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REVIEW ARTICLE

AN OVERVIEW OF VISCOSUPPLEMENTS: THERAPEUTIC MODALITY FOR THE AILMENT OF OSTEOARTHRITIS**Kapoor D*, Vyas RB, Lad C, Patel M**

Dr. Dayaram Patel Pharmacy College, Sardar baug, Station Road, Bardoli, Dist – Surat, Gujarat, India, Pin-394601

*Corresponding Author's Email: dev7200@gmail.com, Contact Info - +91-7874223242

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ABSTRACT:

Osteoarthritis is a multifarious joint disease and is caused by inflammatory mediators, along with a procedure of wear and tear of cartilage. Osteoarthritis outcome in cartilage degradation, synovial inflammation, subchondral bone eburnation, degeneration of menisci, and capsular hypertrophy, which takes part in the pathogenesis of Osteoarthritis. Pain is the leading symptom of Osteoarthritis. However the precise mechanism causing pain is multifactorial and is still not well known. Viscosupplementation with intraarticular hyaluronic acid promotes chondrocyte hyaluronic acid synthesis and prevents the additional cartilage degradation and may possible help to promote the cartilage regeneration. It is also postulated to diminish the production of inflammatory mediators and matrix metalloproteinase involved in Osteoarthritis. Viscosupplementation decline osteoarthritis symptoms in early to judicious Osteoarthritis, and improves functional outcome, if other conservative treatment modalities are ineffective. Hyaluronic acid (HA) is the major constituent of a 1---2µm layer on the surface of articular cartilage; it is also a major constituent of synovial fluid. HA has many properties including exerting an anti-inflammatory effect, it acts as a lubricant when movements in the joint are slow and as a shock absorber when movements are fast effect. Viscosupplementation relieves the symptoms of osteoarthritis of the knee, and this therapeutic effect may last several weeks. However, it is apparently not much greater than that of placebo and, according to some studies, it barely reaches clinical significance. Its pain-relieving effect seems comparable to that of other non-surgical options. The modest clinical benefit of viscosupplementation may never be great enough to outweigh its disadvantages, which include slow onset of action, the need for several weekly injections, the low but present risk of adverse reactions and the relatively high cost of this treatment. It helps in improving the function in early osteoarthritis knee joint and might delay the need for future knee surgery

Keywords: Joint disorders, intraarticular hyaluronic acid, non-steroidal anti-inflammatory drugs, osteoarthritis**INTRODUCTION**

Osteoarthritis is the major source of functional disability and reduced autonomy in elderly adults. It involves an estimated 21 million people in the United States and represents an important economic problem. The present mainstay of treatment in osteoarthritis is exercise and non-steroidal anti-inflammatory drugs (NSAIDs) to control pain and stiffness, but neither has the ability to modify the course of the disease. The revision rates in the long term results of THA have been estimated 33 to 45%. Generally young adults suffer from secondary rather than primary osteoarthritis. Several troubles at birth or later during growth may injure the hip joint producing disadvantageous biomechanics, which cause cartilage breakdown. Osteoarthritis is the most common form of chronic arthritis worldwide. Hyaluronan and hylan products provide opportunity to treat OA in individual knee joints.^{1,2} Osteoarthritis mostly affects the cartilage. Cartilage is the tissue that covers the ends of bones in a joint. When healthy, cartilage allows bones to glide

over one another and provides a "shock absorber" function. The normal knee joint also contains a small amount of fluid called synovial fluid, which is a thick, gel-like substance that cushions the joint and provides lubrication to reduce friction. In osteoarthritis, the surface layer of cartilage breaks down and wears away. Adding to the problem, the synovial fluid in your knees loses its ability to lubricate the joint. This combination causes pain and stiffness, limitation of joint motion, and some inflammation in your knees.³⁻⁷

Non-pharmacological modalities are important and include patient education, exercises, weight reduction, sometimes walking with support (crutches) during acute phase, bracing of the knees, shoe modifications and modification of insoles to provide varus or valgus thrust to knee. Local heat and cold, massage, acupuncture, and electromagnetic therapy are also found to be helpful in subset of patients. Pharmacologic treatment is mainstay and includes mostly acetaminophen or paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), sometimes opioids, and drugs which slow down

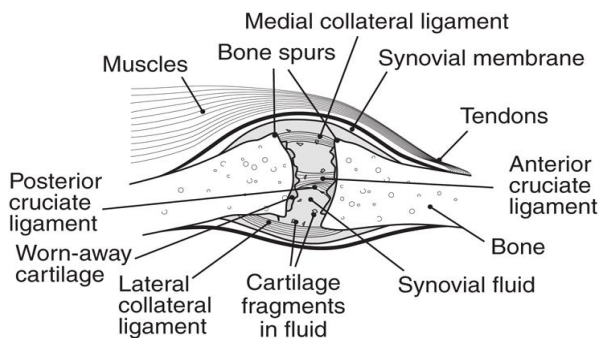
cartilage degeneration like glucosamine and chondroitin sulphate. These drugs which slow down cartilage degeneration are used in oral form, and are usually slow-acting drugs (glucosamine and chondroitin sulphate) and if orally administered, these drugs are usually not much effective. Intraarticular (IA) injection with corticosteroids, Hyaluronic acid (HA) and recently platelet rich plasma (PRP) is the last on list of non operative management. Intraarticular Hyaluronic acid (HA) has the ability of restoring normalization of synovial fluid viscoelasticity and also activates tissue repair process in articular cartilage.⁸⁻¹⁰

In its early stages, arthritis of the knee is treated with nonsurgical methods. Your doctor may recommend a range of treatments, including:

- Changes in activity level
- Weight loss
- Pain relievers, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen
- Physical therapy
- Corticosteroid injections

Another treatment option is a procedure called viscosupplementation. If you have tried all other nonsurgical treatment methods and your pain continues to limit your activities, viscosupplementation may be an option.

The actual changes to the joint surfaces can be seen below:



VISCOSUPPLEMENTATION:

Hyaluronic acid is a naturally occurring substance present in the synovial fluid of your joints. In your knees, synovial fluid, a thick gel-like liquid, helps cushion your joint and absorb the shock of walking, running, twisting, and turning. People with osteoarthritis of the knee have lower levels of hyaluronic acid in their synovial fluid. Therefore, their joints are less “greased” and less able to protect the bones and cartilage from damage and destruction. Viscosupplementation, a popular treatment for Osteoarthritis of the knee, injects hyaluronic acid (also called hyaluron and hyaluronate) into the affected knee in order to hopefully return some mobility to the joint. In this procedure, a gel-like fluid called hyaluronic acid is injected into the knee joint. Hyaluronic acid is a

naturally occurring substance found in the synovial fluid surrounding joints. It acts as a lubricant to enable bones to move smoothly over each other and as a shock absorber for joint loads. People with osteoarthritis have a lower-than-normal concentration of hyaluronic acid in their joints. The theory is that adding hyaluronic acid to the arthritic joint will facilitate movement and reduce pain. The most recent research, however, has not found viscosupplementation to be effective at significantly reducing pain or improving function. Although some patients report pain relief with the procedure, some people are not helped by the injections. Viscosupplementation was first used in Europe and Asia, and was approved by the U.S. Food and Drug Administration in 1997. Several preparations of hyaluronic acid are now commercially available.

MECHANISM OF ACTION

Hyaluronic acid (HA) is a glycosaminoglycan which is naturally occurring and is a normal component of synovial fluid and the cartilage matrix. Moreover, cells from synovium, chondrocytes and fibroblasts synthesis the hyaluronic acid and then secrete it into the joint. Hyaluronic acid enhances the joint function due to normalization of synovial fluid viscoelasticity, and acts as a lubricant and also a shock absorber in nature during the different phases of joint movements. It also has the ability reduces stress on hyaline cartilage and also tends to reduce friction on joint cartilage. Hyaluronic acid is also a important constituent of proteoglycans of the extracellular matrix. Hyaluronic acid also is postulated to be anti inflammatory, mild analgesic and activates the tissue repair process of the articular hyaline cartilage.¹¹⁻¹⁴

ADVANTAGES:

- Safe and effective
- Improves patient assessed pain
- Low rate of complications
- Ha products of higher molecular weight may be more effective than those of lower molecular weight

DISADVANTAGES:

The disadvantages of viscosupplementation were that patients with less recent diagnoses were less likely to advantage than those with more current diagnoses. In other words, patients with more strict radiographic changes also have responded less. The potential adverse events associated with viscosupplementation include joint effusion, joint swelling, arthralgia, joint warmth, and injection-site erythema.

Synvisc injections provide relief through "viscosupplementation". The goal is to restore the natural elasticity and viscous properties of synovial fluid. Synvisc is one of the hyaluronates used in viscosupplementation, other hyaluronates include:

- Euflexxa
- Hyalgan
- Orthovisc
- Supartz

Euflexxa

Euflexxa is one of the hyaluronates used in viscosupplementation. Euflexxa is a treatment for osteoarthritis which is injected directly into the knee joint. Euflexxa is the first hyaluronic acid that is not derived from an avian source.

Euflexxa is a solution of highly purified hyaluronan (also called hyaluronic acid or sodium hyaluronate) in saline. The hyaluronan in Euflexxa is extracted from bacterial cells. It is the first non-avian derived hyaluronan.

Euflexxa is one of the hyaluronates used in viscosupplementation. Euflexxa is injected directly into the knee joint to restore the cushioning and lubricating properties of normal synovial fluid (i.e., joint fluid). Knee joints affected by osteoarthritis lose their lubricating properties.

Indication for Euflexxa:

Euflexxa was approved by the U.S. FDA on December 3, 2004 for the treatment of knee pain associated with osteoarthritis in patients who have failed to respond to more conservative non-drug therapy (e.g., physical therapy) and to simple analgesics, such as acetaminophen. Euflexxa is administered as a series of three weekly intra-articular injections.

Contraindications for Euflexxa:

People with a known hypersensitivity to hyaluronan products should not be treated with Euflexxa. Also, people with an infection in the knee joint, other infection, or skin disease in the area where the injection would occur should not be treated with Euflexxa.

Common Side Effects and Adverse Events:

The most common adverse events associated with Euflexxa treatment during clinical studies included arthralgia (joint pain), back pain, pain in the arms or legs, musculoskeletal pain, and joint swelling. Adverse events that may occur with any intra-articular injection include arthralgia, joint swelling, joint effusion, injection site pain, and arthritis.

Precautions and Warnings:

After receiving an intra-articular injection of Euflexxa, as with any joint injection, it is recommended that the patient avoid strenuous activities or prolonged weightbearing activities for 48 hours. Also, it should be noted that pain or swelling may occur after the injection, but will diminish after a relatively short time period.

Hyalgan:

Hyalgan is a viscous solution that contains purified natural sodium hyaluronate (Hyalectin) in physiological saline. Hyalgan is one of the hyaluronates used in viscosupplementation -- a treatment that involves injecting a gel-like substance (hyaluronate) into a joint to supplement the viscous properties of synovial fluid. The injected viscosupplement helps to cushion the joint and provides lubrication to reduce friction that occurs

with movement. With osteoarthritis, synovial fluid loses its lubricating properties and the goal of viscosupplementation is to restore those properties.

Indications for Hyalgan:

Hyalgan was approved by the U.S. Food and Drug Administration (FDA) on May 28, 1997 as a treatment option for knee osteoarthritis. It is considered a treatment, not a drug. The sodium hyaluronate in Hyalgan is extracted from rooster combs. Hyalgan is indicated for patients with pain related to knee osteoarthritis who have failed to achieve relief with conservative non-drug treatments and with simple analgesics, such as acetaminophen

Administration of Hyalgan:

Hyalgan is an intra-articular injection typically given once a week, one week apart, for a total of 5 injections. Some patients may achieve a successful outcome after 3 weekly cycles, based on study results of patients who received 3 injections and then were followed for 60 days.

Precautions and Warnings:

There are several precautions and warnings associated with Hyalgan intra-articular injections:

- The safety and effectiveness of Hyalgan in joints other than the knee has not been studied.
- If a patient has allergies to avian proteins, feathers, or eggs, injection should be done with caution.
- There may be pain or swelling with the injection that will subside. It is advised, as with all intra-articular injections, that patients not participate in strenuous or weightbearing activity for 48 hours after the injection.
- The safety and effectiveness of Hyalgan injections has not been established in pregnant women, nor in lactating women. Its use has not been studied in children.

SIDE EFFECTS AND ADVERSE EVENTS:

Common side effects associated with Hyalgan injections include gastrointestinal issues, injection site pain, knee swelling or effusion, local skin rash, itching, and headache. Most side effects are injection site reactions which subside after a few days, especially with rest and application of ice. Attention must be paid to symptoms which persist and may be indicative of something more severe, such as infection or systemic allergic reactions. Such severe adverse events are considered rare.

Synvisc:

Synvisc is one of the hyaluronates used in viscosupplementation. Synvisc is a treatment for osteoarthritis which is injected directly into the knee joint. Synvisc injections are approved for the treatment of osteoarthritis of the knee in those who have failed to respond to more conservative therapy.

Synvisc-One (hylan G-F 20):

Synvisc-One is the only viscosupplement approved as a one-dose injection. The FDA indicates that this viscosupplement is designed to provide up to six months of OA relief after just one injection. The most common side effects of a Synvisc-One injection include swelling around the affected joint and pain and stiffness in the joint.

Synvisc (hylan G-F 20):

Unlike Synvisc-One, Synvisc requires three injections of hyaluronic acid. The effects of the injection can last as long as six months. The side effects of Synvisc are similar to the side effects of Synvisc-One — pain, swelling, and fluid buildup around the affected joint.

Orthovisc:

Orthovisc is one of the hyaluronates used in viscosupplementation. Orthovisc is a treatment for osteoarthritis which is injected directly into the knee joint.

Supartz (sodium hyaluronate):

This viscosupplement is given as a three- or five-dose injection. A three-dose injection series provides relief for up to six months. A greater number of injections may provide a longer window of pain relief. The most common side effects of a Supartz injection include pain, effusion (swelling in the joint), redness and bruising at the joint, and injection site pain.

THE MORE SERIOUS SIDE EFFECTS OF VISCOSUPPLEMENTS

Typical side effects of viscosupplement injections are mild — redness, swelling, skin irritation at the injection site — but serious side effects are possible. Contact your doctor's office immediately if you begin experiencing any of the following side effects:

- closing of the throat

- difficulty breathing
- hives
- swelling of the lips, tongue, or face

You may be having a more serious reaction to the injection and need medical attention.

Long term perspective:

Viscosupplements are new to the treatment scene. We know how they work in the short term, but their effectiveness over longer periods of time isn't yet known. Specifically, doctors are uncertain how the use of viscosupplements over the course of a person's life will affect health. Research is also not clear on how viscosupplementation affects the long-term trajectory of osteoarthritis of the knee. While it does provide comfort and pain relief for some people with mild to moderate osteoarthritis, it may not prevent or even delay the likelihood that a patient will need knee replacement surgery at a later point in their life.

Effectiveness:

When successful, viscosupplementation can provide knee osteoarthritis **pain relief for 3 months or even a year**, with the greatest pain relief typically found between 5 and 13 weeks.

Hyaluronic Acid vs. Hylans:

Hyaluronic acid, which is naturally found in joint fluid, is sometimes referred to as **hyaluronan, hyaluronate or HA**.

Substances called hylans are **derivatives of hyaluronic acid**, meaning the two are chemically similar. The term viscosupplementation includes hyaluronic acid as well as hylan injections. Both types of injection therapies aim to decrease pain and improve joint movement.

Table 1: Viscosupplementation Dosing

Drug	Dose
Euflexxa (1% sodium hyaluronate)	20 mg once a week (1 week apart) for a total of 3 injections.
Gel-Syn (0.84% sodium hyaluronate)	16.8 mg once a week (1 week apart) for a total of 3 injections
GenVisc 850 (sodium hyaluronate)	25 mg once a week (1 week apart) for a total of 5 injections
Hyalgan (sodium hyaluronate)	20 mg once a week (1 week apart) for a total of 5 injections.
Monovisc (high molecular weight hyaluronan)	88 mg (4 ml) one time injection
Orthovisc (high molecular weight hyaluronan)	30 mg once a week (1 week apart) for a total of 3 to 4 injections.
Supartz (sodium hyaluronate)	10 mg once a week (1 week apart) for a total of 5 injections.
Synvisc One (Hylan G-F 20)	48 mg one time injection.
Synvisc (Hylan G-F 20)	16 mg once a week (1 week apart) for a total of 3 injections.
Gel-One (Cross-linked Hyaluronate)	30 mg (3 ml) one time injection

Adverse effects of viscosupplementation injections:

The most commonly reported side effects associated with the injections are temporary injection-site pain; swelling, heat, or redness; rash and itching; bruising

around the joint; and fluid accumulation in the injected knee. These reactions are usually mild and don't last long. As with steroid injections, infection and bleeding are also rare complications.[15]

REPORTED WORK ON VISCOSUPPLEMENTS:

- Vignon (2005) concluded that to date, in the absence of placebo-controlled studies, the effectiveness of intra-articular injections of hyaluronic acid or its derivatives in the symptomatic treatment of hip OA can not be determined conclusively. Nevertheless the published data suggest that viscosupplementation may be effective. These researchers stated that double-blind, controlled studies are needed to confirm these data, before viscosupplementation should be included into the treatment paradigm for patients with hip OA.¹⁶
- Migliore et al (2006) reported the effects of hylan G-F 20 administered through ultrasound (US)-guided intra-articular (IA) injections in patients with symptomatic hip OA. They treated 30 patients with symptomatic hip OA. Under US guidance, 7 patients received 1 injection, 21 patients had 2 injections, and 2 patients received 3 injections, each with 2 ml of hylan G-F 20. Lequesne index, visual analog scale (VAS) scale of hip pain, and NSAID consumption were evaluated at baseline as well as 2 and 6 months after the beginning of the treatment. No systemic adverse events were observed.¹⁷
- Van den Bekerom et al (2008) evaluated the effectiveness of viscosupplementation in the treatment of hip OA. A total of 16 articles concerning the effectiveness of a total of 509 patients undergoing viscosupplementation for hip OA were included -- 12 European studies, 3 Turkish studies and 1 American study with levels of evidence ranging from I to IV evaluated the following products: Hylan G-F 20, Hyalgan, Ostenil, Durolane, Fermatron and Orthovisc. Heterogeneity of included studies did not allow pooled analysis of data. The authors noted that despite the relatively low level of evidence of the included studies, viscosupplementation performed under fluoroscopic or ultrasound guidance seems an effective treatment and may be an alternative treatment of hip OA.¹⁸
- Carpenter and Motley (2008) noted that although anecdotal data exist, no long-term studies regarding the use of viscosupplementation in the ankle have been published to date. These researchers compared pain reduction following ankle arthroscopy versus that following ankle arthroscopy combined with weekly intra-articular instillation of hylan G-F 20 during the first 3 post-operative weeks. They found that both treatment groups experienced statistically significantly decreased pain following the intervention ($p = 0.002$ and $p = 0.0009$ for the arthroscopy alone and arthroscopy plus hylan groups, respectively), and that those who received 3 intra-articular injections of hylan G-F 20 following ankle arthroscopy improved statistically significantly ($p = 0.0014$) more than did those who underwent arthroscopy as a sole therapy.¹⁹
- Cleary and colleagues (2008) examined the potential effectiveness of HA injection therapy in the treatment of lumbar facet joint arthritis. A total of 13 patients with symptomatic lumbar facet joint arthritis who met the inclusion criteria were prospectively recruited. Pre-treatment evaluation of patients was by questionnaire, including the VAS and Oswestry Disability Questionnaire. A single injection of HA into affected facet joints was then performed, with correct placement confirmed on fluoroscopy. Patients were similarly evaluated 6 weeks after treatment.²⁰
- Conrozier et al (2009) assessed the effectiveness and tolerability of a single intra-articular injection of non-animal-stabilized HA (NASHA) in patients treated for symptomatic hip OA (HOA). A total of 40 patients suffering from HOA were treated by a single intra-articular injection of NASHA in the painful hip under fluoroscopy.²¹
- Vanelli and associates (2010) evaluated the safety and effectiveness of intra-articular polynucleotides (PN) gel injections in the treatment of knee OA associated with persistent knee pain. A total of 60 patients were enrolled and randomized to receive intra-articular polynucleotides ($n = 30$) or hyaluronan ($n = 30$); patients received 5 weekly intra-articular knee injections and the follow-up period was 3 months after the end of treatment.²²
- Manfredini and colleagues (2010) examined the clinical studies on the use of HA injections to treat temporomandibular joint (TMJ) disorders performed over the last decade. The selected papers were assessed according to a structured reading of articles format, which provided that the study design was methodologically evaluated in relation to 4 main issues: (i) population, (ii) intervention, (iii) comparison, and (iv) outcome. A total of 19 papers were selected for inclusion in the review, 12 dealt with the use of HA in TMJ disk displacements and 7 dealt with inflammatory-degenerative disorders.²³

CONCLUSION:

The price of injection is also a chief issue in India for the multiple doses over the NSAIDs, steroid and Platelet rich plasma intraarticular injections. The Hyaluronic acid (HA) injections had a good safety profile with fewer local reactions. Most of the subjects coming to hospital wherein grade I and II of OA knee. 3 weekly doses of 2ml HA is found to be potentially effective in terms of symptomatic pain relief and functional outcome. This may also prolongs the need of total knee arthroplasty in patient with early OA. But long term study is needed to evaluate its role in cartilage regeneration

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