Intra-articular hyaluronic acid for osteoarthritis of the knee

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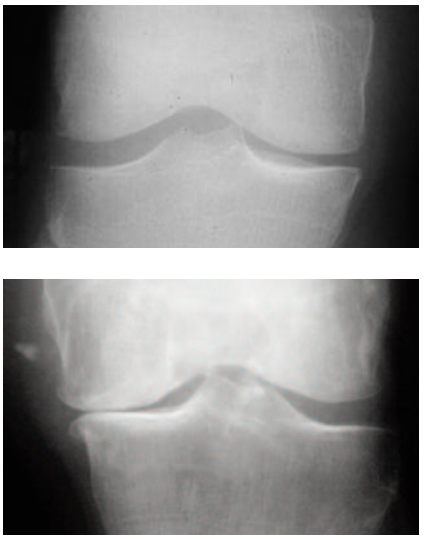
Hyaluronic acid can be a useful therapy for patients with mild to moderate knee osteoarthritis, although its efficacy and mechanism of action are debated. Dr Bagga and Associate Professor March present a guide to current use.



Figures 1a and b. Osteoarthritis of the knee. Hyaluronic acid is indicated for disease of mild to moderate severity (a, top), but is of lesser value in severe disease (b, above).

What is hyaluronic acid?

Hyaluronic acid is a large polysaccharide consisting of D-glucuronic acid and N-acetyl-D-glucosamine residues in an alternating sequence. It is present in high concentrations throughout many tissues but is most abundant in synovial fluid.

Hyaluronic acid is synthesised by specialised synoviocytes in the joints. In healthy adult synovial fluid, it has a concentration in the range of 2.5 to 4 mg/mL and a molecular weight of around 4 to 10 million. At this concentration the molecules overlap extensively and form a highly coiled, tangled network that gives the fluid its elasticity and viscosity. These rheological properties are believed to be important in protecting the cartilage from strong compressive and shear forces.

In osteoarthritic synovial fluid, the concentration and molecular weight of hyaluronic acid are decreased as a result of dilutional effects and impaired synthesis, and the viscosity and elasticity of the fluid are subsequently reduced.[1] It has been postulated that these changes accelerate cartilage damage because the forces on the joint are not mitigated as effectively.

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In the early 1970s, a noninflammatory fraction of hyaluronic acid was extracted and purified from roosters' combs and used to treat equine and subsequently human arthritic joints. The first human study, conducted in 1974, involved 23 osteoarthritic knees and found the injections were well tolerated and that efficacy was maximal when injections were given weekly for three weeks.[2]

Mechanism of action

Studies done in animals and *in vitro* have suggested several potential mechanisms for hyaluronic acid injections, including:

- normalisation of hyaluronic acid synthesis by synoviocytes
- restoration of elastic and viscous properties of synovial fluid
- anti-inflammatory as well as anti-nociceptive effects.

Studies that show these effects in humans, however, are lacking. The mechanism of action of intra-articular hyaluronic acid injections in treating osteoarthritis is currently controversial.

Clinical efficacy

The efficacy of intra-articular hyaluronic acid in treating symptomatic osteoarthritis of the knee has been studied in more than 50 published trials. Approximately half of these trials have been randomised and placebo-controlled and, although of reasonable quality, most were sponsored by industry and some were of small size.

Of these published studies, about one-third reveal no statistically significant benefit for hyaluronic acid and two-thirds report a positive benefit compared with placebo (i.e. injections of normal saline). A review of these has revealed a small but positive effect size when all results are pooled. Subgroup analysis suggests that response rates are higher in those with mild to moderate disease compared to those with end-stage disease (i.e. 'bone on bone' on a standing x-ray of the knee). In fact, response rates tend to be quite low in the latter group, and careful consideration needs to be given to the value of proceeding with this treatment in these individuals. The average duration of pain relief in those who benefit is between six and nine months. In its current guidelines for managing osteoarthritis of the knee, the American College of Rheumatology recommends intra-articular hyaluronic acid as a second line agent for patients who have failed treatment with paracetamol and conventional NSAIDs or COX-2 specific inhibitors.[3]

Several studies have compared intra-articular injections of hyaluronic acid and corticosteroid. The results suggest equal

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efficacy in the short term (up to four weeks), but the duration of benefit was greater (up to three months and beyond) in those who were randomised to hyaluronic acid.

What products are available?

In Australia, the most commonly used preparation is Synvisc, a cross-linked molecule generically known as a hylan. A noncross-linked preparation of sodium hyaluronate with lower molecular weight, Fermathron, is also available (but neither of the authors has experience with the use of this product).

Synvisc

Synvisc is not currently listed on the PBS and must be purchased privately. The price listed in MIMS is $444.50, which covers a course of three pre-packaged injections (2 mL each) to be administered intra-articularly at weekly intervals over a three-week period. Currently Synvisc is approved for injection into the knee, but a clinical trial is underway in the USA to examine the efficacy of injections for osteoarthritis of the hip.

The rationale for using cross-linked molecules is based on their higher intra-articular half-life (about seven days) compared with that of noncross-linked molecules (range, 12 to 48 hours) and the belief that this may lead to production of increased molecular weight hyaluronic acid within the joint.

Fermathron

Fermathron is not currently listed on the PBS but is available on private script. The price listed in MIMS is $97.25, which covers five injections (2 mL each) to be given intra-articularly once weekly for a maximum of five weeks. Fermathron is indicated for symptomatic relief of mild to moderate knee joint osteoarthritis.

Administration

As with arthrocentesis of any joint, it is paramount that injections of hyaluronic acid be administered under sterile conditions in order to minimise the risk of introducing infection. The nature of the solution (a highly viscous, gel-like substance) demands that it be delivered intra-articularly (i.e. not into surrounding soft tissue) so that the risk of an adverse reaction is minimised. It is best attempted only by practitioners who are confident performing arthrocentesis of the knee.

Adverse effects

Adverse events occur in 10 to 15% of patients. These generally involve knee pain and swelling, but large, tense knee effusions occasionally occur. Most patients can be managed with rest, local ice and anti-inflammatory agents. However, it is important to exclude the possibility of infection – the synovial fluid should be aspirated and cultured if any doubt exists.

Systemic reactions are very rare but occasionally occur in patients who have a history of allergy to avian products. For this reason, Synvisc (which is of avian origin) should be avoided in these patients.

Summary

Intra-articular hyaluronic acid is a potentially useful therapy in patients who have mild to moderate osteoarthritis of the knee whose symptoms are not controlled with lifestyle modifications, such as weight loss (for overweight patients) and appropriate exercise, paracetamol and anti-inflammatory agents.

Overall, although evidence for efficacy over placebo injections remains conflicting, there are sufficient data to support a positive effect on pain reduction. Approximately 60% of patients with mild to moderate osteoarthritis of the knee will derive some benefit; however, a reliable way of predicting who will respond is not yet available. MT

Key points for treatment

Who?

Intra-articular injections of hyaluronic acid can be used to treat patients with mild to moderate osteoarthritis of the knee who have failed treatment with:

- appropriate lifestyle modifications, such as weight loss and exercise
- paracetamol, and conventional NSAIDs or COX-2 specific inhibitors
- glucosamine, with or without chondroitin.

The treatment is also worth considering in patients who are not suitable for total knee surgery or want to delay time to surgery. Note, however, that the response rate is low (30%) in those with advanced disease.

Why?

Intra-articular injections of hyaluronic acid have been shown to:

- decrease pain and improve functioning
- improve rheological functioning of joint
- have anti-inflammatory as well as anti-nociceptive actions
- prolong time to total knee replacement (in some patients).

In addition, the treatment may have a role in slowing the progression of knee osteoarthritis.

How?

A course of treatment involves three or five intra-articular injections, depending on the formulation, given once weekly.

References

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