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Use of Viscosupplementation for Knee Osteoarthritis: An Update

Jon G. Divine, MD, MS, FACSM and Michael D. Shaffer, DO

Abstract

Because of the rising numbers of patients affected by osteoarthritis (OA), management decisions on how to minimize pain and improve function in OA patients are important. Intra-articular hyaluronic acid (IAHA) knee injections have become a common treatment in the management of knee OA. In an editorial appearing in the 2007 National Knowledge Week on Osteoarthritis: National Health Service Evidence, four questions were asked about the clinical use of IAHA treatment for OA: 1) Who is the ideal candidate for HA viscosupplementation? 2) Do the mechanical and biological effects differ in importance in different stages of the disease? 3) What is the ideal dose in early- and late-stage OA? 4) Can the biological effect be delivered by means other than injection? These key issues are addressed. On the basis of results from several systemic reviews and metaanalyses, we conclude that IAHA knee injections in patients with knee OA result in modest improvements when measured by validated outcomes.

Introduction

General Osteoarthritis Statistics

Osteoarthritis (OA), or degenerative joint disease, represents a large and growing public health problem in the United States. In the United States, OA is second only to ischemic heart disease as a cause of work disability in men older than 50 years (29). OA continues to be a common cause of disability, as well as a significant financial burden, with costs totaling U.S. \$128 billion annually (48). An estimated 45.8 million adults reported having doctor-diagnosed arthritis in 2003. Current projections suggest an increase from 47.8 million in 2005 to nearly 67 million by 2030 (25). Because of the obesity epidemic, these numbers may become substantially higher. Mokdad *et al.* (37) reported that compared with adults with normal weight, adults with a body mass index of 40 kg·m⁻² or higher had an odds ratio of 4.41

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for arthritis. As the number of older Americans increases, there will be an even greater focus on addressing the overall health and economic impact of OA on the public.

General Description of Hyaluronic Acid and Viscosupplementation

The normal adult knee contains approximately 3.0 mL of synovial fluid (SF), with a hyaluronic acid (HA) concentration of 2.5 to 4.0 mg·mL⁻¹ (51), which decreases during the early stages of the OA disease process. Intra-articular type B synoviocytes and fibroblasts synthesize *in vivo* HA, which is secreted into the joint space. The average molecular weight of HA within the SF is 5 to

 7×10^6 Da (20). With arthritis, the concentration and molecular weight of HA are decreased by 33% to 50% (15,38), resulting in further joint breakdown and articular cartilage degeneration.

SF exhibits non-newtonian flow characteristics; the viscosity coefficient is not a constant, and the fluid is not linearly viscous. HA functions as the primary joint-protective component of SF because it adds viscosity and elastic properties affecting both the protective barrier and the flow characteristics of SF, which are related directly to HA concentration. As an ideal protective barrier, SF with normal HA acts as a lubricant (high viscosity/with reduced elasticity) during slow joint movements, while also acting as a shock absorber (improved flow and more elasticity) during rapid movements (7,16). Basic science research suggests that the therapeutic effect of intra-articular HA (IAHA) supplementation not only improves the viscoelasticity and flow characteristics of SF but also potentially offers a positive effect on the arthritic disease process by promoting in vivo IAHA production and by providing an intra-articular anti-inflammatory effect (19,21,23,38,40,41). If these effects are valid, in the future, clinicians may decide to use IAHA earlier in the disease process.

Viscosupplementation (VS) using IAHA for OA of the knee was approved by the U.S. Food and Drug Administration (FDA) in 1997. Currently approved for clinical use are compounds called hylans — cross-linked hyaluronans

— with a heavier molecular weight and a longer half-life. Hylans have been reported to improve viscoelastic properties and remain in the joint longer, as a function of crosslinking (31). As of this writing, the FDA currently does not approve VS therapy for use in other joints; however, several smaller investigations have shown that IAHA provides a modest reduction in OA-related hip pain (32,33), ankle pain (42), and shoulder pain (14). Synvisc[™] (hylan G-F 20; Genzyme Corporation, Ridgefield, NJ) has received the European approval for treatment of pain due to OA of the ankle and shoulder in 2006 (46).

There are seven forms of injectable HA currently approved by the FDA for clinical use as IAHA in OA of the knee in the United States (Table): Euflexxa[™] (Ferring Pharmaceuticals, Parsippany, NJ), Gel-One[™] (Seikagaku Corporation, Tokyo, Japan), Hyalgan[™] (Sanofi-Synthelabo, Inc, New York, NY), ORTHOVISC[™] (Anika Therapeutics, Woburn, MA), SupartzTM (Seikagaku Corporation), and SynviscTM and Synvisc-OneTM (Genzyme Corporation, Cambridge, MA) (Table). Both Gel-OneTM and Synvisc-OneTM</sup> are "singleshot" injections, whereas the other five are injected in a series of three to five injections on a weekly basis. Few direct comparisons have been published which indicate whether one brand is more efficacious than the other with respect to clinical outcomes (28). Two basic science studies in the early 1990s speculate that, if used earlier in the OA disease process, high-molecular-weight HA (HMWHA, 60×10^5 Da) actually may slow the progression of OA more so than low-molecular-weight (LMWHA, 5 to 10×10^5 Da) agents (1,19). More recently, clinical studies comparing HMWHA and LMWHA use found that HMWHA "might be" more efficacious in treating knee OA but that "heterogeneity of previous studies limited definitive conclusions" (28,43,50,52).

Clinical Efficacy, Research Reliability, and Safety of HA VS

Numerous randomized controlled trials (RCTs) and five published meta-analyses (MAs) (which included many of these RCTs) have supported the clinical effectiveness of using VS (IAHA) in individuals with OA of the knee (5,11,30,35,50). In a novel systematic review, which also included an evaluation of the analytical methods for each of these five MAs, Divine et al. (18) concluded that when the strictest statistical tools for interpretation of data heterogeneity were used, and valid outcome tools applied, the use of IAHA in patients with OA results in modest improvements in pain and function.

Although most RCTs of IAHA for OA of the knee reported positive effects, when reviewed individually, there were several important differences in the clinical research methodology that potentially could cloud the clinician's decision making about IAHA use for OA. A common observation of the individual RCTs was that populations with variable OA severity were included in the trials. Some subjects had unilateral disease, whereas others had bilateral disease. There was variability in study criteria used to exclude test patients with an effusion at time of therapy. Variability also was noted in both timing and method of clinical assessments and in the opportunity for repeat treatment. Each of the HA products studied differed in its origin, method of

Characteristics of se	ven commercially availab	ole hyaluronans.					
	Euflexxa TM	Gel-One TM	$Hyalgan^{TM}$	ORTHOVISCTM	Supartz [™]	Synvisc	Synvisc-(
	Ferring Pharmaceuticals, Parsippany, NJ	Seikagaku Corporation, Tokyo, Japan	Sanofi-aventis Bridgewater, NJ	DePuy Orthopaedics, Inc, Warsaw, IN	Seikagaku Corporation, Tokyo, Japan	Genzyme Corporation, Ridgefield, NJ	Genzyr Corporat Ridgefield
Hyaluronan per series (mg)	60	30	100	06	125	48	48
Active ingredients	1% Na-hyaluronate	1% Na-hyaluronate	1% Na-hyaluronate	1.5% Na-hyaluronate	1% Na-hyaluronate	0.8% Na-hyaluronat	e 0.8% Na-hya
Molecular weight (kDa)	2,400 to 3,600	I	615 to 730	2,000	600 to 1,170	6,000	6,000
njection dose (mg)	20	30	20	30	25	16	48
Vo. injections per series	Series of three injections done per week	Single injection	Series of five injections done per week	Series of three injections done per week	Series of five injections done per week	Series of three injections done per week	Single inje
Amount per injection (mL)	2.0	3.0	2.0	2.0	2.5	2.0	.0
Source	Bacterialfermentation	Rooster combs	Rooster combs	Bacterial fermentation	Rooster combs	Rooster combs	Rooster com

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Viscosupplementation for Knee OA

Table.

production, molecular weight, biologic characteristics, time in the joint, and pharmacodynamic properties. The use of local anesthetic and description of the actual HA injection technique varied. Pain between injections or "breakthrough pain" was treated differently in different studies. Perhaps the greatest clinical differences revolve around trials in which authors reported a "per-protocol" (*i.e.*, only those patients who followed the protocol were included) rather than an "intent-to-treat" (*i.e.*, all patients were intended to be entered whether or not they followed the protocol) analysis (18). Other broader methodological differences included the potential for publication bias and the interpretation of the clinical importance of the observed treatment effects.

All five MAs reviewed used search and analysis techniques that enable the clinician to make a more confident decision regarding the use of IAHA for an individual patient (5,13,30,35,50). In each MA, the authors reported on only those RCTs done in either a single- or a double-blinded fashion, from either single or multiple investigation centers (level I clinical evidence). Although outcome measures varied between several RCT, each of the five MAs only reported on those studies that used a previously tested reliable outcome tool, such as the visual analog scale (VAS), Western Ontario and McMaster University (WOMAC), Lequesne Index, Musculoskeletal Outcomes Data Evaluation and Management System (MODEMS), or numeric rating scale. Most studies also included a VAS score for pain with activities and some type of functionality score. Each MA used a methodological quality assessment. Perhaps most important in an MA is the reported degree of heterogenicity between trials used in an MA. There were small but significant differences associated with the methods used in the search process. Specifically, differences in the assessment of the study methodology's quality and heterogenicity always should be noted when considering conclusions presented within an MA (18). Additional resources describing the MA process are available (36,47).

Although there was variation in the types of outcomes measured and the assessment of study methodology quality and heterogenicity, each MA of studies using IAHA came to the same conclusion that using IAHA offered a broad and vague description of "modest" improvements in OA-related knee pain and improved function. More specifically, most studies included within the five large MA studies used VAS for pain and other validated functional outcomes scores such as WOMAC; a "modest" improvement using VAS, WOMAC, or other relative index scores represents a wide range from 20% to 40% difference in scores from baseline to after IAHA treatment. Risks and mortality associated with HA use were reported to be very low in all of these analyses, and therefore, HA was found to be safe for use in patients with knee OA (10,18).

Who is the ideal candidate for IAHA VS?

The primary goals for clinical management of knee OA are to minimize pain, to maintain and/or improve joint mobility, and to minimize functional impairment (39). The American College of Rheumatology (ACR) suggests an initial conservative noninvasive treatment consisting of physical therapy, weight loss, bracing, and/or assistive devices

followed by pharmacological intervention (3). In a recent analysis, the Osteoarthritis Research Society International (OARSI) (55) completed a systematic literature search of systematic reviews, MAs, RCTs, observational studies, and economic evaluations from 2003 to 2009 that addressed hip and/or knee OA treatment. From the outcomes of the review, the committee developed recommendations physicians could use to approach the treatment of OA. The results of the literature review support previous reports that include the sequential clinical application of lone drug therapy or a combination of nonpharmacological, pharmacological (IAHA), and surgical treatments for OA. Pharmacological intervention may include topical and oral analgesics, nonsteroidal anti-inflammatory drugs (NSAID), COX-2 inhibitors, opioids, and steroids. However, long-term use of these pharmacological agents has deleterious effects, such as hypertension, peptic ulcer and kidney disease, and increased risk of heart attack (5). On the basis of data presented by systemic reviews and MAs on the use of IAHA, the ideal patient should meet the following criteria when considering the use of IAHA:

- Meet the ACR criteria for OA (3) (the ACR criteria are recognized as providing the most comprehensive review of medication toxicity, as well as the use of COX-2 and GI-protective agents).
- Have a documented diagnosis of primary OA of the target knee.
- Demonstrate radiographic evidence of OA in the tibiofemoral compartment of the target knee (17).
- Have a recent history of continued OA pain in the target knee despite attempted nonpharmacological and pharmacological treatments as indicated within ACR "steps 1 and 2, initial and alternative therapeutic approaches" (3).
- Have an abnormal arthritis outcome score (*i.e.*, a score of 2 to 3 of a total of 4 on WOMAC or other evidence-based OA index) (13) (the study by Bellamy *et al.* was based on an original work done by Bellamy for his masters thesis in 1986).
- Be younger than 65 years; in an MA, patients older than 65 years and those with the most advanced stages of arthritic change (*i.e.*, complete loss of joint space) were found to be less likely to improve with HA therapy (50). For those older than 65 years with other medical conditions increasing the risk of medical complications or death due to knee replacement surgery, higher-level evidence comparing safety and pain-reducing efficacy using IAHA versus knee replacement surgery is not available. However, the use of IAHA in this population is safe and offers potential for small to modest improvements in pain and function without the risks associated with knee replacement surgery.

Treatment with HA is ideal for patients who have not had adequate pain relief from oral medications (NSAID, acetaminophen), exercise, and physical therapy.

Other candidates for IAHA include patients with existing renal or gastrointestinal intolerance for NSAID, along with those patients with severe OA who either are poor surgical candidates or must postpone total knee replacement. In a single published study, total knee replacement was delayed by a median of 2.1 years, and for 75% of the treated knees (average of 1.67 treatment cycles), surgery was delayed an average of 3.8 years (49). In this subset of patients who are less-than-ideal candidates for surgery, IAHA injections can provide both pain relief and improved function.

Is Higher-Molecular-Weight IAHA More Ideal for the Patient?

In an earlier MA, Lo *et al.* (30) reported that IAHA "has, at best, modest efficacy in the treatment of knee OA" and that the effect was comparable to that of NSAID over that of acetaminophen, an effect that itself remains controversial. Lo et al. (30) also found "evidence of publication bias, so even this estimate of efficacy may be inflated." Using a broader study inclusion criteria for their MA, Wang et al. (50) — despite significant heterogeneity — demonstrated an overall resting pain control efficacy of 7.9% when comparing IAHA use versus placebo controls (when scoring for sum of pain intensity differences, the following formula was used: (sum of pain intensity differences/maximum scale of pain intensity) \times trial duration). When adjustment for baseline pain level was calculated, the pain control efficacy increased to 13.4%. Increased efficacy in peak resting pain control was 9.9%. In addition to added resting pain control, crosslinked (HMWHA) patients had improved functional pain efficacy (21.9% vs 5.3%), improved function adjusted for baseline function level (38.3% vs 11.7%), and improved peak function (26.8% vs 8.2%) when compared with noncrossed-linked (LMWHA) patients. The summary of Wang et al. (50) indicates that the use of HMWHA offers substantial improvement in pain with activity with an overall activity-related pain control efficacy of 21.9% - a figure commonly described as a "modest" improvement in many reviews of HA efficacy.

Wang *et al.* (50) also note that LMWHA was less effective for pain control in studies of patients who were older than 65 years and with the most advanced radiographic stage of OA (complete loss of joint space). Both Lo *et al.* (30) and Wang *et al.* (50) conclude that, with more severe degenerate disease, highly cross-linked HA (HMWHA) would result in providing improved lubrication and articular cartilage tolerance to compressive forces and thus offer greater pain relief.

Major adverse events were noted in 3 of 1,002 knees treated with injection of LMWHA (one each of severe swelling, vasculitis, and hypersensitivity reaction) and in 1 of 139 knees treated with injection of higher-molecular-weight HA (Synvisc^M) (4,26,41). Minor adverse events consisted of a transient mild increase in local pain or swelling. The relative risk of minor adverse events for all trials was 1.19 (95% confidence interval (CI) = 1.01-1.41). Additional information gleaned from the OARSI review (55) identified that high-molecular-weight hylan used for IAHA resulted in a higher frequency of flares of pain and swelling due to synovial reaction from a high antigen load (rooster combs) when compared with the standard therapy. The authors in the same OARSI analysis also reported that the IAHA therapy cost per quality-adjusted life year was \$13,876, which represents only modest savings when compared with conventional therapy.

Quick Relief of Knee Pain Due to OA From IAHA? Timing of HA Effect on Pain

Authors of three MAs published in 2005 reported a time effect on the relief of pain at rest and on functional pain (6,11,35). All three analyses reported that, in studies of pain ratings at rest, patients receiving IAHA had significant pain reduction during weeks 5 to 12 after injection. In particular, Modawal *et al.* (35) noted improvements in rest pain at weeks 5 to 12; however, IAHA was not more effective than placebo in reducing pain at 1 or at 15 to 22 wk after the last injection.

When IAHA is compared with intra-articular injection of corticosteroids, from week 1 to 4, intra-articular corticosteroids seem to be relatively more effective for pain than IAHA, and after week 4, the two pain control interventions approach equal efficacy (9). In a Cochrane analysis on the early effectiveness of corticosteroid injection use for pain control, there was evidence of significant pain reduction as early as 2 wk (the risk ratio was 1.81 (95% CI = 1.09–3.00)) peaking at 3 wk (the risk ratio was 3.11 (95% CI = 1.61-6.01)), without evidence for efficacy in pain and functional improvement from 4 to 24 wk after injection (12). In another MA comparing corticosteroids and IAHA, beyond 8 wk after injection, IAHA had greater efficacy (9). Arrich et al. (6) also reported a more prolonged reduction in rest pain at 22 to 30 wk after IAHA. Pain reduction with activity also has a postinjection time effect. Bellamy et al. (11) noted reduced pain on weight bearing at 5 to 13 wk after IAHA, whereas Arrich et al. (6) reported an earlier significant reduction in pain during movement after 2 to 6 wk, which continued to improve at each time interval, after 10 to 14 and 22 to 30 wk. Finally, in a recent novel MA highlighting a therapeutic trajectory of IAHA for knee OA pain more than 6 months after intervention (8), IAHA was found to be efficacious by 4 wk, to reach peak effectiveness by 8 wk, and to be with a residual detectable effect by 24 wk. In the same study, the peak effect size (ES) on pain control is 0.46. An ES above 0.20 is considered to be clinically relevant on an individual patient basis in chronic pain conditions such as knee OA. By comparison, ES scores for other OA analgesics include ES = 0.13 for acetaminophen, ES = 0.29 for NSAID, and ES = 0.44 for COX-2 inhibitors (8).

Do the mechanical and biological effects differ in importance in different stages of disease? Basic science data suggest which is the ideal HA dose in early and late OA

Basic science investigations report that the intra-articular [HA] varies inversely with the severity of OA disease: in moderate to severe disease, intra-articular [HA] can be $<1.0 \text{ mg}\cdot\text{mL}^{-1}$. The normal range of [HA] is from 2.5 to $4.0 \text{ mg}\cdot\text{mL}^{-1}$. After injection and dilution with SF and/or a local anesthetic, the intra-articular [HA] has been estimated to increase to slightly $<4 \text{ mg}\cdot\text{mL}^{-1}$. In the arthritic joint, the concentration and molecular weight of HA are decreased by 33% to 50% because of dilution from inflammatory effusion, abnormal synoviocytes, and molecular fragmentation (23,38). Changes in SF composition and dynamics will lead to a less efficient balance between viscous and elastic properties. Decreased lubrication properties result in increased stress on the already-damaged articular cartilage

resulting in further damage to the chondral surface. The loss of "barrier integrity" also adversely affects cartilage nutrition and waste removal and actually may have a proinflammatory effect (7). All of these factors contribute to additional joint pain and dysfunction.

Basic science researchers have reported that, in addition to increasing [HA], IAHA also may offer several other disease-altering benefits. The potentially disease-modifying effects of IAHA are the result of the positive effects of HA on both synoviocyte and chondrocyte metabolism. One of the proposed benefits of IAHA therapy is increased in vivo production and proliferation of chondrocytes. In the bovine model, intra-articular chondrocyte proliferation is felt to be greatest when [HA] is 1.0 to 2.0 mg·mL⁻¹ (2). Using an in vitro model exposure to exogenous HA, de novo HA biosynthesis by fibroblasts occurred (1,19). Also in the bovine model, IAHA reduces the concentration of prostaglandins, fibronectin, and cyclic adenosine monophosphate in the SF (21,34,41). Independent of anti-inflammatory effects, IAHA-mediated pain control seems to occur by direct inhibition of nociceptors and indirectly by binding to bradykinin, substance P, and other hyperalgesic compounds (19,22,38,40). In addition, IAHA provided a protective effect on chondrocytes already exposed to leukocyte proteinases, interleukin 1, or oxygen-derived free radicals (19,23). Both effects on fibroblasts and chondrocytes were HA viscosity dependent, with HMWHA providing superior protection compared with LMWHA formulations (1,19). Thus, in the early stages of OA disease, intra-articular injections of LMWHA may be more ideal for chondrocyte proliferation in early degenerate joints while there is a possibility of restoring articular cartilage (21). Basic science research also suggests that HMWHA exerts several beneficial, disease modifying, anti-inflammatory, analgesic, and possibly chondroprotective effects later in the disease process when the inflammatory process results in greater patient pain (16,21,24,51,53).

Can the biological effect be delivered by means other than injection?

Oral supplements advertised as containing HA, hylan, and other similar HA derivatives are marketed directly to consumers. Currently, only one placebo-controlled RCT with 20 subjects older than 50 years is published (27). Subjects who used oral HA (Hyal-Joint[®]) for 8 wk provided both WOMAC and SF-36 scores as outcomes. Without using a crossover design, differences at 4 and 8 wk in pain control, function, and quality of life were minimal but favored the oral HA. No head-to-head studies comparing oral HA with other pharmacologic agents, including IAHA, have been done.

Bioengineers are taking advantage of HA as a major component of the extracellular matrix in connective tissues. Surgeons are combining HA with other biopolymers (44) to form replacement tissue scaffolding, which is being used in tissue regeneration therapies. Being a polysaccharide and not a protein HA makes it potentially less antigenic. Its supportive role for cell proliferation and differentiation has been confirmed by several *in vivo* and *in vitro* studies (44). HA has been paired with preadipocytes and seeded on HYAFFTM (Fidia Advanced Biopolymers srl, Abano Terme, Italy) and used to serve as a stable tissue scaffold for use in dental and plastic surgeries (15). HA also has been used within a hydrogel scaffold to promote Schwann cell growth (45). Attempts to use HA scaffolds in cartilage tissue regeneration and repair have been less successful than attempts to use them in other areas; however, this is a very popular area for tissue regeneration research (54).

Conclusions

In this review, we attempted to address the important clinical questions regarding the use of IAHA for the potential 50 to 60+ million patients who will experience symptoms of OA during the next 20 years. IAHA is safe, with few risks associated with use - most often localized allergic reaction, most recently reported as occurring with a higher concentration of "rooster comb"-derived single-dose HA. MAs of the use of LMWHA and HMWHA report "modest" clinical efficacy in the control of both resting and functional knee pain. In choosing which agent to use, basic science evidence studies seem to suggest that the use of both LMWHA and HMWHA formulations potentially provides diseasealtering effects; however, MA of clinical studies tends to favor the efficacy of HMWHA for relief of resting and activityrelated knee pain. The ideal candidate for IAHA use in the knee is an individual 65 years or younger, with symptomatic and radiographic evidence of OA, who has attempted to control symptoms with other pharmacologic and nonpharmacologic methods and who does not have severe "bone-on-bone" arthritic changes. Persons older than 65 years, especially those at risk for surgical complications due to chronic medical conditions, also may benefit from IAHA as a safer alternative to the risks associated with knee replacement surgery; however, the pain control efficacy is less than that for individuals younger than 65 years. Because of its essential physical properties within the extracellular matrix, HA lends itself to be paired with other biological substances to provide intraarticular scaffolding for tissue regeneration and in efforts to repair articular cartilage.

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