

**Chang KV, Hsiao MY, et al. Effectiveness of intra-articular hyaluronic acid for ankle osteoarthritis treatment: a systematic review and meta-analysis. Arch Phys Med Rehabil 2013;94(5):951-60.**

Design: Meta-analysis of clinical trials

Purpose of study: to evaluate the effectiveness of intra-articular hyaluronic acid (HA) injections for ankle osteoarthritis (OA)

PICOS:

- Patient populations: Adults with symptomatic ankle OA confirmed by clinical and radiological assessment, lasting six months or more
  - o Articles dealing with ankle osteochondral lesions were excluded
- Interventions: Intra-articular OA
- Comparison interventions: saline control for three studies, exercise for one study, and arthroscopic debridement alone versus arthroscopic debridement plus HA in one study
- Outcomes: (1) Average pain VAS scores before and after treatment, measured in terms of standard deviations, or standardized mean differences (SMD) between pre and post treatment, and (2) the changes in pain SMD between HA and control treatments, using the data closest to the third month after treatment as the time point for the comparisons
- Study types: Randomized trials and prospective cohort studies

Study selection:

- Databases were PubMed, Scopus, the Cochrane Central Register, and ClinicalTrials.gov from January 1995 to June 2012
- Two authors independently evaluated studies for inclusion and evaluated the quality of randomized trials with the 5-point Jadad scale (scores less than 3 were considered low quality)
  - o Prospective cohort studies were rated on a 9 point scale to assess the quality of selection, comparability, exposure, and outcome, where scores less than 4 were considered low quality

Results:

- The pooled effect size of all included studies for improvement from baseline to followup was 2.01 SD with a 95% confidence interval from 1.27 to 2.75 SD
- Pooled comparisons of three randomized trials with saline control showed an advantage of HA over saline of 1.00 SD with 95% CI from -.87 in favor of saline to 2.87 in favor of HA

#### Authors' conclusions:

- There were large and statistically significant improvements in ankle pain from baseline to the 3 month followup with intra-articular OA
- Even though there was some overlap of zero with the 95% confidence interval for the comparison of pain improvements of HA over saline, the effect size remained greater for HA
- Because there was an association between the total number of injections and the effect size of HA, it is appropriate to use multiple injections with appropriate volume to achieve maximum therapeutic value

#### Comments:

- The essential part of the conclusion that increasing frequency and volume of HA is associated with improved efficacy is based on Figure 3, in which the comparisons of HA with saline is displayed
  - o DeGroot 2012, using a single injection of 2.5 ml of HA, reported no effect of HA over saline (the effect size was non-statistically significant in favor of saline)
  - o Salk 2006, using 5 weekly injections of 1 ml HA, had a moderate but statistically non-significant effect in favor of HA over saline
  - o Cohen 2008, using 5 weekly injections of 2 ml of HA, reported a large and statistically significant advantage of HA over saline
- The effect sizes were reported in terms of standardized mean differences (SMD), in which the differences between treatment groups are given as how many standard deviations separate the two groups; when this is done, there is a convention whereby an SMD of 0.2 SD is small, an SMD of 0.5 SD is moderate, and an SMD of 0.8 SD or more is considered large
- Therefore, the effect size for Cohen is extremely large, and even the lower end of the 95% CI of 1.75 SD is extremely and implausibly large
- The difficulty arises from the fact that Cohen's Table 2, which reported the pain improvement scores, gave them in terms of percent improvements plus or minus standard errors, not standard deviations
  - o The standard error is the standard deviation divided by the square root of the number of patients in the sample
  - o This means that the 3 month AOS pain improvement of 34.3 plus or minus 8.9 standard errors, with 15 patients in the group, has a standard deviation of 34.4; similarly, the saline group with 13 patients and a standard error of 9.3 has a standard deviation of 33.5
  - o When these standard deviations are used in place of the standard errors, the SMD for Cohen of 2.79 with 95% CI from 1.75 to 3.83 becomes a SMD of

0.69 with 95% CI from -0.08 to 1.45, a moderate and statistically non-significant advantage of HA over saline

- The consequence of this correction is that there is no advantage of HA over saline from the three randomized trials making the comparison

Assessment: Inadequate for evidence that HA is more effective than saline for treatment of ankle OA

#### References:

Cohen MM, Altman RD, et al. Safety and efficacy of intra-articular sodium hyaluronate (Hyalgan) in a randomized, double-blind study for osteoarthritis of the ankle. *Foot Ankle Int* 2008;29:657-63.

DeGroot H, Uzunishvili S, et al. Intraarticular injection of hyaluronic acid is not superior to saline solution injection for ankle arthritis: a randomized, double-blind, placebo controlled study. *JBJS Am* 2012;94:2-8.

Salk RS, Chang TJ, et al. Sodium hyaluronate in the treatment of osteoarthritis of the ankle: a controlled, randomized, double-blind pilot study. *JBJS Am* 2006;88:295-302.