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ORIGINAL ARTICLE • HIP - ARTHROPLASTY

Efficacy of a single intra-articular injection of ultra-high molecular weight hyaluronic acid for hip osteoarthritis: a randomized controlled study

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Abstract

Background Viscosupplementation with hyaluronic acid (HA) is increasingly used for the treatment of hip osteoarthritis (OA). The purpose of this study was to compare the efficacy of intra-articular injections of an ultra-high molecular weight viscosupplement (UHMW-HA, Fermathron S) with a medium molecular weight hyaluronan (MMW-HA, Hyalubrix 60) in hip OA.

Methods Fifty-four patients with hip OA grade 3 on the Kellgren/Lawrence scale were randomized. All infiltrations were performed under ultrasound guidance. Evaluation was performed preoperatively and at 1, 3, 6 and 12 months after infiltration. Patients were clinically evaluated using Lequesne index, VAS and WOMAC score.

Results Fifty patients, including 27 in the MMW-HA group and 23 in the UHMW-HA group, completed the follow-up. No significant difference was found between the two groups in terms of VAS, WOMAC or Lequesne index preoperatively or at 1, 3, 6 and 12 months after viscosupplementation. A stratified analysis was performed to study the development over time of Lequesne index of patients aged ≤ 55 years, > 55 and, ≤ 70 years and > 70 years and Lequesne index was different between the three age-stratified subgroups only in the MMW-HA group. The subgroup of older patients showed a higher Lequesne index than the subgroups of younger patients ($p < 0.05$).

Conclusions UHMW-HA is a safe and effective treatment for hip osteoarthritis. A single dose of UHMW-HA was as effective as two doses of MMW-HA resulting in similar reductions of pain and disability.

Study design Multicenter, independent, prospective, randomized controlled trial with level of evidence 1.

Keywords Hip osteoarthritis · Regenerative medicine · Hyaluronic acid · Biology of cartilage · Randomized clinical trial

Introduction

Osteoarthritis (OA) is the most common joint disease in humans and is characterized by the progressive destruction of articular cartilage, joint space narrowing, subchondral bone remodeling, joint marginal osteophyte formation and synovitis [1]. Viscosupplementation with hyaluronic acid (HA) is approved for the treatment of osteoarthritis of the knee in both Europe and the USA, but it is not yet approved for the treatment of hip OA [2].

However, the use of HA in hip OA has increased over the past few years. Treatment of the hip with HA has proven to be safe and well tolerated with a reported complication rate of between 10 to 30% of patients [3]. Moreover, the use of ultrasound (US) guidance favors an improved and accurate delivery of the injected product [4].

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HA is used in the treatment of OA for its anti-inflammatory effects and cell stimulation. However, its effectiveness and durability depend largely on the length of its chains and its molecular weight [5].

HA can be divided into three categories: low molecular weight (MW) (MW < 1,000,000 Da) medium MW (MW between 1,000,000 and 3,000,000 Da) and high MW (MW > 3,000,000 Da) [6]. Low MW hyaluronic acids are more sensitive to the free radicals, enzymes and cytokines present in the synovial fluid of the arthritic joints; this causes a rapid deterioration of the chains of HA with a reduction in the effect of the treatment.

In addition, the increase in the half-life of HA itself, the increase in length, and thus the MW of the molecule of HA, make these molecules more similar to the physiological HA present in a healthy joint, which normally has an MW of about 4,000,000–5,000,000 Da [7].

Despite the development of HA molecule formulations, to date in the literature there is no consensus over which is the ideal viscosupplementation for the treatment of hip OA [8]. Recently, cross-linked HA with an ultra-high MW in which most molecules of HA are linked to one other has been put on the market; the cross-linking process, in addition to increasing the overall MW of the molecule, makes it particularly resistant to degradation with a lasting viscoelastic effect [9].

The purpose of this study was to compare the effectiveness of infiltrative treatment with a new ultra-high molecular weight HA, versus infiltrative treatment with medium molecular weight HA in the hip OA. We believe that a single infiltration of ultra-high molecular weight HA could give better clinical results than two infiltrations of medium molecular weight HA.

Material and methods

Patients

Patients with a primary osteoarthritic hip joint were recruited at two centers. The radiological classification was performed with anteroposterior pelvic radiography according to the Kellgren score [10]. The inclusion criteria were: patients with hip OA grade 3 on Kellgren/Lawrence scale; patients capable of giving their informed consent; patients capable of understanding the conditions of the study and participating for its entire duration; nonpregnant female patients with no intention of becoming pregnant in the year following treatment; patients older than 40 years.

Exclusion criteria were: patients with OA of the hip grade 4 on Kellgren/Lawrence scale with exposure of subchondral bone; patients with avascular necrosis of the femoral head; patients with a history of neoplastic disease, patients undergoing chemotherapy, radiation treatment or immunosuppressive therapy; patients with autoimmune disease; women who are already pregnant or who do not rule out the possibility of becoming pregnant within a year of the start of treatment; patients that the surgeon believes to be mentally incapable and/or unlikely to adhere to the planned program of postoperative evaluation; patients receiving chronic therapy with steroids or NSAIDs; patients with severe metabolic disorders.

All subjects gave their written informed consent to participate in the study, which was approved by the Ethical Review Committee.

Recruitment started in January 2013 and was completed in June 2015. Of 75 patients screened for eligibility, 54 patients were judged to be eligible and randomized: 27 patients to the treatment group with MMW-HA (Hyalubrix 60, Fidia Farmaceutici) and 27 patients to the treatment group with UHMW-HA (Fermathron S, Biomet). Of the 54 participants randomized, 50 completed clinical follow-up. Four patients in the UHMW-HA treatment group were lost to follow-up.

Study design

In this 12-month, prospective, randomized, comparative study, patients were randomly assigned to one of two treatment groups. Patients in the first group received 2-dose intra-articular injections of MMW-HA solution (Hyalubrix 60, a linear hyaluronic acid with a molecular weight of between 1.3 and 3.6 MDa). It is a temporary replacement for synovial fluid obtained by bacterial fermentation from a fraction of high molecular weight HA. The treatment was repeated after 3–4 weeks for beneficial long-term pain relief and functional improvement. Each syringe contained 60 mg/4 ml of MMW-HA.

Patients in the second group received 1-dose intra-articular injections of UHMW-HA (Fermathron S) consisting of several folded chains of sodium hyaluronate molecules cross-linked to one another with ether links, obtained from a process of continuous bacterial fermentation followed by a process of cross-linking in the presence of BDDE (1,4-Butanediol diglycidyl ether). Fermathron S is therefore an ultra-high molecular weight hyaluronic acid, whose molecular weight is not quantifiable because it is fully cross-linked with random cross-links, wherein the starting molecule is Fermathron Plus, whose molecular weight is 2 MDa. Each syringe contains sodium hyaluronate 69 mg/3.0 ml.

A power analysis was performed based on the effects of HA treatment (viscosupplementation) on hip function.

The primary outcome measure of the study was the Lequesne algofunctional index [11], hypothesizing that the Lequesne algofunctional index would be 3 points higher in the Fermathron S group than in the Hyalubrix 60 group.

Considering the standard deviation of 3 points, 46 participants were needed (23 in each group) to detect a difference of 3 points in the Lequesne algofunctional index between the two groups. These numbers were based on a power (1-b) of 0.80 and a significance level of 5% (2-sided). With an expected dropout rate of about 15%, this number was increased to 54 participants.

A block randomization procedure was used to generate a randomization list. The block randomization list was generated by dedicated software (StatsDirect Ltd, Cheshire, UK). An independent operator not involved in the treatment prepared sequentially numbered opaque sealed envelopes containing the treatments assigned.

Following verification of the exclusion or inclusion criteria, the surgeon was provided with a sealed envelope containing the treatment assigned to each patient.

Injection technique

Treatment with HA was administered by two surgeons at two different centers. No anesthesia was necessary. The infiltrative procedure consisted of preliminary diagnostic ultrasound to evaluate the joint, and to rule out joint effusion (which, if present, is to be completely aspirated before injecting the hyaluronic acid) and the presence of femoroacetabular osteophytes. Having prepared the sterile field, the infiltrative procedure started. The infiltration was performed under ultrasound guidance on the sterile field, using a special 7.5 MHz linear probe and a 20G spinal needle. At the discretion of the operator, as an aid, use could be made of a 45° biopsy guide, mounted on the ultrasound probe, to which was applied a sterile disposable sheath and sterile disposable 20G needle pointer. Special software showed the path of the needle by means of a dotted line visible on the ultrasound monitor picture. A 20G spinal needle (9 or 15 cm in length depending on the size of the patient) was inserted in the biopsy guide. The needle was introduced into the anterior capsule, at the level of the femoral head. Once in contact with the femoral head, the needle was retracted by about 1 mm and the drug was injected into the hip joint. Verification of its presence in the intra-articular joint space was highlighted by real-time monitoring. The procedure thus performed usually enables the patient to get up, get dressed and go for a short period of observation to the day hospital department where an ice pack will be applied and the BP will be monitored. The patient was discharged about 2 h after the procedure allowing him/her to bear his/her full weight without any need for aids and recommending 2–3 days of relative rest.

Assessment

All assessments were performed by a clinician who was blinded to the type of preparations injected. Each patient was subjected to a preoperative clinical evaluation, as well as at 1, 3, 6 and 12 months of treatment. The clinical evaluation consisted of the subjective global pain assessed by VAS pain score [12]. Pain relief was evaluated using a 100-mm horizontal VAS, on which 0 corresponded to no pain or normal activity and 100 to unbearable pain. The intensity of pain, walking capacity and activities of daily life were assessed by the Lequesne algofunctional index [11]. The Western Ontario and McMaster Universities' Osteoarthritis index (WOMAC) were also used [13]. The WOMAC index is a self-administered questionnaire for the evaluation of patients with osteoarthritis of the knee and hip. It measures changes in health after the surgical procedure. The minimum score is 0, which indicates a state of severe osteoarthritis that limits the activities of daily living. The maximum score is 100, which indicates a condition of well-being and excellent joint function. Any adverse effects of the injections were recorded after each injection during the first month.

Statistical analysis

Values are given as mean ± SD. The differences between the two groups of patients for continuous variables were assessed using an unpaired Student's *t* test or Mann–Whitney test according to the characteristics of the data distribution. The differences for categorical variables were tested with the Chi-square test. A paired sample Student *t* test or nonparametric sign test was used to test pre- and postoperative values of continuous variables. Since clinical outcome variables were repeatedly measured over time, a multivariate analysis of variance (MANOVA) for repeated measures was carried out. MANOVA allowed an overall time effect, general group effect, and time by group interaction effect to be investigated. Furthermore, analysis of variance was performed in order to investigate the influence of dependent factors on the clinical outcomes. Statistical analysis was carried out using SPSS software (SPSS version 17, Chicago, IL). For all analyses, a value of p value < 0.05 was considered significant.

Results

A total of 54 patients were included in the study. During the follow-up period, four patients withdrew from the UHMW-HA group study for personal reasons. The remaining 50

patients, including 27 in the MMW-HA group and 23 in the UHMW-HA group, completed the final follow-up study.

The two groups of patients were matched for age, gender, side affected and body mass index (Table 1). All infiltrations in both groups were unilateral.

No significant difference was found between the two groups in terms of VAS score, WOMAC score and Lequesne index preoperatively or at 1, 3, 6 and 12 months after viscosupplementation (Table 2).

A clinical improvement was observed as early as 1 month after viscosupplementation in both groups of patients ($p = 0.002$). In MMW-HA group, VAS ranged from 6.3 ± 2.1 preoperatively to a final value of 4.9 ± 1.6, Womac score improved from 69.8 ± 21 to 57.1 ± 16 at final follow-up, while Lequesne index changed from 11.5 ± 4.4 before infiltration to 9.5 ± 3.3 12 months after treatment. In UHMW-HA VAS, Womac score and Lequesne index ranged, respectively, from a value of 6.4 ± 1.7, 69.3 ± 19.6 and 12.5 ± 4.1 to a final value of 4.8 ± 1.6, 57.2 ± 13.7 and 9.8 ± 3.3.

Table 1 Demographic data and comparison between the two different groups of treatment

	MMW-HA group	UHMW-HA group	*p* value
Age	67.4 ± 10.3	65.9 ± 10.02	0.7
Body mass index	26.2 ± 5.15	27.2 ± 2.38	0.4
Female—no. (%)	16 (59.3%)	15 (65.2%)	0.6
Dominance—no. (%)	15 (55.6%)	17 (73.9%)	0.1

The values are expressed as mean ± SD or number (%)

MMW-HA medium molecular weight hyaluronan (Hyalubrix 60), *UHMW-HA* ultra-high molecular weight hyaluronan (Fermathron S), *No.* number

MANOVA analysis showed a significant change over time in the Lequesne index for both the MMW-HA group and the UHMW-HA group (Fig. 1).

The development over time did not differ between the two groups: The mean values decreased linearly over time ($p < 0.001$); however, a quadratic component was also observed, implying that the improvement levelled off at the lowest measurements ($p < 0.001$).

Analysis of variance showed a significant correlation between Lequesne index and the patient's age ($p < 0.001$); furthermore, the interaction between age and treatment group was also found to be significant ($p = 0.01$).

A stratified analysis was subsequently performed to study the development over time of the Lequesne index of patients aged ≤ 55 years, > 55 and, ≤ 70 years, > 70 years for each treatment group. Overall, the Lequesne index was found to differ between the three age-stratified subgroups at a significant level ($p = 0.05$) in the MMW-HA group. However, the improvement over time did not differ between the three age subgroups (Fig. 2).

Conversely, no association was found between age and the Lequesne index in the UHMW-HA group. Overall, the Lequesne index did not differ between the three age-stratified subgroups, who also had a similar improvement over time (Fig. 3).

Furthermore, clinical scores were significantly related to the patients' gender. Overall, the Lequesne index was lower for male than for female patients ($p = 0.004$).

However, the development over time was different between male and female patients: A significant linear improvement was observed in female patients only ($p = 0.001$). No significant change over time was seen for male patients (Fig. 4).

Table 2 Clinical outcomes in the MMW-HA and UHMW-HA groups before viscosupplementation and after 3, 6 and 12 months of follow-up

	Pre-op.	1 month	3 months	6 months	12 months
VAS					
MMW-HA group	6.3 ± 2.1	4.9 ± 1.8	4.5 ± 1.5	4.7 ± 1.3	4.9 ± 1.6
UHMW-HA group	6.4 ± 1.7	5.1 ± 1.6	4.7 ± 1.3	5 ± 1.5	4.8 ± 1.6
p value	0.8	0.7	0.6	0.5	0.9
Womac score					
MMW-HA group	69.8 ± 21	59.5 ± 18.8	57.1 ± 17.4	57.4 ± 17.3	57.1 ± 16
UHMW-HA group	69.3 ± 19.6	60.1 ± 18.3	56.8 ± 14.5	56.5 ± 14.3	57.2 ± 13.7
p value	0.9	0.9	0.9	0.8	0.9
Lequesne index					
MMW-HA group	11.5 ± 4.4	9.8 ± 4.4	9.3 ± 3.5	9.6 ± 3.4	9.5 ± 3.3
UHMW-HA group	12.5 ± 4.1	10.6 ± 3.7	9.9 ± 3.3	9.7 ± 3	9.8 ± 3.3
p value	0.4	0.4	0.5	0.8	0.7

Plus-minus values are mean ± SD. A value of $p < 0.05$ was considered significant

VAS visual analog score for pain, *MMW-HA* medium molecular weight hyaluronan (Hyalubrix 60), *UHMW-HA* ultra-high molecular weight hyaluronan (Fermathron S)

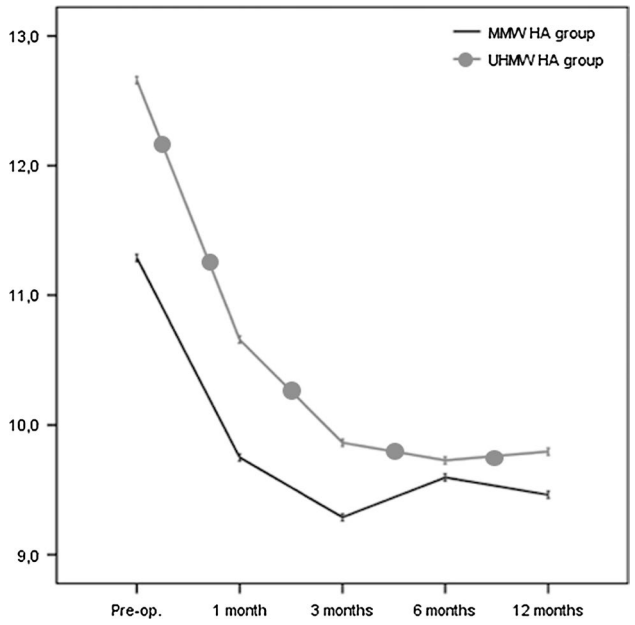

Fig. 1 Lequesne index for the medium molecular weight hyaluronan (MMW-HA) group (Hyalubrix 60) and ultra-high molecular weight hyaluronan (UHMW-HA) group (Fermathron S) at the preoperative baseline and after 1, 3, 6 and 24 months of postoperative follow-up

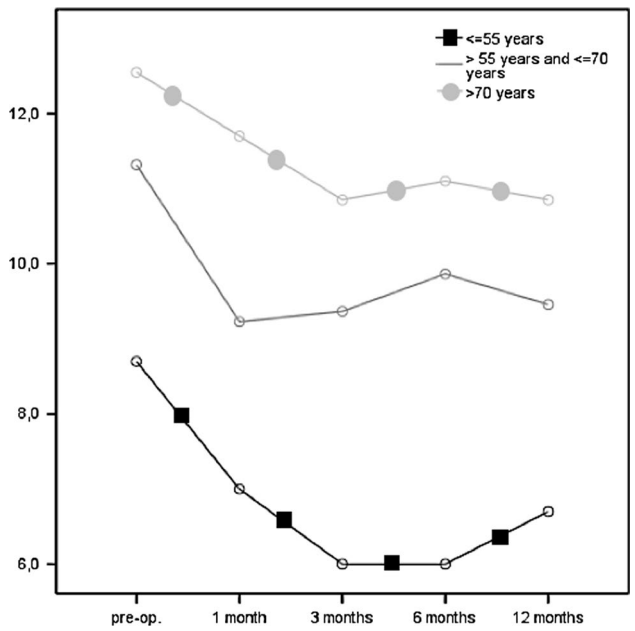

Fig. 2 Lequesne index in the MMW-HA group for each age-stratified subgroup at the preoperative baseline and after 1, 3, 6 and 24 months of postoperative follow-up

Complications

No complications were observed in either of the two groups

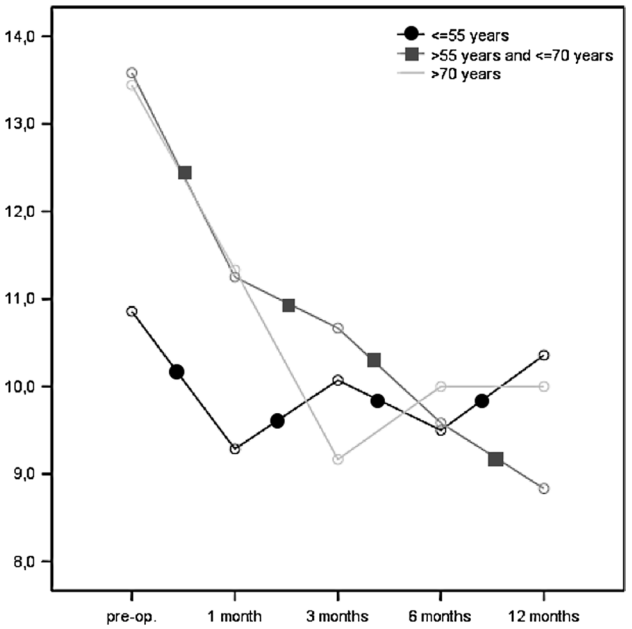

Fig. 3 Lequesne index in the UHMW-HA group for each age-stratified subgroup at the preoperative baseline and after 1, 3, 6 and 24 months of postoperative follow-up

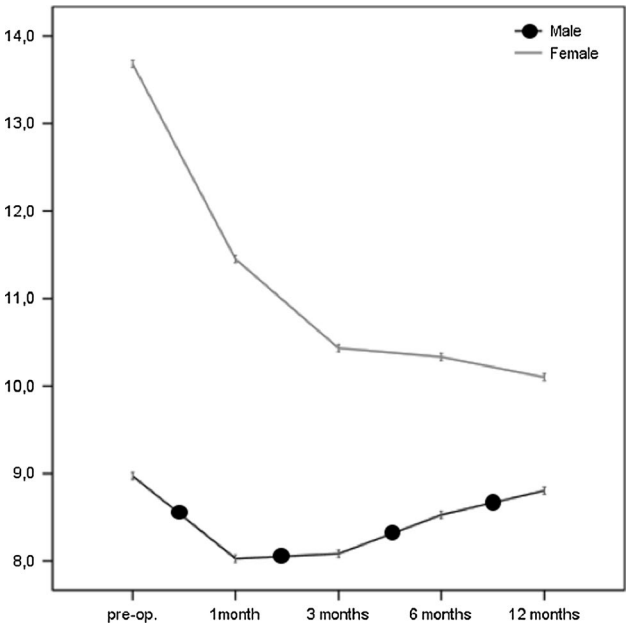

Fig. 4 Lequesne index for the male and female patients at the preoperative baseline and after 1, 3, 6 and 24 months of postoperative follow-up

Discussion

This study showed excellent results after viscosupplementation of hip OA grade 3 on the Kellgren/Lawrence scale

without any kind of complication in patients.

HA stimulates various cellular activities, such as migration and proliferation and also has an anti-inflammatory effect, reducing the expression of various inflammatory cytokines, and relieves pain by acting directly on nociceptors [14]. Furthermore, HA can enhance proteoglycan synthesis and suppresses the production and activity of proinflammatory mediators and proteases [15]. Lurati showed that HA injections can modify knee or hip joint metabolism in patients with OA resulting in a decrease in proinflammatory T-cell concentrations, reducing synovial inflammation and restoring the rheological properties of the synovial fluid [16].

Viscosupplementation is considered one of the best conservative treatment of the knee while only in recent years has its use in the treatment of osteoarthritis of the hip increased [1, 2]. Dıraçoğlu supported the use of viscosupplementation for hip osteoarthritis by demonstrating that clinical results were comparable to those of viscosupplementation of the knee [17].

In support of the use of viscosupplementation, a recent retrospective study shows that hyaluronic acid given by ultrasound-guided injection seems to delay total hip replacement in symptomatic hip OA; moreover, hip viscosupplementation should be considered as conservative treatment to be performed before candidating patients for arthroplasty [18].

Although a recent systematic review of the existing literature affirms that HA injections do decrease hip pain associated with OA, there is a paucity of RCTs assessing the efficacy of HA; furthermore, most of the data available are inadequate to determine the duration of pain relief or which HA formulations provide better and longer lasting pain relief [8].

Molecular weight is a factor that influences the inflammatory effect: Under ideal molecular weight conditions, interaction with cell surface receptors effectively creates a sort of barrier between the cell and the altered articular environment, protecting the cell against the harmful effects of proinflammatory and chondrodegenerative substances [19].

To our knowledge, this RCT is the first to assess an ultra-high molecular weight hyaluronic acid that can be administered in a single infiltration, reducing the risks associated with the procedure. The random cross-links of Fermathrons S are obtained from a process of continuous bacterial fermentation followed by a process of cross-linking in the presence of BDDE; this fermentation creates a fully cross-linked HA starting from a molecule of 2 MDa. Once in the synovial compartment, the flexible structure of the Fermathron S molecule has an excellent lubricating and shock absorbing effect. In addition, the cross-linking that makes the hyaluronic acid more resistant to degradation determines an increase in the residence time in the articulation and allows the molecule to be administered in a single injection into the synovial space of the affected joint.

Tikiz compared the efficacy of intra-articular injections of an LMW-HA (Ostenil, 1.2–1.4 $\times$ 10^6 DA) with a higher molecular weight viscosupplement (Hylan G-F 20, Synvisc, 7 $\times 10^6$ DA) in hip osteoarthritis. Fifty-six hips were evaluated at 1, 3 and 6 months by VAS, WOMAC and Lequesne index [20]. The intra-articular injections produced a significant reduction in VAS, WOMAC and Lequesne index scores in both groups. After three injections, an improvement was achieved at 1 month and maintained for 6 months in both groups. However, there were no significant differences in outcomes of any of the measurements made at 1, 3 and 6 months between the two groups. No systemic adverse effect was recorded.

In 2008, van den Bekerom compared the use of three different hyaluronic acids (Adant® Synthetic hyaluronic acid with an average molecular weight of 0.6–1.2 million Da, Synocrom® Sodium hyaluronate with a average molecular weight of 1.6 million Da and Synvisc® Hylan GF 20 with an average molecular weight of 6.0 million Da) [21] evaluating hip function, time of satisfactory pain relief and also the delay in undergoing a total hip arthroplasty. One hundred and twenty-six hips received viscosupplementation with one of the three hyaluronate formulations, and patients were assessed 6 weeks after each infiltration using the VAS and Harris hip score (HHS). The HHS increased significantly in two of the three groups compared to the baseline, but no statistically significant difference was noted between the groups. The positive effect was still in progress at the end point of the study in 46 hips: 3 years after viscosupplementation, 51% of the patients had not undergone total hip arthroplasty.

Rivera recently assessed the efficacy of a high molecular weight hyaluronic acid for hip osteoarthritis reporting results on 207 patients treated with a single HA (Coxartrum, 2800 kDa) administration of 2.5% high molecular weight sodium hyaluronate (75 mg/3 mL) [22]. Patients were evaluated before IA injection (T0), and at 3, 6 months and 1 year after the injection. The author concludes that a single IA injection of HMW-HA is effective from the third month on and that the results are stable or continue to improve for up to 1 year. The limitation of this study is the lack of a control group that demonstrates the actual effectiveness of a single injection of hyaluronic acid.

In accordance with the existing literature, this RCT conducted on 50 patients (27 in the MMW-HA group and 23 in the UHMW-HA group) showed no significant difference between the two groups in terms of VAS score, WOMAC score and Lequesne index at 1, 3, 6 and 12 months. A clinical improvement was observed early at 1 month in each treatment group and continued until 1 year with no

difference in the development over time between the two treatment groups.

Overall, better clinical outcomes for male patients were observed in this study. The effect of female gender on the risk of OA has been estimated in a number of studies; this may explain the worse outcomes than in men, due to a more rapid progression of the disease [23]. Despite these negative prognostic factors, the results of this study showed that female patients can benefit from viscosupplementation as the HA treatment reduced pain and increased function in this gender subgroup.

In our study, we decided to perform all the infiltrations under ultrasound guidance and did not observe any kind of complications or side effects related to the infiltration technique.

The safety and reproducibility of ultrasound-guided infiltration is confirmed by numerous studies in the current literature: First of all, US guidance favors an improved and accurate delivery of the injected product [24, 25]. Furthermore, ultrasound guidance is cheaper and faster than CT or fluoroscopic guidance and does not require the use of contrast agents, so it can be used in patients allergic to iodinated contrast agents. Another benefit is the lack of radiation, allowing to repeat the procedure without problems both for the operator or the patient. The major limitation of the technique is related to the operator's experience, in fact, performing an US-guided intra-articular injection requires an intermediate level of skill at a minimum, in particular as regards needle positioning [26].

Unlike Qvistgaard, we used an anterosuperior approach for the injections [27]. This approach is commonly used for arthrocentesis. The position of the needle in the lowest part of the joint allows effusion to be dried up as completely as possible. However, we believe that the anterior approach is preferred as it allows the drug to be injected to the femoral head, in order to reach the articular cartilage of the femoral head and acetabulum through gravity.

In this study, we found that in the MMW-HA group, older patients (aged > 70 years) showed a higher overall Lequesne index than the subgroups of younger patients (≤ 55 years, > 55 and ≤ 70 years) (mean difference: 4.5 and 1.7). This can be explained as reported in the study conducted by Loeser [28]. Age-related changes in the cartilage matrix and chondrocyte senescence are key contributors to the aging processes that promote age-related OA. OA is characterized by an imbalance between catabolic and anabolic activity driven by local production of inflammatory mediators in the cartilage and surrounding joint tissues. The senescent secretory phenotype probably contributes to this imbalance through an increased production of cytokines and MMPs and a reduced response to growth factors. Moreover, oxidizing agents play an important role in the correlation between aging and OA.

Despite the overall difference, a similar positive effect was observed after HA treatment as the development over the time did not differ between the three age-stratified subgroups.

Conversely, no difference in the Lequesne index was found between the three age-stratified subgroups in the UHMW-HA group, suggesting that older patients with higher levels of pain and disability could benefit in the medium term from an ultra-high molecular weight formulation.

The study presents several limitations. First of all, we evaluated patients only with the Kellgren–Lawrence scale for radiological assessment, while the MRI would be better suited to evaluate the degree and extent of the cartilage degeneration. In fact, a new MRI hip osteoarthritis grading system (SHOMRI) has recently been developed, that is practical in image acquisition and scoring; this new grading system demonstrated good intra- and inter-reader reproducibility and found a significant correlation with radiographic and clinical scores, which are the current standards of reference for hip OA such as KL [29].

Another limitation of the study is the lack of a placebo group. Placebo injections may cause an important reduction in pain relief, especially during the first week [30]. Moreover the effect of the injections was only evaluated using subjective clinical scores and no objective evaluation or imaging of the progress. Sample size was too small to draw accurate conclusions from the comparison between the two treatments. Furthermore, the follow-up period of 1 year did not allow an assessment to be made of whether treatment with UHMW-HA determined a delay in the need for total hip arthroplasty.

Conclusions

The results of this study showed that a single dose of UHMW-HA is a safe and effective treatment for hip OA. No significant difference in the clinical outcomes was found between ultra-high and medium molecular weight hyaluronan, showing that a single dose of UHMW-HA is as effective as two doses of MMW-HA, resulting in similar reductions of pain and disability during the 12-month follow-up period.

Local tolerability was good and no adverse effects were reported for UHMW-HA viscosupplementation, which suggests that a single infiltration can reduce the risk related to the procedure. Furthermore, the ultra-high molecular weight HA formulation could be beneficial to older patients with higher levels of pain and disability. Future studies with a larger sample size are necessary to confirm the long-term efficacy of a single infiltration of the UHMW-HA formulation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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