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Clinical Outcome of Hylan G-F 20 Injections in Shoulder and Hip Osteoarthritis: A Retrospective Review

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Abstract

Objective: To evaluate the safety and efficacy of Hylan G-F 20 in recalcitrant shoulder and hip osteoarthritis-related pain and function.

Design: Retrospective review of patients undergoing fluoroscopically-guided intra-articular Hylan G-F 20 injections for management of shoulder and hip osteoarthritis-related intractable pain. Age, gender, body mass index, number of co-morbidities, use of opiates, severity, and location of osteoarthritis (OA) were assessed as possible contributing factors to the outcome. Months of pain relief and degree of symptomatic improvement were used to assess clinical outcome.

Setting: Metropolitan area Veterans Affairs Medical Center

Subjects: 26 adults (undergoing 53 consecutive injections, 31 of hip, 22 of shoulder, performed over a 4 year period) suffering from symptomatic OA who had previously failed conservative management measures, including prior corticosteroid injections.

Methods/Results: Injections provided effective pain relief for up to 4 months in approximately half of the patients with a few patients experiencing pain relief during the whole analysis period of 24-30 months. No adverse events were reported. Higher body mass index had a statistically significant association with worse clinical outcome (shorter symptomatic relief and clinical improvement in both joints). Age, race, number of comorbidities, use of opiates, location (hip versus shoulder) and severity of joint disease showed no significant effects on clinical outcomes.

Conclusions: In this retrospective review, intra-articular Hylan G-F 20 injections for the symptomatic management of hip and shoulder osteoarthritis-associated intractable pain appear to be safe; better efficacy was observed in lean individuals (particularly interesting for the non-weight-bearing shoulder joint) regardless of disease.

Keywords: Osteoarthritis; Hip pain; Shoulder pain; Hylan; Visco supplementations

Introduction

Osteoarthritis (OA) affecting the hip and shoulders is a common problem seen in patients with polyarthralgias or following joint trauma [1,2]. Management methods include conservative measures such as weight loss, physical therapy modalities (cold, heat, electrical stimulation, etc.), various analgesics (including opiates and nonsteroidal anti-inflammatory drugs (NSAIDS)), and intra-articular injections of corticosteroids [3]. Operative management of OA can help to decrease pain, recover joint function and increase mobility. However, surgical interventions such as joint replacement and the required post-operative rehabilitation, are expensive and not without risks and morbidity. Furthermore, due to age and co-morbidities, some patients are poor candidates for surgical management.

Intra-articular (IA) injection of hyaluronan (HA) has been proposed as a mode of restoring the normal viscoelastic properties of the synovial fluid in patients with OA. Intra-articular hyaluronan injections (also referred to as visco supplementation) are considered safe and generally effective as a management modality for symptomatic mild to moderate knee OA [4,5].

A recent meta-analysis including a total of 29 studies representing 4,866 unique patients showed that visco supplementation was safe and efficacious for 26 weeks in patients with symptomatic OA of the knee [6]. Despite these findings and extensive anecdotal evidence, the efficacy of hyaluronan injections is still debated [7].

The use of visco supplementation in joints other than the knees is not approved by the Food and Drug Administration (FDA) in the United States. However, it has been approved by the European Union for several years, including hips, shoulders, and ankles. In their systematic review of eight studies on the efficacy and safety of hyaluronic acid (HA) for the treatment of OA of the hip, Fernández

López and Ruano Ravina [8], stated that relief of pain was around 40–50% in many studies but the duration of this effect was not known.

The use of viscosupplementation for shoulder OA is also controversial. Blaine and colleagues [9] conducted a multi-center randomized trial of individuals with glenohumeral OA, rotator cuff tears or adhesive capsulitis. The authors randomized a total of 660 participants to either a course of 3 or 5 injections of hyaluronan or placebo. After 13 weeks, all three groups showed significant decrease in pain without significant difference between two groups. After 26 weeks, the hyaluronan injection group had a statistically significant reduction in symptoms compared to the placebo group.

The goal of the present study was to review all cases where fluoroscopically-guided viscosupplementation of the shoulder and hip joints performed during a 4-year period (2010-2014) to determine the safety and efficacy of these injections and to provide pragmatic recommendations for their use. By systematically reviewing these cases, we expected to obtain information that would help guide future clinical uses for this treatment modality. The two objectives of this retrospective review were to determine the safety and efficacy of Hylan G-F 20 (Synvisc-One®) injections for hip or shoulder OA, and to determine the possible effects of patient characteristics including Body Mass Index (BMI), age, gender, race, opiate medication use, comorbidities and the severity of radiographic joint disease on clinical outcome (duration of pain relief and symptomatic improvement) after injections in the hip or shoulder of patients suffering from intractable pain associated with OA. We hypothesized that higher BMI would be associated with worse clinical outcome (duration of pain relief and symptomatic improvement) following Hylan G-F 20 injections of the hip of patients with OA. We also hypothesized that the use of opiates and greater severity of disease would be associated with a worse clinical outcome in both groups.

Methods

Approval to conduct a retrospective chart review as a quality improvement project was granted by the Scientific Advisory Board of the Research & Development Committee of the West Palm Beach Veterans Affairs Medical Center. The study design allowed waving IRB approval. The use of hyaluronan injections in these non-FDA approved joints had previously been approved by the institution's Pharmacy and Therapeutics Committee for cases of intractable pain related to joint disease that had failed to respond to oral analgesics, physical therapy modalities, and intraarticular corticosteroid injections for patients who were either not considered surgical candidates or who declined surgical interventions. Informed consent in these cases always involves a clear explanation of the fact that these injections have not been approved for injection into these joints. Retrospective review of all cases involving fluoroscopically-guided Hylan G-F 20 injections of shoulders (glenohumeral) and hips was performed by systematically reviewing the patient charts for all available information including but not limited to clinical visits, radiological imaging, and pharmacological treatment. Medical record review included gathering data on patient demographics, medical comorbidities, medications used, Body Mass Index (BMI), and response to injections using numerical (0-10) pain scales and other patient reports. Additionally, the charts were carefully reviewed to detect any untoward events or complications from the injections and to assess clinical outcomes after each injection. Age, BMI, race, gender, number of other medical and psychiatric co-morbidities, opiate analgesics being used at the time of injection (and afterwards) and degree of radiographic OA lesion were used as independent variables and assessed as possible contributing factors (Table 1). Assessment of symptomatic improvement was performed on scale of 1 to 5. The scores were assigned based on the number of months of pain relief, the degree of symptomatic improvement, reported numerical pain score, use of analgesic medication, and patient self-reported functional activities. These scores were used as dependent variables to assess the clinical outcomes. A reduction in pain scores (on a scale of 0 to 10) of greater or equal than 50% from baseline pain score for greater than 3 months was considered a favorable or positive response. Pain assessment functional measures were initially considered but variability in documentation patterns by various providers made it impossible to utilize these measures in our analysis. Data was tabulated with no patient-identifiers and statistical analysis was performed. Patient records were reviewed by one of the investigators who was not involved in performing the injections. Hylan G-F 20 was used because it was available as a formulation that required only a single injection (as opposed to others that require 3 to 5 weekly injections). This facilitates patient compliance and reduces radiation exposure that would be otherwise administered due to multiple procedures.

Gender (No of patients out of 26)	
Male	23
Female	3
Race (No of patients out of 26)	
Caucasian	24
Hispanic	1
African American	1
Age, mean (SD), y (n=26)	65.8 (13.0)
BMI, mean (SD), kg/m2 (n=26)	30.2 (7.7)
Number of comorbidities, median (IQR) (n=26)	6 (5,7)
Location of injection (No of patients out of 26, No of injections out of 52)	
Hip	15, 31
Shoulder	11, 21
Severity of the lesion, median (IQR) (n=26)	4 (1)
Use of opiates (n=26)	
Yes	12
No	14

Table 1: Distribution of patients by gender, race, BMI, number of comorbidities and injection location. No, number; SD, standard deviation; IQR, interquartile range.

Radiological assessment

Degree of OA severity was performed by two of the investigators to ensure interatter reliability. The Kellgren-Lawrence numeric scale (on scale of 1 to 4) for grading knee OA was used [10]. This global visual radiographic assessment based on osteophytes, cysts, subchondral sclerosis, and joint space narrowing is most widely used for OA of the knees but is also commonly used in the assessment of other large

synovial joints [11]. In this review, the scale was applied to the hip and shoulder digital radiographic images (Figure 1).

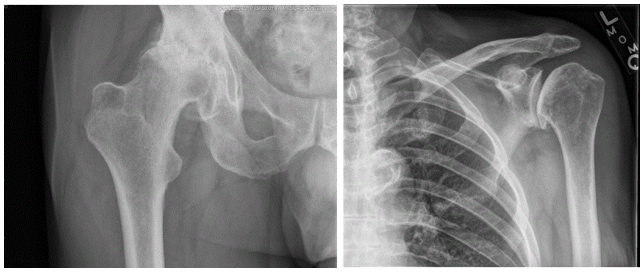

Figure 1: Representative plain radiographs of the hip and shoulder joints of patients treated.

Hylan G-F 20 injections

Hylan G-F 20 injections were performed for the management of symptomatic intractable pain associated with OA of the shoulder and hip joints during 2010-2014. No adverse events were reported within these four years. All Hylan G-F 20 injections were performed by two experienced physiatrists using fluoroscopic guidance and using visual confirmation of intra-articular localization by use on non-ionic contrast (Figure 2). Hylan G-F 20 was used in all patients in the course of our standard clinical practice due to ease and convenience of only one injection for the patients and staff. The option reduces the risk of complications from repeated procedures, radiation exposure, and number of visits. All patients signed informed consent as clinically established by the institutional clinical protocols. Pre-procedural education included clear education about the fact that these injections were not approved by the FDA for use in the injected joints. The protocol used included injections under local anesthesia. Spinal needles (5" in length) were generally used with some exceptions where 6" needles were used in very obese patients. An anterolateral approach was used for the hips and a straight anterior approach for injections of the shoulders. For both joints, the full dose of 6 mL was injected following aspiration of an effusion (when present). In cases where there was significant build-up of pressure felt by the injector while injecting Hylan G-F 20, less than the full amount of 6 mL was injected. This only occurred twice, resulting in 4.5 and 5mL of injectate respectively.

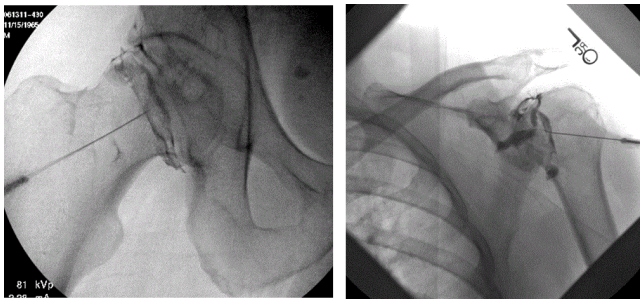

Figure 2: Fluoroscopic images of the hip and shoulder showing intra-articular contrast during procedure.

Statistical analysis

The collected data was assessed using a correlated data regression modeling. Specifically, we employed the Generalized Estimating Equations (GEE) methodology. This methodology is very robust to an assigned correlation structure leading to stable estimates of the parameters. Compared to repeated measures using Analysis of Variance (ANOVA), his methodology was felt to be the best fit, since in-depth chart review showed missing values for some measurements. We used two models: first, where the dependent variable is a total assessment of clinical outcome (Table 2); and, second, where the dependent variable is time of pain relief. The possible prognostic factors were considered to be age, BMI, gender, race, lesion severity, and anatomical location (hip vs. shoulder). The effects of opiate use (users vs. non-users) and the number of any medical and psychiatric comorbidities were also analyzed but were removed from the model given a high non-significant p-value. The final model contains the six covariates mentioned above. The significance of the prognostic factors was examined using Wald statistics, under the GEE methodology. Time-to-treatment failure between hip and shoulder was analyzed using the Kaplan-Meier product-limit method and the Generalized Wilcoxon test (Figure 3).

Source	DF	Chi-Square	Pr > ChiSq
Age	1	1.25	0.2636
BMI	1	5.83	0.0157
Gender	1	1.93	0.1651
Race	2	2	0.3681
Location	1	1.92	0.1656
Severity	2	3.21	0.2012

Table 2: Score Statistics for results of GEE Analysis of effects of prognostic factors on total improvement.

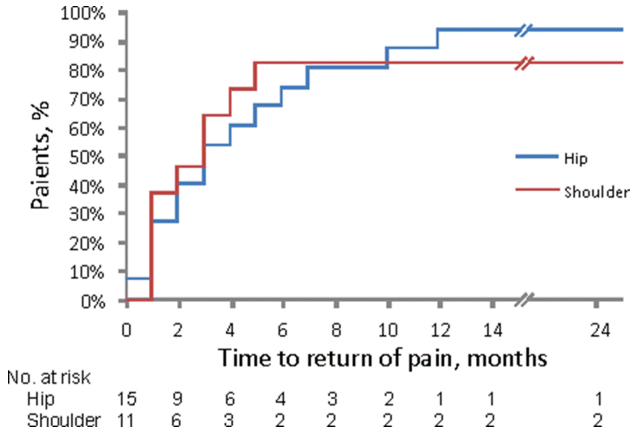

Figure 3: Wald statistics of time-to-treatment failure.

Results

Fifty-two injections (31 hip, 22 shoulder) were performed in 26 patients suffering from symptomatic OA who had previously failed

conservative management measures such as physical therapy, pharmacological treatment and intra-articular corticosteroid injections. In the majority of the patients (n=17), we performed only one injection into the same joint. Some patients (n=9) requested and were granted additional injections into the same joint. However, under our clinical practice protocol, no subsequent injections of Hylan G-F 20 into the same joint were performed until at least 4 to 6 months had elapsed from the prior injection. Maximal numbers of injections in the same joint for a patient within this four-year period was 6 for the shoulder and 4 for the hip. The general distribution of the patient population by demographics, BMI, number of comorbidities, use of opiates, disease severity and anatomical location is provided in Table 1.

The data indicates that Hylan G-F 20 injections provided effective pain relief (greater than 50% reduction in pain scores) for up to 4 months in approximately half of the patients (60% hip and 55% shoulder) with a few patients (7% hip and 18% shoulder) experiencing pain relief during the whole observation period of 24-30 months (Figure 3).

In this retrospective review a lower BMI was associated with better symptomatic improvement (p=0.0157) for those who received either shoulder or hip injections of Hylan G-F 20 (Table 2). Additionally, a lower BMI was associated with longer pain relief interval (p=0.0564) for those who received either shoulder or hip injections of Hylan G-F 20. Effect of BMI can be considered statistically significant "at the border" given the small sample size with only 26 subjects.

The analysis did not show statistically significant difference in favorable responses and the length of pain relief time between injections for the hip or the shoulder (Figure 3). Additionally, we did not find a significant effect relationship to any of the other variables studied (Tables 2).

Discussion

In this retrospective review, we report that there were no adverse events after Hylan G-F 20 injections to the shoulders and hips in patients with OA, that these injections showed to provide effective pain relief for up to 4 months in approximately half of the patients with a few patients experiencing pain relief during the whole observation period of 24-30 months and that a higher BMI was associated with worse clinical outcome (shorter duration of pain relief and less symptomatic improvement) following Hylan G-F 20 injections of the hip and shoulder in patients with intractable pain related to OA.

One important and re-assuring finding was the absence of adverse events. Hylan G-F 20 has been associated to a significant number of pseudo-septic reactions when used in knees [12,13]. The findings in this retrospective review support the safety of using these injections in other large synovial joints.

We observed that Hylan G-F 20 injections provided effective pain relief for longer than 3 months in approximately half of the patients with a quarter of the patients experiencing 6 months or longer pain relief periods and a few patients experiencing pain relief during the whole observation period of 24-30 months. This happened despite managing a group of patients with intractable pain that had failed multiple other treatment modalities including intra-articular corticosteroid injections (CSI's) and generally had greater severity of disease.

Our review points towards a significant relationship between positive responses to intra-articular Hylan G-F 20 injections performed using fluoroscopic guidance in individuals with lower BMI who suffer from intractable shoulder and/or hip OA-related pain.

The relationship of response to BMI appears intuitive when considering hip injections given that hips are weight-bearing joints. However, when considering the favorable response to shoulder injections, this relationship is not clearly apparent. One possible explanation for the equally strong association between higher BMI and worse clinical outcome after Hylan GF-20 injection into both hip and shoulder could be due to the lower exercise tolerance and potentially worse functional baseline of obese individuals. On the other hand, an alternative explanation may be related to the concept of metabolic osteoarthritis where inflammatory mediators in obesity may be causing a greater degree of pain and disability as reported in population studies where OA is observed more commonly in obese individuals even in non-weight-bearing joints [14-17].

Surprisingly, the severity of joint disease (as classified by the Kellgren-Lawrence scale) in our review does not appear to be a predictive factor for response to Hylan G-F 20 injections for either shoulder or hip OA.

The conclusions drawn for this retrospective review has some important limitations. The clinical protocol used at our institution where patients who are referred for these injections are those who have failed several other conservative measures (including intra-articular CSI's) introduces a selection bias towards the patients being a harder to manage population. The great majority of the participants were Caucasian male veterans and therefore the results may not be applicable to other populations. This further affects the applicability of the results to females given the small sample.

In summary, in this retrospective review, fluoroscopically-guided intra-articular Hylan G-F 20 injections (single injection) for the symptomatic management of shoulder and hip pain related to OA appear to be safe. There were no adverse events reported during or after Hylan G-F 20 injections in shoulders and hips of patients with OA. Efficacy was variable but appears to be better in more lean individuals suffering from shoulder and hip OA, regardless of disease severity. We expect that this information will help guide future prospective clinical trials that may validate these conclusions in larger randomized controlled trials with more heterogeneous population cohorts.

Conflicts of interest

None of the authors has any conflicts of interest to declare.

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