# Hip osteoarthritis treatment with intra-articular injections: hyaluronic acid versus glucocorticoid

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## ABSTRACT

**Objective:** To compare the effects of intra-articular injection of glucocorticoid (GC) and hyaluronic acid (HA) on pain and disability caused by hip osteoarthritis (HO).

**Materials and methods:** A systematic review of the literature was carried out within MEDLINE (via PubMed), Web of Science, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) databases, using the keywords (MeSH words): "hip osteoarthritis", "glucocorticoid", "corticosteroid", "corticoid", "hyaluronic acid" and "viscosupplementation". Two independent authors applied inclusion and exclusion criteria, selecting randomized clinical trials with direct comparison between intra-articular injection of GC and HA in patients with HO.

**Results**: 157 articles were found in the initial search. After applying the exclusion criteria, 36 articles were read, with final selection of 3 randomized clinical trials (n = 484). Two studies compared the administration of these products with placebo (saline) - and one also compared it with a fourth group of patients undergoing only physical therapy. Qvistgaard *et al.* demonstrated clinical superiority of GC (moderate clinical benefit) and HA (marginal clinical benefit) in pain, at 4 weeks, both compared to placebo; however, there was no statistically significant difference between GC and HA during the 12-week follow-up. Atchia *et al.* reported a statistically significant improvement in pain and function in patients treated with GC during 8 weeks. Spitzer et al. demonstrated an overall clinical response in patients in both groups throughout the study, with a faster response for those treated with GC. However, the authors highlight the superiority in all outcome measures of HA compared to GC in cases of moderate HO, at 26 weeks.

**Conclusion**: Few studies directly compare the clinical effect between intra-articular injections of GC and HA in HO, showing heterogeneity in the type of population, number of administrations, formulation of HA and follow-up period. The analyzed studies had a short follow-up time. The results obtained seem to demonstrate a superiority of GC compared to HA in managing pain, namely in the speed of clinical response. However, Spitzer *et al.* demonstrated an overall superiority of HA in patients with moderate HO, which suggests that optimal selection of patients remains to be defined.


**Keywords:** Glucocorticoid; Corticosteroid injection; Intra-articular injection; Hip osteoarthritis; Viscosupplementation; Hyaluronic acid.

## INTRODUCTION

Osteoarthritis is an osteoarticular disorder caused by damage to articular cartilage[1-8]. Its onset and progression is associated with aging, changes in metabolism, hormonal and genetic factors, biomechanical changes and inflammation[5,9,10]. Osteoarthritis is the most prevalent rheumatologic disease globally[8] and occurs most commonly in older adults, being estimated to affect up to 80% of patients older than 65 years-old[1-7]. It usually causes pain, various degrees of inflammation, effusion, reduced mobility, disability and loss of functionality[1-5,10,11].

The hip is the second most common localization of osteoarthritis, after the knee[10]. The distinct pathogenesis of hip osteoarthritis (HO) is usually linked to the femoroacetabular morphology, with abnormal articular shearing and tearing forces resulting in a chronic in-

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flammatory process[10,12]. Also, a proinflammatory state due to homeostatic imbalance in adipokines and cytokines can lead to cartilage degradation. Interleukin--1b, tumor necrosis factor- , and interleukin-6 seem to mediate this process, stimulating metalloproteinases and inhibiting proteoglycans[12]. So, although osteoarthritis is described as a noninflammatory disease, inflammation has been recognized as having an important role in its symptoms and progression[13,14]. Thus, blocking proinflammatory pathways may reduce cartilage destruction, leading to better pain control and functionality in patients with HO[12].

Nowadays, there are no effective therapies for reducing disease progression, so management is primarily focused on optimizing pain control and maintaining function[15]. Nonsurgical therapies for HO include physical therapy, exercise, activity modifications, walking aids, topical agents, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections[1,7,8,16-22]. Oral analgesic therapy is restricted by duration, degree of efficacy and considerable associated toxicities[10,11,15]. NSAIDs are associated with significant side effects, exacerbated by the frequent co-morbidities present in a typical HO population[11,15].

As these treatment options are only modestly effective, surgery such as total hip replacement is often considered the best option for treating HO[5,10]. However, this invasive treatment is aggressive and brings out the risks of surgical complications such as nerve injuries and dislocation[5]. Many symptomatic HO patients are not yet candidates for hip arthroplasty, despite experiencing pain and limited function[18]. In these cases, and after non effective conservative treatments, intra-articular injections can be considered, since they target the affected joint directly, with few systemic effects[6,10,23]. Currently, two generally accepted products are used for intra-articular injection of the hip: glucocorticoid (GC) and hyaluronic acid (HA)[10,17,24,25].

Unlike the knee joint, the access to the intra-articular compartment of the hip is rather difficult,[9,24,26] mainly for anatomical features of the joint and the proximity of important structures such as the femoral artery and nerves[4]. For such reason, intra-articular injections in HO have not been widely used in the past[9,24,26]. Even though this procedure may be performed "blindly", failure rate is significant. So, it has been suggested to perform it under radiological or ultrasound control[4,10].

Current guidelines produced by European League Against Rheumatism (EULAR),[27] the American College of Rheumatology (ACR)[28] and Osteoarthritis Research Society International (OARSI)[29] recommend intra-articular GC therapy use in the management of symptomatic HO,[10,15] since they produce anti-inflammatory, immunosuppressive and antinociceptive effects, providing immediate pain relief and reducing joint effusions[1,23]. Clinical experience has shown that glucocorticoids (GCs) are very useful for the treatment of exacerbations of osteoarthritis, although they do not seem to modify its underlying process. Despite the utility, its effect only lasts for a relatively short period of time,[23] which may lead to the need of repeated injections. Although it has been established that GC injections are fairly safe, there are concerns regarding their possible adverse effects following repeated injections. The most frequent side effects are post-injection flare, infection, local fat atrophy, tendon rupture and/or skin hyper- or hypopigmentation[6,16,23,24,30]. Avascular necrosis of the femoral head has been reported on rare occasions[1]. Repetitive GC injections have been shown to damage the cartilage by thinning it[7,12,18]. These injections can also lead to some systemic effects such as increased glucose levels and hypothalamic-pituitary-adrenal axis suppression[1].

HA is a glycosaminoglycan molecule that integrates the normal synovial fluid and cartilage extracellular matrix, being one of its main components[1,5,6,9,10,16,25,30,31]. Its function is to provide lubrication, shock absorption and viscoelastic properties[1,5,16,20,21,31]. It is known that during the aging process, HA concentration in the human body is reduced by 33%-50%[1].

Intra-articular injection of HA derivatives, also known as "viscossuplementation", aims to restore the visco-elastic properties of joints, such as cushioning, lubrication and elasticity[4,6,7,16,24,30,31]. In addition to those properties, HA is thought to have anti-inflammatory and/or antinociceptive effects on the synovial cartilage, decreasing joint effusion[1,21,23,24,32,33]. It may also have chondroprotective effects, but these have only been studied *in vitro*[1,24,31].

HA injections have been used in humans for more than 30 years, mainly in knee osteoarthritis, but increasingly in other joints such as the hip[31]. In clinical practice, there are several preparations of HA available, which range from low-molecular-weight (e.g., Hyalgan® or Synvisc®) to high-molecular-weight (e.g., Durolane®), with the latter being produced by cross-linking hyaluronic acids, also known as hylans[23,30]. All of them are generally well tolerated, with low incidence

of side effects[20,21] such as post-injection flare (that usually resolves without treatment within 72 hours), superficial itching and headache[1,20,21,24,30,31]. Rarely, more serious side effects include severe inflammatory reactions, pseudogout and pseudosepsis[1,20,23,24].

Nevertheless, the effectiveness of HA in comparison to GC remains unclear. This study aims to compare intra-articular injections of GC and HA for the treatment of HO.

## METHODS

### AIM AND INCLUSION CRITERIA

This systematic review was conducted according to the guidelines of the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) Group[34]. The goal was to include all randomized controlled trials concerning the head-to-head comparison of intra-articular injections of GC and HA in the treatment of HO, which reported at least one of the defined outcome variables (pain, disability and quality of life).

HO diagnosis was established according to the ACR criteria[35] with all degrees of severity of osteoarthritis included.

### EXCLUSION CRITERIA

Exclusion criteria were: ineligible publications (book chapters, reviews, editorials, comments, conference proceedings, meeting abstracts or guidelines without relevant information), non-human studies (e.g., *in vitro* or animal research), non-Portuguese, English or Spanish languages, case reports, studies concerning osteoarthritis in other joints (e.g., knee), studies merely describing HA or GC administration technique, studies comparing different HA formulations with a non-GC intra-articular injection and studies comparing different GC formulations with a non-HA intra-articular injection.

### OUTCOMES

The outcomes established for this study were: pain, disability and quality of life. The minimum criteria for inclusion of the trial was the adequate reporting of at least one of the outcome variables. Information regarding other outcomes and adverse events was extracted and analyzed, when feasible. All tools routinely used to assess the referred outcomes were accepted. When the trial reported more than one tool for the same outcome (e.g., visual analog scale [VAS], Western Ontario and McMaster Universities [WOMAC] Osteoarthritis Index and Lequesne Index), a hierarchy proposed by Juhl *et al.*[36] was used to select one of them.

### SEARCH STRATEGY

A search was conducted on the December 13th, 2019 with no date restrictions, within the following databases: MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus and Web of Science.

The search terms used were "hip", "osteoarthritis", "glucocorticoid", "corticosteroid", "corticoid", "hyaluronic acid" and "viscosupplementation". The controlled specific vocabulary of each database was also used (e.g., MeSH in MEDLINE).

Data was independently extracted by two authors. Discrepancies were resolved by discussion or with arbitration by a third reviewer when differences remained. All articles had their title and abstracts analyzed. Articles were not blinded for author, affiliation or source.

All studies that could potentially match the inclusion criteria, or that the title or abstract revealed insufficient information to determine appropriateness for inclusion, had their full text extracted. The papers were then critically read and data was extracted using purpose-made data-extraction tables.

## RESULTS

The initial search of literature databases identified 157 potentially relevant papers (MEDLINE: 17; Scopus: 106; Web of Science: 29; CENTRAL: 5). Based on the title and abstract, 53 papers were included. After removal of 17 duplicates, 2 conference abstracts and 2 studies written in other languages, 32 records remained for full text review, with 3 studies meeting the inclusion criteria[18,26,37] (Figure 1). A published protocol for one trial,[24] if performed accordingly, would have met the review inclusion criteria and be potentially relevant to this review. However, no published results were identified, and the corresponding author did not reply to a request for further information.

A summary of the characteristics of included trials is shown in Table I. The studies were published between 2006 and 2015. Across all three included trials, 484 participants were randomized. The average age was between 59 and 69 years. The studies had a population of 78,[37] 101[26] and 305[18] patients. Three different

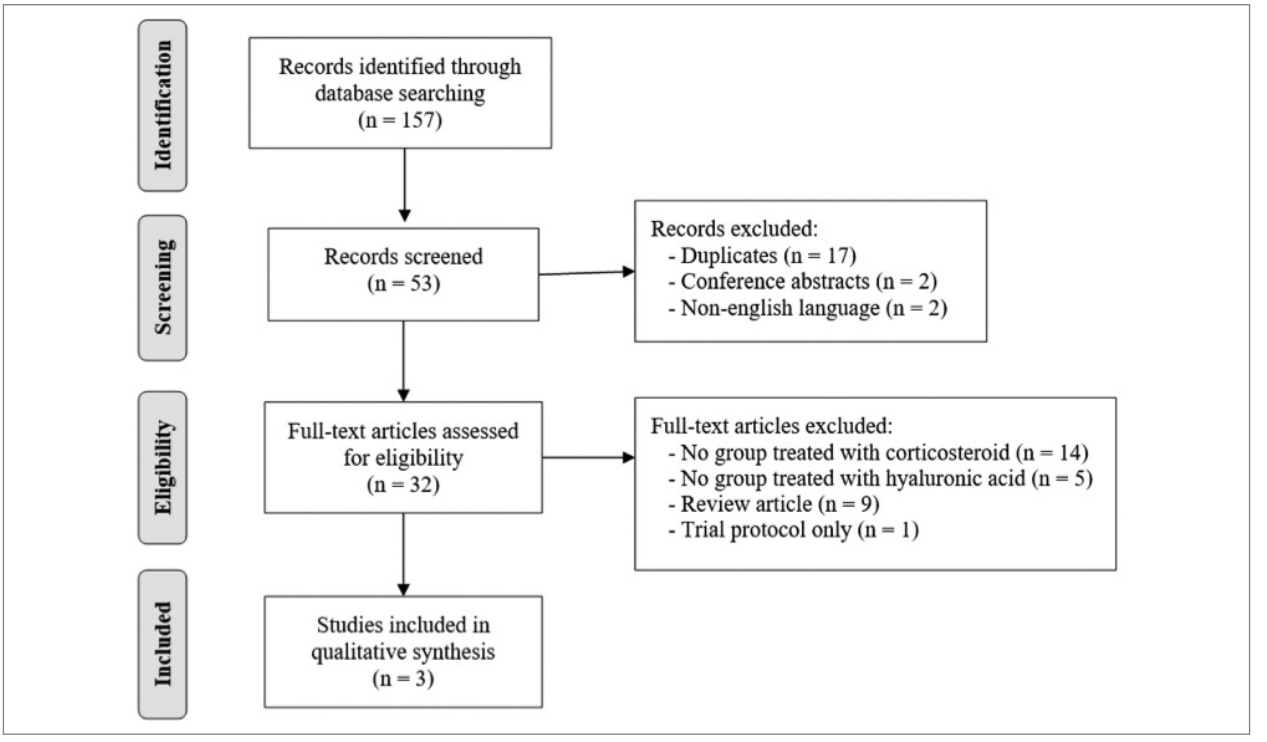


**FIGURE 1.** PRISMA flow diagram of article selection.
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HA formulations (Hyalgan®,[26] Durolane®[37] and Synvisc®[18]) were chosen, but all studies used the same GC preparation (methylprednisolone). The dosing of methylprednisolone was variable throughout the studies. Two studies compared the administration of these products with placebo (saline)[26] - and one of these also compared it with a fourth group of patients undergoing physical therapy, only[37]. Two studies used ultrasound[26,37] as a procedure guide, while one used fluoroscopy[18]. The studies showed heterogeneity regarding the number of injections administered and the time interval between each one (Table I). The duration of follow-up ranged between 12-26 weeks. In all studies, post hoc analysis using the Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society International (OMERACT-OARSI) criteria[38] allowed comparison of positive treatment responses.

Qvistgaard *et al.*[26] performed a prospective double blind study, using a randomized controlled trial with a three-armed parallel-group design (methylprednisolone versus Hyalgan® versus saline). Three ultrasound-guided intra-articular injections were given at two weeks interval (group 1: first injection with GC, following two saline injections; group 2: three HA injections; group 3: three saline injections). Patients continued their usual analgesic consumption throughout the study, but those who demanded therapy changes were secondarily excluded. The primary outcome measure was "pain on walking", registered using VAS, and secondary outcome measures were "pain at rest", using VAS, Lequesne score and WOMAC index for osteoarthritis; and "patient global assessment", on a VAS. Assessments were performed at baseline and after 2, 4 and 12 weeks. The secondary drop-out rate was 13%. Patients treated with GC experienced significant improvement in "pain on walking" at 4 weeks of intervention (p=0.006) with an effect size indicating a moderate clinical effect; standardized mean differences (SMD) = 0.6 (95% confidence interval [CI]: 0.1-1.1, p=0.021). Although a similar significant result could not be shown in the HA group, the effect size indicated a marginal clinical benefit; SMD = 0.4 (CI: -0.1 to 0.9; p=0.13). However, there was no statistically significant difference between the three groups on any outcome measure, at 12 weeks (p=0.29); SMD (GC) = 0.3 (CI: -0.1 to 0.8; p=0.17); SMD (HA) = 0.0 (CI: -0.5

**TABLE I. SUMMARY OF THE CHARACTERISTICS OF STUDIES MEETING THE INCLUSION CRITERIA**

| Study (year) | Design and Follow-up duration | Sample size (n) | Mean age (years) | Study population | Intervention groups | HA brand | Follow-up (weeks) | Injection guidance | Primary outcome | Secondary outcome | Oral analgesics allowed |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Qvistgaard et al. (2006) | Double blind, three-armed parallel-group design. 12 weeks. | 101 | 66 ± 12 | age >18 years, HO defined by the ACR criteria, radiographic changes HO, stable medication for ≥ 3 weeks | 3 injections, 2-week intervals: •40mg MP + 2x sham injections • 3x HA •3x saline | Hyalgan® | 2, 4, 12 | Ultrasound | Pain on walking (VAS) | Pain at rest (VAS, Lequesne score and WOMAC) and patient global assessment (VAS) | Usual analgesic consumption permitted |
| Atchia et al. (2010) | Single blind, four-armed parallel-group design. 16 weeks. | 78 | 69 ± 8 | age ≥ 50 years, unilateral HO defined by the ACR criteria, pain duration > 1 month, and either listed or warranting consideration for THR | 1 injection only: •120mg MP •HA •Saline Standard care - no injection | Durolane® | 1,4,8,16 | Ultrasound | Worst pain (NRS) | Pain and function (WOMAC) and patient global assessment. | No restrictions |
| Spitzer et al. (2010) | Double-blind, two-armed parallel-group design; multicenter. 26 weeks. | 305 | 59 ± 12 | Age ≥ 35 years, unilateral HO defined by the ACR criteria, radiographically confirmed KLG 2 or KLG 3, who had moderate hip pain walking on a flat surface and need medications for hip pain. | 2 injections, 2-week intervals: •40mg MP + sham injection •2x HA | Synvisc® | 4,8,12,16, 20,26 | Fluoroscopy | Pain (WOMAC) | Blinded clinical observer global assessment (VAS), patient global assessment (VAS) and pain on walking, stiffness and function (WOMAC) | Analgesics were suspended 3–21 days before treatment (acetamino--phen was allowed for pain flares) |

HO, hip osteoarthritis; ACR, American College of Rheumatology; THR, total hip replacement; KLG, Kellgren–Lawrence Grade; MP, methylprednisolone; HA, hyaluronic acid; VAS, visual analog scale; NRS, numeric rating scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index

to 0.5; p=0.97). Responder analysis demonstrated that, at 4 weeks, 53% patients responded to HA, 66% to GC, and 44% to placebo. The authors found that GC had significant effect in "pain on walking" on both patients with and without effusion, while HA only had effect in patients without effusion. No significant adverse events were found during the study period.

Atchia *et al.*[37] designed a prospective single blind study, using a randomized controlled trial with a four-armed parallel-group design (methylprednisolone versus Durolane® versus saline versus standard care [non-injection group]). In the three groups allocated to invasive treatment, only one ultrasound-guided intra-articular injection was performed. There were no restrictions regarding medication use, but patients were requested to notify changes in medication during the study. The primary outcome measure was "worst pain" on a numerical rating scale (NRS). The secondary outcome measures were "pain and function global scores" on the WOMAC index for osteoarthritis, and "patient global assessment". Evaluation was performed at baseline, 1, 4, 8, and, when possible, 16 weeks post-injection. At 8 weeks, there were 4 dropouts from the standard care group and 1 from each of the GC and HA groups. There were statistically significant differences throughout the study, with improvements in the GC group for all the outcome measures sustained over the 8-week period (p=0.002 for pain on NRS, p=0.003 for pain on WOMAC and p=0.009 for function on WOMAC), with an effect size indicating a moderate to large benefit (1.5, 1.0 and 0.5 for pain on NRS; 1.9, 1.1 and 0.6 for pain on WOMAC; and 1.3, 0.9 and 0.4 for function on WOMAC, at weeks 1, 4 and 8, respectively). The number of OMERACT–OARSI responders was significantly higher in the GC group, sustained at 8 weeks. The authors highlighted the presence of synovitis (measurement of the bone to capsule distance of over 7mm) as a single predictor of GC response at weeks 4 and 8 (p<0.05, Fisher's exact test). No significant adverse events were found during the study period.

Spitzer *et al.*[18] performed a prospective, multicenter, double-blind study, using a randomized controlled trial with a comparative two-armed parallel-group design (methylprednisolone versus Synvisc®). Two fluoroscopy-guided intra-articular injections were given at two weeks interval (group 1: first injection with GC, following one saline injection; group 2: two HA injections). Patients were required to suspend any pain or osteoarthritis medication 3–21 days before treatment – acetaminophen (4000 mg/day, prn) was allowed for flares of hip pain or post-injection pain management. Patients were asked to discontinue any pain medications 48 hours prior to each evaluation. The primary outcome measure was "pain" on the WOMAC. The secondary outcome measures were "blinded clinical observer global assessment" on VAS, "patient global assessment" on VAS, and "pain, stiffness and function" on the WOMAC. Evaluation was performed at baseline and at 4, 8, 12, 16, 20, and 26 weeks. The percentage of dropouts was 20% for the HA group and 25% for the GC group. Patients in both groups showed a clinical response throughout the study (p=<0.0001) in all outcome measures, with an early response for the ones treated with GC, whereas HA exhibited a more delayed onset of action. Applying WOMAC A and OMERACT–OARSI responder criteria, was demonstrated that patients receiving HA were more likely (31%; p= 0.13, and 34%; p= 0.09, respectively) to have a positive response than patients receiving GC, as it was equally more likely for patients with osteoarthritis Kellgren-Lawrence grade (KLG) 3 (moderate osteoarthritis) treated with HA to have a positive result at 26 weeks (p=0.06). Patients with moderate osteoarthritis had a 50% and 58% greater probability of a positive result with HA versus GC, as measured by WOMAC A (p=0.04; 41%–50%) and OMERACT-OARSI (p=0.01; 48%–58%) criteria, respectively, at all study intervals. There were no significant adverse events during the study.

## DISCUSSION

As several intra-articular medications have been introduced to treat symptomatic osteoarthritis, GCs and HA have been studied the most. Most studies focus on the knee, demonstrating effectiveness of both interventions in reducing knee osteoarthritis symptoms; however, HA seems to have a longer duration of action while GCs have a more rapid onset of action. Some controversy remains over the benefit of HA and GCs in the treatment of HO[24]. Overall, intra-articular injections may be considered safe when given with the aid of ultrasound or fluoroscopic guidance.

Both GC and HA injections should be considered for patients who are delaying or unsuitable for joint replacement surgery. This review indicates an overall superiority of GC compared to HA, namely in the speed of clinical response. However, patients with moderate radiographic osteoarthritis (KLG 3) appear to have

higher response rates to HA.

In the study by Qvistgaard *et al.*,[26] there was no tendency of effect in any outcome measures, during the 12 weeks of intervention, in all groups. Patients treated with GC had a significant but short lasting improvement in "pain on walking", with an effect size indicating a moderate clinical effect. Unlike GC injections, HA showed no effect in pain in patients with joint effusion. Therefore, the authors suggest that the presence of intra-articular effusion may be considered a predictor of good response to GC injections.

Atchia *et al.*[37] reported benefits regarding pain and function of a single injection of GC in patients with advanced HO eligible for arthroplasty, during 8 weeks. However, the authors failed to demonstrate any improvement after injection of a high-molecular-weight HA, at least in moderate to severe HO, as this study did not address early or mild disease. It was also advocated that ultrasound evidence of synovitis is a biomarker of response to GC injection.

Spitzer *et al.*[18] demonstrated that HA was equally as effective, regarding to all outcome measures, as GC in all patients. However, HA patients with moderate radiographic disease responded better overall. As anticipated, GC provided better outcomes early in the study, while HA patients seemed to have surpassed those of GC in a later phase. The authors defend GCs' better response in milder disease, in relation to the presence of soft tissue inflammation.

Many other studies[15,23,32] suggest that intra-articular GCs are efficacious in delivering short term, but clinically significant pain relief, as it can decrease pain and lead to transient function improvement for up to 3 weeks. The overall effect of GCs is the reduction of proinflammatory derivatives such as bradykinin and histamine, which can cause pain by directly stimulating primary afferent nociceptive fibers; and prostaglandins and leukotrienes, which have been shown to sensitize nociceptors. Also, GCs interfere with inflammatory cell adhesion and migration, inhibit synthesis of neutrophil superoxide, and decrease immunoglobulin production. As inflammation is a driver for structural progression of osteoarthritis, the use of intra-articular GCs has been pointed as a possible strategy for its prevention[37]. The reduction of pro-inflammatory mediators, rapidly stabilizing neural membranes and inhibiting C-fiber transmission, may explain why some patients report immediate relief of pain after a GC injection[23]. For such reason, intra-articular GCs are considered a fast-acting symptomatic drug option in HO, as reported by McCabe *et al.*,[15] with a large treatment effect size at 1 week post-injection. Nevertheless, the magnitude of pain reduction and functional improvement tends to decrease thereafter, as GCs have a short-lived effect on pain (1–4 weeks). Despite that, some trials have reported clinically significant differences in both pain and function at 8 weeks post-injection in HO, with a similar pattern of those observed in studies of knee GC injections[15]. Because of its short effect duration, the injection frequently needs to be repeated, jeopardizing the usefulness of this agent in long-term management of osteoarthritis, as it brings concerns about long-term deleterious effects on cartilage. Thus, their use should be limited to the treatment of disease flares, such as exacerbation of pain, nocturnal pain and effusion. The effects of GCs in HO have been demonstrated in several controlled studies,[6,23,24,26] with some authors claiming that GC should be considered as a first-line injectable treatment option after other conservative measures have failed or in case of acutely inflamed osteoarthritis joint[23].

Particulate steroids such as methylprednisolone and triamcinolone have a depot effect, resulting in a longer duration of action due to their ability to remain in the synovial fluid and the maintenance of continuous release of the active drug for longer periods of time[1]. Although all included trials in our review used methylprednisolone as the GC, in our clinical practice, triamcinolone acetonide and hexacetonide are also widely used. Its lower solubility would be expected to prolong intra-articular half-life of the drug and thus the duration of action[1]. Actually, an extended-release of triamcinolone acetonide using microsphere technology was developed, slowing the steroid release in the injection site, possibly until several months[39]. Future studies on intra-articular treatment of HO using other GCs rather than methylprednisolone would be of high importance to clarify this issue.

HA acts as a symptomatic slow-acting drug, with a delayed onset of efficacy of 2 to 5 weeks and a long-lived but modest benefit (4–12 months) on pain and functional outcome[23,30]. Although it was initially believed that the effects of HA were due only to its mechanical properties, numerous studies have showed that HA acts through CD44 suppression of metalloproteinases, cyclooxygenase-2, and reactive species of oxygen[4,12,21,25]. HA is taken up by specific joint receptors, providing moderate anti-inflammatory and antioxidant action, reducing cytokine-induced enzyme

production, anabolizing effect on cartilage, and inducing direct analgesia by masking the joint nociceptors[10,20-22,25,31]. Moderate osteoarthritis seems to be the indication of choice for viscosupplementation with HA, since efficacy seems to be better in moderate joint space narrowing (KLG 3), whichever the joint. Its efficacy on severe HO does not seem to be valuable, being that arthroplasty would be recommended for most patients. Even though viscossuplementation is not a replacement of surgery, it could delay surgical intervention and be useful in patients unsuitable for surgery. In cases of severe effusion, indicating acute inflammation, viscossupplementation is not indicated. Synovitis has been associated with accelerated joint cartilage degradation and it seems to impair the efficacy of HA, both due to enzymes and oxidants (hyaluronidases, free radicals) degrading the HA chains, and due to dilution effect in the effusion fluid. So, the selection of appropriate candidates for HA treatment is crucial to achieve the desired outcomes. Unfortunately, the ideal candidate for viscosupplementation has yet to be well-defined, although current literature tends to point HA injections as being more effective for patients with no or minor joint effusion and moderate loss of joint space width.

A recent study[40] indicates that combined injections of GC and HA can safely lead to rapid pain reduction, which appears to be maintained over time. Thus, combining the two agents seems to lead to a "best of both worlds" scenario, when using intra-articular injections for HO treatment. If more studies arise pointing to this conclusion, maybe the answer is to use both GS and HA together for certain patients, instead of trying to figure out which one is superior.

## CONCLUSIONS

There have been studies on non-operative treatment of HO, but the methodological quality is often poor. Therefore, the need for more rigorously designed controlled trials on HO treatment, with a minimum of 100 patients in each group, and with high methodological quality is growing, as this subject is still very much under debate. Future research should focus on sufficiently powered randomized trials to compare intra-articular treatment of HO with GC injections versus HA injections, as well as with GC combined with HA. Future studies should also aim to compare GC and HA with other types of intra-articular or non-surgical treatments, since there is not any strong evidence favoring one over the other.

There is also the need to conduct studies that may allow to determine which patients with HO are suitable for intra-articular injections with HA or GC, taking into consideration the good and durable results of a total hip arthroplasty, and its cost effectiveness. For such reason, long-term studies are needed to determine the long-lasting benefits of HA and GC injections and the possibility to avoid surgical intervention, by acting as a disease-modifying agent.

Treatment decisions must be made on an individual basis, carefully weighing the benefits and disadvantages of each option. Considering the costs and relative invasiveness of the procedures, injections cannot be recommended as standard therapy in HO for wider populations, and therefore their indication remains a highly personalized matter.

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