# Randomized Prospective Evaluation of Adjuvant Hyaluronic Acid Therapy Administered After Knee Arthroscopy

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## Abstract

**Intra-articular injections of hyaluronic acid products may eliminate pain, improve mobility and quality of life, and delay osteoarthritis progression.**

**In this study, we evaluated the safety and efficacy of sodium hyaluronate injections given after knee arthroscopy. Forty-six patients with early osteoarthritis and a symptomatic meniscus tear were prospectively randomized into study (injection) and control groups and underwent knee arthroscopy. Study patients received 3 sodium hyaluronate injections after surgery.**

**Study and control outcomes were compared 3 and 6 months after surgery. The injection patients had significantly less pain (visual analog scale) at 3-month follow-up and more flexion at 6-month follow-up. Tenderness, pain on motion, and crepitus were significantly more likely to be absent from injection patients at the 3- and 6-month follow-ups.**

**Patients with osteoarthritis and a symptomatic meniscus tear may experience more pain relief and functional mobility after arthroscopic surgery plus hyaluronic acid injections than after arthroscopy alone.**


It is widely accepted that patients with symptomatic meniscus tears can respond well to treatment with knee arthroscopy and partial meniscectomy, but some of these patients have chondromalacia of the knee noted before or during surgery. In some cases, preoperative magnetic resonance imaging (MRI) demonstrates chondromalacia in the same compartment as the meniscus tear as well as in other compartments of the knee; in other cases, preoperative MRI demonstrates only the meniscal pathology, and the surgery reveals the chondromalacia. In either scenario, the patient's outcome may be adversely affected by early osteoarthritis, in spite of the treatment for the meniscus tear.

Osteoarthritis, the most common form of arthritis, affects approximately 15.8 million US patients between the ages of 25 and 74.[1] Treatments for osteoarthritis vary widely, according to disease stage. Patients with osteoarthritis have a low concentration of hyaluronic acid in the synovial fluid, which makes them more susceptible to cartilage injury involving significant pain and swelling.[2] Treatment with sodium hyaluronate has been shown to increase the viscoelastic properties of the synovial fluid and repair the articular cartilage by improving cellular metabolism.[2-7] In patients who have osteoarthritis and symptomatic meniscus tears and who have not improved with standard treatment regimens, such as anti-inflammatory medications, physical therapy, weight loss, and exercise programs, viscosupplementation consisting of intra-articular injections of hyaluronic acid may be used.

We conducted this randomized, prospective study to evaluate the safety and efficacy of combining knee arthroscopy with a series of sodium hyaluronate injections in patients with early osteoarthritis and meniscal pathology.

## Materials and Methods

The study was approved by our institutional review board, and all participants signed a consent form. Patients who had symptomatic, MRI-confirmed meniscus tears and who were indicated for knee arthroscopy were screened for inclusion in this study. To qualify, patients had to be 40 years old or older, report a minimum pain intensity of 4 or higher on the visual analog scale (VAS) for pain (0 = no pain, 10 = excruciating pain) in the signal knee and less than 3 in the contralateral knee after walking 50 feet on a flat surface, have no recent trauma, have radiographic evidence of Kellgren-Lawrence stage II or III osteoarthritis,[8] have osteoarthritis-compatible symptoms for at least 6 months, have pain in the signal knee for at least 50% of the days during the month before screening, and have flexion of 90° or more. Participants had to be willing to refrain from using all nonsteroidal anti-inflammatory drugs (NSAIDs) for 14 days before the study, agree not to use any NSAID besides acetaminophen (up to 1,000 mg 4 times per day as needed), and discontinue use of acetaminophen at least 24 hours before each office visit for the

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**Table I. Significant Outcomes at 3-Month Follow-Up**

| Outcome | Control | Injection | *P* |
|---|---|---|---|
| Visual analog scale | 2.33 (SD, 2.311) | 0.76 (SD, 1.490) | .015 |
| Swelling | 16/20 (80%) | 3/23 (13%) | <.001 |
| Tenderness | 17/20 (85%) | 2/23 (9%) | <.001 |
| Pain on motion | 13/20 (65%) | 2/23 (9%) | <.001 |
| Effusion | 12/20 (60%) | 1/23 (4%) | <.001 |
| Bulge sign | 7/20 (35%) | 0/23 (0%) | .002 |
| Patellar ballottement | 4/20 (20%) | 0/23 (0%) | .039 |
| Crepitus | 15/20 (75%) | 5/23 (22%) | .001 |

**Table II. Significant Outcomes at 6-Month Follow-Up**

| Outcome | Control | Injection | *P* |
|---|---|---|---|
| Flexion in treated knee (°) | 123.53 (SD, 7.199) | 128.37 (SD, 6.465) | .036 |
| Tenderness | 10/19 (53%) | 3/19 (16%) | .038 |
| Pain on motion | 10/19 (53%) | 1/19 (5%) | .003 |
| Crepitus | 16/19 (84%) | 7/19 (37%) | .007 |

duration of the study. Patients taking low-dose aspirin (325 mg/d or less) had to remain on a stable dose throughout the study and not take aspirin 24 hours before office visits. Patients had to be willing to abstain from nonstudy intra-articular or periarticular injections in the study knee for the duration of the study. Ability to complete efficacy questionnaires and to understand and read English or Spanish was also necessary for study participation.

Exclusion criteria included medical conditions that would confound attempts to measure the effectiveness of the study injections (osteoarthritis of either hip, rheumatoid arthritis, infection, arthritis of metabolic origins, acute fracture, severe loss of bone density, avascular necrosis, severe deformity, lower limb axial deviation of more than 15° in valgus or varus, fibromyalgia, osteonecrosis, severe peripheral neuropathy, instability, hemiparesis, active skin infection, vascular insufficiency), prior hyaluronic acid injections (within 12 months in the study knee or 6 months in another joint), and known hypersensitivity to sodium hyaluronate. Patients were also excluded if they were women who were pregnant, nursing, or not using reliable contraception; if they had allergies to hyaluronan or related products; if they had excessive alcohol consumption or known current addiction to pain medications; if they had a flare of gout or calcium pyrophosphate disease (pseudogout) within 6 months before screening; if they had undergone intra-articular or local periarticular corticosteroid injections or oral corticosteroid use within the previous month (3 months in study knee), an arthrogram of the signal knee within 3 months of screening, major injury or surgery to the study or contralateral knee within 1 year, or ligament reconstruction within 3 years or ever undergone articular procedures; or if their doses of glucosamine- or chondroitin sulfate–containing products or biphosphates had been inconsistent or their physical therapy regimens unstable.

Fifty patients were enrolled and assigned to the study or control group using a randomization table provided by the institutional statistician before surgery. Patients were not notified of their assignment until their surgery had been completed. The first visit included screening, informed consent, and preoperative assessments including knee radiographs and preoperative MRI evaluation. Mean age was 59.3 years (range, 42-81 years), and mean body mass index was 29.0 (range, 19.8-38.2). Four patients were enrolled and completed the first visit but did not schedule arthroscopy and were excluded from all data analysis. Forty-six patients completed all 3 injection (or control) study visits.

All patients underwent a knee arthroscopy with partial meniscectomy and débridement. A high-molecular-weight fraction of purified sodium hyaluronate, the study medication, was provided by Sanofi-Aventis (Paris, France) in sterile injection kits. Study group patients received their first intra-articular sodium hyaluronate injection immediately after knee surgery in the operating room. The second injection was given 10 to 14 days later, and the final injection was given 1 week later (17-21 days after surgery). All patients were assessed at each of these postoperative visits and at 3 and 6 months after surgery. Repeat radiographs were obtained at the final 6-month follow-up for comparison with the initial radiographs. Forty-three (23 injection, 20 control) patients completed the 3-month follow-up assessment, and 39 (20 injection, 19 control) completed the 6-month assessment. All patients who completed the 3-month follow-up assessment were included in the data analysis, even those who did not complete the 6-month follow-up assessment.

The primary outcome measures were severity of knee pain evaluated by pain VAS and the timed 50-foot walk test. The secondary outcome measures were range of motion, pain on motion, and presence of swelling, effusion, tenderness, crepitus, quadriceps atrophy, popliteal/Baker cyst, bulge sign, patellar ballottement, inflammation, redness, anserine bursitis, prepatellar bursitis, and synovitis. Other aspects of the routine postoperative clinical knee examination

were assessed and documented, including meniscus injury (McMurray maneuver), patellar alignment, and stability of anterior/posterior cruciate ligaments (drawer sign). All patients were examined by the same surgeon at all follow-ups. Pain VAS, 50-foot walk test, and patient assessment questionnaire were administered by a research assistant with training in this area. Radiographic review was performed at the baseline and 6-month follow-ups to assess changes in severity of osteoarthritis over the course of the study. Operative findings on severity of osteoarthritis in the medial patella facet, lateral patella facet, lateral femoral trochlea, central femoral trochlea, medial femoral trochlea, lateral femur, medial tibia, and lateral tibia as well as any ligament tears were recorded during the knee arthroscopy. There were no significant differences between injection and control groups in severity of osteoarthritis or presence and location of ligament tears found during arthroscopy. In the control group, 15 medial meniscal tears and 15 lateral meniscal tears were found; in the study group, 22 medial meniscal tears and 18 lateral meniscal tears were found.

Statistical analysis was performed using SPSS for Windows 13.0 (Chicago, Ill) by our hospital statistician. Chi-square analyses were performed to evaluate the relationships between the injection and control groups for categorical outcomes of interest (eg, swelling, tenderness). A 2-tailed independent-samples *t* test was used to evaluate associations between the injection and control groups for continuous outcomes of interest (eg, pain VAS, flexion). An analysis was also undertaken to ensure that the randomization adequately distributed potential confounding variables, such as age and body mass index. An a priori power analysis was conducted to achieve 80% power for all primary and secondary outcomes of interest with differences believed to be clinically relevant.

## Results

Thirty-nine of the 46 patients completed all 4 postoperative visits (at 10-14 days, 17-21 days, 3 months, and 6 months after surgery). The visits 3 and 6 months after surgery were designated follow-ups because the patients had already received all 3 study injections by then. Three patients did not complete either follow-up: One passed away from an unrelated illness, 1 came in for the 3-month visit out of the acceptable time window, and 1 left the country because of a family emergency. Four patients did not complete the 6-month follow-up: Two refused to come in for the final visit, 1 came in for a visit out of the time window, and 1 had hip surgery, which would have interfered with analysis of knee functioning.

*P*s for clinical variables at the 3- and 6-month follow-ups are listed in Tables I and II. At 3-month follow-up, pain (VAS), effusion, bulge sign, and patellar ballottement were significantly less for the injection group than for the control group. At 6-month follow-up, the injection group had significantly more flexion than the control group. Tenderness, pain on motion, and crepitus were significantly more likely to be absent from the injection group at both follow-ups. There were no significant differences in the timed 50-foot walk test at either 3- or 6-month follow-up (*P*s = .350 and .230, respectively). Radiographs showed no significant differences between the groups in change in severity of osteoarthritis as graded by the Kellgren-Lawrence scale at 6-month follow-up.

## Discussion

Osteoarthritis is a widespread and debilitating disease that affects millions of people in the United States. There are a variety of treatment options, each with its advantages and disadvantages. Although patients with osteoarthritis tend to be older, the population is still diverse and maintains a constant need for new treatments and improvements on existing modalities. Patients with symptomatic meniscus tears may respond well to treatment with knee arthroscopy and partial meniscectomy, but some may also demonstrate chondromalacia of the knee. Such cartilage degradation may be initially noted either before surgery (with preoperative MRI) or during arthroscopy. As image quality varies considerably, preoperative MRI may demonstrate only the meniscal pathology, and the chondromalacia may become evident only during surgery. In either scenario, the patient's response to knee arthroscopy may be adversely affected by early osteoarthritis, in spite of the treatment for the meniscus tear. Hyaluronic acid treatment has the potential to improve outcomes for patients with early osteoarthritis.

**"This study demonstrated that 3 sodium hyaluronate injections given after knee arthroscopy...are more effective than arthroscopy alone for alleviating pain and restoring motion and function to patients with early-stage osteoarthritis and meniscal tears."**

Hyaluronic acid is a major natural component of cartilage and synovial fluid, which is produced by chondrocytes and synoviocytes. It protects the articular cartilage surface and the inner lining of the synovial membrane by contributing to joint lubrication and restoring the overall quality and concentration of the synovial fluid.[9] There are 2 types of hyaluronic acid products: synthetic Hylan and naturally occurring hyaluronan. Several clinical studies have shown that both types of products provide months of pain relief for most patients with knee osteoarthritis.[10-15] These products in development and in use around the world include Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease, Euflexxa, Nuflexxa), Durolane, Fermathron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20),

Hyruan, NRD-101 (Suvenyl), Orthovisc, Ostenil, Replasyn, SLM-10, Suplasyn, Synject, and Zeel compositum.[16]

Hyaluronic acid treatment has the potential to help patients who have not improved with nonpharmacologic treatment regimens, such as physical and occupational therapy, weight loss, and exercise programs. Hyaluronic acid treatment may also help patients in whom NSAIDs have failed or are intolerable or contraindicated. Several clinical studies have shown that this treatment has the potential to relieve pain, improve mobility, and increase quality of life.[1,7,9,13,17] Sodium hyaluronate has demonstrated the highest degree of pain relief and functional improvement in patients with severe, symptomatic osteoarthritis and primary (as opposed to secondary) osteoarthritis.[7,9]

Previous studies demonstrating the benefits of sodium hyaluronate have varied widely with respect to treatment framework, including differences in number of injections, duration of observation period, and target patient population. Altman and Moskowitz[7] and Kotz and Kolarz[17] showed that 5 weekly injections significantly relieved pain in patients with clinically diagnosed osteoarthritis over a 6- or 12-month period. Listrat and colleagues[13] observed the benefits of sodium hyaluronate injections for knee arthroscopy patients. In their study, sodium hyaluronate injections were given weekly over 2 weeks beginning 1 month after arthroscopy and subsequently every 8 months for a total of 9 injections. The treatment indication needs to be evaluated further to determine the most beneficial and cost-effective regimen.

Two recent studies examined use of artificial synovial fluid substitutes to counteract the loss of synovial fluid during knee arthroscopy. Mathies[18] found that Viscoseal, a hyaluronic acid–containing substitute synovial fluid, significantly decreased swelling and NSAID intake during the 4 weeks after surgery. In a longer term study, Hempfling[19] found that introduction of Viscoseal (0.5% sodium hyaluronate) into the knee joint immediately after arthroscopic débridement led to more favorable outcomes 1 year after surgery. The addition of artificial synovial fluid maximized the benefits of knee arthroscopy. Although both these studies used only intraoperative hyaluronic acid product injections and not a series of postoperative injections, they support our hypothesis that use of hyaluronic acid products improves short- and long-term outcomes more than arthroscopy alone does.

In a European investigation, Listrat and colleagues[13] examined the effect of 3 cycles (2 intra-articular injections per cycle) of sodium hyaluronate injections over 1 year after knee arthroscopy. They found statistically significant ($P<.05$) differences in quality of life between patients who received sodium hyaluronate and patients who did not receive injections. This study and our study have shown that the combination of knee arthroscopy and sodium hyaluronate injections is promising. Additional randomized prospective studies are needed to define the most effective number and timing of injections after arthroscopic surgery.

Part of the data collection and analysis for this study involved evaluation of radiographs at 6-month follow-up. There were no significant differences between the injection and control groups in severity of osteoarthritis visible on radiographs, in spite of the fact that previous studies[3,6,20-26] have suggested sodium hyaluronate may slow osteoarthritis progression. Several animal studies[3,6,20-22,24,25] reviewed by Marshall[26] found that hyaluronan induced chondrocyte proliferation and increased their proteoglycan synthesis, which implies that intra-articular hyaluronan may slow progression of osteoarthritis even after it has been cleared from the joint. Ronchetti and colleagues[27] found that, 6 months after 30 patients with primary and secondary osteoarthritis were treated with sodium hyaluronate, the synovial membrane clearly exhibited improved fibrotic activity. This change in structural variables of the synovial membrane suggests that hyaluronan injections slow the evolution of the disease. Listrat and colleagues[13] showed a tendency toward more deterioration in structural parameters in their control group than in a group of patients who received sodium hyaluronate injections, though this difference was not statistically significant.

The major strength of the present study is its randomized, prospective design. As the same surgeon treated all patients, operative techniques and assessments were consistent across subjects. Study weaknesses include the relatively small group sizes, lack of long-term follow-up results, and lack of blinding of patients, surgeon, and research assistant.

## Conclusions

This study demonstrated that 3 sodium hyaluronate injections given after knee arthroscopy (with the first intra-articular injection given at the end of the arthroscopic procedure) are more effective than arthroscopy alone for alleviating pain and restoring motion and function to patients with early-stage osteoarthritis and meniscal tears. The combination of arthroscopic surgery and hyaluronan product injection may have the potential to yield better outcomes than either treatment on its own. Longer follow-up would be necessary to determine if the combination of knee arthroscopy and sodium hyaluronate injections has the potential to further slow the advance of osteoarthritis in addition to providing more pain relief and functional ability than knee arthroscopy alone.

## Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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