INTRODUCTION

The purpose of visco-supplementation in an osteoarthritic joint is to introduce hyaluronic acid into the joint to provide an initial lubrication and shock absorption along with a long-term goal of changing the disease process of the joint.

Hyaluronic acid (HA) is a high molecular weight polysaccharide and a major natural component of the synovial fluid and the extracellular matrix of the cartilage. It is a glycosaminoglycan consisting of repeating units of glucuronic acid and N-acetylglucosamine, bound together by a glycoside bond beta. HA is synthesized by chondrocytes in the cartilage and fibroblasts of the synovial lining known as synoviocytes. The HA synthesized by the former becomes integrated in the cartilage matrix, whereas the synoviocyte HA is released in the synovial cavity. In degenerative joint diseases the average molecular weight and concentration of HA in the synovial fluid is reduced, as well as the HA and proteoglycan content of the extracellular matrix of the cartilage. The rationale for use of HA is based not only on the concept of fluid replacement or viscosupplementation, but also on the mounting evidence that HA plays a major role in biological activation or biosupplementation that may decrease the symptoms, as well as the disease progression. The fact that all injected HAs are gone within days and yet the clinical benefit lasts for months suggests that biological activation is the dominant mechanism by which HAs mediate their clinical benefit.

PATHOLOGY OF OSTEOARTHRITIS

With respect to the ankle, arthritis is predictable after repeated soft tissue injuries or an intra-articular fracture. The incidence of ankle arthritis after ankle fracture is seen even after surgical anatomic reduction, yet anatomic repair may delay the onset due to restoration of optimal function and alignment. Patients are informed of this from their initial injury and understand this is an unfortunate sequelae of their injury.

CHARACTERISTICS OF COMMERCIAL VISCOSUPPLEMENTS

There are currently 5 visco-supplements that are approved by the Food and Drug Administration (FDA). These are Hylgan, Supartz, Synvisc, Orthovisc, and Euflexxa. The hyaluronic acid in the first 4 is extracted from chicken combs, while Euflexxa is bioengineered and thus absent of any proteins that may cause reactions in some patients. Although these are FDA approved for use in the body, they are not specifically FDA approved for use in the foot and ankle.

The molecular weight of physiologic HA is 4-5 million Daltons. In a diseased joint however, molecular weight of the HA is reduced as the intrinsic HA starts to degrade. The molecular weight of the visco-supplements available in the US range from 0.6-6 million Daltons. What is interesting, is some studies show an advantage to using low to intermediate-weight HA. The weight (in millions of Daltons) of the available viscosupplements is: Hylgan 0.5-0.7, Supartz 0.6-1.2, Synvisc 6, Orthovisc 1-2.9, and Euflexxa 2.4-3.6. Synvisc contains 8 mg/ml of HA while Hylgan, Supartz, and Euflexxa contain 10 mg/ml of HA. Orthovisc contains 15 mg/ml of HA.

Are all the hyaluronans created equal? Will all the injected materials produce the same clinical response? As discussed earlier, the half-life of all these products is only several days, yet the clinical response is often seen for much longer, sometimes upwards to one year. The efficacy of the injections is not just due to lubrication and cushioning of
the diseased joint. Smith and Ghosh discussed the optimum molecular weight to facilitate the maximum amount of receptor binding. The receptor binding serves to provide the "biologic activation" of the joint and its synovial and chondrocyte receptors. This should equate to the maximum stimulation of intrinsic hyaluronic acid production, which seems to relate directly to the disease modifying properties of these medications. As soon as the half-life wears off, it is important for the HA receptors inside the cell to be tightly bound. For optimum signal and binding, it is recommended for the Hyaluronan to be between 0.5–4 million daltons, whereas suboptimal binding seems to occur when the MW is under 0.5 million daltons or over 4 million daltons. Due to this fact, the lower molecular weight products may be more ideal for the optimum binding to occur. Synvisc possesses the highest viscosity and possibly the best for joint cushioning, but that is only part of the picture.

Hyalgan and Supartz require 5 weekly injections while Synvisc, Orthovisc, and Euflexxa require 3 weekly injections. The well known clinical trial from Altman and Moskowitz, which gained FDA approval in the knee was performed with a 5 injection protocol. Therefore, other investigators have also recommended 5 injections with the lower molecular weight (Hyalgan, Supartz) hyaluronans. Three injections have usually been reserved for the higher weight products.

**PHYSIOLOGY OF VISCO-SUPPLEMENTS**

Besides the mechanical qualities of increasing viscosity and elasticity in the synovial fluid, HA injections also produce several favorable physiological changes. They decrease inflammation within the joints. They also increase the synthesis of endogenous hyaluronic acid by stimulating the production by the synovium. These qualities seem consistent with the fact that the HA placed within the joint is absent after a short period of time, but long-term clinical benefits are observed well after the product is gone.

Studies have also shown the disease modifying benefits of visco-supplementation. The 3 parameters that have been well documented to show joint repair are: slow down of joint space narrowing, improvement in cartilage lesions from arthroscopic examination, and improvement in structural features of the biopsied chondrocytes. There is no placebo or injectable material that boasts these modifying benefits, and long term cortisone injections have been shown to be detrimental to cartilage viability.

**RESEARCH OF HYALURONIC USE IN THE FOOT AND ANKLE**

There are few controlled trials involving the lower extremity. Salk et al used a double-blinded, placebo-controlled trial to show the efficacy of five weekly injections of HA (Hyalgan) in the ankle compared with normal saline. The patients were allowed to continue their activities of daily living with no assistive device. This study showed that the study group receiving HA had a clinically significant decrease in pain compared with the placebo, which was phosphate-buffered saline. This particular study was the first well-designed, carefully controlled study to have been performed to assess efficacy of HA for foot or ankle osteoarthritis.

In addition to the therapeutic effects of hyaluronans before surgical treatment there have been studies that have shown its positive effects with perioperative and postoperative use. Carpenter and Moxley performed a study that showed that postoperative injections of HA (Synvisc) for 3 weeks after ankle arthroscopy was efficacious compared with ankle arthroscopy alone. The first injection was given 1 week after the arthroscopic procedure. The patients were allowed to be partial weight bearing with the use of crutches and a walking cast for the first week postoperatively, then full weight bearing for the next 2 weeks. The walking cast was then discontinued after the third week.

Petrella et al performed a placebo-controlled study on acute lateral ankle sprains. In this study, they performed peri-articular injections of either HA or saline on the day of and four days after the injury. Their study showed an overall decrease in pain and a quicker return to activity. Pons et al performed a study comparing the single injection of 1 ml of HA (Ostenil) into the first metatarsophalangeal joint to 1 ml of corticosteroid (triamcinilone acetonide) in the treatment of hallux rigidus. The patients in both arms of the study were to refrain from strenuous activity for a day after the injection. This study, which was single-blinded, showed an improvement in pain and function in the HA group compared to the corticosteroid group at 12 weeks follow-up. This study, conducted in Spain, did not involve a hyaluronate approved for use in the US.
ADMINISTRATION OF VISCOSUPPLEMENTS

The administration of HA can be performed in the office without the need of ultrasound or fluoroscopic guidance. Considering that the protocol requires at least 3 weekly injections (3 for Orthovisc, Euflexxa, Synvisc; 5 for Supartz and Hyalgan), it may be helpful to alternate the injection site between the medial and lateral arthroscopic portals. The medial portal is medial to the tibialis anterior tendon and the lateral portal is lateral to the dorsal cutaneous nerve. An anterior central portal between the tibialis anterior and EHL tendon may also be helpful depending on the areas of damage.

At times, it is extremely difficult to find multiple portals of entry into an arthritic joint. Once an entry point is found for deep administration into the joint, it may be necessary to stay with the same approach throughout the treatment series. First, an aseptic prep is performed over the site. Next, a subcutaneous injection of local anesthetic is given to ease the placement of the larger gauge needle. The needle is inserted into the ankle joint and an aspiration is performed to make sure it is indeed within the joint. Then, all 3 milliliters of the HA are injected into the joint. The authors have also injected directly into the joint using a 25G needle without a preinjection wheal, and have found the viscosity of the fluid easily travels through the needle without the need for a larger diameter. Fluoroscopic guidance may also be beneficial, but not necessary with careful clinical and radiographic evaluation prior to injection.

It may be more beneficial to use fluoroscopy when injecting into the subtalar joint. Due to the general lack of this imaging within the clinic, the posterolateral portal is a possible option used for this joint. The patient is placed in the prone or lateral position while the needle is inserted towards the subtalar joint between the peroneal tendons and the Achilles tendon at the level of the tip of the fibula. Another approach is into the anterior aspect of the posterior facet from the sinus tarsi.

The first metatarsophalangeal joint is injected utilizing a dorsomedial and dorsolateral portal, with an option to alternate the approach each visit. The technique is the same as an injection of cortisone, which requires an angles approach that is proximal-dorsal to distal-planter. This will help to avoid additional damage to the articular cartilage. The technique of this injection enjoys the benefit of being able to distract the hallux to aid placement.

The patient does not need transportation arrangements and can carry out their activities while not engaging in high impact activities such as running. The most common side effects of HA injections are pain, local swelling, and erythema around the injection site. Patients who are allergic to chicken or egg products should not use any HA besides Euflexxa due to the risk of a reaction to the non HA proteins.

At this time, the use of viscosupplementation in the foot and ankle is not FDA approved for these locations. Salk et al showed both safety and efficacy in their ankle study and anecdotal reports have also showed the same. Hopefully these initial reports will stimulate interest for the companies to pursue further clinical trials and multicenter studies and seek FDA approval. Currently, patients will pay for the actual material used for each injection, although the patient visit and injection procedure is covered. The cost of each vial is roughly $100 to the medical office and adds up quickly when the recommended multiple injections are involved.

SUMMARY

In the recent past, nonsurgical treatment of osteoarthritis remained limited to rest, immobilization, physical therapy, activity modifications, nonsteroidal anti-inflammatory drugs, analgesics, weight loss, assistive devices for walking, and corticosteroid injections. The use of viscosupplementation is a welcome addition to the nonsurgical armamentarium that physician have to treat osteoarthritis. Additional studies are required, however, to test the safety and efficacy of this treatment in other parts of the foot.

REFERENCES


