38 CHAPTER

Role of Viscosupplementation in Osteoarthritis

Himanshu Bhayana, Mandeep S Dhillon

INTRODUCTION

For centuries, degenerative pain and stiffness of joints has contributed to the development of frailty in the elderly. Osteoarthritis (OA) affects various aspects of an individual's life ranging from social and functional activities, socioeconomic status, and emotional well being.

Shakespeare's description of an old man in his famous work "***Seven Ages of Man***" read as: "*For his shrunk shank, and his big manly voice, turning again towards childish treble, pipes and whistles in his sound*": ascribing that the old man becomes dependent on others for activities of daily living.

Over the last century, however, several developments in medical science have started to challenge the ingrained image of old age as equivalent to age of physical decline. The pathophysiology of many diseases is clearer now, and for Osteoarthritis we have a myriad of pharmacological and nonpharmacological modalities to halt or delay the course of the disease.

The ACR (American College of Rheumatology) and EULAR (European League Against Rheumatic Disease) recommendations for OA now includes the use of intra articular hyaluronate injections. In this chapter, we shall review the basic science of action of Hyaluronic Acid (HA) in the joint and how intra articular HA injection creates its effect in individual joints.

HA is ubiquitously found in the human body and provides viscoelastic properties to synovial fluid. With the progression of OA, the natural concentration and distribution of HA inside the joint deviates towards lower molecular weight HA which causes degradation of mechanical and viscoelastic properties of synovial fluid.[1] Lower molecular weight distribution of HA (LMWHA) also have strong correlation to pain[2]. Intra articular injections of Hyaluronic Acid aim to restore the decline in average molecular weight distribution as well as concentration of HA in the joint synovial fluid[3].

Intra articular HA injection works for early OA by improving shock absorption, providing anti-inflammatory effects, joint lubrication, cartilage matrix alteration, proteoglycan synthesis, and chondroprotection. Today, we have a better understanding of the mechanism of action of intraarticular Hyaluronic acid administration, which can be broadly classified into six different subsets.

1. Anti-inflammatory effects
2. Chondroprotection

3. Subchondral bone alteration
4. Analgesic action
5. Enhanced proteoglycan and glycosaminoglycans
6. Mechanical modifications

1. ANTI-INFLAMMATORY EFFECTS

The anti-inflammatory actions of HA are mediated through inter-relating relationship through actions of CD 44, TLR 2, ICAM 1 and lyalin cell surface receptor. High Molecular Weight HA (HMWHA) promotes anti-inflammatory responses while LMWHA promotes pro inflammatory responses.

A: HA-CD 44 Receptor Binding

CD 44 is the primary receptor of HA ligand. CD 44 receptor expression is related to cartilage homeostasis, and initiates a signaling cascade which is associated with HER 2 (human epidermal growth factor 2) and proto oncogene c-Src kinase tyrosine kinase pathways[4-6]. The affinity to CD 44 is dependent on molecular size and weight of HA; larger size molecule has higher avidity of binding to CD 44[7]. Noble et al.[8] reported the effects of LMWHA fragments in eliciting a pro inflammatory response; Kawana et al. [9] also demonstrated that CD 44-HA binding suppresses in vivo pro-inflammatory cytokine production. Several other studies have also shown that pro inflammatory response is enhanced by fragmented HA, while presence of HMWHA helps develop an anti-inflammatory response.[10–12]

HMWHA (more than 20 units) occupy multiple binding sites of CD 44 and promotes anti-inflammatory effects, while LMWHA (smaller than 10 units) binds only to limited sites of CD 44.[7] HMWHA also decrease levels of MMP (matrix metalloproteinase) level by increasing TIMP (tissue inhibitor of metalloproteinase-1)[13]. Campos et al. demonstrated that inhibition of degradation of HA contributes to reduction in CD 44 activation and inflammatory mediated response.[11]

B: HA-TLR Receptor Binding

Toll Like Receptors (TLR) are involved in coordination of immune system.[14] Scheibner et al. demonstrated that fragmented HA leads to activation of innate immunity through TLR-2, causing pro inflammatory response while high molecular weight HA inhibits TLR-2 signaling thereby promoting anti-inflammatory actions.

C: HA-ICAM Receptor Binding

Intercellular Adhesion Molecule (ICAM-1) is the cell surface receptor for Hyaluronic Acid. Increased expression of ICAM receptors leads to inflammation[15]. Shao et al.[16] demonstrated that elevation in ICAM-1 was observed in inflammation in rat models; Yasuda et al. demonstrated HMWHA suppressed production of pro inflammatory cytokines through ICAM-1 downregulation.

2. CHONDROPROTECTION

Intra articular injection of HA is known to increase chondrocyte proliferation and reduction in chondrocyte apoptosis[17,18]. The chondroprotective mechanism is dependent on CD 44 pathway. HA binds to CD 44 leads to inhibition of IL 1B expression, which leads to a decline in the expression of MMP 1,2,3,9 &13[19]. As mentioned in the text (*in the previous section above on anti-inflammatory action*), the binding of HMWHA to CD 44 is greater. HA also has affinity to RHAMM (Receptor for Hyaluran Mediated Motility) which aids in chondroprotection [20]. HMWHA is proven to have greater inhibitory action on MMP.[21]

Hyaluronate also provides chondroprotection by decreasing chondrocyte apoptosis. Chondrocyte apoptosis is dependent on ADAMTS expression (A Disintegrin And Metalloproteinase with ThromboSpondin motifs).[22] ADAMTS are involved in cleavage of various synovial components such as Versican and Brevican.[23] The process leads to production of ROS (reactive oxygen species) and NO (nitric oxide) production which results in cartilage apoptosis.[24] Hyaluronate decreases the ADAMTS expression via CD 44 pathways.[22]

CD44-HA binding also results in reduction in PGE2 (prostaglandin E2) synthesis and increased HSP (heat shock protein) overexpression, both of which leads to reduction in chondrocyte apoptosis. [25,26,27] HMWHA has higher chondroprotective action by creating greater inhibition of PGE2 expression compared to LMWHA. [26]

3. ALTERATIONS IN SUBCHONDRAL BONE

Intraarticular installation of HA creates suppression of MMP13 and IL6 through CD 44 binding pathway [28]. Various basic science investigations have supported the fact that suppression of MMP-13 causes inhibition of effects of osteoarthritis within subchondral bone.[28–32] HA improves subchondral thickness and bone density which results in more compliant subchondral bone which reduces the stress on cartilage during impact loading.[33]

4. ANALGESIC ACTION

The analgesic effect of HA is shown to occurs by its binding at the mechanosensitive stretch activated ion channel which leads to blocking the pain response.[34] The action is less pronounced with the use of LMWHA[34]. HA causes reduction of nociceptor action in joints; thereby creating the analgesic effect.[35] Gotoh et al. [36] also demonstrated the interaction of HA and free nerve endings in the joint tissue.

5. ENHANCED PROTEOGLYCAN AND GLYCOSAMINOGLYCANS

With the progression of osteoarthritis, the intrinsic glycosaminoglycans (GAG) and proteoglycans (PG) concentration decreases within the cartilage. Studies have reported that intra-articular administration of HA stimulates PG synthesis, thereby delaying progression of osteoarthritis [37,38] Homandberg et al.[39] demonstrated that HMWHA has more pronounced effect of increasing PG

synthesis compared from LMWHA and the mechanism works through stimulation of IGF (Insulin like growth factor)-1.

6. MECHANICAL MODIFICATION

The viscosity of HA is shown to aid in lubrication of joint capsule which prevents degeneration by decreasing friction [40]. HA also acts as a shock absorber to absorb vibration and pressure changes inside the joint which otherwise can cause degradation of chondrocytes.[41] Improved protection to cartilage against mechanical degradation is provided by HMWHA because of its viscous properties.[42]

As discussed above, various basic science studies have established the beneficial role of Intra-articular hyaluronic acid (IA-HA) for osteoarthritis, working through a variety of mechanisms and pathways; however, which one of these actually predominates in the clinical scenario is yet to be established.

After IA HA injection, the majority of exogenous HA products are retained in the joint for few days only; however the therapeutic action can last for six months or even more[43]. The proposed mechanism of action of HA is therefore divided into two stages i.e. mechanical stage and pharmacological stage[45]. In mechanical stage, action is imparted by the directly added HA, which imparts better viscosity to the joint and enhances mechanical effects such as shock absorption and lubricating effects.

The pharmacological stage involves the disease modifying properties by stimulating endogenous production of HA by synovial cells, which aids in normalization of synovial fluid. This property of exogenous HA aiding in endogenous HA production has been termed as visco-induction.[45]

JOINT SPECIFIC CLINICAL APPLICATION OF HA

Knee Joint

Most of the clinical work in the literature regarding visco-supplementation has been done on knee joints. Various international agencies have given their recommendation for HA specifically for the knee joint. (Table 38.1)

TABLE 38.1 Recommendations by various agencies for IA HA injection in knee joint for OA

International Agency	Recommendation
EULAR; 2003	Evidence is present to support (LEVEL 1B); Limitations include cost issues and logistics
OARSI; 2014	"Uncertain"; depending on patient-physician interaction in the context of risk benefit ratio and patient profile Not appropriate in the scenario of multi joint OA
ESCEO; 2014	For advanced pharmacological treatment if patient still symptomatic despite use of NSAID's
ACR; 2012	Recommended if failure to prior pharmacological treatment
ACR; 2019[85]	Conditionally recommended *against* in patients with knee OA

EULAR: European League Against Rheumatism; OARSI: Osteoarthritis Research Society International; ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; ACR: American College of Rheumatology

EVIDENCE OF EFFICACY OF IA HA IN KNEE

Bellamy et al.[46] did a Cochrane review in 2006 which involved 76 trials of viscosupplementation in comparison with placebo, NSAID's, IA steroid injection and other therapies. A Cochrane analysis revealed that viscosupplementation is an effective treatment for the management of OA of knee joint, and the benefits include effects on function, pain and patient's self global assessment at various post injection time period. This is most notable at 5 to 13 weeks after injection during which the improvement was 9% to 32% for functional outcome and 28 to 54% for pain. The authors also reported that a series of 3 to 5 HA injections were efficacious by 4 weeks, reached its maximum efficacy at 8 weeks and the effect lasted up to 24 weeks. Bannuru et al.[47] did a systematic review in 2015 on 137 studies which included 33,243 participants to demonstrate comparative efficacy of various pharmacological interventions in osteo arthritis of knee. The authors reported that the most efficacious pharmacological intervention for OA knee was IA HA. For functional improvement, all interventions were significantly superior to placebo except for IA steroid injection and PCM (paracetamol). The authors reported IA HA to have significantly significant effect when compared to IA placebo for pain at 3 months.

Miller et al.[48] also conducted a meta-analysis of 29 studies on US approved IAHA injections and placebo, involving 4866 subjects. The authors reported "large treatment effect" from 4th week to 26th week for pain in knee joint and function as compared to pre injection values. Bannuru et al.[49] compared the therapeutic trajectory curve of IA HA and placebo and documented that IAHA is efficacious by 4 weeks, with the curve peaking at 8 weeks; there was a detectable effect on pain in knee even at 6 months after injection. IA HA induces longer lasting control of pain when compared to IA corticosteroid injection.[45] (Table 38.2)

TABLE 38.2 Comparative chart of IAHA and IA corticosteroid on pain in OA knee [49]

Weeks from injection	Favors
Week 2	CS > HA
Week 4	CS = HA
Week 8	HA = CS
Week 12	HA > CS
Week 26	HA > CS

The above observation depicts that clinical effects of HA extends for a significant time. AMELIA (osteoArthritis Modifying Effects of Long term Intra-articular Adant) study evaluated the long-term effects of IA HA on progression of knee OA of 40 months duration.[50] The study involved 306 patients with OA knee who were injected with either four cycles of five injections, either placebo or IAHA; follow up was done at one year after fourth cycle. The authors reported that the number of responders progressively increased in IAHA after each treatment cycle, whereas the response to placebo was roughly stable. There was a significant difference between the two groups (IAHA vs placebo) from one year onwards.

Further long-term outcome in terms of eventual delay in knee arthroplasty was reported by Altman et al.[51] in 2015. In their retrospective analysis involving 182022 patients with OA of knee joint, the authors reported that in patients receiving IA HA injections, there was a definitive dose dependent increase in

time to TKR (Total knee arthroplasty). Similar observations regarding delay in knee replacement by HA supplementation was made by Waddell et al.[52] in 2007 and Mar et al. in 2013[53].

SHOULDER JOINT

The three common indications of viscosupplementation in shoulder joints are OA (glenohumeral arthritis), adhesive capsulitis and rotator cuff tendinopathy. Blaine et al.[54] in 2008 published their experience with 606 patients with shoulder pain which was chronic and resistant to standard conservative management. The authors reported that three to five IA HA injections was effective compared to placebo at 2, 3 and 6 months in the subgroup of OA with or without RCT (rotator cuff tear). However, HA injection in cases with isolated rotator cuff tear did not show any improved efficacy compared to placebo therapy. Saito et al.[55] conducted a meta-analysis of 19 RCT's for efficacy and safety of IA HA injection in cases of chronic shoulder pain, which included 2120 participants. The authors recommended that HA is more effective compared to NSAID's, corticosteroid or rehabilitation in chronic shoulder pain.

Several other preliminary studies have also supported the efficacy and safety of HA for persistent shoulder pain. Silverstein et al.[56] published their report on 30 patients with idiopathic glenohumeral arthritis who received three weekly HA injections (3 cycles). The authors reported beneficial effects of HA up to 6 months after the third cycle. Shibata et al.[57] compared the efficacy of HA versus corticosteroid injection in 78 patients with chronic shoulder pain, the injections were given once weekly for five weeks in both the groups. The authors reported that therapeutic efficacy of both groups was equivalent till 24 weeks after completion of treatment. Other authors have supported the role of IAHA for adhesive capsulitis[58,59]. Lee et al.[60] reported that Ultrasound guided IA injections might be advantageous compared to the blind technique. AAOS guidelines (2020)[85] for glenohumeral arthritis have reported that there is no benefit to the use of hyaluronic acid in the treatment of glenohumeral arthritis. Despite early results favoring the use of HA in chronic persistent pain, the correct indications and appropriate etiology of application of HA injection needs to be better delineated by further well controlled comparative studies.

HIP JOINT

There are limited case studies mentioned in literature, which have focused on viscosupplementation of the hip joint. The anatomical features of this joint, and its proximity to femoral vessels make the IA injections a tricky affair. Pourbagher et al.[61] reported that Ultrasound guided HA injections are easy to perform, safe and well tolerated for management of hip OA. Various reviews and meta-analysis have attempted to clarify the indications and identify advantages of IA HA in hip OA[62–64]. Gatson et al. reported some evidence in favor of IA HA in cases with early radiographic changes in hip. Migliore et al.[66] reported on long term efficacy of viscosupplementation and demonstrated that the effect can last up to 18 months after the first injection. On the other hand, Qvistagaard et al.[67] reported no significant difference between 3 cycles of HA and saline at follow up of 3 months. Similarly, Richette et al.[83] in

their study of 85 patients reported no significant difference between IA HA and placebo at 3 months follow up.

Lieberman et al.[82] reviewed 23 studies to evaluate role of IA HA for OA hip joint. The authors reported that although HA decreases the hip pain in OA, the overall quality of data was insufficient for claiming consistent benefits. The authors also commented that they cannot recommend its routine use for hip OA. ACR (American College of Rheumatology) have reported there is no evidence to support use of HA in hip OA.

We believe that future multi-center randomized control trials regarding IAHA may alter the recommendations; at present there is no definite indication for the use of IA HA in OA hip joint.

ANKLE JOINT

Viscosupplementation has been tried as an adjunct for management of ankle osteoarthritis as reported by Sun et al.[68]. The initial results of viscosupplementation in ankle joint have been rather contradictory. A recent meta-analysis by Chang et al.[69] reported on the efficacy of HA in OA ankle; the authors recommended multiple doses with appropriate volume of injection to achieve maximum efficacy. The ideal patient for viscosupplementation is not yet known, but various other systematic reviews have also supported the role of HA for management in early OA ankle in terms of pain relief and improvement in functional outcome for short duration.[70–72]

Viscosupplementaion has also been shown to accelerate the process of soft tissue healing. Studies by Petrella et al.[73,74] have advocated the role of periarticular HA injection in acute ankle sprain. The authors reported patients receiving HA injection experienced lower recurrence rate of ankle sprain and better pain relief when compared to placebo group. Utility of HA has also been studied as an adjuvant in the treatment of osteochondral lesion of talus, and in management of acute ankle sprain.[75]

VISCOSUPPLEMENT PREPARATIONS

There are numerous FDA approved viscosupplementations available commercially for use in USA (Tables 38.3 and 38.4)[76]. Each preparation differs in terms of molecular weight, concentration, half life, molecular structure, and volume of injection. The preparations are produced either from rooster combs or by bacterial fermentation.[76,77]

HA can be classified into either low molecular weight (LMWHA) or high molecular weight (HMWHA). HMWHA is proposed to have higher clinical efficiency[77] and longer half life[78]. Colen et al. in their systematic review reported that they were unable to recommend superiority of one type of HA over another. Altman et al. [79] conducted a meta-analysis focusing on product differencesin various types of HA, looking at difference in safety and efficacy. The authors reported that HMW HA (>3000 KDa) and biologically fermented HA have better efficacy and safety profile.

TABLE 38.3 US FDA Approved Avian HA

Brand Name	Proprietor	Mol wt (In Million Daltons)
Synvisc	Sanofi Aventis	5.0-6.0
Hyalgan	Fidia Pharma	0.5-0.73
Gel one	Zimmer	NA
Supartz	Bioventus	0.62-1.17
Synvisc one	Sanofi Aventis	6
Visco 3	Zimmer	0.62-1.17

TABLE 38.4 US FDA Approved Bacterial derived HA

Brand Name	Proprietor	Mol wt (In Million Daltons)
Orthovisc	DepuyMitek	1-2.9
Genvisc 80	Orthogen	0.85
Durolane	Bioventus	1
Monovisc	Depuy Synthes	1.0-2.9
Hymovis	Fidia Pharma	0.5-0.73
Gelsyn-3	Bioventus	1
Euflexxa	Ferring Pharma	2.4-3.6

ADVERSE EFFECTS OF VISCOSUPPLEMENTATION

Viscosupplementation classically has been known to have very few serious adverse effects. Petrella et al.[73] in their study reported higher rates of adverse effects with avian derived HA compared to non avian HA. The adverse reactions include joint swelling, pain and warmth and self-resolving pain.[80] The authors also reported of higher risk of adverse reaction with repeated injection. Rare but serious adverse effects include severe inflammatory response, pseudosepsis and pseudogout.[81]

SUMMARY

On the basis of review of the available literature, supplemented with our personal experience, we conclude that intra articular hyaluronic injection is definitely an adjunctive tool in our armory for non-operative management of osteoarthritis of various joints. Judicious patient selection and proper counseling regarding expected benefits and realistic goals is important to achieve optimum efficacy of hyaluronate injections.

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