Study protocol

Comparison of Hyaluronic Acid and Corticosteroid intra-articular injections for the treatment of Osteoarthritis of the hip controlled with intra-articular injections with Bupivacaine. Design of a double blinded prospective randomized controlled study.

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Abstract

**Background:** The effect of intra-articular treatment of hip osteoarthritis with hyaluronic acid in the hip joint is not based on large randomized controlled trials. Hyaluronic acid is a well established treatment for osteoarthritis of the knee.

**Methods:** Randomized controlled trial with three-armed parallel-group design. The patients meeting the inclusion criteria will be randomized into one of the following groups: infiltration of the hip joint with hyaluronic acid, with corticosteroids or with bupivacaine 0.125%.

Pain VAS, Harris Hip Score and HOOS were scored during follow-up. The patients will be asked to determine their situation as worse, stabele or better then at the time of enrollment. There will be asked if they use painkillers and if they have complications/adverse events.

These outcome measure instruments will be used at the time of enrollment in the study prior to any injection, and then again at six weeks, 3 and 6 months after the initial injection. The six-month follow-up period begins for all patients on the date the first injection will be administered.

**Conclusion:** There is a need for more rigorous designed studies on hip osteoarthritis treatment as this subject is still very much under debate.

**Trial registration:** NCT01079455
**Background**

Generally, socioeconomic costs have increased dramatically in the last ten years (1). Osteoarthritis (OA) is one most important cause of it. OA is a very common problem in the older population (2,3). It affects almost 5% of people over 65 years old (4). OA of the hip is one of the most common causes of functional impairment in the elderly (5,6). Despite the immense impact of this disease on many people, there are not many effective non-surgical options to handle it. In this regard, (intra-articular) pharmacological treatment is of special interest: on the one hand as basic agent of relief and for flares of pain in more acute situations, on the other hand as a way to postpone any surgical intervention by improving the patients’ subjective quality of life. In contrast to the knee, the access to the intra-articular compartment of the hip is rather difficult as a result of which injection therapy for OA of the hip has not been commonly used in the past. Nowadays, two generally accepted products are used for intra-articular injection in the hip: corticosteroids (CS) and hyaluronic acid (HA). The effects of CS in the hip have been proved by several controlled studies (7,8), however the widespread use of it remains controversial because of a rather temporary effect and some reports of adverse effects following the injection (8,9).

The effect of intra-articular treatment of HA in the hip joint is yet not really controlled. HA is well established for intra-articular treatment of OA in the knee). Although studies have shown that HA injections provide prolonged relief from symptoms in patients with OA of the knee (10,11,12), some controversy exists over the benefit of HA in the treatment of OA in the hip. The conclusion of a review of the literature showed absence of placebo-controlled studies treating OA of the hip with intra-articular HA or its derivatives (13). This means that the symptomatic treatment of hip OA cannot be determined conclusively. Nevertheless the published data suggest that intra-articular injections of the hip may be effective. Another review of the literature showed relatively low level of evidence of the included studies, although intra-articular injection of HA performed under fluoroscopic or ultrasound guidance seems an effective treatment and may be an alternative treatment of hip OA (14). Double-blind, controlled studies with a higher level of evidence are required to confirm these data.

The effectiveness of HA in comparison to CS is also not very clear. One study compared the results of HA with that of CS in patients with an osteoarthritic hip, but a higher number of patients was needed to clarify their conclusion (15). Most studies do not have a reliable control group, have too short follow-up periods, or a bias in outcome measure (16,17).
The aim of our study is to compare in a randomized, controlled, double blind design the effect of intra-articular hip injections with HA and CS compared with a control group, which will receive an intra-articular infiltration with bupivacaine. To our knowledge there are no studies which made a same comparison.

**Hypothesis**

(1) There are differences in functional outcome (Harris Hip Score (HHS) (18)) and the Visual Analog Score (VAS) (19) between the treatment groups (HA and CS infiltration) and the control group (Bupivacaine) in favour of the treatment groups, for the treatment of OA of the hip at 6 months follow-up.

(2) There are differences in secondary outcome measures (Hip disability and Osteoarthritis Outcome Score (HOOS) (20)) between the treatment groups and the control group in favour of the treatment groups, for the treatment of OA of the hip at 6 weeks, 3 and 6 months follow-up.

(3) There are differences in functional outcome and the VAS between the treatment groups and the control group in favour of the treatment groups, for the treatment of OA of the hip at 6 weeks and 3 months follow-up.

**Methods/design**

All patients will be evaluated at the outpatient clinic at our department. After checking if the patients can be included in the study (the in- and exclusion criteria will be checked (table1)), they will be informed about the study and the study design. They will also be well informed about the disadvantages and adverse effects of the products. The patients then have to sign the informed consent and will get an inclusion number. Approximately 2 months later they will have their treatment (=infiltration). At day 0 (the day of the infiltration (table 2)) there will be checked which kind of treatment the patient will receive. A nurse working at our day hospital will check the inclusion number and links this number at a randomized list downloaded from the internet site [www.randomizer.org](http://www.randomizer.org). Three sets with 163 patients in each set.

Injection of the viscosupplementation will be performed under sterile conditions by the same experienced orthopaedic surgeon and senior author (MM) in all patients. After skin cleaning a lumbar puncture needle is inserted in a lateral approach. Layer by layer local anaesthesia is performed using lidocaine 1%. Arthrocentesis is carefully performed prior to each injection to remove any effusion. Iodinated contrast agent Ultravist® (Schering, Berlin, Germany) will be injected. The needle positioning into the joint cavity will be fluoroscopically controlled when the contrast is injected. When the position is good the injection will be performed. Another option to perform the injection of the hip is using ultrasound (21,22). The skin is cleaned and
a lumbar puncture needle is inserted in an anterior approach. Layer by layer local anaesthesia is performed using lidocaine 1%. Arthrocentesis is performed followed by the injection. After resting for 2 hours, the patient is allowed to walk and to return home. The patient is advised to rest at home until the next morning. Oral symptomatic slow acting drugs for OA (for example glucosamine and chondroitin) are authorized if they are taken at a stable dose for more than 3 months prior to inclusion in the study. These drugs are continued at a stable dose during the VS treatment.

There will be 3 different groups of treatment:

1. Infiltration of the hip joint with Hyaluronic Acid (Ostenil plus 40mg/2ml).
2. Infiltration of the hip joint with Corticosteroids (Depo-Medrol 80mg/2ml).
3. Infiltration of the hip joint with Bupivacaine 0,125% (Marcaine 0,125%/2ml).

All the products used in our study are already used in our department. In the past there were never problems using these products.

“Post-operative” data collection will be performed by a person who is blinded to the treatment received by each patient and who is skilled in the administration of the study outcome instruments. Demographic data including height, weight, body-mass index (BMI), side of involvement, age and the use of nonsteroidal anti-inflammatory drugs during the study period will be recorded.

There will also be a diary filled in by each patient included in the study for the first two weeks after the infiltration to show if all treatments have an effect on OA of the hip. Side effects will be reported. This diary includes the VAS score and the use of pain killers each day.

In summary we can conclude that both the patient and the person who will collect the “post-operative” data do not know which kind of infiltration the patient has received. This means that the study is double blinded.

The findings on the initial radiographs will be graded by a musculoskeletal radiologist, experienced in reviewing orthopedic X-rays using the Kellgren-and-Lawrence grades.

Ethical approval has been obtained from the Ethical Commission of the University of Leuven, Belgium.
### Table 1: Eligibility criteria

#### Inclusion criteria:

1. An age between 30 and 70 years,
2. Radiographic evidence of OA of the hip (Kellgren-Lawrence grading scale 1-3),
3. Chronic pain for at least 3 months prior to study entry (day 0),
4. Dissatisfaction with prior attempts at non-operative management including nonsteroidal anti-inflammatory drugs.

#### Exclusion criteria:

1. Kellgren and Lawrence grade 4,
2. An intra-articular hip injection (with any corticosteroid, hyaluronic acid preparation or other) within the previous three months,
3. Non-compliance to the study procedures and or non-completion of the study according to investigator’s judgment,
4. Rapid destructive hip.
5. A history of crystalline arthropathy or inflammatory arthritis, neuropathic arthropathy,
6. A current other problem in the affected extremity,
7. Psychiatric anamnesis, herpes simplex or zoster (viremic stadium), varicella, 8 weeks before and 2 weeks after immunization, amebism, systemic mycosis, poliomyelitic except of bulbar encephalitic form, lymphadenitis after BCG-vaccination, parenteral depot medication, closed- and wide-angle glaucoma),
8. Allergy or hypersensitivity to any of the study medications or to contrast solutions.

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**Hyaluronic acid**

One of the non-operative options used for reducing pain and maintaining mobility of the hip in patients with OA is viscosupplementation. Viscosupplementation is the administration of HA preparations into the synovial fluid of the joints.

Intra-articular HA is widely used in the treatment of OA of the knee. However, still some controversy exists about the cost/benefit of treatment with HA. Many studies show that HA
injections provide prolonged relief of symptoms in patients with OA of the knee (10,11,12). The underlying mechanisms of HA in osteoarthritic joints are not completely understood. There is an increasing evidence to believe that clinical efficacy is mediated through several pathways: anti-inflammatory effects, anti-nociceptive effects, normalization of endogenous HA synthesis and chondroprotection (23).

It takes less than a day to clear the injected HA from the osteoarthritic joint (24). To increase average longer intra-articular half-life TRB Chemedica produced Ostenil Plus which will be used in our study. Ostenil Plus is using a concentration of hyaluronic acid (40 mg/2ml) twice as much as used before and Ostenil Plus contains also 10 mg of Mannitol which is an antioxidans and protects hyaluronic acid molecules against free radicals and inhibits degradation of HA (25). Ostenil Plus is a low molecular weight hyaluronic acid (LMW HA)(1.6 million Dalton).

One meta-analysis showed no important evidence for a clinically relevant benefit of a high molecular weight hyaluronic acid (HMW HA) compared with LMW HA used in patients with OA of the knee (26). The authors concluded that with the lack of a superior effectiveness of HMW HA over LMW HA and the increased risk of local adverse events associated with the first, it is better to use intra-articular LMW HA in patients with OA of the knee in clinical research or practice. For the treatment with intra-articular HA in OA of the hip there is one study (27) comparing low and high molecular weight HA. They concluded that both treatments had a statistical approved effect but there was no statistical difference between the two groups. This study had small groups of patients (32 hips LMW HA and 24 hips HMW HA) and they did not use a power calculation to prove that they included enough patients.

For the hip, viscosupplementation performed with the use of fluoroscopy or ultrasound guidance is an effective treatment of OA, and can be an alternative method for other conservative treatments or total hip arthroplasty (14,28,29).

Intra-articular injection of HA or its derivates into the hip joint is safe and well tolerated. However, local adverse reactions (hot, painful, swollen joint) were reported, typically occurring 24-72 hours after injection of HA in the knee (30-33). Ten to thirty per cent of the patients treated with intra-articular injections of HA reported adverse effects, which is slightly higher than in OA of the knee (13). Some patients experienced transient hip pain after the infiltration but all of them fully recovered in the following days without any treatment or with the use of NSAIDs. Although a single case of septic arthritis was reported after multiple intra-articular injections (13). Gout, pseudogout and chondrocalcinosis have not been reported after hip infiltrations with HA.
Corticosteroids
Since years, CS are used in the treatment of OA of the knee, because of their anti-inflammatory effects. Intra-articular infiltrations with CS in the hip can also reduce pain, stiffness and disability. Clinical experience showed that CS are very useful for the treatment of exacerbations of OA, but they don’t influence the underlying process of OA. In osteoarthritic hips, CS are useful for acute periods of pain, but this effect only lasts for some months (7,8,34). A significant pain reduction in rest and during activity was seen at 3 and 12 week follow-up. The range of joint motion increased significantly for all directions and functionality improved significantly after the injection of CS (35, 36).
It is well known that intra-articular injections with CS have some side effects, particularly with repeated injections. These include thinning of the cartilage, a higher risk of infection and weakening of the ligaments of the injected joint.
Two doses of CS are used: a dose of 40 mg and 80 mg of intra-articular CS injection. At 6 weeks, the benefit of 40 mg and 80 mg was equal for improving pain and stiffness of the hip, but functionality didn’t improve with the use of the 40 mg dose. Only with use of a dose of 80 mg the functionality was improved (34).
In this study we will use Depomedrol 80mg/2ml.

Bupivacaine
Bupivacaine is a member of the amide group in the local anesthetic family and has a molecular weight of 342,9 g/mol. Because the loss of the amount chondrocytes has been implicated in the development of OA (37), it is important to determine whether bupivacaine may also has cytotoxic effects on articular chondrocytes. In cartilage with an intact surface it is demonstrated that bupivacaine has a less depth of cell death after exposures than cartilage in OA. It is thought that the intact articular surface may provide a partial barrier to bupivacaine (38). A rabbit shoulder model showed no permanent impairment of cartilage function 3 months after intra-articular infusion of bupivacaine. The metabolism in the cartilage was higher than before, indicating a reparative ability to recover from the damage caused by bupivacaine (39). No difference in clinical outcome was seen between bupivacaine 0,5% and placebo (40,41). After a total knee arthroplasty, the use of bupivacaine reduced pain and the need for narcotics during the first 24 hours. Microscopic evaluation of human articular chondrocytes showed cellular death of more than 95% after exposure to bupivacaine 0,5% for 30 minutes. Chondrocytes exposed to bupivacaine 0,25% resulted in a time-dependent reduction in chondrocyte viability, with longer exposure resulting in more cellular
death, which even continued after removal of bupivacaine. Finally, exposure to bupivacaine 0,125% for up to 60 minutes did not influence the viability of chondrocytes in comparison to a saline solution. So, human chondrocytes may tolerate bupivacine 0,125%. Large human joints have a peak absorption of bupivacaine occurring within the first hour (42,43). The combination of systemic absorption and either lavage fluid or effusion is sufficient to dilute the injected bupivacaine to a concentration of less than 0,125%, which reduces the potential for chondrotoxicity (44). In this study we will use Marcaine (bupivacaine) 0,125%/2ml. All the products used in our study are already used in our department. In the past there were never serious adverse events using these products.

**Description methodology**
Randomized controlled trial with three-armed parallel-group design. The patients meeting the inclusion criteria will be randomized into one of the following groups:

1. Infiltration of the hip joint with Hyaluronic Acid.
2. Infiltration of the hip joint with Corticosteroids.
3. Infiltration of the hip joint with Bupivacaine 0,125%.

A block randomization scheme with blocksize equal to 8 will be used for the randomization to avoid at random imbalances in group size. No stratification variables are considered in the randomization. Measurements are taken at baseline and at planned follow-up of 6 weeks, 3 months and 6 months after intervention.

**Planned Statistical Analysis & Sample size calculation**
A linear regression model for repeated measures will be used to compare the evolution of the scores between the groups. Appropriate transformations will be considered if needed to meet the statistical assumptions of the regression model. Timepoint-specific comparisons between the groups of the changes with respect to baseline will be made based on this model. To protect against an inflated type-I error (due to the presence of two outcomes and two pairwise comparisons), an alpha-level of 0.01 is used for each comparison with respect to the control group (Bonferroni correction). A sample size calculation is performed to have 80% power for each group (HA and CS) to detect a difference with the placebo group, assuming effect sizes of 0.4 in each group (15). In total 444 patients are needed, i.e., 148 subjects in each group. The number of included subjects will be increased with 10% to anticipate drop-out (163 subjects per group will be recruited). Interim analyses after 1/3 and 2/3 of the included
patients reached the total follow-up are planned to allow early stop of the study (or accrual of patients in a specific treatment group) due to rejection of the null hypothesis. Using the O’Brien-Fleming method (O’Brien and Fleming 1979) results in respectively |4.495|, |3.178| and |2.595| as critical values for the Z-statistic at the three analysis moments. Otherwise stated, p-values are declared significant if <.000007, <0.00148 and <0.0095 at respectively the first interim analysis, the second interim analysis and at the final analysis1.

Primary outcomes
Assessment of group differences after 6 months on:

• Harris Hip Score (HHS) (18): this score will be used as a self-administered questionnaire in accordance with the developers’ instructions. The Harris Hip Score was first developed in 1967 and is accepted as one of the best used questionnaires dealing the hip function. It is a disease-specific scoring system which was introduced to provide an evaluation system for various hip disabilities and methods of treatment. This Score gives a maximum of 100 points, with domains of pain, function, deformity and motion. Pain and function were the two basic considerations and received the heaviest weighting (44 and 47 points, respectively). Range of motion and deformity are seldom of primary importance, and therefore received five and four points, respectively. Function was subdivided into activity of daily living (ADL, 14 points) and gait (33 points).

• Visual Analog Score (VAS) (19): this score is a self-assessment of variation in pain intensity, measured on a simple 100-mm-long continuous scale of absolutes ranging from “no pain” to “extreme pain”. The percentage of pain is determined by physical measuring from the end of the line to the patients’ mark on the pain scale, and divided by total length of the line. The advantage of the VAS is that you can determine the change in pain by taking the difference between any two recordings of pain severity.

Secondary outcomes
Assessment of group differences on:

• Hip disability and Osteoarthritis Outcome Score (HOOS) (20): this score will be used as a self-administered questionnaire with the help of the developers’ instructions. The HOOS

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1 Note that the ‘price to pay’ for performing the interim analysis is a slightly more conservative alpha-level at the final analysis, i.e. alpha=0.0095 instead of alpha=0.01.
is an adaptation of the Knee disability and Osteoarthritis Outcome Score (KOOS) intended to evaluate symptoms and functional limitations related to the hip. The HOOS consists of 40 items, assessing five different patient-relevant groups: Pain (P) (ten items); Symptoms (S) including stiffness and range of motion (five items); Activity limitations-daily living (A) (seventeen items); Sport and Recreation Function (SP) (four items); and Hip Related Quality of Life (Q) (four items). The HOOS contains all Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questions in unchanged form. The WOMAC scores are often used in scientific literature and it is important that if needed the WOMAC scores can be calculated from the HOOS questionnaire. To answer each question, five options were used (no, mild, moderate, severe, extreme). All items were scored from zero to four, and each of the five subscales will be calculated as the sum of the items included. The HOOS is transformed into a 0–100 worst to best score.

- VAS, Harris Hip Score on all follow-up moments, except after 6 months
- The patients will be asked to determine their situation as worse, stable or better then at the time of enrollment. There will be asked if they use painkillers and if they have complications/adverse events. When they have complications they will be seen in our department sooner as normal.

These outcome measure instruments will be used at the time of enrollment in the study prior to any injection, and then again at six weeks, 3 and 6 months after the initial injection. The six-month follow-up period begins for all patients on the date the first injection will be administered.
Table 2: Flowchart

<table>
<thead>
<tr>
<th>Day</th>
<th>Day of inclusion:</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>??</td>
<td></td>
<td>Informed consent, controlling in- and exclusion criteria.</td>
</tr>
<tr>
<td>0</td>
<td>Day of infiltration:</td>
<td>VAS, HOOS and HHS-score, randomization and infiltration.</td>
</tr>
<tr>
<td>1-14</td>
<td>Diary:</td>
<td>daily VAS and use of pain killers per day.</td>
</tr>
<tr>
<td>6</td>
<td>Second consultation:</td>
<td>VAS, HOOS and HHS-score.</td>
</tr>
<tr>
<td>12</td>
<td>Third consultation:</td>
<td>VAS, HOOS and HHS-score.</td>
</tr>
<tr>
<td>26</td>
<td>Fourth consultation:</td>
<td>VAS, HOOS and HHS-score, end follow-up.</td>
</tr>
</tbody>
</table>

Ethical review committee and informed consent requirements

Ethical approval was necessary because it is a prospective randomised study. Ethical approval has been obtained by the ethical committee of the K.U.Leuven. Informed consent papers will be signed by the patients before including in our study. If patients, after reading the patient information, have any questions about the protocol of our study, they can contact dr. Sascha Colen or dr. Michiel Mulier.

Discussion

This study is primarily designed to evaluate the effectiveness of non-operative treatment of hip OA using HA and CS infiltrations. A comparison is made between HA, CS and bupivacaine (control group) infiltrations. There have been studies and even randomized clinical trials on non-operative treatment of hip OA but the methodological quality is often low. There is a need for more rigorous designed studies on hip OA treatment as this subject is still very much under debate. By publishing our protocol we wish to show our care for a profound design and methodological quality of our protocol. Moreover, when the design of a study is published it will help to achieve transparency about why and how studies are
undertaken. The publication of a study design may help to reduce the problem of publication bias, i.e. selective publication of positive associations and disregarding negative and weak associations, prevent unnecessary duplication of research efforts and duplicate publication. To our knowledge, there has never been a design study published on the same subject. By making this design study we wish to contribute to more profound research on non-operative treatment of osteoarthritis of the hip and prevent publication bias for this double blinded randomized trial. Results of the trial will be disseminated through publication in relevant peer-reviewed journals and conference proceedings.

Authors' contributions
All authors were involved in the design of the study. For all of them there are no competing interests according to the products used. SC was responsible for drafting the paper, and all authors commented on the draft. All authors have read and approved the final manuscript.

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In 2010 the authors received funding from Ostenil© to pay article-processing charge for publishing their article in BMC musculoskeletal disorders. This funding company has absolutely no role in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, division, centre, clinical practice, or other charitable or non-profit organization with which the authors, or a member of their immediate families, are affiliated or associated.

References


