

Rutjes AWS, Juni P, et al. Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review and Meta-analysis. Ann Intern Med. 2012;157:180-191.

Design: Meta-analysis of randomized clinical trials

PICOS:

- Patient population: adults with symptomatic knee osteoarthritis
- Intervention: Any type of intra-articular viscosupplementation with hyaluronic acid or a derivative
 - o Data were extracted for type of viscosupplementation , average molecular weight, number of cycles, and number of injections
 - o Three classes of molecular weights were considered: high (>6000), intermediate (between 1500 and 6000), and low (<1500)
- Comparison: sham viscosupplementation or no viscosupplementation
 - o Sham was defined as saline or as a minimal viscosupplementation solution such as 1% of the active injection
- Outcomes: pain intensity was the primary outcome and physical function was a secondary outcome
 - o A minimally clinically important difference (MCID) of 0.9 cm on a 10 cm VAS pain scale was prespecified for pain scores; this was equivalent to a treatment effect of 0.37 standard deviations (SD) between groups
 - o The primary safety outcome was a flare-up of the injected knee, defined as a hot, painful swollen knee within 24 to 72 hours after injection
- Study types: randomized or quasi-randomized controlled trials without language restrictions

Study selection:

- Two authors independently evaluated studies for inclusion, resolving disagreements through consensus or discussion with a third reviewer
- Databases were MEDLINE from 1966, EMBASE from 1980, and the Cochrane Central Register of Controlled Trials from inception to present
 - o Additional searches were done with Science Citation Index, reference lists of all obtained articles, and selected clinical trials registries
- Quality items were concealment of allocation, blinding of participants and outcome assessors, and analysis by intention to treat
- Analyses of effectiveness were stratified on some trial characteristics: concealment of allocation, blinding of patients, use of a sham injection, intention-to-treat analysis, trial size, number of injections, average molecular weight, number of treatment cycles, and molecular structure (cross-linked or not cross-linked)

- One analysis was restricted to large trials (100 or more patients per group) and blinded outcome assessment because of the fact that these characteristics were associated with the measurements of treatment effects

Results:

- 187 reports describing 89 trials in 12,667 patients met inclusion criteria
- The average age of patients ranged from 50 to 72, with a median of 63 years
- Only 13 trials (15%) reported adequate allocation concealment, 16 (18%) had adequate blinding of patients, and 48 (54%) had blinded outcome assessment; 17 trials (19%) analyzed all patients by intention-to-treat, while 23 trials (26%) had 100 or more patients in each group
- Knee pain was measured in 71 trials with 9617 patients for the overall meta-analysis of treatment effect
 - The effect of viscosupplementation was for all 71 trials was moderate with a size of 0.37 SD (95% confidence interval between 0.28 and 0.46), which was equal to the prespecified MCID
 - The effect size for 21 large trials with 6085 patients was smaller (0.16 SD, 95% CI from 0.07 to 0.26), and the high end of the CI did not reach the MCID
 - In contrast, the effect size for 50 smaller trials with 3532 patients was 0.52 SD with a 95% CI from 0.39 to 0.67; the low end of the CI exceeded the MCID
 - Concealment of allocation was adequate in 13 trials with 3006 patients, and the effect size was 0.18 SD with 95% CI from 0.01 to 0.36 SD; the high end is close to the MCID, but the low end indicates no effect
 - In contrast, allocation concealment was inadequate or unclear in 58 trials with 6611 patients, and the effect size was 0.43 SD with 95% CI from 0.32 to 0.53 SD, making the pooled effect greater than the MCID
 - Blinded outcome assessment also made a difference in the effect size; in the 46 adequately blinded trials, the effect size was 0.25 SD; in the 25 inadequately blinded trials, the effect size was 0.66 SD
 - There were 18 trials with 5094 patients which were both large and had adequate blinding of outcome; the effect size for these trials was 0.11 SD with 95% CI from 0.04 to 0.18 SD, which is less than the MCID of 0.37 SD
 - In 7 of these 18 trials, there was also adequate allocation concealment; the effect size was 0.09 SD with confidence intervals between 0.24 SD in favor of viscosupplementation and 0.07 SD in favor of control
 - Only one large trial (with 242 patients) was funded independently of industry; it had an effect size of 0.14 SD in favor of control with 95% CI from 0.11 in favor of viscosupplementation to 0.40 in favor of control; this exceeded the 0.37 SD which is the MCID

- Physical function was measured in 52 trials with 7904 patients
 - o A moderate effect size of 0.33 SD for viscosupplementation had a 95% CI from 0.22 to 0.44 SD when all trials were pooled
 - However, when large adequately blinded trials were pooled, the effect of viscosupplementation was much less; it was 0.09 SD with 95% CI from 0.00 to 0.17 SD, again much less than the MCID of 0.37 SD
- Safety as assessed by post-injection flare-ups was available in 6 trials with 811 patients; the relative risk of viscosupplementation compared to control was 1.51, but the 95% CI was wide and the RR was not statistically significant
 - o The RR was 2.39 in large trials with blinded outcome assessment, but again the 95% CI was wide enough to include a non-statistically significant value
- There was evidence of publication bias, which was seen in a funnel plot showing that trials favoring viscosupplementation were more likely to be published than trials favoring control
- In contrast to what has been reported elsewhere, there did not appear to be any time period of followup in which a clinically meaningful effect was seen, whether at 1, 3, 6 or 12 months

Authors' conclusions:

- A small, clinically irrelevant effect of viscosupplementation on pain was seen in a meta-analysis of large trials with blinded outcome assessment
- There were more adverse effects of viscosupplementation than of control (even though not statistically significant)
- Many trials were poor in quality and some gave unrealistic effect sizes in favor of viscosupplementation
- Because the benefits of viscosupplementation are minimal or nonexistent, and because of risks of local adverse events, the administration of these preparations should be discouraged

Comments:

- This meta-analysis is more recent than the 673 page Cochrane review by Bellamy et al 2006, and is much better organized and presented; the Cochrane review did not assess publication bias, and did not effectively assess the influence of study type on effect size
- There is some lack of clarity in the presentation of safety data; Figure 4 gives relative risks for the included trials, but does not give the number of events
 - o Supplement appendix 14 displays relative risks with numbers of serious adverse events for several trials, but does not show numbers of events for the large trials with blinded outcome assessment, even though it does display a

relative risk of 1.55 whose 95% confidence interval excludes the null value of 1.0

- Appendix 8 is helpful because it is restricted to large trials with blinded outcome assessment, and breaks these down by other study characteristics such as allocation concealment and blinding of patients
- Appendix 13 displays the time from treatment effect as being short of the MCID at 1, 3, 6, and 12 months; this stands in contrast to what has been reported elsewhere for the time period of about 3 months
- Although blinding of outcome assessment had a noticeable influence on the reported size of the treatment effect, blinding of patients appears to have had only a small influence on this measurement

Assessment: High quality meta-analysis with strong evidence that in the setting of knee osteoarthritis, the effectiveness of viscosupplementation is clinically unimportant, and may impose a risk of adverse events on the patient

Reference:

Bellamy N, Campbell J, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005321