

Intra-articular hyaluronans: the treatment of knee pain in osteoarthritis

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Abstract: The etiology of pain in osteoarthritis is multifactorial, and includes mechanical and inflammatory processes. Intra-articular injections of hyaluronans (HAs) are indicated when non-pharmacological and simple analgesics have failed to relieve symptoms. The HAs appear to reduce pain by restoring both mechanical and biomechanical homeostasis in the joint. There are five FDA-approved injectable preparations of HAs: Hyalgan[®], Synvisc[®], Supartz[®], Orthovisc[®] and Euflexxa[®]. They all appear to relieve pain from 4 to 14 weeks after injection and may have disease-modification properties. 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 HA injections in the treatment of osteoarthritis.

Keywords: hyaluronans, knee, pain, osteoarthritis

Introduction

Osteoarthritis (OA) is the most common form of arthritis. It has been reported that 40% of people over the age of 80 will have at least one joint involved and 27 million people in the United States have clinical OA.^{1,2} 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. The etiology of OA remains unknown; however, significant risk factors have been identified with OA development.^{1,3} These include joint trauma, hypermobility, mal-alignment and genetic abnormalities. 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, weight loss and low-impact exercises.⁴⁻⁷ Pharmacological treatment options include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs, glucosamine and/or chondroitin sulfate and intra-articular (IA) corticosteroids. Opioid and non-narcotic analgesics may be prescribed in refractory pain patients. IA hyaluronans (HAs) have recently been used for the treatment of painful knee joints with OA.⁸ Surgical intervention should be considered only after pharmacological and non-pharmacological treatment have failed.³ The purpose of this review is to address the role of IA HAs treatment for pain in OA of the knee.

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Pain mechanism in OA

The etiology of pain in the joint with OA is complex but a brief summary of the pathophysiology of pain production is helpful to understand the role of HAs in its treatment.¹ Studies have identified the three major types of pain. Acute pain is directly associated with the activation of peripheral nerve receptors. Chronic pain is associated with an ongoing inflammation of peripheral tissues.⁹ When there is a significant chronic pain, damage occurs to the pain pathways either peripherally or centrally, which results in the third type of pain, neuropathic.¹⁰ Synovial joints are innervated by nerves that originate in primary sensory neurons located in the dorsal root ganglion.¹¹ 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 recognition.¹¹ The result is an enhanced discharge of nerve impulses that are perceived as a painful stimuli. IA HAs have been shown to have a pain-reduction effect through a number of mechanisms which will be discussed later.

Hyaluronans

Hyaluronan or hyaluronic acid (HA) is a complex glycosaminoglycan composed of repeated disaccharide units to form a linear polymer. It is widely present in mammalian tissues and has the highest concentration in synovial fluid. 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.¹⁰ Further, 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.¹² The synthesis of HA in OA is disrupted by increased levels of pro-inflammatory cytokines, free radicals and proteinases, resulting in an HA with a significantly reduced molecular weight, more molecular polydisaccharides, and a reduction in synovial fluid viscoelasticity.¹² This abnormal hyaluronic acid increases the potential for articular cartilage wear and accelerates progression of the disease. The progression of OA results from the disruption of the mechanical, biochemical and homeostasis of the diarthrodial joint, in part provided by ultra-high molecular weight

HA. HA functions in articular cartilage as a supramolecular aggregate to retain proteoglycans, aggrecan and link protein. It therefore acts as a scaffold for these important extracellular matrix molecules. Loss of this normal HA disrupts cartilage matrix stability and perpetuates the destruction of the articular cartilage. Mechanically HA provides viscoelastic properties to the joint allowing for normal fluid flow, lubrication and smooth joint motion. When the ultra-molecular weight HA is enzymatically cleaved by the increased levels of the proteinases observed in OA, the lower-molecular-weight HA no longer can maintain the mechanical integrity of the joint. Further, this lower-weight HA may be proinflammatory, further accelerating the disease. The goals of IA HA injections are to improve function, reduce pain and possibly modify disease activity. Potential disease-modifying activities of the HA include promotion of healing and repair by stimulating chondrocyte growth, decreasing apoptosis and stimulating synthesis of cartilage matrix components: collagen, proteoglycans and endogenous hyaluronans.¹²⁻¹⁴ There are data that suggests a potential inhibition of the synthesis and activity of the chondrodegrading enzymes, eg, metalloproteinases as well as the inhibition of matrix destructive inflammatory processes.¹⁵⁻¹⁷

Exogenous HA with a molecular weight of 500 to 4000 kDa increases synovial fluid viscosity and enhances shock absorption and the lubricating capabilities of synovial fluid.¹⁸ HA has been shown to have an effect on reducing pain by several mechanisms.¹⁹ HA binds neuropeptides, creating a boundary layer around nociceptors which is one mechanism to reduce pain. Additional mechanisms that potentially can reduce pain in OA include inhibition of inflammatory mediators, eg, cytokines and prostaglandin. HA has been shown to stimulate endogenous HA synthesis by synovial sites through CD 44 receptor binding.^{12,20} Exogenous HA downregulates matrix metalloproteinase-3 expression and inhibit metalloproteinase synthesis which results in decreased cartilage destruction. Exogenous HA restores metabolic homeostasis thereby enhancing synovial fluid flow and reducing pain. The synergistic effect of exogenous HAs reduces the mechanical, chemical or thermal noxious stimuli to the innervated tissues of the synovial joint restoring normal homeostasis and reducing pain and stiffness.

HAs in clinical use

There are currently five FDA-approved injectable preparations of HAs used for the painful knee in OA: Synvisc[®], Hyalgan[®], Supartz[®], Orthovisc[®] and Euflexxa[®]. Table 1 summarizes their product characteristics.²¹⁻²⁴

Table 1 US-approved hyaluronan (HA) therapies: summary of product profiles

Product distributor	Manufacturing	Active ingredient	Number injections per course	Molecular weight (kDa)	Labeling precaution on efficacy/safety
Hyalgan (Sanofi-Aventis)	Naturally derived, purified HA	1% sodium hyaluronate (20 mg)	3 or 5	500–730	No
Synvisc (Genzyme Biosurgery)	Hylan polymers derived from HA	0.8% sodium hyaluronate derivative (16 mg)	1 (6 mL) or 3 (2 mL)	6000 + gel	No
Supartz (Smith and Nephew)	Naturally derived, purified HA	1% sodium hyaluronate (25 mg)	3 or 5	620–1170	Yes
Orthovisc (DePuy Mitek)	Naturally derived, purified HA	0.7% sodium hyaluronate (30 mg)	3 or 4	1100–2900	Yes
Euflexxa (Ferring)	Fermented, bacterial derived HA	1% sodium hyaluronate (20 mg)	3	2400–3600	Yes

Notes: Product profiles based on package insert of Hyalgan (2001), Synvisc (2006), Synvisc I (2008), Supartz (2004), Orthovisc (2005), Euflexxa (2005).

The available HAs range in molecular weight from 500 to 6000 kDa. HAs with molecular weights less than 500 kDa have not been effective in either pain relief or improvement of function. The active ingredients are sodium hyaluronate in a concentration of about 20 mg per dose. The recommended number of injections per course range from a single injection for Synvisc to five for Hyalgan or Supartz. The total dose of HA per series varies from 45 mg for Orthovisc to 125 mg for Supartz. There have been no well done randomized controlled head-to-head studies reported, so conclusions on the outcomes of different dosages are difficult to make. Hyalgan, Synvisc, Supartz and Orthovisc are naturally derived products from purified HA extracted from rooster comb. Euflexxa and the recently introduced Supartz are made by a different process in which their HA is derived from an engineering-based process that extracts HA from fermented bacterial sources.

The current guidelines for the treatment of OA of the knee suggest the use of IA HAs for the treatment of pain in patients who have failed to respond adequately to non-pharmacological therapy as well as simple analgesics.^{1,3–5,7} IA HAs are contra-indicated if there is known hypersensitivity to HA preparations, if there is a IA infection or a skin problem in the area of the injection site. As a class the HAs are relatively safe with no significant systemic adverse events. There have been no drug interactions reported.²⁵

Five meta-analyses have been published on IA HA treatment in knee OA with the primary outcome being pain relief.^{25–29} Table 2 summarizes these meta-analyses. In general the studies support the efficacy of IA HAs in reducing pain; however, the data indicate only a small but clinically important effect. The outcome metrics of most studies centered upon the improvement of pain measures,

eg, WOMAC A or VAS scores; however, in some studies when function was also assessed usually by WOMAC Scores, similar parallel improvements of function and stiffness were seen. The improvement did not last beyond 14 weeks after treatment and the effect size was no more than 0.3. Issues that reduce the value of these meta-analyses include the lack of head-to-head comparisons, the high variability because of different outcome measures and the use of different outcome scales. One study has suggested that IA HA injections provide a longer-term pain benefit than IA corticosteroids.⁸ The recent introduction of Synvisc I, a single 6 mm injection of Hyalran G-F 20, was shown to be effective in a randomized, double-blind placebo controlled trial. This is a unique formulation and demonstrated after one injection a significant decrease in WOMAC A pain scores.³⁰

The 2006 Cochrane Review reviewed 76 trials, and is the most comprehensive review to date.⁷ Many different HA products were examined for effects from 1 to 52 weeks. In assessing the pooled effect size in comparison to placebo at 1 to 4 weeks after treatment, the reduction in pain was significant and physical function also improved as joint stiffness declined. There is 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.^{14,15,18,19,25,31} Further, the data suggested that pain reduction diminished with time and was no longer significant after 14 weeks. A number of trials have compared IA HAs to IA corticosteroids.^{4,32–34} The data indicate that IA corticosteroids significantly improved pain during the first 4 weeks after injection but that IA HAs were shown to be more effective

Table 2 Intra-articular hyaluronan therapy in knee osteoarthritis: summary of meta-analyses

Reference	Lo ²⁷	Wang ²⁹	Arrich ²⁶	Modawal ²⁸	Bellamy ²⁵
Total no. of studies	22	20	22	11	76
Efficacy outcome measures	Effect size (change from baseline pain vs placebo)	Mean difference, ASPID vs placebo	WMD in pain during/after exercise (VAS) vs control	VAS	WMD in pain on weight bearing vs placebo
Key pooled results	Effect size: 0.32 ($P < 0.001$)	Mean difference for ASPID: 13.4%	WMD 10–14 wk: -4.3 mm ($P = 0.013$) WMD 22–30 wk: -7.1 mm ($P = 0.013$)	WMD 5–7 wk: 17.6 (95% CI, +7.5, +28.0) 8–12 wk: 18.1 (95% CI, +6.3, +29.9) 15–22 wk: 4.4 (95% CI, -15.3, 24.1)	% Change 5–13 wk: +26% for pain; +23% for function
Conclusion	Small treatment effect	Safe and effective	Not effective in measured outcomes	Moderately effective at 5–10 wk, not effective at 15–22 wk	Effective treatment for pain, function, pt, global assessment at 5–13 wk

Abbreviations: ASPID, adjusted sum of pain intensity differences; WMD, weighted mean difference; VAS, visual analog scale; pt, patient.

from 5 to 13 weeks post-injection. Pain relief was greatest following IA corticosteroids at 2 weeks, but not at 4 weeks after injection. By contrast IA HAs demonstrated superior reduction in pain at 8 weeks and continued to be significant until 14 weeks after the injections.

IA HAs have an excellent safety profile with few serious side-effects.²⁵ Systemically there is no differences observed in gastrointestinal and cardiovascular events between HAs and controls. There have been reported a number of local adverse events such as transient pain and swelling at the injection site and in some circumstances, IA injections of HAs were followed by a greater frequency of pain and swelling when compared to placebo.^{9,35–37} Pseudoseptic reactions after injections have been reported primarily with Hylan G-F 20 treatment.³⁸ Pseudosepsis is characterized by a severe inflammatory response in the joint with significant cellular infiltration and painful effusion occurring within 72 hours after the injection. It usually occurs after a second or third injection in the treatment course and appears similar to an infectious process or a gouty response so that sepsis or pseudogout should be excluded. The synovial fluid may have a high number of mononuclear cells with some neutrophils, but with an increased number of eosinophils and macrophages.⁶ It generally is not self limiting and requires some clinical intervention such as arthrocentesis and an IA steroid injection, with the addition of oral NSAIDs. If there is a concern about infection, while awaiting cultures, one should consider administering prophylactic oral antibiotics. If the condition does continue to deteriorate, intravenous antibiotics may be indicated. If a chronic granuloma develops, surgical intervention may be required. Data from clinical and

pre-clinical studies suggest that there is an immunological basis for this reaction; however, more studies in this area are needed to substantiate this mechanism and their long-term consequences.³⁸

IA HAs are indicated in the US for use in knee OA. However, there have been a number of physician directed uses of HA in other joints. Qvistgaard in a randomized controlled trial of HA compared to isotonic saline in hip OA demonstrated a significant improvement in pain and an overall improvement in clinical activities.³⁹ Another study utilizing a population of patients who were total hip replacement candidates demonstrated a significant improvement in both pain and Harris Hip Scores.^{40,41} More randomized control trials are necessary to establish the risk/benefit of the use of IA HAs in hip OA. Other joints have been studied including the carpal-metacarpal joint, shoulder and ankle.^{42–44} The results have been variable and it is difficult to conclude anything from these studies without further randomized control trials. One orthopedic application is the injection of HA in the post-arthroscopy period to enhance pain and accelerate rehabilitation. One recent study evaluated the safety and efficacy of a high-molecular-weight sodium hyaluronate after a knee arthroscopy for treatment of a symptomatic meniscus tear.⁴⁵ The study utilized 3 injections after arthroscopy and randomized patients into a group treated with the IA HA compared to a group using only acetaminophen, up to 1000 mg 4 times a day. The patients in the treated groups 3 and 6 months after surgery had significantly less pain and more flexion than the comparative control group. This is an area that is fertile for additional randomized controlled trials.

In conclusion pain is a central symptom of OA and requires an integrated approach to its treatment. Both non-pharmacological and pharmacological treatments offer the best chance for pain relief. Pharmacological treatments include NSAIDs, cox-2 inhibitors, opioids, anti-inflammatory creams and IA corticosteroids. IA corticosteroids have been shown to be effective in relieving pain during the first 2 weeks after treatment. IA HA injections have a longer onset of action and longer duration of effect. The exact mechanism of action is still to be delineated, although it is clear that IA HA reduces pain through its effect on peripheral pain receptors as well as an impact on the synovial tissue and its role in enhancing the viscoelastic properties of synovial fluid. 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. The use of IA HA in other joints requires additional well structured clinical studies.

Disclosures

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