

Managing knee osteoarthritis: efficacy of hyaluronic acid injections

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ABSTRACT

Osteoarthritis (OA) is the most common form of chronic arthritis worldwide. The etiology of pain in osteoarthritis is multifactorial, and includes mechanical and inflammatory processes. The use of intra-articular viscosupplementation in the nonoperative management of patients with osteoarthritis has become quite popular. Recent clinical data have demonstrated that the anti-inflammatory and chondroprotective actions of hyaluronic acid viscosupplementation reduce pain, from 4 to 14 weeks after injection, while improving patient function. Viscosupplements are comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events, and hyaluronic acid has more prolonged effects than IA corticosteroids. Although several randomized controlled trials have established the efficacy of this treatment modality, additional high quality randomized control studies with appropriate comparison are still required to clearly define the role of intra-articular hyaluronic acid injections in the treatment of osteoarthritis. We review the basic science and development of viscosupplementation and discuss the mounting evidence in support of its efficacy and safety profile.

Keywords: Viscosupplementation; Osteoarthritis; Knee; Pain; Hyaluronic acid

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthri-

tis and a clinically significant cause of disability. OA is a slowly evolving process, characterized by joint pain, stiffness and loss of range of motion. Weight bearing usually worsens the pain and it is improved with rest. OA results from a complex interaction of biomechanical, biochemical and genetic factors and is characterized by degradation of cartilage and hypertrophy of bone. Increasingly recognized is the presence of synovitis in a significant proportion of patients with primary OA, and based on this observation, further studies have gone on to implicate joint inflammation and synovitis in the pathogenesis of OA. However, clinical OA is not one disease but a final common pathway secondary to many predisposing factors, most notably age, joint trauma, altered biomechanics, and obesity. How such biochemical and mechanical processes contribute to the progressive joint failure characteristic of OA is tightly linked to the interplay of joint damage, the immune response to perceived damage, and the subsequent state of chronic inflammation resulting in propagation and progression toward the phenotype recognized as clinical OA^{1,2}. On physical examination patients usually have a swollen joint with warmth, palpable osteophytes, crepitus with movement, tenderness and reduced range of motion. The treatment of OA includes non-pharmacological interventions such as patient education, physical therapy, bracing, wedged shoe insoles, walking aids, weight loss and low-impact exercises³⁻⁵. Pharmacological treatment options include paracetamol, non-steroidal anti-inflammatory drugs (NSAID), topical NSAID, glucosamine and/or chondroitin sulfate and intra-articular (IA) corticosteroids. Opioid and non-narcotic analgesics may be prescribed in refractory pain patients. In September 2000, the American College of Rheumatology guidelines for the treatment of osteoarthritis of the knee recommended that one treatment option to be considered is the use of intra-articular injections of hyaluronic acid for the relief of osteoarthritic pain^{4,6,7}. Since then, hyaluronic acid viscosupplementation has become one of the

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more popular nonoperative treatment options for symptomatic osteoarthritis⁸⁻¹⁰. More recently, in 2008, the Osteoarthritis Research Society International (OARSI) cited intra-articular hyaluronic acid as a useful therapeutic modality, that has delayed onset, but prolonged duration of symptomatic benefit, in treating patients with osteoarthritis of the knee or hip³. In addition, although marketed as analgesics, viscosupplements have been postulated to have potential chondroprotective effects as well¹¹. Surgical intervention should be considered only after pharmacological and non-pharmacological treatment have failed. Although surgical treatment of osteoarthritis can reduce pain and improve joint mobility and function, the operative management of osteoarthritis is associated with significant cost and potential morbidity. Furthermore, not all patients are candidates for surgical intervention, and they may wish to delay or avoid it if possible^{2,12}.

The purpose of this review is to address the role of IA hyaluronic acid treatment for pain in OA of the knee and discuss the mounting evidence in support of its efficacy and safety profile.

PAIN MECHANISM IN OSTEOARTHRITIS

The etiology of pain in the joint with OA is complex but understanding the pathophysiology of pain production is helpful to understand the role of Hyaluronic acid (HA) in its treatment. Synovial joints are innervated by nerves that originate in primary sensory neurons located in the dorsal root ganglion⁷. The tissues of synovial joints that are innervated by nerve endings are the capsule, ligaments, synovial membrane and subchondral bone. Hyaline cartilage does not have nerve endings. The nerves of the synovial joint are sensitive to the detection of both noxious and non-noxious stimuli. Activation of the nerve endings can begin with any mechanical, chemical, or thermal process. The pathophysiology of OA involves the release of a large number of inflammatory mediators and these directly act on the nerve endings and reduce their threshold to pain recognition⁷. The result is an enhanced discharge of nerve impulses that are perceived as a painful stimulus.

HYALURONIC ACID

Hyaluronic acid, also known as hyaluronan or hyaluronate, is a high-molecular-weight glycosaminoglycan

made up of repeating disaccharide units of N-acetylglucosamine and glucuronic acid¹³. The average molecular weight of synovial fluid HA is 5 to 7 × 106 Da. It is widely present in mammalian tissues and has the highest concentration in synovial fluid. Type B synoviocytes and fibroblasts synthesize HA and secrete it into the joint space. HA molecules occupy a large spheroidal space while in their fully hydrated state. Therefore, the viscoelasticity and flow characteristics of synovial fluid are intimately tied to its HA content^{7,12}. Its function in the diarthrodial joint is both mechanical and metabolic. HA provides important viscoelasticity and lubricating properties to synovial fluid, thereby reducing articular cartilage wear and acting as a lubricant during slow movements and as a shock absorber during rapid movements^{7,12-14}. Furthermore, HA molecules restrict large plasma protein from entering into the synovial fluid while facilitating the passage of small molecules into the joint for maintenance of nutrition.

The normal adult knee contains approximately 2 mL of synovial fluid, with a HA concentration of 2.5 to 4.0 mg/mL. In the arthritic joint, the concentration and molecular weight of HA are decreased by 33% to 50% because the synthesis of HA in OA is disrupted by increased levels of pro-inflammatory cytokines, free radicals and proteinases^{12,15}. These alterations lead to dramatically poorer viscous and elastic properties and, thus, distorted joint mechanics. Decreased lubrication leads to increased stress on the already diseased cartilage, which further disrupts the collagen network and the integrity of the chondral surface. The loss of barrier integrity also adversely affects cartilage nutrition and waste removal. Finally, fragmented low-molecular-weight HA may actually have a proinflammatory effect¹².

The goals of IA HA injections are to improve function, reduce pain and possibly modify disease activity⁷. Hyaluronic acid exerts its anti-inflammatory effect within the joint space by influencing a variety of leukocyte functions both in vivo and in vitro. These include inhibition of migration, chemotaxis, phagocytosis, adherence, and proliferation¹⁶. Furthermore, intra-articular injection of HA reduces the concentration of inflammatory mediators, such as prostaglandins, fibronectin, and cyclic AMP in the synovial fluid of patients with arthritis¹⁷. Of even greater significance are the various positive effects of HA on both synoviocyte and chondrocyte metabolism. Potential disease-modifying activities of the HA include promotion of healing and repair by stimulating chondrocyte growth and stimulating synthesis of cartilage matrix components: colla-

gen, proteoglycans and endogenous hyaluronans^{7,12}. Ghosh¹⁸ demonstrated de novo HA biosynthesis by fibroblasts upon in vitro exposure to exogenous HA. This effect was dependent on both concentration and molecular weight of exogenous HA. In this same study, the authors also demonstrated that high molecular weight, cross-linked derivatives of HA actually provided a protective effect on chondrocytes exposed to leukocyte proteinases, IL-1, or oxygen-derived free radicals. The synergistic effect of exogenous HA reduces the mechanical, chemical or thermal noxious stimuli to the innervated tissues of the synovial joint restoring normal homeostasis and reducing pain and stiffness⁷.

DEVELOPMENT OF VISCOSUPPLEMENTS

Balazs and associates¹³ pioneered the concept of viscosupplementation in the 1960s. They believed an ideal viscosupplement should meet 4 specific criteria: 1) permeability to metabolites and macromolecules, 2) non-immunogenic, 3) similar molecular weight to native synovial fluid, and 4) a long half-life. Viscosupplementation with intra-articular (knee) HA was approved by the Food and Drug Administration (FDA) in 1997. Viscosupplementation therapy in joints other than the knee is not approved at the moment⁷. The available HA range in molecular weight from 500 to 6000 kDa. The first HA formulations required multiple injections, because they were relatively lower in molecular weight. HA with molecular weights less than 500 kDa have not been effective in either pain relief or improvement of function. To address this issue of shortened half-life, crosslinked hyaluronans, called hylans, were developed. Hylans have been reported to have improved viscoelastic properties and an increased duration within the joint, as a function of cross-linking^{7,12,19,20}.

HYALURONIC ACID IN CLINICAL USE

The clinical efficacy of hyaluronic preparations has been published in numerous clinical outcome studies. The 2006 Cochrane Review, the most comprehensive review to date, reviewed 76 randomized placebo-controlled trials that fulfilled strict methodology and study design criteria²¹. Many different HA products were examined for effects from 1 to 52 weeks and based on their careful analysis of the literature, the authors concluded that viscosupplementation is an effective treatment for

osteoarthritis of the knee with favorable effects on pain, function, and patient global assessment, especially during the 5- to 13-week postinjection period.

Five meta-analyses have been published on IA HA treatment in knee OA with the primary outcome being pain relief^{8,21-24}. In general the studies support the efficacy of IA HA in reducing pain. Wang et al⁸ performed a meta-analysis to determine the effects of intra-articular injection of HA on knee osteoarthritis and to elucidate the therapeutic efficacy and safety of the procedure. They evaluated 20 randomized controlled trials that compared both cross-linked (hylan G-F 20) and noncross-linked hyaluronates with placebo. All trials used validated outcome measures and safety was assessed by the relative risk of an adverse event. The authors reported that both cross-linked and noncross-linked hyaluronates do indeed have a therapeutic effect in patients with osteoarthritis of the knee when compared with placebo. They found significant improvements in pain on activity, pain at rest, and function. Furthermore, trials that involved cross-linked hyaluronates showed much greater pooled estimates of efficacy than did the trials involving non-cross-linked hyaluronates. Overall, clinically meaningful improvements with crosslinked hyaluronans have been demonstrated by pain improvements from baseline of 33% to 80% compared with 21% to 26% with placebo²⁵.

Four randomized, placebo-controlled trials investigated the use of 3 weekly intra-articular injections of HA for the treatment of knee osteoarthritis²⁶⁻²⁹. In a 26-week study, Wobig et al²⁶ reported significant improvements on visual analog testing versus placebo for pain during weight-bearing, pain at rest, pain during most painful knee movement, and treatment success. At the end of the 26 weeks, significantly more HA treated patients versus placebo treated patients were symptom free and required less use of NSAIDs or steroid as rescue therapy.

HYALURONIC ACID VERSUS NSAIDS

Increasing attention has shifted toward comparing HA with other nonoperative knee osteoarthritis treatment strategies. These include NSAIDs and intra-articular steroid injections. Several randomized controlled trials comparing HA viscosupplementation with NSAIDs have reported that the benefit obtained with intra-articular HA was similar to or greater than that observed with NSAIDs, with fewer gastrointestinal side ef-

fects^{30,31}. In a multicenter Canadian trial, Adams and colleagues³² compared three treatment groups: oral NSAIDs alone, HA treatment (3 weekly injections), and a combination of oral NSAIDs and HA treatment. At 6 months, both the HA only and the combined NSAID and HA groups were statistically superior to the NSAID only group. These findings are further supported by the previously mentioned Cochrane review, which reported that when HA was added to pre-existing NSAID therapy, combination therapy was associated with greater improvement in pain and joint function than use of NSAIDs alone²¹.

HYALURONIC ACID VERSUS INTRA-ARTICULAR THERAPY WITH CORTICOSTEROIDS

A number of trials have compared IA HA to IA corticosteroids^{21,33}. The data indicate that IA corticosteroids significantly improved pain during the first 4 weeks after injection but that IA HA were shown to be more effective from 5 to 14 weeks post-injection. Pain relief was greatest following IA corticosteroids at 2 weeks, but not at 4 weeks after injection. By contrast IA HA demonstrated superior reduction in pain at 8 weeks and continued to be significant until 14 weeks after the injections. Two recent prospective trials have compared intra-articular HA to intra-articular corticosteroids. Leopold et al³⁴ prospectively compared 2 treatment arms. The first groups received 3-weekly injections of HA, and the second group received 1 injection of intra-articular betamethasone. At the 6-month follow-up, both groups improved and there was no statistically significant difference between the two groups for VAS and WOMAC scores, or the Knee Society Scoring System. Caborn and associates³⁵ also studied similar cohorts. In their comparison of intra-articular HA (3 weekly injections) and intra-articular triamcinolone (1 isolated injection) they found that although the maximal benefit of corticosteroids appeared more rapidly (week 2), pain reduction and functional improvement were significantly superior ($p < 0.01$ and $p < 0.001$, respectively) with HA viscosupplementation at the 3- to 6-month follow up periods.

LOW VERSUS HIGH MOLECULAR WEIGHT PREPARATIONS

A large number of different studies explored the effect of the high versus low molecular weight preparations of

HA. In a randomized, controlled, blinded study, Karlsson et al³⁶ evaluated 3 parallel cohorts of patients with knee osteoarthritis. The patients in each group received 1 of 3 treatments: 3-weekly injections of low molecular weight HA, 3-weekly injections of high molecular weight HA, or placebo. No significant differences were noted between those treated with low or high molecular weight preparations. Kotevoglou et al³⁷ also examined the efficacy of different molecular weight preparations. Their 6-month follow-up data revealed no statistically significant difference in clinical efficacy between the preparations. Finally, in a 2005 review, Goldberg and Buckwalter³⁸ stated that, to date, no substantive clinical evidence has been put forth to suggest that differences in the molecular weight of currently available viscosupplements have any impact on clinical efficacy.

Through the years there has been considerable diversity in the outcomes between many of these trials. Previous data had suggested that the higher-molecular-weight products had a greater efficiency, especially in pain relief, but recent studies indicated that the pooled effect size of higher molecular weights were not more effective in relieving pain. Furthermore, the data suggested that pain reduction diminished with time and was no longer significant after 14 weeks^{18,21,39}.

MULTIPLE COURSES OF TREATMENT

Multiple studies of intra-articular HA have confirmed the benefit of treatment with more than one course of HA. In a prospective open-label study, Waddell et al⁴⁰ evaluated the efficacy and tolerability of a second course of HA for the treatment of osteoarthritic knee pain over a 12-month period in patients who previously experienced a beneficial initial course of therapy. Most patients experienced continued pain relief as all efficacy parameters significantly improved ($p < 0.001$) from baseline at weeks 1, 2, 4, 8, 12, 26, and 52. Furthermore, Raynauld and colleagues⁴¹, in a randomized controlled trial also demonstrated the safety of repeat treatment with no evidence of higher incidence of local mild adverse events than with a first course of therapy. This safety profile of viscosupplementation is also supported in a recent meta-analysis by Pagnano et al⁴².

CLINICAL SAFETY

The safety profile of HA viscosupplementation has

been well established over its 20 years of clinical use. In fact, no viscosupplement product has been withdrawn because of safety concerns. Intra-articular HA is generally well tolerated with low incidence of local adverse events⁴³. The overall incidence of adverse events has been reported to be approximately 1% to 4% per injection^{31,44}. The most common adverse event is local reaction at the injection site, consisting of mild pain, swelling, or effusion, and warmth or redness, or both. Such injection site reactions are usually mild and self-limited, resolving with 1 to 3 days and generally respond to NSAIDs and local modalities. Other mild adverse effects that have been reported include post-injection itching, headaches, and calf pain⁴⁵. Furthermore, the incidence of adverse events with viscosupplementation is similar to that observed with other intra-articular procedures. The incidence of adverse events has been proved to being significantly related to the injection technique used: a medial approach to a partially bent knee was associated with 5.2% adverse events by injection, compared with 1.5% with straight lateral injections. Interestingly, injection laterally has also been shown to have a higher incidence of intra-articular injection accuracy when compared with injection into the flexed knee using conventional arthroscopic portal approaches⁴⁶. Brockmeir and Schaffer¹⁶ postulated that adverse reactions are related more closely to the accuracy of intra-articular injection than to the substance itself.

Overall, HA has a very good tolerability profile in clinical trials and practice. However, there is growing evidence to suggest that hylan G-F 20 (crosslinked hyaluronate) in particular may be associated with a specific adverse event termed pseudosepsis or severe acute inflammatory reaction (SAIR)⁴⁵. Its clinical presentation may be difficult to differentiate from a true septic knee or even pseudogout episode without joint fluid aspirate studies. The syndrome itself is characterized by the following: 1) severe pain occurring 1 to 3 days after an injection; 2) usually occurring after the first injection or treatment course (prior exposure); 3) highly cellular joint effusion without crystals or bacteria by culture; 4) usually requires clinical intervention (NSAIDs, arthrocentesis, or intra-articular steroid injection)⁴³. Although severe, pseudosepsis seems to be a relatively rare occurrence. It is characteristically seen after previous exposure, prompting some investigators to postulate that the cause of pseudosepsis may be immune-based and possibly reflective of immunologic sensitization^{46,47}.

Although the cause of local adverse events associated with HA injection is not clear, these events are typically mild-to-moderate in nature, resolve spontaneously or after treatment of symptoms, and do not result in any longterm sequelae. Therefore, it is often difficult to clinically distinguish the symptoms of a reaction from the symptoms of osteoarthritis. Additionally, the types of usual local adverse events observed after viscosupplementation are not as potentially serious as the systemic adverse effects that may occur with NSAIDs or COX-2 inhibitors⁴⁸.

INDICATIONS

Knee OA is associated with symptoms of pain and functional disability. Physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity and mortality. Current treatments aim at alleviating these symptoms by several different methods:

- Non-pharmacological treatments (for example, education, exercise, lifestyle changes)
- Pharmacological treatments (for example, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), topical treatments)
- Invasive interventions (for example, intra-articular injections, lavage, arthroplasty).

Managing knee OA is based on:

- Educating the patient about OA and its management
- Alleviating pain
- Improving function and decreasing disability
- Preventing or retarding progression of the disease and its consequences.

Guidelines on the management of knee and hip OA have been published by the Royal College of Physicians⁴⁹ and the American College of Rheumatology⁵⁰. In 2003, EULAR commissioned a steering group to review the evidence for the treatment of knee OA⁵¹.

The treatment of knee OA should be tailored according to:

- Knee risk factors (obesity, adverse mechanical factors, physical activity)
- General risk factors (age, comorbidity, polypharmacy)
- Level of pain intensity and disability
- Sign of inflammation—for example, effusion

- Location and degree of structural damage⁵²

The ideal candidate for intra-articular viscosupplementation has yet to be clearly defined. Previous guidelines for the treatment of knee osteoarthritis recommended the use of HA only in patients who have not responded to nonpharmacologic therapies and simple analgesics, and after the unsuccessful trial of NSAIDs and selective COX-2 inhibitors^{47,50}. However, given the cardiovascular, gastrointestinal, and renal side effects of selective and nonselective NSAIDs, the use of HA products earlier in osteoarthritis treatment paradigm should be considered. Again, despite failure to identify the optimal cohort, there is evidence suggesting that the greatest potential benefit of HA would likely be among younger patients and those in the earlier stages of osteoarthritis⁵⁰. In the meta-analysis by Wang et al⁸ patients older than 65 and those with the most advanced stages of osteoarthritis were less likely to benefit from HA therapy. Evanich et al⁵³ also reported greater improvement in pain scores for patients with less severe radiographic disease compared with those having more severe disease. Last, a short-term safety study of 4253 patients given hylan G-F 20 revealed that those patients who were most recently diagnosed with knee osteoarthritis were more likely to have an early benefit of therapy compared with those who had been diagnosed at a later time point in the disease course⁵⁴. As a whole, these studies support the use of HA earlier in the osteoarthritis treatment regimen. The most recent OARSI guidelines state that optimal management of patients with knee osteoarthritis requires a combination of nonpharmacological and pharmacological modalities of therapy³. Physicians should therefore consider incorporating the use of HA into a comprehensive treatment program for knee osteoarthritis. The best evidence to support this idea are the studies conducted by Kahan et al⁵⁵ and Raynauld et al⁴¹ demonstrating significant improvements in knee osteoarthritis symptoms when HA was added to usual therapy. HA may also decrease the use of concomitant corticosteroids and NSAIDs when added to standard care for knee osteoarthritis. A few studies also indicate that the use of HA may even delay the need for total knee replacement. For example, Waddell and colleagues⁵⁶ demonstrated the ability of HA to delay the need for total knee replacement by approximately 2 years in patients with grade IV osteoarthritis.

Finally, the dosing regimen can be as important as the timing of HA injections. Different dosing regimens of IA HA can limit the availability of treatment and af-

fect patient compliance. Yet the appropriate number, dose, and timing of HA injections have yet to be determined.

IA HA are contra-indicated if there is known hypersensitivity to HA preparations, if there is an IA infection or a skin problem in the area of the injection site. As a class the HA are relatively safe with no significant systemic adverse events. There have been no drug interactions reported²¹.

CONCLUSION

In conclusion pain is a central symptom of OA and requires an integrated approach to its treatment. Both nonpharmacological and pharmacological treatments offer the best chance for pain relief. As a result of increased interest and scientific investigation of intra-articular viscosupplementation, its use in the nonoperative management of patients with osteoarthritis has become well accepted. Numerous prospective, randomized, placebo-controlled studies have proven the efficacy of HA. Cumulative evidence also affirms its clinical safety. The exact mechanism of action is still to be delineated, further clinical studies are necessary to prove the potential disease-modifying effects of HA.

Although there have been many studies, there still is a need for additional high quality, randomized control trials with placebos or comparators to clearly delineate the role of IA HA in the treatment of pain in OA. Viscosupplementation as a whole must expand beyond pain relief and joint preservation and evolve to encompass therapies that restore normal cartilage and joint homeostasis, arrest the progression of osteoarthritis, interfere with cartilage-degrading mechanisms, and reverse existing damage.

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