Current Concepts

The Use of Hyaluronan After Arthroscopic Surgery of the Knee

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Abstract: Viscosupplementation is defined as the use of intra-articular hyaluronan therapy for symptomatic osteoarthritis (OA). Originally used for the treatment of ophthalmic disorders, viscosupplementation has been available for over a decade in the United States for the treatment of pain secondary to OA of the knee in patients who have not responded adequately to conservative oral pharmaceuticals including nonsteroidal anti-inflammatories and simple analgesics. The majority of patients with symptomatic knee OA will have evidence of meniscal and/or articular surface pathology, and most orthopaedic surgeons include arthroscopic surgery as a possible treatment modality for the symptomatic patient. Although arthroscopic meniscectomy is the most commonly performed orthopaedic procedure in the United States, in patients with concomitant OA, disease-related pain can persist after arthroscopic surgery. This article reviews some of the more recent evidence recommending the use of viscosupplementation for the management of symptomatic knee OA and pain relief after arthroscopy.

Osteoarthritis (OA) is the leading cause of disability in the United States[1] and one of the leading causes of disability throughout the world.[2] It is a chronic degenerative disorder recognized by joint pain, stiffness, and effusion. OA can be idiopathic (primary) or secondary to trauma, and it can be contributed to by anatomic congenital abnormalities or other diseases, such as metabolic or neuropathic illnesses. Obesity, anatomic abnormalities, and loss of joint stability place abnormal stresses on the joint, leading to cartilage changes and degradation. Aging, genetic predisposition, inflammation, and immune system activity can also play a role in abnormal cartilage changes. In addition, cartilage degradation can be caused by biochemical changes, such as an increase in levels of proteolytic enzymes or a reduction in their inhibitors. Collectively, the previously mentioned factors contribute to chronic low-grade inflammation, swelling, and pain in the symptomatic disease state.

VISCOSUPPLEMENTATION FOR OA TREATMENT

Viscosupplementation has been used for more than 2 decades internationally for the treatment of OA. Hyaluronan products are indicated in the United States for the treatment of pain in OA of the knee in patients who have not responded adequately to conservative nonpharmacologic therapy and to simple analgesics, such as acetaminophen.[3-7]

Viscosupplementation had been accepted by the American Academy of Orthopaedic Surgeons (AAOS), American Pain Society, and American College of Rheumatology, as well as Medicare and private third-party payers, as a treatment for osteoarthritic knee pain. However, in December 2008 the AAOS stated, "We cannot recommend for or against the use of intra-articular hyal-

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uronic acid for patients with mild to moderate symptomatic OA of the knee." The AAOS study group determined the Level of Evidence of the studies reviewed to be Level I and II, and their grade of recommendation was regarded as "inconclusive."[8] However, the use of viscosupplementation in the treatment of OA of the hip, shoulder, ankle, elbow, and back is common in other countries, and expanded indications are limited to off-label status in the United States. Viscosupplementation has been supported by numerous clinical trials and postmarketing studies,[9-27] and the efficacy of hyaluronic acid has been supported by several meta-analyses.[28-30]

Hyaluronan is a unique macromolecule, having a number of distinct biophysical, biochemical, and cell regulatory functions in synovial cells as well as other tissues. Hyaluronan is highly coiled at rest, such that when a force is rapidly applied to the molecule, it cannot uncoil and acts as an elastic body. If a direct force is applied slowly, as would occur while walking, the molecule unwinds and acts as a viscous lubricant. The combination of these two properties is critical for resisting compressive forces and reducing friction between opposing surfaces of cartilage and depends on the presence of a physiologic concentration of hyaluronan in the synovial fluid. Initially, these rheological properties were believed to be the primary mechanism by which hyaluronan therapy was beneficial in treating OA pain.

However, during the past decade, researchers have shown a number of other properties that likely play a dominant role in the efficacy of this treatment. Rather than being merely a device, as hyaluronan is registered with the Food and Drug Administration, it is also a biologically active molecule. It is well known that joint residence times range from several hours to several days, depending on the product, which may explain why efficacy dosing protocols vary from 3 to 5 injections.

The biochemical effects of hyaluronan (Table 1) include inhibition of tissue nociceptors, stimulation of endogenous hyaluronan, direct anti-inflammatory effects, and inhibition of matrix metalloproteinase (MMP) activity. Hyaluronan has been shown to inhibit nociceptive action potentials when applied to the sciatic nerve[31] and to inhibit the effects of the pain mediator substance P.[32] Increased production of endogenous hyaluronan with exogenous hyaluronan has recently been shown in a study from Australia in which concentrations of hyaluronan were measured in knee aspirates at the time of viscosupplementation and again 3 months and 6 months later.[33] The mechanism by which this effect was shown has yet to be explained, but correlates with the positive clinical effect of the therapy, which can last from 6 to 12 months or longer after initial treatment. In a repeat treatment study, Waddell et al.,[34] showed a mean time to the second course of hylan G-F 20 of 19 months in 70 patients. One patient in this study did not require repeat treatment until 39 months after the first course of therapy.

Another mechanism-of-action study, by Marino et al.,[35] showed a significant reduction in MMP activity after interleukin 1β stimulation. Under the direction of an IRB approved protocol, human synovial cells obtained at the time of surgery and commercial obtained human immune globulin 82 rabbit synovial cells were cultured. After incubation with interleukin 1β, the supernatant was placed on a standardized collagen cell plate and allowed to digest the collagen. MMP activity was calculated from optical density measurements as previously validated.[36] Both native hyaluronan and cross-linked hylan (hylan G-F 20) were shown to inhibit MMP activity when their concentrations exceeded 2 mg/mL. Higher–molecular weight substances such as hylan G-F 20 were shown to be more effective in producing this effect. By showing an ability to inhibit MMP activity, this study raises the possibility of the disease-modifying capability of viscosupplementation, although further laboratory data and long-term studies using radiographs and possibly magnetic resonance imaging cartilage assessment will be necessary to substantiate this theory.

TABLE 1. *Biochemical Effects of Hyaluronan*

Inhibits tissue nociceptors
Stimulates endogenous hyaluronan formation
Has anti-inflammatory effects
Inhibits MMP activity

INTRA-ARTICULAR HYALURONAN AFTER ARTHROSCOPIC SURGERY

Arthroscopic knee surgery, specifically meniscectomy, is the most commonly performed orthopaedic procedure in the United States.[37] Creamer and Hochberg[38] proposed a widely accepted treatment paradigm that incorporated intra-articular hyaluronan injections together with other treatments, including nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors, analgesics, physical therapy, intra-articular steroids, and surgery (e.g., arthroscopic debridement, lavage, meniscectomy, and total joint replacement). Arthroscopic surgery, used in the treatment of OA, has generated

Table 2. *Clinical Effects of Hyaluronan*

Author	Type of Study	Findings
Marshall et al.[45] (1996)	Meta-analysis	68% with severe OA did not progress to TKA S/P tx
Chen et al.[46] (2002)	Level I study: hyaluronan S/P scope	VAS scores increased in hyaluronan patients
Dai et al.[47] (2002)	Level I study: hyaluronan S/P scope	VAS scores increased in control group
Rolf et al.[48] (2005)	Level I study: hyaluronan *v* placebo	Patient symptoms improved with hyaluronan and hylan
Mathies[49] (2006)	Viscoseal S/P meniscectomy	Decreased effusion and pain
Hempfling[50] (2007)	Level I study: hyaluronan *v* control	Decreased pain up to 1 yr
Ulucay et al.[51] (2007)	Level I study: hylan G-F 20, Orthovisc, Adant, and S/P scope	Improved pain relief
Huang et al.[52] (2007)	Level I study: hyaluronan S/P anterior cruciate ligament repair *v* saline solution	Hyaluronan increased results
Zietz and Selesnick[53] (2008)	Level I multicenter study	Increased VAS scores S/P scope for OA

Abbreviations: TKA, total knee arthroplasty; S/P, status/post scope; tx, treatment.

much discussion as to its efficacy in this treatment algorithm. Moseley et al.[39] reported no difference between placebo arthroscopy, arthroscopic debridement, and arthroscopic lavage in a randomized, prospective, double-blind study of 180 patients. However, recent studies confirm that in patients with preoperative mechanical symptoms secondary to loose bodies, chondral flaps, and meniscal pathology, arthroscopic surgery is beneficial.[8,40]

More than 90% of patients with symptomatic knee OA will have magnetic resonance imaging evidence of meniscal pathology.[41] Contrary to the report of Moseley et al.,[39] Matsusue and Thomson[42] reported an 87% positive response in patients with arthroscopic meniscectomy in the presence of OA grade I or II. Furthermore, Bin et al.[43] noted in a patient population with a mean age of 63 years that 25% had grade IV Outerbridge[44] changes on the femoral condyle at the time of arthroscopic meniscectomy, yet 90% had subjectively improved after arthroscopic meniscectomy by use of visual analog scale (VAS) scores and Lysholm scores. Most orthopaedic surgeons include arthroscopic surgery as a treatment modality offered to patients with meniscal pathology with mild or moderate OA. However, in patients with symptomatic OA, pain can still persist after arthroscopic meniscectomy and/or debridement of chondral lesions. Treatment combining arthroscopic surgery and viscosupplementation has been widely used for patients with combined intra-articular mechanical and articular surface pathology.

Marshall et al.[45] were one of the first groups to report the use of intra-articular hylan G-F 20 in patients with continuing pain after arthroscopic debridement (Table 2). This study, published in 1996, included patients who had undergone arthroscopic debridement and intra-articular steroid injection. Most of these patients had "marked" or "severe" OA. Patients not progressing to total knee replacement were rated as "salvaged"; 68% of those studied were included in this group.

In 2002 Chen et al.[46] reported on 77 patients with OA receiving sodium hyaluronate after knee arthroscopy. In this Level I study one group received sodium hyaluronate and the other group received no injections. Knee muscle strength index and patient VAS pain score were statistically better in the hyaluronate group ($P < .05$). It was concluded that hyaluronic acid was a positive factor in the rehabilitation of these patients with knee OA after arthroscopy.

In 2002 Dai et al.[47] studied the use of hyaluronan injections postoperatively in both arthroscopic and open knee surgery. Of the patients studied, 134 had undergone arthroscopic knee surgery and 91 open knee surgery. A control group of 85 patients received no injections, whereas the remaining patients were injected with 4 mL of hyaluronan at the end of the procedure and 2 mL of hyaluronan at 5 days postoperatively. VAS scores determined the endpoint for pain and were significantly lower in the hyaluronan group. Painless range of motion was reached at day 6 postoperatively in the hyaluronan group and at day 9 in the control group. The authors concluded that hyaluronan was effective in reducing postoperative knee pain. This study, however, did not address OA or long-term pain relief associated with the intra-articular injections.

Rolf et al.[48] reported the results of a study in 2005 comparing hyaluronan and placebo in patients with symptoms after a diagnosis of OA was confirmed

arthroscopically. The 272 patients received Synvisc (hylan G-F 20; Genzyme, Cambridge, MA), Artzal (sodium hyaluronate; Seikagaku, Tokyo, Japan), or saline solution injections. At week 26, 44% of the patients receiving hylan G-F 20 were symptom free, whereas 43% of those receiving sodium hyaluronate and 30% of those receiving placebo had no complaints. Synovial fluid from the 3 groups was studied, and no changes were found.

In 2006 Mathies[49] assessed the use of Viscoseal (0.5% sodium hyaluronate, TRB Chemedica International, Geneva, Switzerland) immediately after arthroscopic surgery. Ten milliliters of sodium hyaluronate was injected immediately after arthroscopic partial meniscectomy. Joint swelling was judged to be less at day 12 ($P = .0093$) and day 28 ($P = .0072$). Diclofenac intake was less in the sodium hyaluronate group as well as at postoperative days 3 and 7. No adverse events were reported. The authors concluded that the use of Viscoseal may be of benefit in reducing postoperative pain and swelling.

In 2007 Hempfling[50] reported the results of a randomized, controlled, double-blind study of 80 patients undergoing arthroscopic knee joint lavage with Ringer's lactate. Forty of the patients also received 10 mL of hyaluronan. Both the control and study groups had positive effects at 3 months, but the treatment effect was maintained in the hyaluronan group for up to 1 year.

Ulucay et al.[51] in 2007 published a prospective, randomized, controlled study of 77 patients with knee OA receiving either hylan G-F 20, Orthovisc (sodium hyaluronate; Anika Therapeutics, Woburn, MA), or Adant (synthetic hyaluronic acid; Tedec-Meiji Failma, Madrid, Spain) 3 weeks after arthroscopic surgery. Patients in all groups showed statistically significant improvements from baseline at week 3 after injection.

In 2007 Huang et al.[52] reported a prospective, randomized, controlled study of 120 patients undergoing isolated anterior cruciate ligament reconstruction. The study attempted to determine the optimum time for hyaluronan injection. The active groups received 2 mL of hylan G-F 20 at week 4, 8, or 12 after reconstruction, whereas the control group received saline solution. The authors concluded that hyaluronan therapy resulted in more functional muscle rehabilitation. The group receiving hyaluronan at week 8 had the most improved clinical results 1 year after surgery.

Zietz and Selesnick[53] in 2008 published a small, prospective, multicenter, open-label study of 15 active, athletic patients with knee OA who underwent knee arthroscopy for mechanical symptoms. If patients reported residual pain or activity limitations postoperatively, they were treated with hylan G-F 20 with a mean initiation of treatment 3.4 months after arthroscopy. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and International Knee Documentation Committee scores significantly improved at baseline and at 3 and 6 months postoperatively compared with scores before arthroscopy. The authors also reported improved activity levels associated with hylan G-F 20 administration at 3 months' follow-up.

Huskin et al.[54] in 2008 published a multicenter, prospective, open-label study evaluating the safety and efficacy of hylan G-F 20 in patients with knee OA presenting with pain after arthroscopic meniscectomy. The study was performed in several centers in Belgium, France, and Spain and was the first study to prospectively evaluate the efficacy and safety of intra-articular injections of hylan G-F 20 in patients with symptomatic knee OA not responding to simple analgesics 4 to 12 weeks after arthroscopic meniscectomy. At the time of initial surgery, arthroscopic procedures, in addition to meniscectomy, included resection of unstable flaps and superficial mechanical shaving. To be eligible for the study, OA had to be shown at the time of surgery. Patients with Outerbridge grade I, II, and III OA were enrolled in the study, whereas those with grade IV OA were excluded. Of those enrolled, 84% of the knees showed patellofemoral grade I OA, whereas 16% had grade II changes. Medial and lateral OA changes were mostly limited to grade I, although 40% had grade II medial changes and 20% had grade II lateral changes. The mean time to viscosupplementation after surgery was 53 days (range, 27 to 107 days). The initial study population consisted of 62 patients, but only 43 patients completed the study. Statistically significant improvement was noted in mean VAS pain score while walking, which was reduced from 65.0 mm to 28.0 mm at week 26 ($P < .0001$). WOMAC scores, VAS walking pain scores, physician global assessment, and patient assessment all showed statistically significant positive results at all other time points. The authors concluded that viscosupplementation with hylan G-F 20 had a favorable risk-benefit profile in patients with symptomatic knee OA presenting with persistent pain after arthroscopic meniscectomy.

DISCUSSION

This review is not intended as a formal meta-analysis of the literature regarding viscosupplementation

after arthroscopic surgery but rather is intended to report the relevant literature that has been published to date in this area. Viscosupplementation has become a major treatment available for the management of symptomatic OA of the knee in the United States. Expansion of its indications for use has occurred in countries throughout the world. For years, the use of viscosupplementation with arthroscopy has been anecdotally advocated. However, experience documented in randomized, double-blind studies showing the efficacy and safety of the combination of arthroscopy and viscosupplementation has now been published. Some physicians are now using intra-articular hyaluronan in active athletes. Mandelbaum and Waddell[55] have coined the term "chondropenia" to describe the early osteoarthritic changes associated with extreme, high-performance athletic activities. It is unknown whether viscosupplementation plays any role in the prophylactic treatment of the etiology of this disease.

We currently use a protocol of viscosupplementation for treating patients after arthroscopy. If a patient has had an arthroscopic procedure for mechanical problems and is found to have Outerbridge grade I to III OA changes intraoperatively, viscosupplementation after arthroscopy is considered. If the patient's symptoms abate and a normal recovery/rehabilitation course is achieved, viscosupplementation usually will not be recommended. However, if after arthroscopy the patient with OA remains symptomatic and is found to have Ahlback[56] grade I radiographic changes without complete joint space collapse on a standing knee radiograph, then he or she would be considered a candidate for hyaluronan injections.

The time interval from arthroscopy until viscosupplementation injection in these patients is generally 4 to 8 weeks. The WOMAC scores for such patients are usually between 40 and 60, with a score of 2 or greater on question A-1 (pain walking on a flat surface). If the patient has Ahlback grade II or Kellgren-Lawrence[57] grade IV OA, indicating complete joint space collapse, total knee arthroplasty should be seriously contemplated. Some patients with early grade IV OA who either do not or cannot have total knee arthroplasty because of medical comorbidities represent another group in which viscosupplementation after arthroscopy may be considered. Viscosupplementation after arthroscopic surgery will generally be performed in a person having Ahlback grade I or Kellgren-Lawrence grade II to III radiographic OA before arthroscopy on their standing knee radiographs with or without flexion views, in whom meniscal pathology or significant chondral lesions or loose bodies are felt to be the primary cause of symptoms. Symptoms may have only developed briefly preoperatively in these individuals, with the diagnosis of OA concurrent with that of their meniscal, chondral, or loose body intra-articular pathology.

CONCLUSIONS

The literature reviewed supports the use of viscosupplementation for symptomatic OA after arthroscopy. Some surgeons anecdotally advocate immediate intra-articular hyaluronan for postoperative pain relief or improved muscle rehabilitation. However, additional studies will be necessary to support the use of viscosupplementation beyond its OA indications. Currently, it appears that in the presence of symptomatic OA after arthroscopic treatment of pathology causing mechanical knee symptoms, viscosupplementation serves a definitive role in helping to reduce symptoms of pain and improve function in a significant number of patients.

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