Intra-articular hyaluronic acid injections

Are they effective treatment for osteoarthritis of the knee?

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Petrella RJ, DiSilvestro D, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med* **2002;162:292-8.**

Research question

Can sodium hyaluronate (eg, Suplasyn®) injections alleviate pain and improve physical function in patients with unilateral knee osteoarthritis (OA) more effectively than diclofenac/misoprostol (Arthrotec®) and placebo?

Type of article and design

Multifactorial, randomized, double-blind, placebo-controlled trial

Relevance to family physicians

The overall prevalence of arthritis in Canada is 21.2% for women and 15.7% for men and can be as high as 51.2% in people 75 and older.[1] For those with OA, the knee is the most commonly affected joint, and patients experience disability and pain.[2,3] Knee pain in older adults is thought to be the latest musculoskeletal "silent epidemic."[4] About 25% of people older than 55 will report an episode of severe knee pain in the past year, and about half of them will report associated disability.[2] Osteoarthritis is associated with mild to moderate disability in up to 10% of adults older than 55.[1]

Osteoarthritis is the second most common diagnosis and the most common cause of disability among older people consulting general practitioners.[2] Age is the factor most strongly and consistently associated with OA; other accepted risk factors include being female, genetic predisposition, mechanical stress, repetitive joint use, joint trauma, obesity, congenital and developmental disorders, and prior inflammatory joint disease.[1]

The goals of OA therapy are to decrease pain, maintain or improve joint function, and educate patients.[3] Managing moderate-to-severe knee OA is difficult, although some pharmacologic and nonpharmacologic therapies have been shown to be effective. Once severe disability and pain emerge, however, surgery remains the only option.[3] Treatment aims to control symptoms rather than modify the disease.

Hyaluronic acid, a viscous component of synovial fluid, acts as a lubricant and cushion for joints. In OA, the hyaluronic acid in the articular matrix is depleted. Pharmacologic companies have tried to replicate this component so that it can be injected into the articular space and provide relief of pain. Some consider this a maneuver to delay surgical intervention in a degenerating knee joint, but regular use is controversial.

Overview of study and outcomes

Participants were enrolled from a primary care referral centre in London, Ont, if they had radiographic evidence of unilateral OA and pain at rest. They were excluded if they had non-OA arthritides, showed previous intolerance to nonsteroidal anti-inflammatory drugs (NSAIDS), had gastrointestinal bleeding, had peptic ulcer disease, had avian allergy, used herbal remedies regularly, or had had an intra-articular injection in the previous 6 months. Patients discontinued all OA medications 2 weeks before baseline assessment. At baseline, age, sex, body mass index (BMI), comorbidity, pain--scale ratings, and physical functioning at rest and following a functional task were recorded. One hundred twenty participants were randomized to four groups: group 1 had sodium hyaluronate injections and oral placebo; group 2 had sodium

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hyaluronate injections and oral diclofenac/misoprostol (75/200 twice daily); group 3 had saline injections and oral diclofenac/misoprostol (75/200 twice daily); and group 4 had saline injections and oral placebo.

Three injections were given at baseline, week 1, and week 2. Medications were taken until week 12. At baseline, all subjects were documented and given instructions and a video showing a 10-minute home-based resistance exercise program they were to do at least three times weekly. Pain and physical functioning were measured at weeks 3 and 12. Rescue analgesia (acetaminophen up to 650 mg four times daily) was given to all groups. All data were collected by investigators blinded to treatment.

Results

Most (90%, 108/120) participants completed the study. Participants' characteristics were similar across the four groups at baseline, and drop-outs were not statistically different from those who completed the study. One drop-out was lost to follow up, two had moderate gastrointestinal irritation, one was noncompliant, and eight left for unknown reasons. Compliance with the exercise program was similar in all groups; an average of 75% of participants were compliant at week 12.

The main study outcome was pain at 4 weeks and 12 weeks. Other outcomes were physical functioning, stiffness, and pain with activity. Pain, disability, and stiffness improved significantly in groups 1, 2, and 3 from baseline to week 4. The authors mention that group 2 showed further significant improvement from week 4 to week 12, but actual measures were not reported. After 4 weeks, all groups reported significantly less pain with activity following a self-paced walking test, but only groups 1, 2, and 3 reported less pain after a similar stepping test.

Analysis of methodology

Study design was rigorous. Response rate was good, and blinding was adequate. Each randomized group was small (four groups of 30), however, and the study lasted only 12 weeks.

The results are questionable. Many statements of benefit from sodium hyaluronate injections were not clearly defined in the tables (eg, the tables give data only up to 4 weeks, even though improvements from weeks 4 to 12 were described in the text). *P* values in the tables refer only to within-group comparisons (eg, baseline to week 4) and not comparisons between groups. Thus, comparisons are pretest–posttest within a group, rather than between groups. Main outcomes were either not different among groups or, in the case of 12-week pain scores, not given.

In an editorial with this study, Felson and Anderson question the results.[5] They performed a posthoc repeat analysis of the available data as a factorial experiment, comparing outcomes between groups after controlling for cotreatment of half the participants with NSAIDs. They made a few statistical assumptions based on previous OA studies and concluded that the effect of the NSAIDs was approximately 48 times the effect of the sodium hyaluronate in this study. At the very least, the main effects of sodium hyaluronate, NSAIDS, or their interaction would not be statistically significant.

The accompanying intervention of strengthening exercises was not evaluated, but could explain why the placebo group experienced significant improvement in disability and pain at rest at week 4. Use of rescue acetaminophen was not documented in any group.

The conclusion of the abstract to this paper states, "For resting pain relief, hyaluronate sodium seems to be as effective as NSAIDS. Further, for pain with physical activity and functional performance, hyaluronate sodium may be superior to placebo alone or NSAIDs alone." The paper, however, does not give evidence for such statements. We should also note that the study was supported by Bioniche Life Sciences Inc of Belleville, Ont, who make Suplasyn.®

Application to clinical practice

An average patient in this study was known to a family physician, was 65 years old, had a BMI of 31, had up to two other conditions, and had moderate unilateral OA of the knee. We know from other studies that conditioning exercises are efficacious in knee OA and could explain the positive results in all groups.[3] The positive effects of NSAIDS were also supported in this study. This study does not provide evidence that sodium hyaluronate injections are better than NSAIDS or placebo alone for knee OA.

Bottom line

- Sodium hyaluronic injections have no obvious benefit.
- These injections are not known to be harmful, but have not been evaluated long term.
- Sodium hyaluronic injections are expensive, as are the health care costs of administering three injections in 3 weeks.

Points saillants

- Les injections d'hyaluronate de sodium ne présentent aucun bienfait évident.
- Ces injections ne sont pas reconnues pour être néfastes mais elles n'ont pas fait l'objet d'une évaluation à long terme.
- Les injections d'hyaluronate de sodium sont coûteuses, tout comme le sont les coûts des services de santé pour administrer ces trois injections en trois semaines.

References

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