Review

Is there evidence to support the inclusion of viscosupplementation in the treatment paradigm for patients with hip osteoarthritis?

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ABSTRACT

Objective. *Viscosupplementation with hyaluronic acid (HA) or its derivatives for the symptomatic relief of osteoarthritis (OA) of the hip joint has never been studied in placebo-controlled, double-blinded trials and conflicting results have been obtained from the published open trials. The aim of this study was to review the literature on viscosupplementation as a symptomatic treatment of hip OA.*

Methods. *Data sources: Clinical trials in Medline (1966-2005) and Cochrane Controlled Trials Register using the key words: hip osteoarthritis AND hyaluronic acid or HA preparation trade name. All trials aimed to assess intra-articular hyaluronic acid injection for the treatment of hip OA were analyzed. In the absence of placebo-controlled trials, and because of the very wide variety of the study designs it was not possible to apply strictly the conventional rules of meta-analysis.*

Results. *Nine studies, including a total of 287 patients, were identified. Eight studies were uncontrolled-open trials. One was a randomized double blind study comparing two HA preparations.*

Five open-label prospective studies, including a total of 141 patients with symptomatic hip OA, assessed the safety and efficacy of 1 to 3 x 2mL intra-articular (IA) injections of hylan G-F 20 under fluoroscopic or ultrasound guidance. The overall success rate was about 50% at 3 to 12 month follow-up. In 31 subjects with symptomatic hip OA who received 1 x 3mL IA injection of non animal stabilized hyaluronic acid (NASHA) under fluoroscopy, pain and disability were reduced by 59% and 47% respectively at month 3. Six to 11 months after treatment the results remained satisfactory (42% and 39%). Hyaluronan injections, performed 3 to 5 times at weekly intervals in 44 patients, were effective in controlling pain in 68% of the patients over the 6 month follow-up period. In contrast, 1 to 3 ultrasound guided IA injections of HA preparations with 0.5-0.75 or 1.0 million MW induced only a very weak benefit in 28 patients.

In all studies IA injections of HA were safe and well tolerated. Transient pain at the injection site and mild increase in hip pain for a few days was more frequent with NASHA. In the only double blind controlled trial no difference between hyaluronan and hylan was found regarding both efficacy and safety.

Conclusion. *To date, in the absence of placebo-controlled studies, the efficacy of IAinjections of HA or its derivatives in the symptomatic treatment of hip OA cannot be determined conclusively. Nevertheless the published data suggest that viscosupplementation may be effective. Double-blind, controlled studies are required to confirm these data, before viscosupplementation should be included into the treatment paradigm for patients with hip osteoarthritis.*

Introduction

Viscosupplementation is a therapeutic concept which aims to restore joint homeostasis via the intra-articular (IA) injection of exogenous hyaluronic acid (HA) into osteoarthritic joints (1-3). Intra-articular injections of viscoelastic solutions of HA or its derivatives have been widely studied in the symptomatic treatment of knee OA. To date, the literature supports the clinical efficacy and safety of this therapeutic class for this indication, although there are differences between the marketed products (4-7). Most of the placebo-controlled, double-blinded trials of a high

MW, cross-linked HAderivative showed significant improvement in pain, activity levels, and function. The studies using low MW HA had more conflicting results (8,9).

Despite the fact that the precise mechanism of action (10, 11) and true efficacy of viscosupplementation remain unclear (12), viscosupplementation has been recommended by several expert panels for the management of patients with knee OA (13,14). The American College of Rheumatology recommends IA injection of hyaluronan derivatives as an alternative to oral analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) for the symptomatic treatment of pain associated with OAof the knee (15).

Osteoarthritis of the hip is one of the most common causes of pain and functional disability in subjects aged 55 years and older (16). The age and sex standardised-incidence rate for the disease was estimated between 47.3 to 88/100,000 person-years (17,18), increasing with age to reach 445/100,000 in women aged 70-79. Guidelines have been proposed for the management of hip OA that provide recommendations to control patients'pain, improve function and health-related quality of life, and avoid therapeutic toxicity (19, 20). Paracetamol remains the first line pharmacological therapy to control pain, with non selective NSAIDs given only to patients unresponsive to paracetamol therapy. However the use of NSAIDs, including cyclo-oxygenase-2-selective inhibitors, in elderly patients is limited by their potential for serious adverse events. A number of therapies for the prevention or treatment of OA (disease-modifying OA drugs) are currently under investigation but are already widely used in several countries (e.g. glucosamine and chondroitin, diacerrhein). Intra-articular steroid injections may be used as monotherapy, or as an adjunct to oral analgesia. Lastly, total hip arthroplasty is often necessary in the late stages of OA, in patients who remain or become unresponsive to medical management.

Considering the positive results achieved by IA injections of HAin knee OA, it appears justified to assess the treatment in patients suffering from hip OA but, as yet, viscosupplementation of the hip joint has not been studied in controlled, double-blinded placebo trials, and conflicting results have been obtained from the published, non-controlled open trials. Characterisation of the different HA commercial preparations shows marked differences in MW, elastoviscous properties, residence time in the joint, and recommended dosing regimen. One can roughly classify HA preparations according to their MW and the type of preparation: solution of low MW (500 – 1,200 kDa) HA, high MW (6,000 kDa) cross linked HA (80% solution, 20% gel-hylan GF-20) and gel of non-animal stabilised HA (NASHA). Methods and results obtained with each of these in the published studies on viscosupplementation in hip OAare discussed below.

Table I. Characteristics of included trials.

Source	Year	Hyaluronic acid	No. of pts.	Outcome measure	Follow-up (months)	No. of injections
Bragantini	1994	Hyalgan	44	P/GA/NSAIDs	6	3-5
Brocq	2002	Synvisc	22	LI	1-6	1-2
Conrozier	2003	Synvisc	57	P/W/GA	3-6	1-2
Vad	2003	Synvisc	22	P/AAOSLLCS	12	3
Migliore	2003	Hyalgan	28	P/LI/NSAIDs	NG	1-3
Caglar-Yagci	2004	Synvisc	14	P/LI/15mWT	3	3
Berg	2004	Durolane	31	W/GA	3	1
Migliore	2005	Synvisc	26	P/LI/NSAIDs	12	1-2
Tikiz	2005	Synvisc vs Ostenil	43 (25/18)	P/W/LI	6	3

P: pain on VAS; GA: global assessment of the disease; LI: Lequesne index; W: WOMAC index; NSAIDs: non-steroidal anti-inflammatory drug intake; 15mWT: 15 meter walking time; AAOSLLCS: American Academy of Orthopaedic Surgeon Lower Limb Core Scale; NG: not given.

Patients and methods

Data sources

We searched for human clinical trials in MEDLINE (1966 through February 2005) and the Cochrane Controlled Trials Register, using the following key words: hip osteoarthritis or hip osteoarthrosis or coxarthrosis AND hyaluronic acid or viscosupplementation or viscosupplement trade name (Hylan GF-20, NASHA, Synvisc®, Durolane®, Hyalgan®, Orthovisc®, Ostenil®, Supartz®, Suplasyn®).

Results

We selected only published, English or non-English language, papers. Since no single- or double-blind-randomized placebo controlled trials has not been yet published we analyzed all trials aimed to assess intra-articular hyaluronic acid injection for the treatment of hip OA. Nine studies, including a total of 287 patients, were identified. Eight were open trials with Hylan GF-20 (5 studies), hyaluronan (2 studies) or Non-Animal-Stabilized-Hyaluronic Acid (1 study). One was a randomized double-blind trial comparing Hylan to 1.2MDa-hyaluronan.

Outcome variables and study design

The outcome measures were pain on visual or numeric analogue scale (6/9), Lequesne index (5/9), patient's global assessment (3/9), WOMAC index (3/9), NSAIDs consumption (3/9), physician's global assessment, American Academy of Orthopaedic Surgeons Lower Limb Core Scale, 15 meter walking time (1/9). The mean follow-up was 5.4 months, ranging from 1 to 12 months. Intent-to-treat analysis was performed in only one study. The number of HA injections varied from 1 to 5, and the time interval between two injections ranged from 7 to 90 days (Table I).

Analysis

In the absence of placebo-controlled trial, and because of the very wide variety of the study designs (outcome measures, follow-up duration, number of

injections …) it was not possible to apply strictly the conventional rules of meta-analysis. For these reasons the following data are only descriptive and can not allow drawing conclusion on the real efficacy of the treatment.

Results

Hylan GF-20

Five open studies, including a total of 148 patients, were published.

In an open-label prospective study, Brocq *et al.* (21) studied 22 patients with symptomatic hip OA(pain > 40 mm on VAS and/or Lequesne index > 6) who received 1 (14 patients) or 2 (8 patients) IAinjections of 2mLof hylan G-F 20 under fluoroscopic guidance. After injection, patients had to stay in bed for 2 hours. At day 30 after the first injection, 11 patients experienced a > 50% improvement in VAS pain scores and/or the Lequesne index. The success rate reached 14 after a second injection was performed in patients who did not experience adequate benefit with the first injection. Thirteen and 6 of the 11 evaluated patients still reported a > 50% improvement at day 90 and 180 respectively. Three patients reported a worsening of pain after injection that fully recovered with NSAID therapy within 48 hours.

Similar results were obtained in an open label pilot study (22) whose primary aim was to obtain prospective data on the safety of IA injections of hylan G-F20. Fifty-seven patients with hip OA, Kellgren-Lawrence grade II-III, aged ≥ 40 and with walking pain of 50-90 mm on VAS were enrolled in this multi-centre pilot trial. 2mL of hylan G-F20 were injected into the hip under fluoroscopy, using an anterior or lateral approach, and follow-up visits were performed at days 7-30-60-90. Patients who reported pain levels equivalent to baseline received a 2nd injection at day 30 or 60 or 90 and were followed for 3 months after the last injection. Twenty-five patients received 1 injection and 32 received 2 injections. Transient hip pain was reported following 10.1% of injections, but no patient withdrew from the study as a result of safety issues. Walking pain decreased at day 7 (–27.3 mm, range –86 to +12) even in patients who required a second injection. At end-point, 29 patients (51%) had a 50% or more improvement in walking pain. Three patients reported a worsening of pain (>10% on VAS) during the course of the study. The decrease in walking pain and disability was much better in patients who required 1 injection only (pain at end point: 27.5 mm ± 26.5) than in those who needed 2 injections (49.2 mm ± 28.6), regardless of the time between the first and second injection. The percentage of responders according to the OMERACT-OARSI response criteria was 59% at end point. One third of the patients experienced a 75% or more improvement in pain. The decrease of pain was found to be negatively correlated with the joint space narrowing score. No difference in adverse events and efficacy was detected between the patients injected using the anterior and lateral approaches.

Caglar-Yagsi *et al.* (23) performed 3 hylan G-F injections (2mL) using a lateral approach under ultrasound guidance, in 14 patients with hip OA and evaluated efficacy via VAS pain score, Lequesne index, patient's satisfaction and 15-metre walking time at baseline and at 30 and 90 days after injections. They found a significant improvement for all outcome variables at both day 30 and 90. No adverse events were reported.

Vad *et al*. (24) studied 22 patients with mild to severe hip OA who had failed to obtain pain relief from conservative methods such as physical therapy, exercise, and steroid IAinjections. All were injected (25 hips) with 2mL of hylan G-F 20 at 2, 3, and 4 weeks after a fluoroscopic lavage with 100mL of normal saline at week 1. All patients had a standard hip exercise regimen after the injection. Clinical assessment was made using American Academy of Orthopaedic Surgeons (AAOS) Lower Limb Core Scale score and visual numeric pain score. At 1-year follow-up, the AAOS Lower Limb Core Scale score improved significantly from a pre-injection mean of 44.2 to a follow-up mean of 86. Pain score improved from 8.7 at baseline to 2.3 at end-point. The overall success rate was 50% in severe OA, reaching 90.5% in patients with mild to moderate OA. There were no adverse events related to the injection.

In a prospective, open, uncontrolled pilot study, including 24 patients (25), Migliore *et al*. investigated the safety and effectiveness of intra-articular injection, under ultrasound control, of hylan G-F 20 for the treatment of OA of the hip. Twelve patients with symptomatic hip OA were treated with one injection of 2 ml of hylan G-F 20 under ultrasound guidance. Treatment efficacy was assessed through Lequesne index, VAS pain quantification, and NSAID intake at the timepoint zero (baseline), and after 2, 6 and 12 months. A statistically significant reduction of all considered parameters was observed at the time points 2 and 6 months, when compared to baseline. At 12 months the changes were still statistically significant for all parameters for about 50% of the patients. No side effect was observed, nor systemic complication.

NASHA

Only 1 study has been published to date. Berg and Olsson (26) included 31 subjects with symptomatic hip OA (Kellgren Lawrence grade II and III) who received 1 IA injection of 3mL of NASHA under fluoroscopy. Clinical assessment (WOMAC A B C index, patient's assessment of global status) was made at baseline, 2 weeks and 3 months. Eighteen patients were evaluated from 6 to 11 months after injection. Exacerbation of hip pain (3 severe and 6 moderate) occurred in 8 patients (25.8%) in the days immediately after injection (day 0 to day 3). All resolved within 7 to 22 days without any treatment (5 patients) or with NSAIDs (3 patients). At month 3, pain (WOMAC A) and disability (WOMAC C) were reduced by 50% and 44% respectively. Six to 11 months after treatment the results remained satisfactory (respectively -42% and -39% compared to baseline). At end-point 68% of the patients considered their condition to have improved with only 1 patient indicating his condition has worsened.

Low MW HA

Bragantini and Molinari (27) reported the results of low MW (500-750 kDa)

HA injections (2mL), performed 3 to 5 times at weekly intervals in 44 patients suffering from unilateral or bilateral symptomatic hip OA(50 hips). Clinical outcome (pain, walking ability, joint motion, NSAID intake, patient and physician global assessment) was followed up at day 30, 60, 120 and 180. The treatment was effective in controlling pain in 68% of the patients over the 6 month follow-up period. Indeed at month 1, 17 patients reported no hip pain, and 17 reported only slight pain at the end of follow-up. The result was maintained in 33 patients at month 6. Efficacy was considered excellent to good by 53.1% and 49% of the patients at month 1 and 6 respectively. Nevertheless no reduction in NSAID consumption was noted.

In contrast with these promising results, Migliore *et al*. (28) have recently demonstrated only a very weak benefit from hyaluronan preparations with 0.5-0.75 or 1.0 million Da MW, in 28 patients with Kellgren-Lawrence grade II to IV hip OA. All received 1 to 3 ultrasound guided IA injections (2mL), at 2 week intervals (78 injections). Pain relief was evaluated using a VAS, and function was assessed using the Lequesne index. NSAID consumption was recorded. No details were given on the follow-up duration. The authors reported a 48% reduction in NSAID consumption and a 28% decrease in pain after treatment. Neither systemic effects nor septic adverse events were observed. Four patients (14.3%) experienced a sensation of heaviness and pain in the hip for 2 to 5 days after injection, but none of them required any medication or needed to suspend daily activity.

Comparison Hylan – Low MW HA

In a double-blind randomized trial (29), Tikiz C *et al*. compared the efficacy of intra-articular injections of a 1.2 MDa -hyaluronan and hylan GF-20 in 43 patients (56 hips) with hip osteoarthritis. Patients had a VAS pain score higher than 50 mm, a Lequesne index greater than 6, and persistent pain for longer than 3 months. Twenty-five (32 hips) received 1.2MDa -HA and the remaining 18 patients (24 hips) received hylan G-F 20. Three injections were administered once weekly under fluoroscopic guidance. Efficacy was assessed with pain on VAS, WOMAC and Lequesne indices. Pain on VAS was reduced by 38 and 40%, WOMAC by 43 and 40%, and Lequesne index by 47 and 49% in the 1.2MDa-HA and hylan G-F groups at the 6th month, respectively. Improvement was prominent at the 1st month and maintained for 6 months in both groups. There were no significant differences in outcomes between any of the measurements at the 1st, 3rd, and 6th month between the two groups. Local adverse effects consisting of pain and/or swelling were noted in 9% of the hips injected with 1.2MDa HA and in 12.5% injected with hylan G-F 20.

Discussion

Intra-articular injection of HA or its derivatives into the hip joint appears to be safe and well tolerated. Treatment-related adverse events (AEs) were strictly localised at the target hip and none were serious. The AEs frequency ranged from 10 to 30%, which is slightly higher than the rates reported in viscosupplementation in the treatment of knee OA. Transient exacerbation of hip pain was reported with all HA products, but its frequency seems to be higher with NASHA, probably because of the viscous gel nature of the device. The present data suggest that repeated injections did not increase the risk of adverse events. The number of injections needed to obtain optimal clinical response seems to be different (1 to 5) between products and MW dependent (more injections are needed in case of low MW). The optimal dose regimen should be investigated further for each HA compound but it is clear that the increased number of injections may increase the septic risk, even if there were no reports of infectious adverse events or serious systemic reactions in the prospectively followed patients.

The only 2 isolated cases of septic arthritis were reported in the literature with hylan GF-20, and each was preceded by steroid IA injections (30, 31). After extensive use of HA in knee OA, the rate of septic arthritis reported is very low and there is no particular reason it would be different in the hip, if injections are performed under strict aseptic conditions.

However, when HA is injected under fluoroscopic guidance, there is the possibility of systemic reactions to the iodine contrast media. An alternative to fluoroscopy would be ultrasonography and this might address some of the reservations concerning repeated fluoroscopy and use of radiation. Using a 7 MHz linear or 3.5 MHz convex transducer, and colour Doppler vision to avoid injecting blood vessels, the needle insertion and progression into the articular space is visualised by on-screen guidance (28). Unlike the fluoroscopic technique, ultrasound does not require the use of radiation, which can be of importance in young patients. Nevertheless this method may not be available routinely in many centres and requires an experienced operator (32). If fluoroscopic guidance is used, HA preparations needing a single injection appear preferable to avoid repeated radiation exposure.

Of course, in the absence of placebo-controlled studies the efficacy of viscosupplementation in hip OA cannot be determined conclusively. Furthermore all the studies were performed on small samples (total number of evaluated patients 221, range 24 to 57), with variable dosing regimens (1 to 5 injections at different time intervals), with different follow-up periods, using various HApreparations and different injection techniques. A number of small open trials have also been presented in abstract form and their results cannot be satisfactorily used in this review. Finally it is very difficult to compare these data to others, since no long term placebo-controlled study has ever been published on IA treatment in hip OA, and only very few data are available regarding steroid injections as a treatment of hip OA.

In a prospective open study, Plant *et al*. (33) reported that 80 mg methylprednisolone and lidocaine injected under X-ray guidance into painful hips gave a 24% and 17% decrease of pain at 2 and 12 weeks respectively, but pain levels had returned nearly to baseline by 26 weeks, and functional ability did not change during the course of the study.

Hips with an atrophic pattern of arthritis on plain radiography gained negligible pain relief at 2 weeks compared with hips with a hypertrophic or mixed bone response. The degree of pain relief was not influenced by radiographic severity or by the direction of migration of the femoral head. Margules (34) reported 510 triamcinolone acetonamide hip injections in patients suffering from mild to severe hip OA. A significant improvement of pain was obtained for 8 weeks in patients with mild to moderate OA, but not for severe OA. Flanagan *et al*. (35) carried out a double blind randomised trial to ascertain whether IAinjections of saline, bupivacaine or bupivacaine plus triamcinolone would be of value in the relief of hip pain in patients awaiting total hip replacement for OA. The majority of patients had good pain relief for 1 month but in general this was not maintained and some patients were much worse after the injection.

Conversely, HAstudies support the fact that IA hip injections of HA provide significant improvement in pain and function in a majority of patients for more than 3 months. As has been shown in knee OA(36), viscosupplementation of the hip appears to have a slower onset of action than IA steroids, but its effect seems to last much longer. In the hylan study (22), the mean decrease in the pain score (-29.8 mm at month 3, –43% versus baseline) was much higher than the mean placebo effect observed in other hip OA clinical studies (10.4 mm, 16%) (37). At month 3, 58.9% of the patients fulfilled the OMERACT-OARSI responder criteria (38). Furthermore the mean variation in pain and patient's global assessment (-18.8 mm) were similar to those considered as a fair response to therapy (-26.2 and -19 mm respectively) by Ehrich *et al*. (39).

In summary despite the absence of placebo controlled trial, the small size of the samples and the high heterogeneity of the study designs, the review of the literature suggests IA injections of HA may have a symptomatic effect in patients with painful hip OA. In order to confirm these promising data, large scale double-blind controlled studies must be performed. Further studies should also be performed to determine why some patients respond very well and demonstrate significant signs of symptomatic improvement while others experience little or no benefit from the treatment. Furthermore, the differences of safety and efficacy between HA preparations, and the best dosing regimen to apply (1 or more injections, time between repeat injections, technique of injection) remain to be studied, before viscosupplementation could be recommended for the treatment of patients suffering from hip OA.

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