

Penning LIF, de Bie RA, Walenkamp GHIM. The effectiveness of injections of hyaluronic acid or corticosteroid in patients with subacromial impingement. J Bone Joint Surg Br 2012;94-B:1246–52.

Design: randomized clinical trial

Study question: does injection of hyaluronic acid improve symptoms of subacromial impingement more effectively than either corticosteroid or placebo injection?

Population/sample size/setting:

- 159 patients (75 men, 84 women, mean age 53) treated for shoulder impingement syndrome at a university orthopedics department in the Netherlands
- Eligibility criteria were age over 18 with pain in the shoulder and a clinical diagnosis of impingement based on a painful arc with or without scapulohumeral movement; ultrasound was not used to make the diagnosis
- Exclusion criteria included pain less than 6 weeks, injection with steroids in the past three months, flexion $<100^\circ$ in the frontal plane, external rotation limited by $>50\%$ compared to the opposite side, rheumatoid arthritis, osteoporosis, previous surgery of fractures of the shoulder, neck, thorax, or upper limb, pain referred from the neck

Main outcome measures:

- All patients received a subacromial injection through a dorsolateral approach using the dorsal acromial ridge as a landmark; injections could be repeated if needed at 3 and 6 weeks; most patients had a full course of three injections
 - o All injected solutions contained 8 ml of 1% lidocaine
 - o Syringes were masked with black adhesive tape to protect the blinding of the injections
 - o No added treatment was allowed for 12 weeks except for self-medication with acetaminophen
- Randomization was to injection with either 2 ml hyaluronic acid (n=51), 2 ml triamcinolone 10mg/ml (n=53), or 2 ml normal saline (n=55)
- Followup after baseline was done at weeks 3, 6, 12, and 26
- Primary outcome was pain VAS expressed as the proportion of patients with a reduction in or a resolution of pain
 - o Numerous secondary outcomes were measured, including disability/function questionnaires, Constant scores, painful arc, and range of motion
- There were 22 patients who withdrew from the study, and were about equally distributed between groups

- For the main outcome, the pain VAS scores for all three groups were statistically similar at baseline and at 26 weeks, but there were some differences at earlier followup points
 - o Corticosteroids were more effective than hyaluronate at weeks 3 and 6
 - o Placebo injections were more effective than hyaluronate at 12 weeks
 - o Steroids were more effective than placebo at 6 weeks
 - o The mean reductions in pain were modest in all three groups at 26 weeks: 15% for hyaluronate, 20% for steroids, and 21% for saline
 - o At 26 weeks, a reduction in pain was reported by 63% of hyaluronate patients, 72% of steroid patients, and by 69% of saline patients
- Significance levels for secondary outcomes were not reported, but at 26 weeks the saline group had the highest Constant score (82.3), compared to 76.0 for hyaluronate and 80.4 for steroid
- Mild adverse effects were reported by 67 patients, mostly injection site pain; these are not reported separately by group (data supplement on the journal website shows that the distribution of adverse effects is about equal)

Authors' conclusions:

- Steroid injection was associated with faster reduction of pain than for either hyaluronate or saline, but at 26 weeks there were no group differences (although saline had the best mean improvement in pain and function)
- Although the injections were done without imaging guidance, the use of anatomic landmarks is the usual practice in clinical settings
- While steroids can provide fast initial relief of impingement pain, the placebo group had the best long term improvement
- Hyaluronate is a high molecular weight compound which may be broken down into smaller fragments in an inflammatory environment, and these smaller fragments may be pro-inflammatory (Noble 2002)

Comments:

- While the placebo group had the numerically greatest relief of pain and the best Constant scores at 26 weeks, the group differences are small and within the range consistent with chance differences
- The dosage of hyaluronate is not specified, but the preparation used (Ostenil) has 10 mg of hyaluronate per ml; the dosage per injection was 20 mg
- Several sources of bias are controlled more effectively in this study than in some other studies; the blinding is better maintained and the method of randomization is better suited to avoid selection bias at the start of the study
- No rehabilitation or exercise program is reported as part of the treatment plan; it may have been done, but there is no information about how it was implemented

- The sample sizes are sufficient to support evidence statements that hyaluronate is not more effective than saline injection for subacromial impingement symptoms
- Use of landmark rather than image-guided injections is not likely to have had an important influence on the pain and functional outcomes (Bloom 2012)
- Noble 2002, while it does not report on any clinical outcomes, does report on some biological variables which could shed light on the action of hyaluronate in a diseased joint
 - o If hyaluronic acid fragments initiate inflammatory responses in vivo as they apparently do in vitro, it could become less effective when injected into an environment in which it can be catabolized

Assessment: Overall a high quality study supporting good evidence that subacromial injection of hyaluronic acid is not more effective than steroid or placebo for pain relief and functional improvement of subacromial impingement syndrome

References:

Bloom JE, Rischin A, et al. Image-guided versus blind glucocorticoid injection for shoulder pain (Review). Cochrane Database of Systematic Reviews 2012, Issue 8, Art # CD009147.

Noble PW. Hyaluronan and its catabolic products in tissue injury and repair. Matrix Biol 2002;21:25–29.