Blaine T, Moskowitz R, et a. Treatment of Persistent Shoulder Pain with Sodium Hyaluronate: A Randomized, Controlled Trial A Multicenter Study. JBJS Am 2008;90:970-9

Design: Randomized clinical trial

Study question: Does intra-articular injection of sodium hyaluronate (HA) relieve symptoms of persistent shoulder pain?

Population/sample size/setting:

- 660 patients (328 men, 332 women, mean age 63) treated for persistent shoulder pain at 79 sites in the United States
- Eligibility criteria included persistent shoulder pain refractory to standard treatments
    - Standard treatments were defined as physical therapy, at least one steroid injection more than 3 months prior to entry into the study, and oral analgesics
    - A pain VAS between 40 and 90 without analgesics for 24 hours was required
    - Patients were not considered to be surgical candidates
    - Limitation of range of motion in at least one direction was required, but retention of at least 20% of ROM in all directions was also required
- Exclusion criteria were a major injury in the past year, chronic pain lasting more than five years, cervical spine disease, shoulder surgery in the past 12 months, inflammatory joint disease, severe frozen shoulder, gout & calcium pyrophosphate disease, steroid injection of any other joint within the past month, intra-articular HA therapy in the past 12 months, acute fracture of the shoulder, severe loss of bone density, osteonecrosis, or Kellgren-Lawrence Grade IV osteoarthritis of the glenohumeral joint

Main outcome measures:

- All patients received intra-articular injections without imaging guidance
- Randomization was to one of three treatment groups: five weekly injections of 2 ml phosphate-buffered saline (n=221), five weekly injections of 2 ml (20 mg) of HA, or three weekly injections of 2 ml (20 mg) of HA
- The majority (about 60%) of patients in each group had osteoarthritis (OA) diagnosed as the cause of shoulder pain, and about 66% of the patients with OA had other shoulder pathology: rotator cuff tear (full or partial thickness) or adhesive capsulitis
- Followup was done at 7, 9, 13, 17, and 26 weeks

- The primary outcome was the change in pain with movement between baseline and the 26 week followup
- There was high attrition at the time of the 26 week followup: 69.1% of patients had a followup visit at that time (30.9% attrition)
    - Attrition was balanced between treatment groups, and the reasons for withdrawal were also balanced between groups
    - Lack of efficacy and patient withdrawal of consent were the leading reasons for dropping out of the study
    - Most of the attrition was in the first 13 weeks, at which time there had been 20% dropout
- At week 13, all three groups had significant reduction from baseline in VAS ford pain on movement; the between-group differences were not significant; 26.3 points for the three-injection HA group, 26.4 points for the five injection HA, and 23 points for the saline group
- With the use of all data points in a repeated measures mixed linear model (which uses all of the data from all of the repeated measurements), the overall effect of pain reduction was similar for the two HA groups and the effect of HA was greater than for the control group: 4.2 points better for the three injection group and 5.1 points better for the five injection group
- The presence or absence of OA had a significant effect on the response to HA
    - For patients with OA, both HA groups had greater pain relief than the control group at all measurement points (7.5 points better for the three injection group and 7.8 points better for the five injection group)
    - For patients without OA, the HA groups did not differ from the control groups on pain relief (1.2 points worse for the three injection group and 1.2 points better for the five injection group; both had high p values)
- Differences in range of motion between HA and control were less than 10°, which was considered as the minimal clinically important difference
- The injections were generally well-tolerated with few adverse events

Authors' conclusions :

- The primary objective of the study was to evaluate the safety and efficacy of HA for the treatment of persistent shoulder pain
- Although the primary end point was not achieved, significant improvements occurred in several secondary end points
- Patients with OA demonstrated significantly better pain responses to HA than those without HA, supporting the hypothesis that OA is a key factor in the therapeutic effects of HA
- Benefits beyond 26 points cannot be ascertained

- The lack of significant differences between HA and control at the 13 week measurement could have been due to an effect of the phosphate-buffered saline solution
- Although the primary end point was not achieved, the data demonstrate that HA is safe and effective for the treatment of shoulder pain due to OA, either OA alone or OA associated with other shoulder conditions

Comments:

- The primary end point is somewhat unclear: in the "Statistical Methods" part of the Methods section, the pain response at Week 26 is designated the primary dependent variable; in the "Primary Efficacy Outcome" part of the Results section, week 13 is the primary end point
- The longitudinal data analysis was done with a mixed-model, repeated measures ANOVA, which deserved more emphasis than it received in the Discussion section; the authors may not have appreciated its importance
    - Unlike measurements at a single time (week 13 or week 26), mixed models make use of all of the available data, and may avoid problems which often arise with imputation of missing data and with the vagaries of what can happen at a particular time point in the study
    - The mixed model did show a greater pain reduction for the two HA groups than for the control group, and this finding should not be neglected
        - Part of the purpose of a mixed model with repeated measures in a longitudinal study is to allow the researcher not to base the analysis on what is measured at only one time point
- The finding that OA is a predictor of HA response is of potential importance, but it may not have been planned at the outset of the study as one of the purposes of the investigation
    - A study protocol does not appear to be available, since the trial does not appear to have been registered at clinicaltrials.gov where the original protocol might have shown whether the effect of OA was one of the planned variables
- The study had a fairly high rate of incomplete data due to attrition, and was carried out in 79 centers
    - Multicenter trials may control some biases more effectively than single-center trials, but are often at a higher risk of incomplete outcome data due to logistic and practical issues (Dechartres 2011)
- The high response to buffered saline (if it represents an effect on the arthritic joint) means that the advantage of HA over "placebo" represents a conservative estimate of its therapeutic effect
- Most OA patients had concomitant shoulder pathology; a separate analysis of the effect of HA on "pure" OA was not done as was done in Kwon et al 2013

Assessment: adequate for some evidence that three weekly injections of HA alleviate the symptoms of glenohumeral osteoarthritis for up to 26 weeks

Reference:

Dechartres A, Boutron I, et al. Single-Center Trials Show Larger Treatment Effects Than Multicenter Trials: Evidence From a Meta-epidemiologic Study. Ann Intern Med. 2011;155:39-51.

Kwon YW, Eisenberg G, Zuckerman JD. Sodium hyaluronate for the treatment of chronic shoulder pain associated with glenohumeral osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. J Shoulder Elbow Surg 2013; 22: 584-594.