Can Viscosupplementation Be Used in the Hip? An Italian Perspective

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abstract

Viscosupplementation is the intra-articular administration of preparations containing hyaluronic acid or hyaluronate intended to restore the normal biological properties of hyaluronic acid normally found in synovial fluid. Infiltration of hyaluronic acid in the arthritic hip is a more recent technique than viscosupplementation of the knee due to the greater technical difficulty of infiltration to the hip, which requires fluoroscopic or ultrasound guidance. The introduction of high-molecular-weight hyaluronic acid in the treatment permits a single administration and has helped diffuse hip infiltration treatment. A single infiltration reduces patient discomfort caused by the procedure and allows treatment of a larger number of patients. Although the literature has unequivocally proven the possibility of reducing pain in patients affected by hip arthritis following infiltration, the molecular weight and density, the number of infiltrations required for long-term results, and the most appropriate indications for infiltration treatment have yet to be clarified. Selecting the patient is the first obstacle to be overcome. Therefore, infiltration should be considered as an option for patients with initial pain symptoms who have not yet been listed for joint prosthesis surgery. The radiographic criteria require at least a partly preserved joint space, and the clinical criteria of persistent hip pain and full joint mobility seem to be sufficiently effective for selection. [Orthopedics. 2014; 37(1):48-55].

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Osteoarthritis in the hip is a major cause of pain and disability in adult and elderly patients. The incidence rate is estimated to be 48 to 88 per 100,000 people per year, depending on sex and age, increasing to 445 per 100,000 women 70 to 79 years old per year. Several guidelines exist for treating the various phases of hip osteoarthritis, all of which include pharmacological and nonpharmacological treatment for the purpose of reducing pain and increasing joint mobility. Pharmacological treatment includes the use of nonsteroidal anti-inflammatory drugs, painkillers, chondroprotective drugs, and infiltration treatment. Rehabilitation treatment and the use of ambulatory aids may help improve mobility. When medical therapy fails, surgery then becomes necessary and may include osteotomy or joint prosthesis.

Viscosupplementation is the intra-articular administration of preparations containing hyaluronic acid or hyaluronate intended to restore the normal biological properties of hyaluronic acid normally found in synovial fluid. As described in the literature, the intra-articular molecule has several properties and functions: physical properties (elasticity and viscosity that make synovial fluid pseudoplastic), anti-inflammatory effects (prevents leukocyte activity and inhibits phagocytosis and cellular adherence), anabolic effects (stimulates the production of endogenous hyaluronic acid by fibroblasts), analgesic activity (inhibits bradykinin levels and nociception), and chondroprotective potential (increases the cartilage matrix). The concentration of hyaluronic acid in an arthritic joint has been found to decrease from one-half to one-third of normal levels, and includes a reduction in molecular size. Molecular interaction has also been observed, with a consequent decrease in elasticity and viscosity of the synovial fluid.

**Characteristics and Mechanism of Action**

The various physical and chemical properties of hyaluronic acid are based on its unique macromolecular structure. It is a long (3-30 µm) chain of repeating disaccharides, joined by N-acetylglycosamine and glucuronic acid linked at points 1 through 4. Intra-articular hyaluronic acid molecules are composed of approximately 12,500 disaccharides. Hyaluronic acid molecules inside joints are prevalently synthesized by type B synovial cells. These cells produce and disperse molecules into the synovial fluid with a variable molecular weight of 2 to 10×10^6 Da depending on the joint and the species. In a healthy adult, the molecular weight of hyaluronic acid in synovial fluid varies between 4 and 5×10^6 Da. Its concentration ranges from 2.5 to 4 mg/mL, which, if the presence of approximately 0.5 to 4 mL of synovial fluid in the human body is assumed, corresponds to a total quantity of hyaluronic acid in a healthy person of approximately 4 to 8 mg.

Several hyaluronic acid formulations for intra-articular infiltration are currently available on the market. Meanwhile, research on preparations, cell response, and short- and long-term efficacy continues. The first difference between commercially available products is their origin. Hyaluronic acid can be derived from an animal (eg, extracted from chicken combs) or can be synthesized by bacterial fermentation. Therefore, hyaluronic acid is available in a number of preparations with widely differing molecular weights (from 500 Kd to more than 90 million D). Cross-linked hyaluronic acid (using a chemical process) has recently been proposed for medical use. The purpose of creating further links within the long polysaccharide chain is to increase the drug’s half-life inside the synovial fluid and, according to some authors, to slow down the inflammatory process by using links to receptors that are found in leukocytes. The behavior of cross-linked hyaluronic acid in vitro has been found to be more viscoelastic and more efficient in creating links with the proteins contained in synovial fluid. However, other studies have shown that the clinical results obtained with non-cross-linked hyaluronic acid are comparable with those obtained with cross-linked preparations, making further clinical trials necessary to verify the real advantage of using cross-linked hyaluronic acid.

The concept of viscosupplementation (ie, aspirating synovial fluid from the affected joint and replacing it with purified high-molecular-weight hyaluronic acid to restore viscoelasticity to the synovial fluid) was introduced in the early 1990s and is based on the reduction properties of hyaluronic acid molecule in the synovial fluid of arthritic joints. Viscosupplementation is the effect of the molecule’s rheological characteristics. The rheological behavior of a preparation containing hyaluronic acid depends heavily on the molecular mass and concentration of the molecule in the preparation. Based on this fact, introducing very-high-molecular-weight or partly cross-linked hyaluronic acid into the arthritic joint is the best therapeutic strategy for optimizing the viscoelastic characteristics of synovial fluid.

Furthermore, some authors have illustrated the gap between the moment of the infiltration treatment’s highest clinical efficacy and clearance of the hyaluronic acid from the treated synovial membrane. Studies in animals have found a half-life of 10 to 13 hours for the radiolabeled drug injected into rabbit joints and a half-life of 20.8 hours for the drug injected into sheep with induced osteoarthritis. In particular, the half-life of high-molecular-weight hyaluronic acid (molecular weight, >6×10^6 Da) was found to be lower (13.2 hours) than the half-life of low-molecular-weight hyaluronic acid (molecular weight, 0.09×10^6 Da) (10.2 hours). Different results were obtained by measuring the half-life of the drug after intra-articular infiltration in the metacarpophalangeal joints of healthy horses: a half-life of 8.9 hours was obtained with high-molecular-weight hyaluronic acid (pm, 2.5×10^6 Da), whereas the average
Other authors suggest record that the possibilities of efficacy, although the half-life has been as long as 1.5 to 9 days. A correlation between the molecular weight of the various preparations available on the market and the clinical efficacy of the treatment could not be found from an analysis of the clinical results published in the literature. The beneficial effects are likely due to the pharmacological and physical properties of the molecule. Not all authors accept the theory that hyaluronic acid has specific receptors in cartilage. However, the function of cell mediator has been proven because it can link to the CD44 receptors, the intracellular adhesion molecule-1, and the receptor for hyaluronic-mediated motility, which are expressed in many cells. This link can activate a number of intracellular signals that can cause cytokines to be released and stimulate protein production. The concept of viscoinduction was introduced on the basis of these findings, which is the molecule’s capacity to induce endogenous hyaluronic acid synthesis. This theory explains the long-term benefit of the treatment, notwithstanding the rapid catabolism of the chains injected into the synovial fluid during infiltration therapy. The presence of cytokines (interleukin-1 alpha and beta, tumor necrosis factor alpha) and interleukin-1 antagonist receptors, the quantity of both that is directly proportional to the severity of the pathology, has also been confirmed in patients affected by osteoarthritis. 

**INDICATIONS**

The problem of identifying whether a patient is suitable for hyaluronic acid infiltration treatment in the hip is increased by the various selection criteria in trials. Some authors consider success with infiltration therapy to be a reduction in pain, proven by the decrease in the use of drugs. Other authors suggest recording the time gained by patients treated with hyaluronic acid infiltration therapy before undergoing joint prosthesis surgery to compare it with that of patients undergoing a different treatment. Although no study has been conducted of the variability in the efficacy of intra-articular hyaluronic acid infiltration therapy in the hip compared with the gravity of the arthritis in the treated joint, it can reasonably be assumed, as in the case of knee joint arthritis, that the possibilities of efficacy and duration of the beneficial effects of the treatment are inversely proportional to the gravity of the disease. Therefore, infiltration should be considered an option for patients with initial pain symptoms who have not yet been prescribed joint prosthesis surgery so that the properties of the drug can be used as effectively as possible to improve the quality of life of coxarthrosis-affected patients. The selection criteria for the candidate patient for infiltration are the following:

1. Hip pain for at least 3 weeks;
2. Radiographic proof of at least partially preserved joint space; and
3. Good or full joint mobility.

Absolute contraindications or nonindications for infiltration therapy due to the negative cost/benefit ratio, where the cost is not merely the financial aspect but also the discomfort of the patient during the infiltration procedure, her/his exposure to radiography, and the possibility of complications, are the following:

1. Severe hip arthritis (coxarthrosis) where no joint space can be found on radiographs;
2. Presence of inflammation, autoimmunity, or septic conditions (rheumatoid arthritis, connective tissue diseases, osteomyelitis); and
3. Surgical indications for a total joint prosthesis.

Observing the indications reduces the number of patients with coxarthrosis who are suited to undergo infiltration, therefore increasing the probability of treatment success.

**INFILTRATION TECHNIQUE**

The anatomical structure of the hip joint makes intra-articular infiltration difficult without the help of radiological guidance. Performing blind hip infiltration is not recommended due to the narrow intra-articular space, the depth of the joint capsule, and the difficulty in identifying the anatomical landmarks compared with other joints. Recommended radiological guidance can be obtained using ultrasound, fluoroscopy, and computed tomography. Direct control over the intra-articular position of the needle and drug ensures safety of the treatment. Ultrasound does not need contrast media and can be repeated without causing problems of radiation load for the patient or operator. Fluoroscopy requires an iodized contrast medium that highlights the capsule before administering the preparation to the patient to spread through the joint after administration (Figures 1-2). There is no difference in the infiltration speed between the 2 techniques when performed by experts. Exposure to radiation during fluoroscopy is minimal. The choice between ultrasound or fluoroscopy is based on the experience of the operator in using both methods. Like the previous 2 methods, computed tomography ensures the correct performance of the treatment. It requires contrast medium and longer preparation and performance times.

A sterile field is required in all cases.

**COMPlications AND Side Effects**

The possible complications are not connected to the pharmacological activity of hyaluronic acid but to the invasive procedures.
nature of the infiltration technique. Septic arthritis is the worst complication, but it can be prevented by performing infiltration in a sterile field. Two cases of intra-articular infection are reported in the literature. Nallamshatty et al. described a case of infection from alpha-hemolytic Streptococcus that appeared 3 weeks after infiltration with cortisone. Two months after the onset of sepsis, the infection process made joint prosthesis surgery necessary. The second described case is an intra-articular infection following an infiltration cycle composed of 1 cortisone infiltration and 10 hyaluronic acid infiltrations. The risk factor in this case appears to have been the increased exposure to contamination caused by the repeated infiltrations in a short time span. Osteonecrosis of the femoral head is only reported in the literature following cortisone infiltration.

The use of intra-articular hyaluronic acid is also associated with minor complications such as transient synovitis, which causes pain, skin reddening, and joint effusion. These complications are described with an incidence that varies from 2% to 10% of cases. Two different types are usually described: synovitis with the presence of microcrystals, or pseudogout, if there are calcium phosphate crystals in the synovial fluid when observed under an electronic microscope; and the crystal-free form, which can be classified as giant-cell granulomatous synovitis. Although the correlation with the reaction to a foreign body is evident, the molecular mechanisms behind the pathogenesis are still unknown. However, these are transient episodes that are prevalently resolved in 24 to 48 hours following infiltration.

**LITERATURE REVIEW**

Although the hip is the most frequently studied joint in the literature regarding hyaluronic acid infiltrations, if the knee is excluded from consideration, only a small number of scientific articles contained statistically significant results up until the early 2000s. Conrozier et al. retrospectively evaluated a group of 56 patients with moderate or severe osteoarthritis using the Outcome Measures in Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria after administering 1 or 2 high-molecular-weight hyaluronic acid infiltrations. Ninety days after infiltration, 58.9% of the patients responded to the evaluation criteria, thus also supporting the potential benefit of single-administration infiltration treatments.

In a prospective, double-blind study that compared the effect of high-molecular-weight hyaluronic acid and low-molecular-weight hyaluronic acid, together with a placebo, 59 patients were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and patients’ and physicians’ global assessments at time intervals of 1, 3, and 6 months after the first infiltration. Improvement of scores was noted at 1 month and remained significant up to 6 months in the groups treated with sodium hyaluronate and high-molecular-weight hyaluronic acid compared with the placebo group ($P<.001$). No significant differences were observed between the results obtained in the 2 study groups treated with the different molecules of hyaluronic acid.

Berg and Olsson performed a pilot study evaluating 31 patients at 2 weeks and 3 months after a single administration of nonanimal, stabilized hyaluronic acid. Three months after administration, symptom improvement was statistically significant (68%; $P<.007$).

In 2005, the Galician Agency for Health Technology Assessment performed a systematic review to evaluate clinical evidence from the use of hyaluronic acid in arthritis of the hip. The authors identified 7 clinical trials and a systematic review corresponding to the evaluation criteria. The number of patients in the various trials ranged from 22 to 104. Five trials had no control groups, 1 trial compared 2 acids with different molecular weights, and others compared the results with those obtained by infiltration of cortisone. A reduction in pain was observed in between 40% and 50% of the cases. The authors concluded that a need existed for more accurate clinical trials before the method’s clinical efficacy could be validated.

Migliore et al. reported the effects of ultrasound-guided administration of high-molecular-weight hyaluronic acid in patients with symptomatic hip arthritis. The trial involved 30 patients: 7 patients underwent 1 infiltration procedure, 21 patients underwent 2 infiltration proce-
dures, and 2 patients underwent 3 infiltration procedures. Evaluation was performed using the Lequesne index, visual analog scale (VAS), and patient use of nonsteroidal anti-inflammatory drugs. Preinfiltration was performed. Follow-up occurred at 2 and 6 months. All evaluation parameters showed a statistically significant improvement. This trial demonstrates the efficacy and safety of the treatment in patients with symptomatic arthritis.

The Canadian Agency for Drugs and Technologies in Health’s 2007 report on the efficacy of treatment for osteoarthritis of the hip concluded that the clinical evidence currently available suggests that hyaluronic acid may provide pain relief in moderate and mid-range coxarthrosis, should other conservative treatment fail or not be possible due to contraindications. Clinical evidence of better quality is currently needed so that final conclusions can be drawn.

van den Bekerom et al\(^5\) evaluated the efficacy of hip viscosupplementation by analyzing the results of 16 trials with a total of 509 patients, with evidence levels varying from I to IV, and using various types of preparations. The heterogeneous nature of the trials considered did not provide for a cumulative analysis. Notwithstanding the relatively low level of evidence in the trials, the authors concluded that viscosupplementation may be an alternative therapy for treating coxarthrosis, both by fluoroscopy-aided and ultrasound-guided administration. Intra-articular infiltration has proven to be safe and well tolerated. However, the authors state the need for trials in a larger number of people to avoid having to consider hyaluronic acid infiltration in the hip as an extremely selective choice that depends on the experience of the operator.

In 2009, Conrozier et al\(^5\) analyzed the efficacy and tolerability of a single nonanimal hyaluronic acid infiltration. The trial involved 40 patients treated by fluoroscopy-guided administration. All patients were evaluated by patients’
global assessment, walking pain, VAS, WOMAC, and Lequesne index. A total of 39 patients were included, with a follow-up of 156 days. All evaluation parameters showed a statistically significant reduction. If radiographic criteria are excluded, the evaluation using the Lequesne index (P=.04) and WOMAC (P=.04) at 0 time (preinfiltration) predicted the treatment’s efficacy. Treatment was well tolerated and no adverse events were observed, but 15 patients reported transient pain during the first week following treatment. The authors concluded that viscosupplementation is a safe, easy-to-perform, well-tolerated procedure in clinical practice despite the possibility of hip pain during the first few days following infiltration. However, prospective trials to evaluate the efficacy and safety, as well as the efficacy and safety of treatments that are repeated in time, are necessary.

A trial performed in 2010 analyzed the efficacy of a single 75-mg administration of sodium hyaluronate by 3-mL syringe in a group of 207 patients.34 Each patient underwent fluoroscopy-guided infiltration and was evaluated by Brief Pain Inventory (BPI) score, VAS score, and Harris Hip Score (HHS) preinfiltration and 3, 6, and 12 months after infiltration. The results obtained for each BPI category were analyzed statistically, calculating the average, SD, and Student’s t test. At 3-month follow-up, all patients were analyzed by the HHS and BPI, and 165 patients were evaluated by the VAS. At 6-month follow-up, 150 patients were analyzed by the HHS and BPI, and 128 patients were evaluated by the VAS. At 1-year follow-up, 121 patients were analyzed by the HHS and BPI, and 104 patients were evaluated by the VAS. Mean VAS at preinfiltration and at 1 year were 6.21±1.27 (range, 10-6) and 2.85±2.01 (range, 10-3), respectively, a statistically significant difference (P<.001) (Figure 3). Fifty-three (41%) patients reported a minimum 50% reduction in pain at 6-month follow-up. Mean HHS at preinfiltration and at 1 year were 68.35±8.37 (range, 23-65) and 81.76±15.8 (range, 47-91), respectively, a statistically significant difference (P<.001) (Figure 4). Mean BPI score at preinfiltration and at 1 year were 30.40±13.65 (range, 16-60) and 14.17±9.78 (range, 8-34), respectively, a statistically significant difference (P<.05). Each entry on the BPI showed a statistically significant difference at 6 months and 1 year (P<.001). Considerable reductions occurred in the entries of nighttime rest (from 3.80±2.23 preinfiltration to 1.31±1.17 at 1-year follow-up) and mood (from 4.11±2.18 preinfiltration to 1.83±1.62 at 1-year follow-up) (Figure 5).

Migliore et al35 performed a retrospective study in patients with hip osteoarthritis treated with ultrasound-guided intra-articular injections of high-molecular-weight hyaluronic acid. All patients were previous candidates for total hip arthroplasty (THA) by 4, 5, or 6 orthopedic surgeons. At 1-year follow-up, 17 of 79 patients had undergone surgery, with survival results of 82%. At 48 months, this percentage reduced to 66%. The authors suggest that hip viscosupplementation should be considered as conservative treatment before proposing patients for hip arthroplasty.35

Despite van den Bekerom et al9 reporting that 51% of patients had not undergone surgery 3 years after viscosupplementation, how long THA can be postponed remains unclear. However, no evidence exists in the literature of increased rates of infection or general complications in patients who underwent THA after undergoing a prior hyaluronic injection in the same hip. A study on intra-articular steroid injection of the hip showed no increase in the risk of infection in patients subsequently undergoing THA.36 Although not statistically significant, McIntosh et al37 observed an increased risk of deep infection in patients receiving a steroid injection within 6 weeks of THA. The authors recommend that caution be used before giving an intra-articular injection within 2 months of THA.

CONCLUSION

The increase in the population’s average age is driving research toward new solutions to control arthritic pain. Infiltration of hyaluronic acid in the arthritic hip is a more recent technique than viscosupplementation of the knee due to the greater technical difficulty of infiltration to the hip, which requires fluoroscopic or ultrasonic guidance. The introduction of high-molecular-weight hyaluronic acid permits a single administration and has helped diffuse hip infiltration treatment. A single infiltration reduces patient discomfort caused by the procedure and allows treatment of a larger number of patients. The choice of radiological guidance tool during the infiltration procedure depends on the personal choice of the operator. Current problems with infiltration are the choice of the preparation to be administered, the number of infiltrations to be performed, and the selection of patients. Although the literature has unequivocally proven the possibility of pain reduction in patients affected by hip arthritis following infiltration, the molecular weight and density of the preparation to use depending on the gravity of the arthritis, the number of infiltrations required for long-term results, and the most appropriate indications for infiltration treatment have yet to be clarified. Patient selection is the first obstacle to be overcome. The radiographic criteria require at least a partly preserved joint space (Tönnis type II and III), and the clinical criteria of persistent hip pain and full joint mobility seem to be sufficiently effective for selection. Doubts concerning the characteristics of the infiltrated preparation and the number of infiltrations to be performed to obtain the best clinical result remain to be solved. New prospective studies are required on broader populations.

REFERENCES

1. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip and knee osteoarthritis among patients in health maintenance organizations. Arthritis
Feature Article


52. Dagenais S. Intra-articular hyaluronic acid (viscosupplementation) for knee osteoarthri-
tis. In: *Issues in Emerging Health Technologies.* Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2006.


55. Sankar B, Seneviratne S, Radha S, Rajeev A, Banaszkiewicz P. Safety of total hip replacement following an intra-articular ster-

56. McIntosh AL, Hanssen AD, Wenger DE, Os-
mon DR. Recent intraarticular steroid injection may increase infection rates in primary THA. *Clin Orthop Relat Res.* 2006; 451:50-54.

57. Tönnis D, Heinecke A. Acetabular and femo-
ral avetension: relationship with osteoarthri-