of the evidence and potential for bias in the review, the findings regarding the safety and efficacy

of hyaluronate injections should be interpreted with caution. The authors' conclusion on the need for further research seems appropriate.

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

**Practice:** The authors stated that hyaluronate injections were a safe treatment for chronic painful shoulder.

**Research:** The authors stated that larger and longer term trials were needed to ascertain the long-term efficacy of hyaluronate injections.

### **Funding**

Not stated.

### **Bibliographic details**

Saito S, Furuya T, Kotake S. Therapeutic effects of hyaluronate injections in patients with chronic painful shoulder: a meta-analysis of randomized controlled trials. *Arthritis Care and Research* 2010; 62(7): 1009-1018

### **PubMedID**

20235211

### **DOI**

10.1002/acr.20174

### **Original Paper URL**

<http://onlinelibrary.wiley.com/doi/10.1002/acr.20174/abstract>

### **Indexing Status**

Subject indexing assigned by NLM

### **MeSH**

Chronic Disease; Humans; Hyaluronic Acid /administration & dosage; Injections, Intra-Arterial; Pain Measurement; Randomized Controlled Trials as Topic; Range of Motion, Articular; Recovery of Function; Shoulder Pain /drug therapy; Viscosupplements /administration & dosage

### **AccessionNumber**

12010005314

### **Date bibliographic record published**

13/10/2010

### **Date abstract record published**

28/09/2011

### **Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.