Viscosupplementation: Therapeutic Mechanisms and Clinical Potential in Osteoarthritis of the Knee

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Abstract

Viscosupplementation by means of intra-articular injections of hyaluronic acid has been used to treat osteoarthritis of the knee. The proposed mechanisms of action result from the physical properties of hyaluronic acid, as well as from its anti-inflammatory, anabolic, local analgesic, and chrondroprotective effects. Adverse reactions from hyaluronic acid injections into the knee occurred in 8.3% of the 336 patients treated in one study, but at a rate of less than 3% per injection. Reactions were almost always local and generally resolved over 1 to 2 days. Hyaluronic acid injections were approved by the US Food and Drug Administration as a medical device; thus, the level of efficacy demonstrated is less than might have been required for approval as a drug. Several studies have failed to show statistically significant benefit compared with placebo. Furthermore, the treatment is relatively expensive; the cost of the drug for a series of injections is more than $500 per knee. Therefore, widespread use of these agents should be limited until more convincing data on their efficacy are available from well-designed clinical trials.

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Osteoarthritis, the most common form of arthritis, can be a major cause of disability. Medical management of osteoarthritis of the knee with analgesics is effective for many patients, but morbidity is common for those utilizing nonsteroidal anti-inflammatory drugs (NSAIDs). The economic burden of NSAID-associated acute gastrointestinal disorders is enormous, with an estimated excess medical care cost of $500 million.[1] Surgical treatment of osteoarthritis of the hip or knee is effective, but is not appropriate for all stages of the disease or for all patients. It is also costly and not without risk. With increased understanding of the pathogenesis of osteoarthritis, new therapies are being developed, one of which is viscosupplementation with hyaluronic acid.

Properties of Hyaluronic Acid

Hyaluronic acid is a polysaccharide chain made of repeating disaccharide units of *N*-acetylglucosamine and glucuronic acid. Type B synoviocytes or fibroblasts synthesize hyaluronic acid and secrete it into the joint space.[2] Most articular hyaluronic acid is made of approximately 12,500 disaccharide units, giving a molecular weight of approximately 5×10^6 daltons (d). The healthy human knee contains about 2 mL of synovial fluid, with a hyaluronic acid concentration of 2.5 to 4.0 mg/mL. In osteoarthritis of the knee, the concentration of hyaluronic acid is reduced to one half to one third of the normal value. The molecular size of the hyaluronic acid is also reduced, and there is decreased interaction between the hyaluronic acid molecules. This results in much lower dynamic viscous and elastic properties of the synovial fluid and reduced barrier and filter effects (Table 1). The loss of lubrication causes increased stress forces, which further disrupt the collagen network that is essential to the integrity of the articular surface. The loss of barrier integrity influences nutrient availability and waste removal from articular cartilage.

Viscosupplementation with hyaluronic acid may benefit patients

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Table 1
Rheologic Properties of Normal and Osteoarthritic Knee Synovial Fluid*

Rheologic Variable	Healthy Knee	Osteoarthritic Knee
Hyaluronic acid concentration, mg/mL	2.5-4	1-2
Dynamic elastic storage modulus at 2.5 Hz, Pa	23	8
Dynamic viscous modulus at 2.5 Hz, Pa	7	5

* Adapted with permission from Balazs EA, Denlinger JL: Viscosupplementation: A new concept in the treatment of osteoarthritis. *J Rheumatol* 1993;20(suppl 39):3-9.

with osteoarthritis by several different mechanisms of action. These include its anti-inflammatory, anabolic, analgesic, and chondroprotective effects, in addition to its effect on the viscosity and elasticity of synovial fluid.

Physical Properties

Hyaluronic acid has both viscous and elastic properties, and the degree to which either predominates depends on the amount of shear force applied.[3] At high shear forces, hyaluronic acid molecules exhibit increased elastic properties and reduced viscosity; at low shear forces, the opposite is seen. (Elasticity is the ability of a molecular structure to store mechanical energy; viscosity is the ability to dissipate mechanical energy as heat during low shear stresses.) Hyaluronic acid gives synovial fluid a "pseudoplastic" property, being a shock absorber during fast movements and an effective lubricant during slower movements.

The intra-articular kinetics of hyaluronic acid argue against considering the physical effects of replacing the depolymerized hyaluronic acid of an arthritic knee to be the major explanation for the benefits of viscosupplementation. Direct evaluation of hyaluronic acid kinetics within the synovium is difficult. An assay has been developed in sheep models to measure the half-life of hyaluronic acid injected into both healthy joints and joints with collagen-induced arthritis.[4] In sheep, the mean intrasynovial half-life of [^{3}H]acetyl-labeled hyaluronic acid in normal joints was 20.8 hours, compared with 11.5 hours in acutely inflamed joints. Applying these figures as a rough guide to the kinetics in the human osteoarthritic joint, the mechanism of action of viscosupplementation must be more than the simple replenishment of degraded hyaluronic acid.

Anti-inflammatory Effects

Hyaluronic acid has both in vivo and in vitro effects on leukocyte function. These include inhibition of phagocytosis,[5] adherence, and mitogen-induced stimulation.[6] Of interest is that these properties are dependent on the molecular size of hyaluronic acid.[7] However, the effect of the molecular size of hyaluronic acid is probably not related to a physical exclusion or entrapment role, as hyaluronic acid molecules of both high and low molecular weight do not alter other leukocyte functions, such as the formation of oxygen-derived free radicals on exposure to serum-opsonized zymosan.[8] Tamoto et al[8] have theorized that hyaluronic acid is involved in leukocyte signal transduction via cell-surface receptors, which are dependent on the size of the hyaluronic acid molecule.

Intra-articular administration of hyaluronic acid reduces the levels of inflammatory mediators, including prostaglandin and cyclic adenosine monophosphate, in the synovial fluid of patients with arthritis.[9] In vitro evidence has also shown that hyaluronic acid can affect the release of arachidonic acid from human synovial fibroblasts.[10] This property is dependent on both dose and molecular weight. Extracellular arachidonic acid is normally taken up by synovial leukocytes and converted to inflammatory mediators, including prostaglandins and leukotrienes.

Anabolic Effects

Intra-articular injection of hyaluronic acid may affect the synthesis of hyaluronic acid by stimulating synovial fibroblasts. Osteoarthritic joints produce hyaluronic acid at a lower rate than normal joints. In a study by Smith and Ghosh,[11] the effects of several commercially available hyaluronate products were examined for their ability to stimulate hyaluronic acid production in the joints of patients with osteoarthritis. Both the concentration and the molecular weight of these products were shown to be important in stimulating de novo hyaluronic acid production. A molecular weight greater than 5×10^5 d was most effective. Other authors have noted similar findings but have also reported that a very high extracellular concentration of hyaluronic acid can have inhibitory effects on synovial fibroblasts.

Analgesic Activity

The anti-inflammatory effects of hyaluronic acid within the synovium may partially explain some of the analgesic properties. A direct analgesic effect was shown by Ghosh[7] in a rat model. In that study, hyaluronic acid was found to be equivalent to indomethacin in reducing pain arising from the intra-articular

administration of bradykinin. The author concluded that intra-articular hyaluronic acid modulates pain perception directly through inhibition of nociceptors or indirectly through binding of substance P (a small peptide involved in the transmission of pain signals).

Chondroprotective Potential

In animal models, hyaluronic acid has been shown to possess a disease-modifying chondroprotective potential. In a canine model of osteoarthritis induced by anterior cruciate ligament transection, an increase in cartilage matrix production, including hyaluronic acid, was seen.[12] The significance of this phase of "hypertrophic repair" is unknown, but it may play a role in the pathogenesis of osteoarthritis. Intra-articular injection of hyaluronic acid reduced this phenomenon early on in another study in which the same canine model was used.[13] However, by 12 weeks there were no histologic differences between treated and nontreated control osteoarthritic synovium. In a sheep model of osteoarthritis induced by medial or lateral meniscectomy, five weekly injections of high-molecular-weight (2×10^6 d) hyaluronic acid improved gait but did not prevent progression of osteophyte formation and cartilage lesions.[14] Thus, the chondroprotective effect of hyaluronic acid is, at best, unproved.

Hyaluronic Acid Viscosupplements

The use of hyaluronic acid for medical purposes was pioneered in the late 1960s by Biotrics, Inc (Arlington, Mass). The source material was human umbilical cord and rooster comb hyaluronic acid, which could be purified into inflammatory and noninflammatory fractions by using the quantitative monkey vitreous test, a highly sensitive test of the inflammatory inciting nature of a substance. In a canine model of cartilage damage, the noninflammatory fraction of sodium hyaluronate was demonstrated to reduce the synovial inflammatory reaction and capsular pain resulting from injury.[15] Sodium hyaluronate was marketed for use in traumatic joint injury in racehorses under the trade name Hyalartil-Vet.

Recent advances have targeted several properties that a substance must display to be of use as a viscosupplement. These include (1) lack of immunogenicity; (2) the capability of allowing passive diffusion within the synovial fluid; (3) native rheologic properties; and (4) a prolonged half-life within the synovium.

In the United States, two viscosupplements, Synvisc (Biomatrix, Ridgeford, NJ) and Hyalgan (Sanofi, New York, NY), are currently approved for use in patients with osteoarthritis of the knee (Table 2). In Canada, Orthovisc (Anika Therapeutics, Woburn, Mass) is also available for this indication. These products are derived from rooster combs through a purification process that isolates the noninflammatory hyaluronan component. Neovisc (Stellar International, London, Ontario, Canada), another hyaluronic acid product available in Canada, is manufactured from bacterial culture. This product may be useful in patients with poultry allergy and those who are strict vegans.

Viscosupplements are considered medical devices rather than pharmaceutical agents by the US Food and Drug Administration and the equivalent agency in Canada. Thus, the stringent requirements for approval of a drug have not been applied to viscosupplements.

The molecular weight of physiologic hyaluronic acid in the human synovium is approximately 4 to 5 $\times 10^6$ d. The molecular weight of the hyaluronic acid used affects several properties related to its proposed mechanism of action. To increase the molecular weight of

Table 2
Commercially Available Viscosupplements

Proprietary Name	Molecular Weight $\times 10^5$ d	Hyaluronic Acid Concentration, mg/mL	Manufacturer	Treatment Regimen
Synvisc Hylan G-F 20	60 (cross-linked)	8	Biomatrix, Ridgeford, NJ	Weekly ×3
Artzal	6-12	10	Seikagaku-Kaken, Japan	Weekly ×≤10
Hyalgan	5-7.3	10	Sanofi, New York, NY	Weekly ×≤6
Orthovisc	>10	15	Anika Therapeutics, Woburn, Mass	Weekly ×3
Neovisc	5-7.3	10	Stellar International, London, Ontario, Canada	Weekly ×3

the viscosupplement, a process of cross-linking hyaluronan molecules by means of terminal hydroxyl groups has been developed. These polymers are referred to as hylans. The theoretical, but unproven, benefits of this molecule are enhancement of viscoelastic properties and a prolonged residence time within the joint space.[16] Synvisc is the only cross-linked viscosupplement available in North America.

Viscosupplements are not inexpensive. According to the manufacturers, at the time of this writing the suggested non-Medicare prices for three weekly syringes of Synvisc and five weekly syringes of Hyalgan were $517.55 and $661.00, respectively.

Clinical Safety

Although hyaluronic acid preparations have been used to treat osteoarthritis in human knees for 20 years, most of the experience has been much more recent. The overall incidence of side effects is approximately 1% per injection.[17] The most common are local reactions in the treated knee, consisting of pain, warmth, and minimal local swelling. Reactions normally last no more than 1 to 2 days. However, in one small retrospective series, clinically significant local inflammatory reactions were noted in 27% of the 22 patients (11% of injections).[18]

In a large review of viscosupplementation with Hylan G-F (gelfluid) 20 in Canada, local reactions occurred after 42 (2.7%) of 1,537 injections and occurred in 28 (8.3%) of 336 patients overall.[19] Of the 42 reactions, 33 (79%) resolved without sequelae. Five patients had a total of nine reactions with sequelae, including residual swelling and intermittent pain. Interestingly, the rate of adverse events per injection was highest (5.2%) when the medial approach was taken in a partially flexed knee. No systemic adverse effects were reported.

Clinical Efficacy

The efficacy of hyaluronic acid preparations has been evaluated in a number of studies (Tables 3 and 4).

In 1974, Peyron and Balazs[20] published the first clinical trial of intra-articular hyaluronic acid for the treatment of arthritis in humans. Fourteen patients were randomized to placebo or treatment groups. In a 4-month follow-up period, more patients in the treatment group reported some improvement in joint symptoms. Subsequently, there have been numerous uncontrolled trials and a limited number of controlled trials of intra-articular hyaluronic acid. Most of the trials of injected hyaluronic acid have been for the treatment of osteoarthritis of the knee.

The usual requirements for a drug to be approved by the Food and Drug Administration include the demonstration of statistically significant efficacy compared with placebo in two or more well-conducted randomized trials. Study designs to assess the efficacy of hyaluronic acid in the treatment of osteoarthritis of the knee have included the usual outcome measures, such as scales of pain and function and global assessment by patient and physician. Several studies also assessed patient outcomes by using validated, disease-specific instruments, including the Lequesne Index[21] and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[22] The Lysholm Scale used in the trial by Dahlberg et al[23] is not specific to osteoarthritis, but is rather a scale used in evaluation of knee ligament injuries.[24] Similarly, the Larson Scale used as an outcome measure in the trial by Graf et al[25] is not disease-specific, having been developed for grading a variety of knee disorders.[26] Unfortunately, the placebo-controlled randomized trials of hyaluronic acid have produced conflicting results (Table 3).

In an early trial, Dixon et al[34] found that up to 11 injections of hyaluronic acid per patient over a 23-week period produced statistically significant ($P<0.01$) improvement in knee pain at rest but no improvement in two very relevant outcomes, activities of daily living and pain on movement. In a single-blind study of Hyalgan, Dougados et al[33] found that hyaluronic acid was significantly better ($P = 0.03$) than placebo for pain relief and for improvement of the Lequesne functional index; the treatment group also had a significantly ($P = 0.03$) reduced need for local supplemental treatment at 1 year. A double-blind study by Henderson et al[31] found no significant benefits with Hyalgan for more than a dozen outcomes. However, in a large double-blind trial of Hyalgan, Altman et al[35] found a significant ($P<0.005$) benefit compared with placebo for the primary outcome in an efficacy analysis (i.e., analysis of data on only those patients who completed the study) but not the more demanding "intention to treat" analysis (i.e., analysis of data on all the patients who were randomized). In the efficacy analysis, a secondary outcome, the WOMAC measure of pain and disability, showed statistically significant improvement ($P = 0.041$).

A study of Artzal showed absolutely no benefit of hyaluronic acid over placebo in the primary analysis.[28] A post hoc analysis of subjects over age 60 with Lequesne scores greater than 10 showed significant ($P<0.05$) improvement for some outcomes. Post hoc analyses require confirmation by another study.

A study of Hylan G-F 20 by Adams et al[29] was designed to compare this hyaluronic acid preparation with active treatment. However, there was a flaw in the design (acknowledged by the authors of the report) that limited the conclusions that could be drawn. Nonetheless, two arms of the trial remained blinded. In these two arms, patients receiving

Table 3
Randomized Trials Evaluating Hyaluronic Acid vs Placebo in Treatment of Osteoarthritis of the Knee*

Study	Active Treatment	No. of Patients	Patient Characteristics	Study Design	Outcome Measures	Results Favoring Hyaluronate
Wobig et al,[27] 1998	Hylan G-F 20, 3 injections	110	Mean age, 62 yr; K-L, 1-3; VAS Pain, >70	Multicenter, double-blind, 12 wk, 26-wk phone follow-up	VAS Pain and Function	VAS Pain and Function
Lohmander et al,[28] 1996	Artzal, 5 injections	240	Mean age, 58 yr; Lequesne Index ≥4	Multicenter, double-blind, 20 wk	VAS Pain, Activity Level, Lequesne Index	None
Adams et al,[29] 1995	Hylan G-F 20, 3 injections	102	Mean age, 61 yr; K-L, 1-3; VAS Pain, >50	Multicenter, double-blind, 12 wk, 26-wk phone follow-up	VAS Pain, MD Global	None
Scale et al,[30] 1994	Hylan G-F 20, 2 vs 3 injections	80	Mean age, 59 yr; Larson score, 2-4; VAS Pain, >40	Single center, double-blind, 12 wk, 26-wk phone follow-up	VAS Pain and Function, Pt/MD Global	VAS Pain and Function, Pt/MD Global
Dahlberg et al,[23] 1994	Hyaluronic acid, 5 injections	52	Mean age, 45 yr; normal x-ray; arthroscopic evidence of osteoarthritis; VAS Pain, >40	Single center, double-blind, 52 wk	Knee function, VAS Pain, ROM, Activity Level, Lysholm Scale	None
Henderson et al,[31] 1994	Hyalgan 5 injections	84	Mean age, 67 yr; VAS Pain, >30	Single center, double-blind, 20 wk	VAS Pain, RRM, Function	RRM (one subgroup)
Puhl et al,[32] 1993	Hyaluronic acid, 5 injections	195	Mean age, 61 yr; VAS Pain, >50	Multicenter, double-blind, 14 wk, 18-wk phone follow-up	Lequesne Index, RRM, VAS Pain, Pt/MD Global	Lequesne Index, VAS Pain
Dougados et al,[33] 1993	Hyalgan 4 injections	110	Mean age, 68 yr; VAS Pain, >40	Multicenter, single-blind, 52 wk	VAS Pain, Lequesne Index	VAS Pain, Lequesne Index
Dixon et al,[34] 1988	Hyaluronic acid, up to 11 injections	63	Mean age, 69 yr	Multicenter, double-blind, 25 wk	VAS Pain, ADL assessment	VAS Rest and Pain

* Abbreviations: ADL = activities of daily living; K-L = Kellegren-Lawrence (or equivalent) radiographic grade (1 = minimal or no changes; 2 = questionable formation of osteophytes or joint-space narrowing; 3 = osteophytosis and joint-space narrowing; 4 = end stage, with bone-to-bone interface); ROM = range of motion; RRM = Return to Rescue Medication (NSAID or analgesia); VAS = Visual Analog Scale (×100).

NSAIDs were randomized to three knee injections of Hylan G-F 20 or placebo. There were no statistically significant benefits of Hylan G-F 20 injections.

In another study of Hylan G-F 20 in which NSAIDs were discontinued, Wobig et al[27] demonstrated that hyaluronic acid was significantly ($P<0.01$) more effective than placebo. In a 12-week study with 26-week telephone follow-up, Scale et al[30] demonstrated significant ($P<0.05$) improvement in pain, activity, and global assessment

Table 4
Randomized Trials Comparing Hyaluronate Supplement vs Other Modalities in Treatment of Knee Osteoarthritis*

Study	Treatment	No. of Patients	Patient Characteristics	Study Design	Outcome Measures	Results
Altman et al,[35] 1998	Hyalgan vs placebo vs naproxen, 500 mg twice daily	333	Mean age, 63 yr; K-L, 2-3; VAS Pain, >20	Multicenter, double-blind, 26 wk	50-ft walk pain time, WOMAC, MD/Pt Global, RRM	Equal efficacy
Jones et al,[36] 1995	Hyaluronan supplement vs IA steroid	63	Mean age, 71 yr; VAS Pain, >30	Single center, double-blind, 26 wk	VAS Pain, Inflammation	Equal efficacy
Graf et al,[25] 1993	Hyaluronan supplement vs IA MPA	60	Mean age, 55 yr; K-L, >1	Single center, single-blind, 26 wk	Larson score, MD Global	Larson score and MD Global favor hyaluronate supplement
Leardini et al,[37] 1991	Hyalgan vs IA steroid	40	Mean age, 65 yr; K-L, 2-4; VAS Pain	Single center, open label, 8 wk	VAS Pain, NSAID/analgesic intake, MD/Pt Global	VAS Pain favors hyaluronate supplement

* Abbreviations: IA = intra-articular; K-L = Kellegren-Lawrence (or equivalent) radiographic grade (see Table 3); MPA = mucopolysaccharide polysulfuric acid ester; RRM = Return to Rescue Medication (NSAID or analgesia); VAS = Visual Analog Scale (×100).

with Hylan G-F 20. This trial also compared the usual three-injection regimen with a two-injection treatment and found significant improvement favoring the former. A 52-week trial of hyaluronic acid in patients with normal knee radiographs but clinically significant knee pain and arthroscopically demonstrated early osteoarthritis showed no clinical benefit compared with placebo.[23]

Hyaluronic acid has also been compared with other active agents (Table 4). In a single-blind study, Graf et al[25] compared seven injections of hyaluronic acid with 13 injections of mucopolysaccharide polysulfuric acid ester. There was significantly ($P<0.05$) greater improvement in the Larson index (mainly due to improvement in pain) in the hyaluronic acid group at 6 weeks but not at 6 months. In another study, Jones et al[36] demonstrated that intra-articular corticosteroids and hyaluronic acid were of similar efficacy. In a smaller open-label trial, Leardini et al[37] demonstrated the superiority of hyaluronic acid over intra-articular corticosteroids in a study with a short follow-up period of 8 weeks. In the study by Altman et al,[35] an additional study arm permitted comparison of Hyalgan with naproxen, 500 mg twice daily, and found no difference in the primary outcome, suggesting that naproxen and hyaluronic acid are of similar efficacy.

Summary

At a direct cost of more than $500 for the treatment of one knee, hyaluronic acid is not an inexpensive therapeutic regimen. However, the lack of systemic side effects and the potential lasting effects make it an appealing option. The US Food and Drug Administration approval of hyaluronic acid as a device has avoided the need for meeting the more stringent criteria for approval as a drug. Perhaps as a result, the evidence to date for the efficacy for hyaluronic acid is imperfect. Unfortunately, cost-effectiveness data are also lacking.

More scientifically rigorous evidence is needed before viscosupplementation with hyaluronic acid can be generally accepted as an effective treatment for osteoarthritis of the knee. This will require multicenter, randomized, placebo-controlled trials with blinding of both patient and investigator to treatment, as well as intention-to-treat analyses. For clinicians, it is not sufficient for outcomes to achieve statistical significance; it is more important that they be clinically relevant. Such trials are currently under way in North America, with results expected next year.

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