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Intra-Articular Hyaluronic Acid Injection for Osteoarthritis Treatment: A Literature Review

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Abstract: ***Background: Osteoarthritis is a degenerative joint disease involving the cartilage and its surrounding tissues as the result of imbalance between breakdown and repair of articular cartilage. Primary symptoms include joint pain, stiffness and limitation of movement. Disease progression is usually slow but can lead to joint failure with pain and deformity.Risk factors include genetic predisposition, mechanical overload, trauma, overuse, female, and the age >60 years old.It is commonly treated with NSAIDs; however, their use is limited because of serious adverse effects. To improve biomechanical function, viscosupplementation is widely used for symptomatic osteoarthritis by acting as a lubricant and shock absorber. Objectives: The aim of this literature review is to describe the benefits and risks associated with the use of viscosupplementation for symptomatic osteoarthritis in adults. Method: Articles on viscosupplementation treatment in osteoarthritic patients were identified from textbooks and electronic journals. These articles are then discussed and formulated for this literature review. Conclusion: Viscosupplementation can be considered as one of the treatments for patients that are not appropriate with analgetics and steroid due to age, intolerance or other medical conditions.***

Keywords: Hyaluronic acid, NSAIDs, Osteoarthritis, Viscosupplementation

1. Introduction

Osteoarthritis (OA) is a degenerative joint diseaseinvolving the cartilage and many of its surrounding tissues. In addition to damage and loss of articular cartilage, there is remodeling of subarticular bone, new growth bone at the joint margins (osteophyte formation), ligamentous laxity, weakening of periarticular muscles, mild synovitis and capsular fibrosis.[1,2]Although osteoarthritis prevalence and incidence estimates have varied somewhat across studies there is agreement that a substantial proportion of adults are affected;[3]over 50% in people above the age of 60 and known to affect more female than male. The joints often affected are hip, knee, fingers, and spine.[2,3]

2. Etiology and Pathophysiology

The stresses applied to the joints, especially the weight-bearing joints (I.e, ankle, knee, and hip), play an important role in the development of osteoarthritis. Some risk factors for OA include advancing age, obesity, trauma, genetics, repetitive use, infections, crystal deposition, acromegaly, hemoglobinopathies, and neuropathic disorders.[2]

The earliest changes are an increase in water content of the cartilage and easier extractability of the matrix proteoglycans. At a slightly later stage there is loss of proteoglycans and defects appear in the cartilage. The cartilage then softens and loses elasticity thereby compromising joint surface integrity. Microscopically, flaking and fibrillations develop along the normally smooth articular cartilage on the surface of an osteoarthritic joint. As the disease progress, the loss of cartilage results in joint space narrowing. Erosion of the damaged cartilage in an osteoarthritic joint progresses until the underlying bone is exposed. The subchondral bone responds with vascular invasion and increased cellularity, becoming thickened and dense (a process known as eburnation) at areas of pressure. Furthermore, subchondral bone may also undergo cystic degeneration. In the peripheral areas of the joint, cartilage responds by hypertrophy and hyperplasia to form a thickened rim of cartilage around the joint margin, known as chondrophyte. Chondrophyte then undergoes endochondral ossification to become bony outgrowth (osteophyte).[2,4,5]

3. Diagnosis

3.1 Typical Presentation

The usual presenting symptoms are pain, stiffness, swelling, deformity, and loss of function. The pain is aggravated by exertion and relieved by rest, although with time relief is less and less complete. There are several possible causes of pain, including mild synovial inflammation, capsular fibrosis with pain on stretching the shrunken tissue, and bone pressure due to vascular congestion and intraosseous hypertension. Stiffness characteristically occurs after periods of inactivity, but with time it becomes constant and progressive. Swelling may be intermittent (suggesting an effusion)or continuous (with capsular thickening or large osteophytes). Deformity may result from capsular contracture or joint instability. Patient may also complain about the loss of function, such as limping, difficulty in climbing stairs, restriction of walking distance, or progressive inability to perform everyday tasks, that eventually drive the patient to seek help.[1]

3.2 Diagnosis Criteria

OA can be defined by clinical presentation and radiological. In physical examination, joint effusion and deformity can be found. Local tenderness and crepitus can be felt, also restriction in movements. Muscle wasting suggests longstanding dysfunction. Instability is common in late stages of articular destruction. There have been many attempts to accurately identify and grade radiographic disease in OA and it is most widely assessed in studies using the Kellgren and Lawrence (K&L) score. The overall grades of severity are determined from 0 to 4 and are related to the presumed sequential appearance of osteophytes, joint space

loss, sclerosis and cysts.Late features may include joint displacementand bone destruction. CT, MRI, or arthroscopy may be useful for early detections.[1,2]

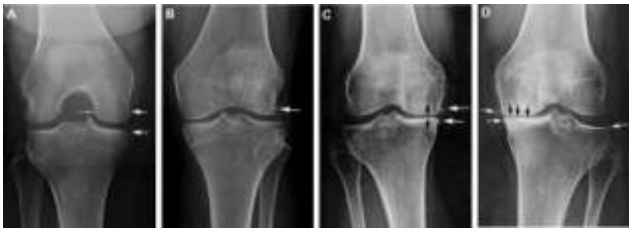

Figure 1: The grading of knee OA based on Kellgren Lawrence classification[6]

A. KL grade 1 (minimal, equivocal osteophyte on joint margins, doubtful joint space narrowing);
B. KL grade 2 (1 or more apparent marginal osteophyte, probable joint space narrowing);
C. KL grade 3 (Apparent joint space narrowing, multiple marginal osteophytes, subchondral sclerosis, joint deformity might be found);
D. KL grade 4 (bone-to-bone contact, apparent subchondral sclerosis, joint space diminished

3.4 Treatment

Management of OA is symptomatic, as there is yet no drug that can modify the effects of OA. The aims of treatment are to maintain movement and muscle strength, protect the joint from overload, relieve pain, and modify daily activities. Physical therapy should be encouraged, especially in the early case, to maintain joint mobility and improve muscle strength. However, activities that increase impact loading should be avoided. Load reduction such as wearing shock-absorbing shoes, weight reduction for obese patients, and using walking stick can also be useful. Pain relief can be achieved by analgesic, such as NSAID. For intermediate stage, joint debridement may be useful. Surgical management such as realignment osteotomy, arthroplasty, and arthrodesis should be considered in late stage of OA.[2,4]

3.5 Viscosupplementation in Osteoarthritis

Viscosupplementation is a medical procedure in which Hyaluronic Acid (HA) derivative is injected into a joint to relieve pain and improve function.[7]HA is not a rapidly acting agent, rather its clinical effect on pain and function shows a carryover effect that extends for a long time after administration.[8] Some patients also will not be helped by viscosupplementation. For those who report pain relief with the procedure, it may take several weeks to notice an improvement.[9]

According to The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm, intra-articular (IA) hyaluronic acid (HA) is recommended for management of knee osteoarthritis (OA) as second-line treatment in patients who remain symptomatic despite use of non steroidalanti inflammatory drugs (NSAIDs).[8] IA HA is not indicated for preventive purposes. IA HA seems to give best efficacy for moderate OA (Kellgren-Lawrence II-III), even though some studies too have reported efficacy in highly advanced knee OA (grade IV), in which HA injection can provide interim relief awaiting arthroplasty.IA HA is recommended for knee OA, especially for femorotibial OA, but the result of this procedure seems uncertain for other locations of OA. Some studies show disappointing results for hip OA, but encouraging for shoulder and ankle OA.[10]

3.6 Mechanism of Viscosupplementation

Hyaluronic acid is a naturally occurring substance found in the synovial fluid surrounding joints. It normally acts as a lubricant to enable bones to move smoothly over each other and as a shock absorber for joint loads. Osteoarthritic patients have a lower-than-normal concentration of hyaluronic acid in their joints.[9,11]The exact mechanisms of action through which IA HAs provide symptomatic relief to some people are unknown, but it is thought that IA HA might work by creating a viscoelastic protection of articular surfaces (the synovial membrane and the cartilage), covering the pain receptors in the articular capsule and diminishes their sensitivity, restoring the filtering property of the synovial fluid, removing free oxygen radicals and inflammatory factors from the articular surface, and inhibiting the migration and phagocytosis of macrophages and granulocytes. IA HA is also thought to be beneficial in the reestablishment of joint homeostasis through induction of endogenous HA production, which continues long after the exogenous injection has left the joint [4,8]

The proposed mechanism of HA activity occurs in 2 stages: a mechanical stage and a pharmacological stage. During the mechanical stage, OA synovial fluid is replaced by higher concentrations of HA thereby improving viscosity. This also restores the shock-absorbing and lubricating abilities of depleted synovial fluid and maintains a boundary layer around nociceptors, reducing pain induction. The pharmacological stage induces the biosynthesis of endogenous HA and extracellular matrix components, which reduces proteoglycan loss in cartilage and apoptosis of chondrocytes. It also reduces inflammatory cell activities to reduce HA degradation and acts by reducing induction of pain mediators.[7]

3.7 Different Kinds and Techniques of Hyaluronic Acids Administration

According to its molecular structure, HA can be distinguished into two groups: low molecular weight linear HA and reticulated HA with higher molecular weight (and probably slower degradation and longer joint residence). Preparations with associated adjuvants (manitol, sorbitol, chondroitin sulfate), reticulated or not, have also come onto the market more recently, with the aim of prolonging joint residence, although this has not been demonstrated.[8] HA derivatives differ not only in reticulation and molecular weight (chain length) but also in origin. Euflexxa is derived from a fermentation process (*Streptococcus*), whereas the source material for some other products is chicken combs. At present, no distinct advantage or disadvantage has been associated with any particular source of HA.[4,8] Characteristics of HA injections can be seen in **Table 1.**

Injection technique is of prime importance for both efficacy and tolerance. Injection must be strictly intra-articular. Different technical characteristics of HA injections is stated in **Table 2**. If there is any swelling (effusion), the excess fluid should be aspirated before injecting the hyaluronic acid because synovitis has been shown to impair the efficacy of HA, less by dilution in the effusion fluid than due to enzymes and oxidants (hyaluronidases, free radicals) degrading the HA chains. For these patients, the acute episode should be treated first. [9,10,11]

Table 1: Characteristics of HA injections[10]

Hyaluronic Acid	Forms
Linear HA	Sodium hyaluronate: (MW 0.5–3 mD) Multi-injection: Adant®, Arthrum®, Euflexxa®, Go-on®, Hyalgan®, Orthovisc®, Ostenil®, Sinovial®, Structovial®, Synocrom® Single-injection: Arthrummonodose®, Coxarthrum®, Synochrom forte®
Reticulated HA	(MW > 3 mD) Hylan GF-20: Synvisc®, Synvisc one® Sodium hyaluronate: Monovisc®, Synocrom forte one® happycross NASHA: Durolane®
Combined HA	Single-injection Mannitol: Ostenil plus® Happyvisc®, Happycross® Chondroitine sulfate: Arthrum HCS®, Synovium surgical®

Corticosteroid can be associated to HA in the same injection in the first of the 3 injections or in a single-injection, especially in case of severe pain or persistent effusion. In patients awaiting arthroplasty, an interval of more than 6 weeks should be left between the last injection and the arthroplasty surgery, to limit the risk of implant infection. Concerning HA, no study has yet been done, but it is considered that a 4 weeks interval before arthroplasty is safe, regarding to the absence of local immunosuppressive effect of HA.[10].

3.8 Side Effects

The HA class in general has demonstrated a very favorable safety profile for chronic pain management in knee osteoarthritis, with the most common adverse event being injection-site pain, warmth, and slight swelling.[4,11]To minimize this effect, it is advised that for the first 48 hours after the shot, patients should avoid excessive weightbearing on the leg, such as standing for long periods, jogging or heavy lifting.[9,11]

Although any intra-articular injection (whether of HAs or of steroids) may elicit an inflammatory response and possible effusion, only the cross-linked Hylan G-F 20 product has been associated with a clinically distinct acute inflammatory side effect (ie, severe acute inflammatory reaction [SAIR] or HA-associated intra-articular pseudosepsis).[4]

In some sources, it is said that IA HA was associated with an increase in risk for flare-ups, as well as with a significantly increased risk for serious adverse events. The most common adverse events were related to the gastrointestinal system, cardiovascular system, and musculoskeletal system. Regarding the various adverse effects that might happen to different patients, it is best to keep in mind that the use of IA HA in OA therapy depends on individual patient features and response to the treatment, therefore wise consideration is needed.[12]

3.9 Controversies Regarding Intraarticular Injections of Hyaluronic Acid

Intraarticular injection of HA claims to improve OA symptoms, reduce the effusion and recurrences after 60 days of treatment, reduce the chondropathy and synovial inflammation, delay the development of cartilage damage, and improve patient's quality of life.[7]In one of the literatures, intraarticular injection of hyaluronic acid for 6 months is proven to decrease pain and stiffness, also to increase patient's physical function.[15]

IA HA is also said to delay patient's progression to the need for Total Knee Replacement (TKR) by approximately 2.2 years.[8] But despite some studies and practices that claim the benefits of IA HA in OA patients, a meta-analysis of "best-evidence" studies found that hyaluronic acid injections do not demonstrate a clinical benefit over placebo in the treatment of knee osteoarthritis. It is also said that despite ongoing use of HA in the treatment of knee OA, the effect size of the injections is not large enough to show a benefit when appropriate blinding and appropriate best evidence are applied to trials involving HA injections.[12,14] Further studies are needed regarding this matter.

3.10 Viscosupplementation versus other treatments

Analgesics- First line treatment in OA according to international guidelines, including paracetamol, opioid and NSAIDs.[10]

Paracetamol is usually well tolerated (although digestive toxicity has recently been highlighted), but effect is slight. Opioids show greater analgesic effect, but with poor tolerance, especially in the elderly (risk of falls). NSAIDs are widely used analgetics in clinical practice. But prolonged use of NSAIDs is not recommended, due to digestive, cardiovascular and renal toxicity. A further analysis of trials directly comparing IA HA and NSAIDs suggests that the effect of IA HA is not significantly different from continuous oral NSAIDs in the short term, at 4 and 12 weeks for pain, function, and stiffness in knee OA.

Injection site pain was the most common adverse event reported in the HA group, and gastrointestinal (GI) adverse events were more common in the NSAIDs group. This result suggests that IA HA might be a good alternative to NSAIDs for knee OA, especially for older patients or in those at greater risk for NSAID-induced adverse effects.[8,10]

Miller et al. found it is perplexing that the AAOS does not recommend HA injections for symptomatic knee OA citing lack of efficacy, but it does recommend non steroidal anti-inflammatory drugs. This is despite numerous reports that HA injections are safe and that efficacy of HA is at least comparable, if not superior, to that of nonsteroidal anti-inflammatory drugs.[16]

Table 2: Different technical characteristics of HA injections[10]

Aspects	Knee	Hip	Shoulder	Ankle	Metacarpo phalangeal
Approach	Lateral latero-patellar	Anterior or antero-lateral	Anterior or posterior	Antero-medial or anterior	Lateral
Guidance	No, except difficult cases	Radioscopy or ultrasonography	Radioscopy> ultrasonography	No, or radioscopy > ultrasonography	Radioscopy or ultrasonography
Quantity per injection	2–6 ml (single-injection)	2-4 ml	2-4 ml	2-3 ml	0.5-1 ml
Schedule	3 injections (1 per week) or single-injection	2–3 injections (1 per month) or single-injection	1–3 injections (1 per week or per month)	3 injections (1 per week)	1–3 injections (1 per week or per month)

Corticosteroids – Corticosteroids effect is fast but short (about 1 to 3 weeks), whereas that of HA is delayed but lasts several months.[10]

4. Conclusion

Osteoarthritis (OA) is a degenerative joint disease involving the cartilage and many of its surrounding tissues. As the disease progresses, it may cause chronic pain, disability, and deformity.

The aims of treatment are to maintain movement and muscle strength, protect the joint from overload, relieve pain, and modify daily activities. Steroid and analgesics (paracetamol, opioid and NSAIDs) can be used as the pharmacological treatments. Viscosupplementation can also be considered as a pharmacological regiment, especially in elderly patients who cannot tolerate the side effects of analgesics. IA HA is recommended for knee OA, but the result of this procedure seems uncertain for other locations of OA, including shoulder, ankle, and hip.

References

[1] Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. British medical bulletin. 2013 Jan 20;105(1):185-99.
[2] Solomon S, Warwick D, Nagayam S. Apley's system of orthopaedics and fracture. 5th ed. London: Hodder Arnold; 2010. p. 83-96
[3] Allen KD, Golightly YM. Epidemiology of osteoarthritis: state of the evidence. Current opinion in rheumatology. 2015 May;27(3):276.
[4] Lozaada CJ. Osteoarthritis Treatment & management [Internet]. Medscape. 2018 [cited 2018 Jul 20]. Available from: https://emedicine.medscape.com/article/330487-treatment#d1
[5] Salter RB. Textbook of disorders and injuries of the musculoskeletal system. Maryland: Lippincott Williams & Wilkins;1999. p.257-66
[6] Hayashi D, Roemar FW, Guermazi A. Imaging for osteoarthritis. J Rehab. 2016 Jun; 59(3): 161-9. doi: 10.1016/j.rehab.2015.12.003
[7] Banciu M, Tuduce P, Marian L. Viscosupplementation in Osteoarthritis. Arad Medical Journal. 2010:5-9.
[8] Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. InSeminars in arthritis and rheumatism 2016 Feb 1 (Vol. 45, No. 4, pp. S28-S33). WB Saunders.
[9] American Academy of OrthopaedicSugeons. Viscosupplementation for knee osteoarthritis [Internet]. OrthoInfo. 2015 Jun [cited 2018 Jul 21]. Available from: https://orthoinfo.aaos.org/en/treatment/viscosupplementation-treatment-for-knee-arthritis/
[10] Legré-Boyer V. Viscosupplementation: techniques, indications, results. Orthopaedics& traumatology, surgery & research: OTSR. 2015 Feb;101(1 Suppl):S101.
[11] American Academy of OrthopaedicSugeons. Viscosupplementation treatment for arthritis [Internet]. OrthoInfo. 2009 [cited 2018 Jul 21]. Available from: https://www.arlingtonortho.com/images/stories/footanklehandouts/Viscosupplementation%20Treatment%20for%20Arthritis%20-%20OrthoInfo%20-%20AAOS.pdf
[12] Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for osteoarthritis of the knee: a systematic review of the evidence. JBJS. 2015 Dec 16;97(24):2047-60.
[13] Kelly JC. Viscosupplementation for knee OA: little gain, big risks [Internet]. Medscape. 2018 [cited 2018 Jul 20]. Available from: https://www.medscape.com/viewarticle/765492
[14] Stanton T. Taking a second look at effectiveness of viscosupplementation [Internet] AAOS Now. 2016 Jan [cited 2018 Jul 20]. Available from: https://www.aaos.org/AAOSNow/2016/Jan/Clinical/clinical2/
[15] Thomas T, Amouroux F, Vincent P (2017) Intra articular hyaluronic acid in the management of knee osteoarthritis: Pharmaco-economic study from the perspective of the national health insurance system. PLoS ONE 12(3): e0173683. https://doi.org/10.1371/journal.pone.0173683
[16] Miller LE, Altman RD, McIntyre LF. Unraveling the confusion behind hyaluronic acid efficacy in the treatment of symptomatic knee osteoarthritis. Journal of pain research. 2016;9:421.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4918943