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.

Design: Randomized clinical trial

Study question: Does sodium hyaluronate (SH) effectively relieve pain from glenohumeral osteoarthritis (OA)?

Population/sample size/setting:

- 300 patients (164 men, 136 women, mean age 66) treated for glenohumeral OA in a multicenter clinical trial in the United States (original cohort had 300 patients)
- Inclusion criteria were age over 36, initial pain on movement score at least 50 mm on a 100 mm VAS, duration of pain more than 6 months but less than three years, willingness to discontinue all pain medication for at least 24 hours prior to each visit, and no modification of medication regimen in the past 4 weeks
- Exclusion criteria were severe joint effusion, structural defects necessitating surgery, steroid injection in any joint in the past 3 months, surgery on the affected shoulder in the past 2 years, and inflammatory disease of the affected joint

Main outcome measures:

- All patients had 3 weekly intra-articular injections
- 300 patients were randomized to injection with HA (n=150) or phosphate-buffered saline (n=150)
    - 37 of these had concomitant shoulder pathologies such as rotator cuff tears in addition to OA
    - The remaining 263 patients with OA only were the focus of a separate analysis of study results
- Followup visits were scheduled at weeks 7, 13, 20, and 26
- For both HA and saline patients, improvements in VAS occurred after treatment, beginning at week 1 and maintained throughout the 26 weeks of observation
- Although the HA patients had greater VAS improvements than the saline patients (19.88 mm for HA and 16.29 for saline) , the difference did not reach statistical significance in the repeated measures longitudinal analysis
- The improvements in VAS were the same for injections done with and done without guidance

- A separate analysis of the 263 patients with OA only demonstrated similar trends on the VAS
    - For the HA group, the improvement in VAS was 21.04 mm; for the saline group, the VAS improvement was 15.67
    - This 4 point difference did reach statistical significance
- A separate analysis was also done of the response to HA/saline in the three different radiographic stages of OA
    - For Grade I OA, there were too few patients to analyze
    - For Grade II patients, the difference between HA and saline was statistically significant in favor of HA (actual VAS reductions not reported)
    - For Grade III patients, HA had a greater VAS reduction than saline, but was not statistically significant
- No serious device-related adverse events occurred and the injections appeared to be safe for both groups of patients

Authors' conclusions:

- For OA of the glenohumeral joint without other shoulder pathologies, there was a greater reduction with HA than with saline
- For all patients analyzed together the difference between HA and saline was not statistically significant
- MRI was not required for entry into the study, and other pathologies were not ruled out; however, the usual treatment of shoulder OA is based on plain x-ray and this is the scenario faced by most clinicians
- The high placebo response in the control group could have been induced by a yet unexplained effect of buffered saline in the setting of OA

Comments:

- The dosage of HA and the volume of buffered saline was not specified in the study and was not in the study protocol at clinicaltrials.gov
    - The reader is left to speculate that the dose of OA may have been 20 mg in a 2 ml solution, as is common in other trials of HA for shoulder OA
- The contrast between OA only and OA with other pathologies may have been planned at the beginning of the study, but the clinicaltrials.gov protocol data is very sparse and this is not clear
- The radiographic grade of the OA was based on the Samilson-Prieto grading system, which has three grades and is designed for glenohumeral OA
    - Grade III of the Samilson-Prieto system may correspond to Kellgren-Lawrence Grade IV
    - Both systems have excellent interrater reliability (Elsharkawi et al 2013)

- Kellgren-Lawrence Grade IV OA was excluded from the study by Blaine et al 2008, but Samilson-Prieto Grade III was present in 142 of the 300 patients who were randomized in this study
- The group differences for Grade II and Grade III OA are reported only as p values and not as effect sizes; the authors may have been placing more emphasis on statistical significance than is necessary or informative
    - The statistically significant difference of 4 mm VAS for HA versus saline in the OA-only analysis may not be clinically very important
- As was the case with Blaine et al, the "placebo" response to buffered saline was fairly large, and comparison with buffered saline may represent a conservative estimate of the effect of HA in the setting of shoulder OA

Assessment: adequate for some evidence that three weekly glenohumeral injections of HA may alleviate the symptoms of OA, especially in the absence of other shoulder pathology

References:

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

Elsharkawi M, Cakir B, et al. Reliability of radiologic glenohumeral osteoarthritis classifications. J Shoulder Elbow Surg 2013;22: 1063-1067.