

# Intra-articular therapy in hip osteoarthritis

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## Summary

**Several therapeutic options have been used in the past for treatment of patients with hip osteoarthritis (HO). In recent years we have witnessed to the introduction of the intra-articular injection (IA) of hyaluronic acid (HA) in clinical practice. This technique was initially used to treat knee arthritis, for which was actually introduced, but hip anatomy itself (deeper joint structure) and technical features (different methods) pose more challenges. However, results look promising in terms of symptoms improvement and delaying prosthetic surgery. Indeed, it does appear mandatory to increase pool of available data with further studies in order to refine techniques, make them more effective, and target patients who could potentially benefit more than others from treatment.**

**KEY WORDS:** osteoarthritis of the hip; intra-articular injection; viscosupplementation; hyaluronic acid.

## Introduction

In last few years, use of intra-articular injections (IA) of hyaluronic acid (HA) for symptomatic treatment of hip osteoarthritis has broadly expanded. At the time of their introduction, IAs were performed "blindly" using external anatomical landmarks as reference. Failure rate was relatively high, and burdened by complications due to the proximity of important anatomical structures (ex. femoral artery and nerves). Ultrasound guidance has implemented the use of the hip viscosupplementation, making it secure and effective. When compared to fluoroscopy, this technique presents significant benefits: absence of radiation, no need for contrast, and an increased sensitivity. As an example, Iliopsoas bursitis present in approximately 2.7% of symptomatic hip osteoarthritis is indeed undetectable with fluoroscopy alone.

## The evidence from randomized controlled trial (RCT)

First comparative study on viscosupplementation of the hip

was performed by Qvistgaard et al. in 2006 (1) and involved 101 patients with diagnosis of osteoarthritis randomized into three arms of treatment: HA, corticosteroids, and saline solution. Three ultrasound-guided injections of HA were administered on intervals of 14 days between each administration. The primary outcome measure considered was the 'walking pain'. It has been observed a significant improvement after treatment with CS compared to saline solution. When compared with saline solution, HA showed a reduced effect without any significant difference between groups of treatment. Authors concluded that CS were more effective than HA, which has shown limited efficacy without reaching a statistically significant clinical improvement.

In another comparative study Tikiz (2) compared efficacy of low molecular weight HA (LMW HA), Ostenil, and a viscosupplementator with a higher molecular weight (Hylan G-F 20) in 43 patients. Three fluoroscopic guided injections have been administered once a week for every patient. Primary outcome measures used were Lequesne, WOMAC and Vas score. Both treatments produced a significant reduction on all pain scales used, without significant differences between two groups measurements recorded at 1st, 3rd and 6th month.

In 2009 Richette (3) performed a three months comparative study comparing groups of patients with osteoarthritis of the hip with radiological Kellgren/Lawrence scale grade of 2-3. Patients received either a single vial of Adant (2.5 ml/mg) under fluoroscopic guide or placebo (2.5 ml of saline isotonic solution). After three months, pain score improvement did not show significant differences between groups treated with HA or placebo.

Conversely, our group has performed a double-blind RCT (4) on 42 patients with symptomatic hip osteoarthritis, comparing injection of Hyalubrix (60 mg/ 4 ml) and mepivacaine 2% (4 ml) both administered under ultrasound guidance. An average of six months follow-up was obtained. Results were statistically in favour of HA compared to the group treated with local anesthetic. All primary and secondary endpoints were significantly improved compared to baseline value.

In 2010, Spitzer (5) compared the efficacy and safety of administration of hylan GF 20 against methylprednisolone acetate (MPA) for the symptomatic treatment of 313 patients with osteoarthritis of the hip and Kellgren-Lawrence (KLG) grade 2 or 3. Patients were treated with two injections of hylan GF 20 or one injection of 40 mg MPA or one simulated injection. Clinical WOMAC response rates were higher with hylan G-20 compared to MPA in patients showing more advanced disease (KLG 3) and were similar between hylan G-20 and MPA in patients with less advanced disease (KLG 2). Adverse events were similar between groups and among patients with KLG of 2 or 3.

In 2011, Atchia et al. (6) evaluated response to a single injection under ultrasound guidance in hip osteoarthritis, considering 77 patients with moderate to severe illness, divided into four treatment groups: conservative management with

no injection, saline solution injection, HA not stabilized on animal model (Durothane), or MPA injection. Indices of pain and function were improved significantly in groups treated with steroids alone.

## Results of cohort studies

From 2005 onwards, several cohort studies (7-9) with progressively increasing number of patients and protracted follow-up period confirmed efficacy of viscosupplementation of the hip. Treatment showed an initial improvement in symptoms, persisting over third month after the first administration. This was evident on the VAS pain index and on comparable algo-functional scales, such as WOMAC and LEQUESNE. Symptoms improvement was described as high as 40-60% compared to baseline. More specifically, anti-inflammatory drug intake showed 50% reduction in patients undergoing infiltrative therapy. Cyclical and targeted treatments repeated every 4 to 6 month allowed pain control for several years, as evidenced by the ANTIAGE registry data on more than 1.000 patients treated for more than seven years with Hyalubrix (in press). Data on over 4.000 cases from ANTIAGE registry have revealed an excellent safety profile of the HA, both systemically and locally, and confirmed protracted 50% reduction of anti-inflammatory consumption by patients.

Three studies (10-12) analysed the length of prosthetic surgery delay after the viscosupplementation; they are retrospective studies on a variable population of about 400 patients, which, even allowing few limitations due to the studies design, there is evidence that viscosupplementation can delay the hip prosthesis for an average of 24 months in at least 80% of treated patients. It would also appear that the lower osteoarthritis grade is at the time of treatment, the longer is the prosthesis surgery delay.

## Discrepancies of treatment efficacy observed in trials

Some recommendations about VS have been developed from three different societies (OARSI, ACR, EULAR) but are still considered controversial in scientific community.

First of all, adequate and standardized HA dosage to achieve an effective result needs to be established. Different doses of HA may lead to different levels of saturation of CD44 and hyaladherine receptors influencing receptor activation. As an example of different dosage reported, Qvistgaard et al. (1) have administered a total of 60 mg of low molecular weight HA (three injections), Richette (3) used only 25 mg of a single vial of Adant, while in our Study of Hyalubrix (4) we injected a total of 120 mg of HA with a molecular weight of > 1500 kDa in two sessions.

Second, choice of alternative agent to inject for the control group is debated and variable in different studies. Sample size and length of follow-up are also both influenced by this type of choice. Placebo in AI therapy should include only the needle itself, without any substance injected, since the injection of saline solution also causes the dilution and removal of proinflammatory cytokines in synovial fluid.

CS act faster compared to HA, but effect wears off more rapidly. This is the reason why in order to fully establish length of both agent effects, we need a longer follow-up. We also need larger pool of patients in order to fully establish

clinical effects of both agents. As an example, Quistgaard (1) study was not statistically significant, despite the good effect of HA documented because of too short follow-up period and the limited size of the sample. Same problem is emerging from the study done by Tikiz (2), where sample size was too small to show statistically significant differences in efficacy of two products – low and high molecular weight respectively. Choice of imaging technique also plays a role in the outcome. The fluoroscopic guidance technique, used by Richette et al. (3), requires injection of 1 ml of contrast, followed by quantity of HA with low concentration and molecular weight (Adant 2.5 ml). Due to low sensitivity of fluoroscopy in identifying bursitis of the iliopsoas, injection of an additional volume of solution in the joint cavity lead to worsening symptoms in a few cases. Henrotin et al. (13) organized in 2015 an international consensus conference which had set out the following statements about VS with hyaluronic acid: VS is not an alternative to surgery in advanced hip OA; VS is a well-tolerated treatment of knee and other joints OA; VS should not be used only in patients who have failed to respond adequately to analgesics and NSAIDs; VS is a “positive” indication but not a “lack of anything better” indication; the dosing regimen must be supported by evidence-based medicine; in 2015 a committee of fifty-two clinicians took part in a Delphi process (14, 15) to obtaining consensus statements among appropriateness of clinical and organizational criteria for intra-articular injection therapies in osteoarthritis. A consensus was reached for agreement on: IA injection therapy is useful in patients with hip OA, High molecular weight HA is adequate for IA injection therapy in patients with hip OA, Mobile Reticulum HA is adequate for IA injection therapy in patients with hip OA, Ultrasound/radiologic guide is useful to perform hip IA injections. In the end experts are quite satisfied about application of IA injection with HA in hip OA even if further data and targeted studies are still necessary.

## Conclusions

Even if evidences about viscosupplementation obtained so far might appear promising, we still have conflicting data that require further targeted studies to determine the real efficacy range and what subgroups of patients may be best candidates to treatments. We should aim to uniform outcome measures and therapeutic protocols in order to obtain better uniform results from dedicated studies.

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