

Viscosupplementation with intra-articular hyaluronic acid for hip disorders. A systematic review and meta-analysis

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Summary

Background: Hip joint diseases are common in adult population and their prevalence increases with age. Osteoarthritis, rheumatoid arthritis and femoroacetabular impingement are the most common chronic diseases in the hip joint. Viscosupplementation with exogenous hyaluronic acid (HA) is one of the most widely used conservative treatment aiming to improve synovial fluid properties and to decrease pain. There is no global consensus on the type of HA, method of injection and frequency, or on its efficacy in hip joint.

Methods: We selected published data in English in the PubMed and Google Scholar electronic databases up to March 2016 about hyaluronic acid injections in hip disorders.

Results: 26 articles were included following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Conclusion: There is a lack of standardization of HA injections for hip conditions. Our results suggest that this is the best conservative therapy before surgery and it can act on pain relief and function however there is no evidence to prove its ability to modify the morphological structure of the pathological hip and the natural history of the disease. There are few data about the use of HA in other hip disorders rather than osteoarthritis. The most relevant evidence seems to show the utility of HA injections in improving synovial inflammation, but only a few studies have been conducted.
Level of evidence: I.

KEY WORDS: hyaluronic acid, hip injections, hip disorders, hip diseases.

Introduction

Hip disorders are responsible for reduced quality of life in terms of pain, loss of mobility and independence, disability, increased use of health care resources and loss of productivity. In the hip, the prevalence of osteoarthritis (OA) increases with age. In the young men are more affected than women, while over the young age of 45 women are the most affected, with severe limitation of the daily activity and quality of life. The success rate of conservative treatment is limited, and it is often necessary to consider surgical procedure like total hip replacement. While OA is the most common hip disease, different disorders can affect the hip joint. Rheumatoid arthritis is associated with significant morbidity, increased mortality and a complex multifactorial pathogenesis¹, resulting in systemic autoimmune destruction of bone and joints². Inflammatory cells active macrophages that release cytokines with a significantly contribute to inflammation and joint destruction³. Femoroacetabular impingement affects the hip and pelvis with abnormal contact between the acetabular rim ("pincer" impingement) or proximal femur ("cam" impingement). It is increasingly recognized as a potential cause of early hip osteoarthritis and labral cartilage pathology^{4,5}. In 1934, Karl Meyer and John Palmer⁶ isolated hyaluronic acid (HA) in humans, identifying it as an endogenous polysaccharide in the extra cellular matrix of many mature tissues including synovial fluid. Various pathological processes change the concentration of HA in synovial fluid. In the early 1960s, Balasz and Denlinger⁷ introduced the idea of visco-supplementation with exoge-

nous HA to improve synovial fluid properties and to treat articular pain. Shortly afterwards, the first studies on animal models and attempts to treat using HA were published. In 1997, HA received Food and Drug Administration (FDA) approval in humans. Visco-supplementation involves the use of HA solution to supplement or replace the synovial fluid in a pathological joint to alleviate pain and promote the healing of intra-articular injuries⁸. This procedure should improve the physiological environment of an osteoarthritic joint by restoring the protective viscoelasticity of synovial fluid⁹⁻¹², reducing friction and improving mobility^{13,14}. Intra-articular hip injections have been attempted for a wide variety of hip disorders, including OA, rheumatoid arthritis¹⁵, acetabular labral tears, femoro-acetabular impingement^{16,17}. The direct injection of hyaluronic acid in the joint space allows to reach a high concentration with low doses, enhancing a longer permanence in the joint that allows a therapeutic response. Hyaluronic acid preparations have a short half-life and the long term effects cannot solely be attributed to the substitution of molecule itself. This can be mediated by a different process, such as the anti-inflammatory and the anti-nociceptive effects, repair of joint rheology, chondroprotection and normalization of endogenous HA synthesis¹⁸.

Aim and Methods

The present review and its procedures were organized, conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁹. We wished to clarify:

- a) the efficacy of HA injections in hip joint diseases;
- b) the possibility to modify the natural history of hip OA or all other hip diseases;
- c) whether there was a global consensus about the type of HA, technique of injection, number and frequency of injections and outcome measures.

Source of studies and search strategy

We performed a systematic search (up to September 2016) in PubMed and Google Scholar electronic databases of articles assessing the association between HA injections and hip joint diseases published in English only. The search strategy covered different type of HA injections in different hip affections. In the search strategy, we used various combinations of the following key words and MeSH terms: hyaluronic acid, hyaluronic injections, hip joint, hip osteoarthritis, hip diseases, rheumatoid arthritis, femoral head avascular necrosis, hip dysplasia, femoroacetabular impingement, hip disorders, hip cartilage, conservative treatment. We only considered for inclusion in the present review the published randomized controlled trials that evaluate clinical outcomes after hyaluronic hip injections performed in any manner. Pilot studies, case reports, editorials, technical notes and narrative review articles were excluded.

Study selection and eligibility criteria

An orthopaedic surgeon and a physiatry resident performed the search and evaluated the articles independently. An experienced researcher in systematic reviews solved cases of doubt. At the beginning of the procedure, each examiner read the abstracts of all the articles, selected the relevant ones according to inclusion and exclusion criteria previously determined, and then compared the results with the other examiner. After four weeks, the same studies were read again to establish the agreement of the researchers on the selection. No disagreement was observed among the investigators.

Data collection

One reviewer extracted the data from the full text articles to Excel spreadsheet structured tables to analyze the studies in a descriptive way. The second researcher independently double checked the extraction of primary data from all the articles. Doubts and inconsistencies were followed and solved by discussion. The following information was extracted from articles: aim of the study, number of patients, hip joint disease, type of hyaluronic acid used, type of injections, follow-up and clinical outcomes.

Results

A total of 35 potentially relevant citations were identified. All of them concerned with hip OA, hip osteoarthritis, rheumatoid arthritis or femoroacetabular impingement. No studies were identified about HA and femoral head avascular necrosis or hip dysplasia. After reviewing titles and abstracts, 10 studies were excluded either because they were not randomized control trials, they were unblinded and uncontrolled studies or they did not clearly investigate the association between HA injections and hip joint disease modifications or because they had very small samples of patients. In addition, some of the excluded studies did not report the presence of a control group. A total of 25 articles were eventually included in the present review. All of them used different models and different protocols, making statistical data analyses impossible. The number of cited references, and other data recruited from the 25 included studies are reported in Table I.

Discussion

About OA, there is no global consensus on the efficacy of HA in the hip joint.

It is still unclear how HA would act in the joint microenvironment during OA. Recently, Lürati et al.²⁰ studied the effects of HA visco-supplementation on peripheral T cells in knee and hip OA and they showed that HA injection results in a decrease in

Table I. HA injections in hip joint diseases.

Reference	Year	Authors	Model	Frequency of injections
20	2015	Lurati et al.	86 pz - 800 and 1200 kDa HA in hip and knee joint -	3 weekly inj
21	2016	Dallari et al.	111 pz - PRP - PRP + HA - HA	3 weekly inj
22	2015	Battaglia et al.	46 pz - hyaluronic acid (Highly Cross-Linked HA) -	2 inj PRP + 2 inj HA
23	2009	Migliore et al.	42 pz - Hyalubrix - Mepivacaine	2 inj (1 per month)
24	2009	Richette et al.	85 pz - HA - Placebo	Single inj
25	2006	Quistgaard et al	185 pz - HA - Corticosteroid - Saline	3 inj HA (each 14 days) 1 inj corticosteroid 3 inj saline
26	2008	Van De Beckerom et al	120 pz - 3 hyaluronate formulations	1 inj 2 or 3 inj if pain relief
27	2005	Tikiz et al	43 pz - Low molecular weight HA - High molecular weight HA	3 weekly inj
28	2016	Atchia et al	77 pz - No inj - Corticosteroid - Non-animal stabilised HA - Saline	Single inj
29	2003	Migliore et al.	28 pz - hyaluronan preparations with molecular weight of 0.5–0.75 or 1.0 million	1 to 3 inj every 15 days
30	2006	Migliore et al	30 pz - HA hylan G-F 20	1,2 or 3 inj
31	2010	Eyigor et al.	21 pz - 2.5 ml HA injection	3 weekly inj
32	2008	Migliore et al.	1887 pz - Low molecular weight HA - High molecular weight HA	1 inj inj every 6 months if pain relief
33	2011	Migliore et al.	2343 pz - Low molecular weight HA - High molecular weight HA	1 or 2 inj every 6 month
34	2006	Conrozier et al.	56 pz - HA hylan G-F20	3-4 inj if pain was unchanged or returned to baseline levels
35	2008	Conrozier et al	34 pz - Non-animal stabilized HA(NASHA)	Single inj
36	2002	Brocq et al.	22 pz - HA hylan G-F 20	1 inj or 2 inj (day 30)
37	2003	Vad et al.	22 pz - HA hylan G-F 20	3 inj at 2, 3, and 4 weeks
38	2007	Gaston et al.	13 pz - synthetic high molecular weight - HA	3 weekly inj

to be continued

Continued from Table I

39	2012	Migliore et al.	176 pz - sodium hyaluronate (MW 1,500– - 2,000 kDa)	single inj every 6 months. Up to 1 inj per 3- month period, in any 1 year
40	2015	Reum Son A et al.	Rats affected by rheumatoid arthritis	Single inj at a volume of 100µL into the articular knee joint
41	2011	Kim KS et al.	Animal model*	Intra-articular injection of HA-Tyr hydrogels encapsulating dexamethasone (DMT)
42	2010	Yasuda T.	Cartilage specimens from patients who underwent total knee replacement who were diagnosed as having RA or OA	Histological evaluation
43	2009	Saito S et al.	4725 patients in the database	Single inj of HA or corticosteroids
44	2014	Abate M et al.	23 pz - 3 bilateral cases	2 inj (time 0 and after 40 days)

*Lack of information

PZ, patients; INJ, injection; PRP, platelet rich plasma; kDa, kilodalton.

proinflammatory T cells concentrations. In particular, HA can reduce synovial inflammation and restore the rheological properties of synovial fluid. Some studies compared HA injections to different drugs for hip pain relief. Dallari et al.²¹ compared Platelet Rich Plasma (PRP) injections to hyaluronic acid (HA) or their association (PRP1HA) at 6 and 12 months follow-up evaluating VAS scale, Harris Hip Score and WOMAC scores in hip OA. Intra-articular PRP injections lead to a significant clinical and functional improvement, with no significant differences between PRP and PRP1HA treatment. Battaglia et al.²² combined HA and PRP injections following a specific protocol for moderate to severe hip OA (4 injections), and they performed laboratory, VAS and radiological evaluation after 1, 3, 6 and 12 months. The results showed that in 93.7% of cases there was a significant reduction of subjective pain (VAS scores) and consumption of NSAIDs greater than the HA or platelet gel alone.

Migliore et al.²³ 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 3 and 6 months after treatment with a significantly reduced pain score (VAS) at 3 and 6 months after treatment when compared with the local anesthetic group.

If compared to placebo, it is not clear whether HA is more effective in the treatment of hip OA. Richette et al.²⁴ performed a single injection of HA or placebo. VAS and WOMAC were evaluated after 3 months and compared to baseline. The results showed that there was no significant difference in terms of efficacy after one injection of HA compared with placebo in patients with hip osteoarthritis.

Comparison between three HA, one corticosteroid and three isotonic saline ultrasound-guided injections was performed by Quistgaard et al.²⁵: the study demonstrated that patients treated with corticosteroids experienced significant improvement in "pain on walking" dur-

ing the 3 months of intervention. No such results were experienced after HA injections probably because corticosteroids act immediately on pain relief.

Van De Beckerom et al.²⁶ compared three different hyaluronate formulations and evaluated functional improvement, pain relief and also the delay in performing a total hip arthroplasty after two injections. They showed that the three HA formulations do not differentiate in terms of clinical and functional outcomes. These data show that it is still unclear how HA products affect OA treatment outcome based on their different molecular weight.

Some Authors compared the efficacy of lower and higher molecular weight visco-supplementation in the treatment of hip OA. Tikiz et al.²⁷ performed three hip injections (one injection per week), and evaluated VAS scale, WOMAC and Lequesne index after 1, 3 and 6 months. Both types of visco-supplementation produced a significant clinical improvement during the 6-month follow-up period, with no significant difference between higher and lower molecular weight hyaluronic acid. Atchia et al.²⁸ reported no significant improvement in pain and function after a single high molecular weight HA injection in moderate to severe hip OA when compared to standard care with no injections or to saline or non animal stabilized HA. This suggests that high molecular weight hyaluronic acids may not have a role to play in moderate to severe hip osteoarthritis.

On a methodological point of view, the latest studies emphasize the importance of ultrasound-guided injections in hip joint. Migliore et al.²⁹ reported that ultrasound-guided IA injection of HA in the hip is well tolerated, the few adverse events were local and resolved spontaneously in a few days. Ultrasound guidance is safe and cheap. In addition, the same group of Authors observed the effects HA administered through ultrasound (US)-guided intra-articular injection in patients with symptomatic hip osteoarthritis at 2 and 6 months follow-up and they demonstrated that

an injection or repeated injections of HA could be effective and acceptable with poor risk³⁰. On the contrary, radiological guide is more expensive and it implies a high radiation load. Eyigor et al.³¹ investigated intraarticular HA injection (three injections) through a lateral approach under fluoroscopic control, and reported that this type of injection provided significant reduction in pain scores, disability scores and analgesic use in advanced hip OA. HA injections in hip osteoarthritis seems to reduce the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs). Migliore et al.³² reported that NSAIDs consumption decreases already after the first hip injection with low and high molecular weight HA showing that hip viscosupplementation may be effective and cost-saving. A few years later, they increased their population, and they reported that the consumption of NSAIDs was reduced of 48.2% at the third month when compared with baseline values with an increased sparing effect at 12th and 24th month³³.

According to clinical outcome after HA injections, different clinical variables have been considered to evaluate the efficacy in hip osteoarthritis. Conrozier et al.³⁴ 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.

A few years later, Conrozier et al.³⁵ determined that the patient self assessment of treatment efficacy (PATE) after one HA injection was correlated with Lequesne index and walking pain decrease after one HA injection at 6 months of follow-up; PATE at month 1 was also highly predictive of the efficacy of the injection at month 6.

In the short term, Brocq et al.³⁶ investigated the safety and efficacy of one or two intraarticular HA injections in patients with symptomatic hip osteoarthritis. Short-term safety was satisfactory, with a self-limited exacerbation of pain during the first few days in three patients but no infections or other side effects. The response rate was 50% after the first injection but only one third of the entire population had a sustained improvement at 6 months.

Vad et al.³⁷ evaluated the outcome after three HA injections at one year follow-up. HA injections are a valid option for mild to moderate OA according to pain relief but they are not useful in severe OA because they are not able to modify the natural history of the disease and they are not able to avoid surgical procedure.

Gaston et al.³⁸ tried to investigate whether there was any relation to pre-injection radiographic changes of osteoarthritis after three visco-supplementations with synthetic hyaluronic acid to the hip joint. HA can alle-

viate patient symptoms in hip OA with no significant radiographic changes. Migliore et al.³⁹ performed HA injections every 6 months with a maximum of one injection per 3-month period in any 1 year in hip osteoarthritis. Visco-supplementation should be considered as conservative treatment to perform before listing patients for total hip replacement.

Concerning other hip joint diseases rather than OA, few studies investigate the role of HA injections in rheumatoid arthritis (RA).

Reum Son et al.⁴⁰ considered different preparations for rheumatoid arthritis treatment in rats: methotrexate-loaded HA (Met-HA), dexamethasone (Dex-M) and dexamethasone dispersed inside methotrexate-loaded HA (Met-HA/Dex-M). Met-HA/Dex-M formulations could serve as an effective injectable drug, as it synergistically enhance local RA repair. Kim KS et al.⁴¹ assessed that intra-articular injection of tyramine modified hyaluronic acid encapsulating dexamethasone (DMT) resulted in successful treatment of RA with reduced pro-inflammatory cytokines such as interleukine-6, prostaglandin E2 and other types of cytokine levels in collagen-induced arthritis animal models. Yasuda⁴² histologically compared the effects of HA in normal, osteoarthritis, and rheumatoid arthritis affected hip joints. In this study, explanted articular cartilage was incubated with heparin-binding fibronectin fragment (HBFN-f) producing higher levels of nitric oxide (NO) compared with normal cartilage. HA seems to block HBFN-f actions in OA and RA cartilages through interaction with some molecular factors such as CD44. HA, which targets CD44 highly expressed on OA and RA chondrocytes, could suppress catabolic actions by fibronectin fragments like HBFN-f in diseased cartilage. Saito et al.⁴³ evaluated the patient-based database from a cross-sectional observational cohort in order to investigate if the intra-articular injection of HA is a potential clinical option for the treatment of RA. 14% of the patients in the database received corticosteroids or HA injections. The patients satisfaction rate of injection was 64 for corticosteroid injections and 59.3 for HA injections. HA and corticosteroid injections generally have similar efficacy rates; HA could be identified as a therapeutic option for RA.

Abate et al.⁴⁴ investigated the role of HA injections in femoroacetabular impingement (FAI).

They reported the short-term results on hip pain and function after 2-ml intra-articular ultrasound-guided injection of hyaluronic acid at baseline and after 40 days in 23 hips affected by mild FAI. They evidenced significant pain reduction, anti-inflammatory medication consumption reduction and function improvement after HA injections.

Conclusions

There is lack of general consensus about the standardization of HA injections in hip OA osteoarthritis and other hip diseases.

We can state that:

- The evidence suggest that this is the best conservative therapy for osteoarthritis before surgery indications, and it can act on pain relief without modifying the morphological structure of the pathological hip and natural history of the disease.
- There is no general consensus on number and timing of hip injections. Studies provide from one to four injections following a variable timing. Ultrasound guided injection is the safest approach.
- There is no relevant difference between low molecular weight and high molecular weight HA. The outcome after injection is comparable. No comparison has been made with medium molecular weight hyaluronic acid injections.
- If HA is associated to PRP o corticosteroids, pain relief is more rapid but it is not clear if this condition is persistent. There is no evidence on the efficacy of PRP and corticosteroid injections alone in hip osteoarthritis.
- The only improvement is on pain and walking distance. Radiographic changes are not present, and the progression towards surgical option is not modified.
- The efficacy on symptoms is demonstrated only in mild to moderate OA. Severe disease does not benefit from this treatment. However, studies on the early disease and on young populations have not been published yet.
- Concerning other hip joint conditions, only a few studies investigated the role of HA injections in rheumatoid arthritis or femoroacetabular impingement. No studies have been published On femoral head avascular necrosis or hip dysplasia.
- It is not clear whether a concomitant rheumatic disease such as rheumatoid arthritis or synovial inflammation could influence the clinical outcome of HA hip injections during osteoarthritis.
- HA in association with methotrexate or dexamethasone injections seems to be able to reduce synovial level of pro-inflammatory cytokines during rheumatoid arthritis.
- Published data do not allow us to consider HA able to modify the natural history of the hip disorders included in our review. We can only speculate about clinical improvement in terms of pain relief.
- Further studies need to be planned about HA injections and other hip congenital or acquired diseases, like femoral head avascular necrosis or hip dysplasia. To our knowledge, only a few case series reported conservative treatment of femoral osteonecrosis, but they investigated adipose-tissue derived stem cells. Considering synovial fluid cartilage metabolism in osteonecrosis of the femoral head, the impact of HA in hip disruption should be investigated.

All the procedures described in the present study comply with the Muscles, Ligaments and Tendons Journal. Basic principles and recommendations in clinical and field science research.

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