

Intra-Articular Hyaluronic Acid (Viscosupplementation) for Hip Osteoarthritis

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Summary

- ✓ **In viscosupplementation, a glycosaminoglycan called hyaluronic acid (HA) is administered via intra-articular injection to patients with osteoarthritis (OA).**
- ✓ **Two systematic reviews found that HA for hip OA may relieve pain and improve function. Randomized controlled trials had differing results. Uncontrolled studies suggest that there are moderate improvements regarding pain and function for three to six months after HA injection.**
- ✓ **There is no evidence regarding the cost-effectiveness of this therapy.**
- ✓ **No serious adverse events have been reported after intra-articular injection of HA for hip OA.**
- ✓ **The best available evidence suggests that HA may offer symptomatic relief in patients with mild to moderate hip OA for whom other conservative therapies are contraindicated or have failed. Currently, there is insufficient good quality evidence to determine this conclusively.**

The Technology

Hyaluronic acid or hyaluronan (HA) is a glycosaminoglycan (GAG) composed of glucuronic acid and glucosamine in a polysaccharide of varying lengths and molecular weights. At high molecular weights, HA is viscoelastic, aiding weight-bearing joints in lubrication, shock absorption, and fluid retention during movement.¹ The mechanism of action is poorly understood, but the effects may be due to regulation of cartilage synthesis, inhibition of inflammatory cytokines and nociception (the ability to feel pain), and stimulation of natural HA synthesis. These effects may depend on the molecular weight of the HA product.¹ This bulletin focuses on the evidence regarding its use for hip osteoarthritis (OA) and complements an earlier bulletin on HA for knee OA.²

Regulatory Status

In Canada, the first HA products for osteoarthritis were licensed in 1999, and several are available. Some are

licensed for use only in specific joints, such as the knee. Other HA products have broader Health Canada licensing that covers use in the knee and other synovial joints, such as the hip. These agents include Durolane[®] (Q-Med AB), Hyalgan[®] (Fidia Farmaceutici SpA), NeoVisc[®] (Stellar Pharmaceuticals), Orthovisc[®] (Anika Therapeutics, Inc.), Ostenil[®] (TRB Chemedica), Suplasyn[®] (Bioniche Teoranta), and Synvisc[®] (also known as Hylan G-F 20, Genzyme Corporation).³ These products are regulated by Health Canada as class III or class IV medical devices, and sold as pre-filled single-use 2 mL (3 mL for Durolane) syringes.³ HA products are divided into low [0.5 to 2.0 megadaltons (MDa)] and high (6 to 7 MDa) molecular weights; Durolane, Orthovisc, and Synvisc are generally considered to be of higher molecular weights.⁴

Patient Group

OA is the most common joint disorder in the world. Hip OA, which is second to knee OA in prevalence throughout North America and western Europe, is estimated to affect 3% to 11% of adults >35 years old, 7% to 25% of white European adults >55 years old, and 10% to 15% of adults >70 years old.⁵⁻⁷ The risk factors that may increase the likelihood of developing hip OA include obesity; excessive or repetitive physical activity; altered walking biomechanics secondary to trauma, injury, or other causes; and hip dysplasia.⁵ Although the pathogenesis of OA is incompletely understood, cartilage degradation is a hallmark of the disease.⁸ Cartilage changes may be related to the loss of synovial fluid viscoelasticity, possibly due to decreased concentrations and molecular weights of HA.⁷

Hip OA is often symptomatic, marked by a gradual development of pain, stiffness, and decreased function, which can restrict the activities of daily living and impair quality of life.^{8,9} Although the severity of hip OA varies, most patients will eventually need total joint arthroplasty (hip replacement) for symptomatic and functional relief.¹⁰ The radiological findings include joint space narrowing, osteophyte formation, and subchondral sclerosis, although such findings may not correlate with the self-reported outcome measures of disease progression.¹¹

Current Practice

Many therapies are available for the symptomatic relief of hip OA. These include non-pharmacological (education,

exercise, walking aids, complementary therapies, weight loss), pharmacological [non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX-2) inhibitors, acetaminophen, opioids, and other analgesics], injection (corticosteroid and HA), and surgical (osteotomy and total joint arthroplasty) approaches.⁵ Evidence-based clinical practice guidelines for the management of hip OA recommend a combination of treatments based on hip risk factors, general risk factors, level of pain intensity, disability and handicap, location and degree of structural damage, and patients' preferences.⁵ The preferred approach is to start treatment with acetaminophen and progress to NSAIDs or COX-2 inhibitors, opioids, guided intra-articular (IA) corticosteroids, osteotomy or other joint-preserving surgeries, and total joint arthroplasty in those with refractory pain or disability. The degree of adherence to these clinical practice guidelines in Canada is unknown.

The Evidence

Clinical studies that have examined the efficacy of HA products for hip OA include two systematic reviews,^{17,18} two randomized controlled trials (RCTs),^{12,13} and several uncontrolled trials.^{7-9,14-16,19,20} Two studies were funded by manufacturers,^{6,7} and one by research foundations.¹² Other studies did not report the funding sources.

A systematic review of viscosupplementation with HA or its derivatives for patients with hip OA uncovered nine studies with a total of 287 participants (including six studies^{6,7,13-16} that are discussed in this bulletin).¹⁷ Five studies with 141 participants treated with one to three injections of Synvisc reported an overall success rate of approximately 50% after three to 12 months. One study of 31 participants each treated with one Durolane injection reported improvements in pain (59%) and disability (47%) after three months. One study of 44 participants each treated with three to five low molecular weight HA injections (product name unspecified) reported that 68% experienced effective pain relief after six months. One trial of 28 participants each treated with one to three Hyalgan injections reported a 28% improvement in VAS (visual analogue score) pain and 48% reduction in NSAID use. The only RCT¹³ reported improvements in pain and disability with low (Ostenil) and high (Synvisc) molecular weight HA products, and no difference in efficacy between the two products. The systematic review concluded that although available evidence suggests the therapy may be effective, there is insufficient evidence to determine this conclusively.

A second systematic review of HA for patients with hip OA identified eight studies with >20 participants and a follow-up >1 week (including six studies^{6,7,12-14,16} and a systematic review).^{17,18} The uncontrolled studies reported improvements in pain (43% to 84%), and in the Western Ontario and McMaster (WOMAC)/Lequesne indices (28% to 59%). The latter are commonly used, validated OA outcome measures. Two of the five studies included additional therapies. One

RCT¹³ compared HA products of different molecular weights, and reported significant improvement in pain and disability with no differences between the two HA groups. One RCT¹² compared HA to corticosteroids and placebo, and reported a higher proportion of respondents in the HA and corticosteroid groups after 14 and 28 days (p values not reported). The review reported that conclusive results regarding the efficacy of HA for hip OA could not be obtained without placebo-controlled studies. The review concluded that although evidence suggests that HA may improve pain and function in hip OA, its use should be restricted to patients in whom other treatments have failed, given the weakness of the available evidence.

In one RCT, 104 participants with hip OA received three weekly IA injections of Hyalgan (n=34), one corticosteroid followed by two placebos (n=34), or saline (n=36).¹² The primary outcome was VAS pain on walking after 14 days, 28 days, and 90 days. In the Hyalgan group, VAS pain on walking was 49.2±24.8 (mean±SD) at baseline, with mean [95% confidence interval (CI)] improvements of -10 (-18 to -2) after 14 days, -11 (-19 to -3) after 28 days, and -11 (-19 to -3) after 90 days. In the corticosteroid group, these values were 44.0±19.7, -12 (-20 to -4), -15 (-23 to -7), and -9 (-16 to -1). In the saline group, they were 42.4±19.7, 2 (-5 to 9), -1 (-8 to 7), and -5 (-13 to 2). The effect size for corticosteroid versus saline was 0.6 (95% CI 0.1 to 1.1) and 0.4 (95% CI -0.1 to 0.9) for HA versus saline. The effect size was not provided for HA versus corticosteroid. The peak effect was noted after 14 days. There were no significant inter-group differences in any outcomes after 90 days (Hyalgan versus saline p=0.57, Hyalgan versus corticosteroid p>0.21, corticosteroid versus saline p=0.58).

The second RCT compared the efficacy of three weekly injections of Ostenil (n=25) or Synvisc (n=18) in 43 participants with hip OA. Thirteen participants had bilateral OA, for a total of 56 hips (Ostenil=32, Synvisc=24).¹³ The primary outcomes were VAS pain, WOMAC index, and Lequesne index measured after one, three, and six months. The VAS pain (mean±SD) for Ostenil versus Synvisc groups at baseline, one month, three months, and six months was 7.2±1.5 versus 6.7±1.7, 4.1±2.6 versus 4.4±2.3, 4.6±2.5 versus 4.7±2.7, and 4.6±2.5 versus 3.4±3.0. This is an improvement of 38% versus 40% from baseline to six months. The Lequesne index (mean±SD) for the Ostenil and Synvisc groups at baseline, one month, three months, and six months was 11.4±4.6 versus 11.8±3.3, 5.9±4.8 versus 7.1±4.5, 6.2±4.8 versus 6.3±4.3, and 6.2±5.8 versus 5.9±5.4. This is an improvement of 43% versus 40% from baseline to six months. The WOMAC index (mean±SD) for the Ostenil and Synvisc groups at baseline, one month, three months, and six months was 63.9±21.3 versus 57.2±16.7, 37.1±28.4 versus 35.6±19.5, 43.6±31.4 versus 39.4±27.9, and 38.7±30.3 versus 32.5±23.0. This is an improvement of 47% versus 49% from baseline to six months. Although all intra-group differences in primary

outcomes were statistically significant ($p < 0.05$) compared to baseline, there were no significant inter-group differences at any points in the follow-up ($p = 0.18$ to 0.96).

Smaller open-label trials of 10 to 57 participants, without a control group, generally reported moderate improvements in pain and function after treatment with Durolane,⁶ Ostenil,^{19,20} or Synvisc.^{7-9,14-16} All studies measured pain (VAS or numerical pain rating scale) or disability (WOMAC, Lequesne, or American Academy of Orthopaedic Surgeons Lower Limb Core Scale). Four trials also measured analgesic use.^{8,9,14,15} The follow-up periods varied from three months^{7,9,15} to six months.^{6,8,14,19} One study had a follow-up of one year.¹⁶ Because there was no control group and no random allocation, these results must be interpreted with caution, with greater weight placed on the evidence from systematic reviews and RCTs.

Most of the clinical efficacy studies included patients with mild to moderate hip OA based on the Kellgren-Lawrence (KL) radiographic assessment scale. Of the eight studies using KL to determine eligibility, six specified a maximum of grade 3 (moderate).^{6-8,13-15} Two included patients with a maximum of grade 4 (severe).^{9,12}

Adverse Effects

The systematic review by Conrozier *et al.* concluded that HA appeared safe and well tolerated, with more transient pain at the injection site reported with Durolane.¹⁷ The systematic review by Fernández López *et al.* concluded that none of the clinical studies reported any adverse events other than local pain, which may occur more often with higher molecular weight HA products.¹⁸ Additional uncontrolled studies reported minor adverse events, most commonly, transient local pain.^{6-9,12-16,19} No evidence was identified regarding the long-term safety of HA products for hip OA.

Administration and Cost

The administration schedules recommended by the manufacturers vary from one injection (Durolane), three to five weekly injections (Hyalgan), three to five weekly injections repeated every six to eight months if necessary (NeoVisc), three weekly injections (Orthovisc, Ostenil), three to six weekly injections (Suplasyn) for chronic conditions, and one injection followed by a second injection one to three months later if there is no symptomatic relief (Synvisc). The manufacturers of NeoVisc, Suplasyn, and Synvisc recommend arthrocentesis (aspiration of joint fluid through a needle and syringe) before injections.

HA products cost approximately C\$100 to C\$400 per vial. The costs vary from C\$300 to C\$600 per course of treatment, depending on the recommended administration schedule (i.e., one to six injections). This cost increases with a repeated

course of injections. These devices are not covered by public health insurance in Canada, although general physician fee codes and radiologic procedure codes are used for the IA injections. IA knee injection is simple compared to IA hip injection, which carries the risk of damage to the femoral neurovascular bundle.¹⁹ Radiological guidance using fluoroscopy, computed tomography, or ultrasound is recommended, adding to the cost of the procedure. Because the effects of HA tend to be short-lived, treatment may be repeated despite a lack of evidence about the efficacy of multiple courses of HA. No evidence was uncovered related to the cost-effectiveness of HA for hip OA.

Concurrent Developments

Other HA products that are available in Canada include Euflexxa[™] and Supartz[®]. Although these products are approved exclusively for knee OA, manufacturers could expand their indications by sponsoring more research. The manufacturers of other HA products that are approved in the US and elsewhere may also seek regulatory approval in Canada for hip OA. Medical devices that are intended for use in partial hip replacement are being tested in clinical studies to assess their effectiveness as less invasive and less costly alternatives to total hip replacement.

Rate of Technology Diffusion

The rate of technology diffusion of HA for hip OA has been low, relative to knee OA, possibly because of insufficient supporting evidence. The HA products that are sold in Canada may face additional competition from other products sold internationally if regulatory approval for these other products is sought in Canada. Such market saturation could lead to more visibility for all HA products from the increased marketing aimed at patients and physicians. Increased competition could lead to additional comparative clinical trials as manufacturers try to distinguish their products through dosage (i.e., one versus three to five injections), repeatability of treatment, duration of effect, or safety. Such research could improve the quality of evidence supporting the use of these products and lead to greater acceptance. The increased prevalence of hip OA in an aging population may accelerate the uptake of the technology.⁶

Implementation Issues

Based on the available evidence, HA seems to be most appropriate in patients with hip OA for whom other therapies are contraindicated or were unsuccessful. The evidence in this bulletin applies mainly to patients with mild to moderate hip OA. Although these criteria may restrict the number of eligible patients, demand may be strong. The repeated office visits required for HA injection will increase the demand for services from primary care physicians, rheumatologists, physiatrists, orthopedists, and others specializing in rheumatic

disease. This will also likely increase the demand for other related medical and diagnostic services such as radiological and laboratory testing.

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Dr. Goldsmith has been a paid consultant for Genzyme Pharmaceuticals, helping to conduct a Canada-wide study on Synvisc in knee OA patients. He has presented the findings from that study for honoraria from Genzyme Corporation and helped I3-Innovus prepare reports on the study. Dr. Goldsmith also helped to develop WOMAC.

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