

Efficacy and safety of viscosupplementation with hyaluronic acid for hip osteoarthritis: results from a cross-sectional study with a minimum follow-up of 4 years

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Abstract. *Background and aim of the work:* Osteoarthritis is the most common cause of disability in elderly. Hip osteoarthritis is the second most frequent form affecting a large joint and the social and economic impact on society of its related disability is expected to increase. The purpose of this study was to verify the efficacy and safety of ultrasound-guided viscosupplementation with high weight hyaluronic acid in hip osteoarthritis. *Methods:* 183 patients with painful hip OA (Kellgren-Lawrence 1-2-3) were treated from January 2014 to December 2016 with viscosupplementation. Patients were evaluated before injection (T0) and after 1,2,3,4 (T1-T2-T3-T4) years through the VAS scale and Harris Hip Score (HHS). Patients who underwent to subsequent injections were followed and assessed. Subjects who underwent prosthesis were analyzed for a minimum of 6 months in order to detect any early postoperative complication. *Results:* The mean improvement of HHS and VAS between T0 and T1 was statistically significant. Patients who underwent subsequent injections showed a higher improvement even if statistical significance was not observed. Results showed that patients with grade 2 of osteoarthritis had the higher change in the scores. No adverse effects were registered. No early complications were reported in those patients who needed prosthesis. *Discussion and Conclusions:* Results observed confirm that ultrasound-guided viscosupplementation with high weight hyaluronic acid could be a possibility in the treatment of hip osteoarthritis, especially in patients with Kellgren-Lawrence grade 2 of disease. Subsequent injections are not characterized by similar positive effects. Outcomes of prosthetic surgery are not influenced by viscosupplementation.

Key words: hip, osteoarthritis, hyaluronic acid, ultrasound, viscosupplementation, prosthesis

Introduction

Osteoarthritis (OA) is the most common cause of disability in the elderly population. Hip pain, which could be the consequence of different pathologies, is reported by 19.2% [95% confidence interval (CI) 17.9-20.6] of people aged 65 years and older (1-4).

Hip OA is the second most frequent form of OA affecting a large joint, and its prevalence ranges from 3 to 11% in populations over 35 years of age (5-7). Risk factors include genetics, female gender, previous traumas, advancing age and obesity. Given that the number of people aged 65 and over will double by 2030 (8), along with escalations in obesity and physical

inactivity (9), the social and economic impact on society of OA related disability is expected to increase.

Despite the improvement in anatomical design and material composition of prosthesis components, total hip arthroplasty (THA) remains an invasive approach that has to be postponed as long as possible (10-12). Non-comparative studies showed short-term pain reduction and functional improvement after intra-articular hyaluronic acid injection (IAHAI) (13). More recent meta-analyses instead reported contrasting findings, ranging from statistically significant pain reduction to no effect, regarding the efficacy of hip IAHAI (14-16). For these reasons more methodologically adequate powered studies are required in order to evaluate the effects of intra-articular agents in OA (14,16).

The purpose of this study was to verify the efficacy and safety of ultrasound-guided viscosupplementation with high weight hyaluronic acid in hip osteoarthritis. Specifically, this study tried to answer the following questions: 1) How long does it last the efficacy of a single injection of IAHA? 2) Is there safe indication to repeat IAHAI and which effect we have to expect from this? 3) Is there an influence of IAHAI on the outcome of a subsequent surgical procedure of total hip replacement (THR)?

Materials and Methods

This study was conducted in accordance with the principles of Declaration of Helsinki and subsequent amendments and the principles of Good Clinical Practice. All patients signed informed consent about the treatment they were subjected and the processing of their personal data. Patients treated for hip OA from January 2014 to December 2016 with ultrasound-guided intra-articular (17) high weight HA (2500 kDa) injection of 2.5% sodium hyaluronate (60 mg/4 mL) were recruited. Inclusion criteria were also age higher than 40 years, mono- or bilateral hip OA with X-ray proof of at least partially preserved joint space (Kellgren-Lawrence grade 1-2-3) (18), good or full joint mobility, and hip disease persisting for at least 3 months. Exclusion criteria were: the presence of severe hip OA for which it was no longer possible to recognize

radiographic joint space (Kellgren-Lawrence grade 4), of inflammatory, autoimmune and septic disease and of previous hip surgeries.

At baseline demographic data (age, gender and body mass index), duration of disease, Kellgren-Lawrence radiological grade of OA, degree of hip pain reported on VAS and Harris Hip Score (HHS) were recorded.

All subjects were clinically evaluated before injection (T0) and then each year for the following four years (T1-T2-T3-T4). Clinical outcomes were registered using HHS and VAS. Furthermore, patients who underwent to subsequent ultrasound-guided IAHAI following the same protocol were identified and their clinical evolution was assessed. Finally patients who underwent to THA were followed for a minimum of 6 months in order to detect any early postoperative complication.

Results were statistically analyzed using SPSS 20.0 software (IBM Corp, Armonk, NY, USA). Univariate analysis with the Mann-Whitney test compared HHS and VAS at the different time of follow-up.

The effects of first and successive IAHAI calculated as mean changing in VAS and HHS were compared using Mann-Whitney test.

Multiple linear regressions evaluated the presence of clinical or radiologic variables as predictive factors of subsequent progression of the disease with positioning of THA. The cut-off value of significance was determined at $p < 0.05$.

Results

Overall 183 subjects (102 female and 81 male) with available complete data were included in the study.

Demographic data and baseline characteristics are reported in Table 1. No adverse events were registered during the entire follow-up.

A total of 72 subjects underwent to a second ultrasound-guided IAHAI with the same technique after a mean time of 20,6 months (range 13-38). All these second IAHAI were performed after at least 1 year from the first one. Moreover in 30 patients a third IAHAI was administered after a mean of 25,8 months (range 19-35) from the first.

Table 1. Demographic data and baseline characteristics.

	<i>N</i> = 183
Age	
Mean	65,8
Standard deviation	+/-12,3
Gender	
Male	102
Female	81
BMI	
Mean	25,1
Standard deviation	+/-3,6
Side	
Right	98
Left	85
Kellgren-Lawrence	
Grade 1	26
Grade 2	115
Grade 3	42
Baseline HHS	
Mean	56,4
Standard deviation	+/-11,9
Baseline VAS	
Mean	7,2
Standard deviation	+/-2,1
Duration of disease (months)	
Mean	8,7
Standard deviation	+/-6,9
Follow-up (years)	
Minimum	4
Maximum	6,2
Mean	4,8
Standard deviation	+/- 0,6

Clinical scores registered at different follow-ups are reported for the entire group of patients in Table 2.

The mean improvement of HHS and VAS between T0 and T1 was respectively 22,5 ($p < 0,001$) and 2,4 ($p = 0,021$).

At T2-T3-T4 the mean improvement of HHS and VAS was not statistically significant both in subjects who underwent one or more IAHAIs. Patients who underwent second and third IAHAIs showed a higher improvement of HHS and VAS than those who

performed only one IAHAIs even if statistical significance difference was not observed.

Considering the different scores registered at the last follow-up and the grade of baseline osteoarthritis a higher improvement in HHS and VAS was reported in patients with Kellgren-Lawrence grade 2 ($p < 0,001$).

In the follow-up after the first IAHA a total of 24 patients out of 183 underwent to THA (Table 2), with a comprehensive percentage of conversion to THA of 13,1% at last evaluation. The mean time between the last IAHA and the surgical procedure was 14,5 months (range 8-32 months). No early complications were reported after THA positioning in the available follow-up (mean 7,2; range 3-12).

Discussion

OA can affect all the synovial joints, but knee and hip are the most frequent localizations. Total joint arthroplasty has reached a progressive increasing relevance in orthopaedic surgery, interesting not only hip and knee but also the upper limb and the distal lower limb (19-22) leading to a definitive relief from symptoms. However, if OA incidence is higher in elderly, this pathology is also observed in young adults, especially in the case of intense sporting (23,24) and working activities, following femoral head osteonecrosis (25,26), hip traumas (27,28) and articular fractures (18).

It is estimated that 25-30% of the population over 45 years of age is affected by a form of OA with alterations of normal visco-elastic behaviour of synovial fluid (29).

At the beginning of the 90s, it was hypothesized that infiltrations with exogenous hyaluronic acid in patients suffering from OA could restore the visco-elasticity of the synovial fluid (30). The concept of viscosupplementation was subsequently developed because of the scientific evidence that the rheological properties of the synovial fluid were altered in OA and that these changes were related to the qualitative modification and quantitative decrease of hyaluronic acid.

In addition, exogenous derivatives seem to have biological activities such as the induction of endogenous high molecular weight hyaluronic acid synthesis,

Table 2. Clinical scores registered at follow-ups.

	Mean HHS (standard deviation)	Mean VAS (standard deviation)
T1 (N=183)	78,9 (+/-6,1)	4,8 (+/-1,8)
T2		
1 IAHA (N=111)	74,1 (+/-10,5)	5,3 (+/-1,5)
2 IAHA (N=60)	77,3 (+/-8,6)	4,9 (+/-1,3)
3 IAHA (N=12)	76,2 (+/-8,3)	4,8 (+/-1,7)
T3		
1 IAHA (N=105 [6 THA])	73,8 (+/-9,8)	5,2 (+/-1,7)
2 IAHA (N=40 [2 THA])	78,9 (+/-8,2)	4,9 (+/-1,4)
3 IAHA (N=30)	75,2 (+/-10,3)	5,1 (+/-1,6)
T4		
1 IAHA (N=96 [15 THA])	74,4 (+/-11,1)	4,9 (+/-1,5)
2 IAHA (N=35 [7 THA])	78,1 (+/-9,5)	4,8 (+/-1,2)
3 IAHA (N=28 [2 THA])	73,8 (+/-8,7)	5,1 (+/-1,4)

interaction with pain receptors and inhibition of pro-inflammatory mediators thus favoring potential disease-modifying effects.

As consequence, the use of intra-articular injections of hyaluronic acid has gained popularity among conservative therapies for OA, with demonstrated beneficial effects on pain and functional parameters and improved outcomes with an absence of clinically relevant adverse effects (31). In routinely clinical practice, IAHA is an accepted treatment for knee OA as supported by a number of evidence-based clinical practice guidelines, consensus statements, and decision algorithms (32,33). Although the onset of symptomatic benefit following IAHA may not be immediate, correspondingly, the therapeutic efficacy is prolonged (carry-over effect), with the effect size peaking by around 8 weeks and persisting for at least 6 months (34,35).

In recent years some studies have investigated the effects of IAHA for hip osteoarthritis.

A meta-analysis by Lieberman et al. (15) showed that viscosupplementation generated a minor but significant improvement over controls. This paper included twenty-three studies that met criteria and the mean decrease in visual analogue scores (VAS) was -1.97 (95% CL, 2.83 to -1.12, $P < 0.0001$). However, the clinical relevance of this change is difficult to

determine since the decrease in VAS was only -0.27 in the six randomized trials in the study and the duration of follow-up in most studies was less than six months.

Migliore et al. (17) compared HA injections to mepivacaine at 6 months follow-up (2 injections); patients in the HA group exhibited a significantly reduced Lequesne's algofunctional index and VAS at 3 and 6 months after treatment when compared with the local anaesthetic group. Conrozier et al. (36) assessed the clinical response of patients presenting with symptomatic hip osteoarthritis to the first intra-articular HA injection at 3 months of follow-up (up to four injections according to symptoms). Clinical response was defined as a 50% reduction from baseline in the Lequesne index one month after treatment. The response rate was 50% after the first injection and about half of the patients experienced significant pain relief during the 3 months following a single injection, and some of the patients who did not respond to the first injection received significant benefit from a second one.

On the opposite, some recent studies appear to reduce the real effectiveness of IAHA for hip osteoarthritis. Liao et al. reported a pooled analysis which did not find differences between viscosupplementation and placebo in pain or in function scores, which might be due to the small sample sizes of the included studies

that failed to detect differences (37,38). However, the benefits of viscosupplementation in hip OA was only demonstrated in open-label cohort studies, most of which included early OA (36,39,40).

Gazendam et al. (41) in a systematic review and network meta-analysis of randomized controlled-trials demonstrated that compared with placebo, no IA injections demonstrated a statistically significant improvement 6 months following the injection for patients with hip OA.

To date, controversy exists regarding possible increased infection risks when performing arthroplasty after previous intra-articular injections. A systematic review on intra-articular corticosteroid prior to THA identified 2 studies that reported higher infection risks for THA after intra-articular injection, and 7 studies that found no difference (42). Of the 2 studies reporting increased infection rates, Kaspar et al. (43) showed prosthetic joint infection (PJI) rates of 10% (4/40 patients) in their CS group, compared to 0% in the control group (0/40 patients), but their study lacked statistical power. Ravi et al. (44) included 37,881 THA patients in their database study, of whom 2468 received an intra-articular injection within 5 years prior to THA (69% <1 year). Patients who had an injection within 1 year of THA showed higher PJI rates than patients who did not receive prior intra-articular injection (3.3% vs 2.4%, $P = 0.04$). Also, controlling for confounders, an elevated hazard ratio of 1.37 of PJI was found after prior injection (44). Additionally, McIntosh et al. found no difference in infection rate in a matched cohort of 448 (224 per group) THAs; in the 3 patients who developed deep PJI, mean time between injection and THA was 44 days (± 23), compared to 112 days (± 23) for the entire cohort, raising concern for increased deep infection risk after intra-articular CS injection within 6 weeks of THA (45).

More recently, Werner et al. (46) showed that the incidence of infection after THA for patients who underwent previous intraarticular injection within 3 months was significantly higher at 3 months (odds ratio [OR] 1.9, $P = 0.004$) and 6 months (OR 1.5, $P = 0.019$) (36). There was no significant difference in infection rates in patients who underwent THA between 3 and 6 months or 6 and 12 months after ipsilateral hip injection, compared to controls (46).

This study has several limitations which includes the low number of participants, the absence of a control group and the absence of a blinded methodology.

However, the results observed, as described in the literature (15,17,30,31,34,35,47), suggest that the use of a preparation with high molecular weight hyaluronic acid allows to obtain satisfactory improvements in pain and joint function.

In particular Authors have documented that ultrasound guided IAHA for hip osteoarthritis is a safe procedure who shows maximum efficacy at first administration, with an effect that is higher within the first year after injection in patients with moderate grade of OA (Kellgren-Lawrence 2) and that the repetition of a IAHA does not lead to a significant adjunctive improvements. Furthermore, this treatment does not influence the outcomes of a subsequent THA implant as documented by the absence of any early postoperative complication in these subjects, thus including infections.

Conclusions

Authors can affirm that a single ultrasound-guided viscosupplementation with high weight IAHA could be a possibility in the symptomatic treatment of low and moderate grade of hip osteoarthritis. Better results are observed in in patients with Kellgren-Lawrence grade 2 OA. The repetition of IAHAIs is not characterized by similar positive effects. Outcomes of subsequent THA surgery are not influenced by this conservative treatment.

Conflict of Interest: Each author declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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