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Role of Viscosupplement in Knee Osteoarthrosis

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Abstract

Degenerative osteoarthrosis (OA) of the knee is a chronic degenerative joint disease characterized by articular hyaline cartilage destruction with resultant para-articular bone changes. Multiple treatment options are available for knee OA, ranging from conservative management to total knee arthroplasty(TKA). Viscosupplementation with intra-articular injection of hyaluronic acid formulations is a valuable option in the gamut of conservative management. It has demonstrated moderate but significant efficacy versus placebo in terms of pain and function, with a high rate of responders (60–70%) in mild to moderate osteoarthrosis knee. In this review article, we had analyze the various types of viscosupplements available,current evidence for use of viscosupplements in OA knee and guidelines for its use of in appropriate situations.

Keywords: Knee; Osteoarthrosis; Viscosupplements; Hyaluronic Acid.

Introduction

Osteoarthrosis (OA) is a age related degenerative joint disease that frequently affects weight bearing joints of the body[1]. Osteoarthrosis is the eighth leading cause of physical impairment, with knee joint being the most commonly affected joint. Globally, the prevalence is estimated at 18% of women and 10% of men among individuals aged 60 years and older[2].In India, the prevalence of osteoarthrosis ranges from 22% to 39% and is the second most common rheumatological disease[3].The pathogenesis of knee osteoarthrosis is characterized by an imbalance between synthesis and degradation of cartilage matrix, resulting in a slow degradation of cartilage occurring over several years. Thinning or erosion of articular cartilage is followed by osteophyte formation, joint space reduction, subchondral bone remodeling with inflammation of the synovial membrane[2]. Clinically, the patient with OA suffers from chronic pain, stiffness, limited mobility and very high medical expenditure, which will have economic burden too[1].

There are more than fifty modalities of treatment for OA, which can be non-surgical or surgical. The main non-surgical treatment options include pharmacological management using analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids and disease-modifying drugs for osteoarthrosis (DMDOA) like glucosamine, chondroitin, avocado and soybean unsaponifiable extracts and diacerein. The physical or mechanical interventions include off-loading orthoses, acupuncture, exercises, body and mind therapies. Another important non-surgical tool is intra-articular injections of corticosteroids and hyaluronic acid formulations (viscosupplementation) [4]. Hyaluronic acid (HA) is a high-viscosity polysaccharide that is produced naturally by the B cells of the synovial membrane[2]. The main functions of synovial fluid such as a lubrication, scavenging free radicals, and regulation of cellular activities such as binding of proteins, are due to the rheological properties of HA[5]. The synovial fluid from osteoarthritic joints is lower in elasticity and viscosity than that from normal joints[6]. The progression of osteoarthrosis results in depolymerization of HA and it changes from a high molecular weight (6500–10,900 kDa) into a lower molecular weight (2700–4500 kDa) substance. This consequently diminishes the mechanical and viscoelastic properties of the synovial fluid in the affected joint[7].

Viscosupplementation consists of injection of exogenous hyaluronic acid into degenerative joints, with the aim of restoring the rheological properties of the synovial fluid, thereby producing mechanical, analgesic, anti-inflammatory and chondroprotective effects[4]. Viscosupplements do not restore or replace the full properties and activities of the depolymerized endogenous HA of the synovial fluid, but it may induce satisfactory pain relief via several mechanisms including anti-inflammatory effect, synthesis of proteoglycan and/or glycosaminoglycan, and viscoelasticity maintenance[1,7]. Real-world functional outcome of exogenous HA is not without controversies, with some studies reporting an overall beneficial effect, while others reporting only a small benefit. The efficacy of intra-articular HA has been investigated extensively in randomized controlled trials (RCTs) and subsequently in various systematic reviews and meta-analyses. Peak effectiveness of intra-articular HA is reached between 1 and 2 months and residual effects exist for up to 6 months[8,9,10]. Few systematic reviews have questioned the benefit of viscosupplementation on pain and function in patients with symptomatic osteoarthrosis of the knee because of increased risks for serious and local adverse events[11,12].

Types of Viscosupplements: Are they all the same?

Based on the molecular weight, HA preparations are of two broad types: hyaluronans (unmodified hyaluronic acid) and hylans. Hyaluronans are low/medium weight fractions of HA obtained from

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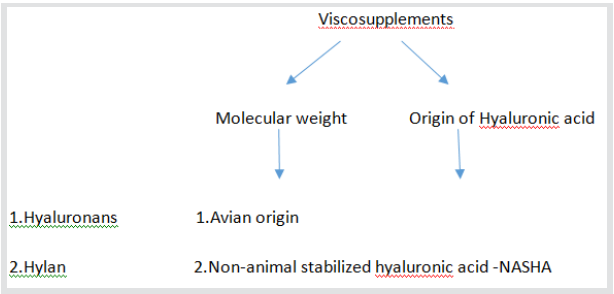
Table 1: Guideline for use of viscosupplements in knee osteoarthrosis.	
Guideline committee	**Recommendation for IA HA**
European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthrosis (ESCEO)	Recommended for advanced pharmacological management in persistent symptomatic patients if still symptomatic after intermittent or longer cycles of oral NSAIDs.
National Institute of Health and Care Excellence (NICE)	Recommends against the use of intra-articular viscosupplementation.
European League Against Rheumatism (EULAR)	Evidence to support efficacy. Limitations: logistic and cost issues.
American College of Rheumatology (ACR)	No recommendation in the initial management. Conditionally recommended if no satisfactory response to prior treatments.
Osteoarthrosis Research Society International (OARSI)	Uncertain but possible for knee OA after physician patient interaction. Not appropriate for multi-joint OA.
IA HA- intra-articular hyaluronic acid; OA- osteoarthrosis; NSAIDs- non-steroidal anti-inflammatory drugs.	



animal-derived raw materials (often rooster combs or bovine). Hylans, on the other hand have high molecular weight and are chemically cross-linked derivatives of hyaluronans[13].

Hyaluronans- There are long-chain molecules of avian or biofermenation origin, with a molecular weight of between 0.5 and 1.8 x 106 Da. As with endogenous HA, hyaluronans are readily degraded by free radicals, and because of their unbranched nature, even a small number of breaks can result in a profound decrease in their molecular size. Consequently, the ability to provide lubricating and shock-absorbing functions may be rapidly reduced. The hyaluronan preparations typically have residence times of <24 hours within the knee joint which was demonstrated in animals studies[13]. Hyaluronan preparations are generally well tolerated, with only minor, transient injection site reactions reported[14]. Hyaluronans are produced using HA extracted from minced rooster combs and although the products are purified, the small risk of eliciting anaphylactic reactions, particularly among patients with known allergies to avian products, cannot be eliminated[15]. With hyaluronans, one injection per week should be applied, for three to five weeks. Certain limitations of Hyaluronans are rapid elimination of hyaluronan preparations from the affected joint, which means the requirement for multiple injections cannot be avoided and they usually have a molecular weight that may not be high enough to restore the rheologic properties of the synovial fluid[13].The need for multiple injections and short residence time of hyaluronans paved the way for Hylan.

Hylan- The hyaluronan molecule is chemically modified by means of cross-links, with a liquid phase (of higher molecular weight (around 6x106 Da), through cross-linking connections between long chains of hyaluronan, and a solid portion (of infinite molecular weight) formed by even greater presence of links[1]. The advantage of hylan is that the molecular size is increased, which improves rheologic properties and increases residence time within the joint. Secondly, because of the large number of cross-links, numerous molecular breaks are required to reduce molecular size.[13].

Non-animal stabilized hyaluronic acid (NASHA)- Non-animal stabilized hyaluronic acid (NASHA) produced by a two-step,bacterial synthesis of HA followed by carefully controlled stabilization (cross-linking). NASHA possesses greater resistance to degradation within the body and consequently increased intra-articular residence time. NASHA may be rheologically superior to the endogenous HA found in young healthy joints and have higher biocompatibility due to absence of animal protein[13].

Current evidence for Viscosupplements in Knee OA

Far from a consensus, there is not even general agreement for the use of exogenous HA in knee osteoarthrosis. A systematic review and meta-analysis by Rutjes came to the conclusion that viscosupplements in patients with osteoarthrosis knee is associated with a small and clinically irrelevant benefit but with an increased risk for serious adverse events[12].A compliant systematic review of overlapping meta-analysis by Xing D demonstrated that HA is an effective intervention in treating knee OA without increased risk of adverse events[16]. Evidence from real-life setting trials and surveys by E. Maheu et al found an improvement in pain or function lasting up to 40 months (12 months after the last treatment cycle). They also observed reduction in use of concomitant analgesia by up to 50% and a delay in the need for total knee arthroplasty by around 2 years. They advised further prospective long-term controlled trials or surveys to confirm the findings of this study[17].A randomized controlled double-blind trial by vander Weegen et al concluded that symptoms improved significantly up to 6 months after 3 weekly injections of HA. However, there was no additional benefit over placebo treatment for patients with radiological confirmed mild to moderate knee OA[18]. An evidence based analysis by Bhandari showed that the full therapeutic value of intra-articular HA therapy is especially pronounced for higher molecular weight preparations. They also concluded that exogenous HA is safe and effective option for patients with mild to moderate knee OA failing first-line pharmacological therapy[19]. Another metanalysis by the French Osteoarthrosis Study Group concluded that intra-articular HA provides a moderate but real benefit for patients with KOA compared to placebo [20]. Another systematic review and meta-analysis to compare the efficacy of multiple versus single hyaluronic acid injections concluded that overall, 2–4 and ≥5 injection regimens provided pain relief over intra-articular saline, while single injection did not[21]. A randomised controlled trial by Hermans on the effectiveness of high molecular weight hyaluronic acid for knee osteoarthrosis in patients in the working age, concludedintra-articular high molecular weight -HA added to usual care and is effective for knee osteoarthrosis in patients in the working age group[8]. Hence, current evidences is very conflicting, being partly for and against the use of exogenous HA. One of the potential reasons for the variable effect of HA treatments on OA patients is level of hyaluronidases in the synovial fluid, which degrade hyaluronic acid through cleaving the β(1–4) linkages of HA, fracturing the large molecule into smaller pieces before degrading

PEARLS OF WISDOM
• Viscosupplements represent a variety of commercially available preparations of Hyaluronic acid. Not all are the same.Their mechanical and chemical properties must be understood before use.
• Intra-articular injection of hyaluronic acid has a role in the conservative management of osteoarthrosis.
• Benefit is greater if used in early to moderate OA only and in the absence of mechanical symptoms.
• Knee effusion if present during injection, must be aspirated to improve efficacy of viscosupplements.
• Inflammatory arthritis is not a good indication of IAHA and must be avoided in this setting.
• The decision to use IAHA in a patient must be made after thorough discussion and understanding the potential benefits of this therapy

it[1].

Guidelines for use

There are a large number of guidelines and consensus statements by scientific societies for the management of knee OA. There remains a non-alignment between guidelines with respect to the recommended role of viscosupplementation for knee OA. Some of these are summarized in Table 1.

European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthrosis algorithm for the management of knee OA suggests that viscosupplementation be positioned after NSAIDs, and considers these agents safe and effective[22]. The National Institute of Health and Care Excellence (NICE) specifically recommends against the use of intra-articular viscosupplementation[23]. The European League Against Rheumatism (EULAR) guidelines recommend intraarticular HA based upon level 1B evidence for both pain reduction and joint functional improvement[24]. The American College of Rheumatology (ACR) recommended the use of intra-articular hyaluronic acid injection for the treatment of OA of the knee in adults and stated that HA injection is clinically indicated for management of OA in patients who are not good candidates for surgery or who do not respond to other treatment options[25]. The Osteoarthrosis Research Society International guidelines for the nonsurgical management of knee OA provide an "uncertain" recommendation based on the heterogeneity of study results in the literature[26].The Royal Australian College of General Practitioners states that there is evidence to suggest that hyaluronic acid is of some benefit for OA of the knee[27].The 2013 American Academy of Orthopaedic Surgeons guidelines for knee OA, which strongly recommended against the use of IAHA in patients with knee OA, changed their stance in 2014, suggesting that IAHA could be used as a supplementary tool in knee OA, based on the surgeon's clinical discretion[3].

Conclusions

The administration of intra-articular hyaluronic acid is an important adjunct in the non-surgical treatment of mild to moderate knee osteoarthrosis. Although there is no strong scientific backing for the use, indication or advantages for this modality of treatment, it nonetheless is an important tool in the armamentarium of the surgeon. The usage is each instance is best discussed with the patient and then a decision made based on discretion.

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