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Are Hylan Injections More Effective In Reducing Stiffness In Primary Knee Osteoarthritis Compared To Hyaluronic Acid Derivative Injections?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not hylan injections are more effective in reducing stiffness in primary knee osteoarthritis compared to hyaluronic acid derivative injections.

Study Design: Review of three published, English language randomized controlled trials published in 2007, 2008 and 2011.

Date Sources: Three randomized control trials were found using PubMed. These studies compared the efficacy and safety of hylan injections and hyaluronic acid derivative injections for reducing stiffness in primary knee osteoarthritis.

Outcome(s) Measured: The efficacy and tolerability of hylan injections for the treatment of stiffness in patients with knee osteoarthritis. The clinical outcome was measured using the Western Ontario McMaster University Osteoarthritis Index (WOMAC). The incidence of serious adverse events including septic arthritis, anaphylactic shock, pain, effusion, erythema and injection site hematoma. Adverse events were patient reported with investigator documentation.

Results: Juni (2007)⁸ found that patients given hylan injections compared to hyaluronic acid derivative injections showed equal efficacy in improving clinical performance in reducing the WOMAC subscores including the stiffness subscore. Raman (2008)⁹ found improvement in the WOMAC stiffness subscale for both hylan and hyaluronic acid derivative injections, but no statistical difference observed between the two injections. Pavelka (2011)¹⁰ found both preparations equally effective in reducing the WOMAC stiffness subscale with no significant difference between the hylan and hyaluronic acid derivative injection treatment groups.

Conclusions: Results from the three randomized controlled studies demonstrate that both hylan and hyaluronic acid derivative injections show equal efficacy in reducing stiffness in primary knee osteoarthritis.

Keywords: Knee osteoarthritis, hylan, hyaluronic acid.

INTRODUCTION

Osteoarthritis is a progressive degenerative joint disease that affects joint cartilage and bone leading to joint pain and stiffness. Osteoarthritis is the most common form of arthritis and frequently occurs in the hand joints, spine, hips, knees and great toes.¹ The diagnosis of osteoarthritis is becoming more prevalent as more people are living longer and the population obesity rates continue to increase. As there is no proven treatment to reverse osteoarthritis, the goal has become to relieve symptoms and improve function as conservatively as possible.¹

Osteoarthritis is one of the most prominent causes of disability in the United States.¹ Knee osteoarthritis is typically managed by primary care practitioners including physician assistants in combination with orthopedic surgeons. In 2010, osteoarthritis accounted for 21.7 million of all arthritis-related ambulatory medical visits.² Patients diagnosed with osteoarthritis have a higher risk of death compared to the general population.³ Osteoarthritis of the knee affects approximately 13% of women and 10% of men aged 60 years and older.³ Knee and hip joint replacements accounts for 35% of total arthritis-related procedures during hospitalization.² According to the CDC, the rate of total knee replacements have increased 217% from 1992 to 2011.² Total knee replacement estimated costs due to hospital expenditures totaled approximately 28.5 billion in 2009.²

While the underlying etiology of knee osteoarthritis is unknown, research has shown that osteoarthritis results from local inflammation, genetics, cellular and biochemical processes.⁴ Risk factors for osteoarthritis include advanced age, obesity, occupation, previous injury and a positive family history.⁴ Osteoarthritis of the knee is a progressive chronic disease with clinical manifestations including joint pain, swelling, instability and stiffness. Osteoarthritic pain is described as a constant dull and aching pain that increases with impact and relieved by rest.⁴

Patients describe their pain as being worse as the day progresses. Limited range of motion and stiffness may be due to osteophyte formation in the knee and capsular thickening. Osteoarthritis of the knee is diagnosed clinically but can be confirmed with radiographic imaging displaying joint space narrowing, osteophytes, and subchondral sclerosis.⁴

The goal of treatment for patients with knee osteoarthritis is to reduce pain and improve function which can be achieved with nonpharmacological treatment, pharmacologic treatment or surgically. Typical nonpharmacologic treatment include physical therapy, aquatic therapy, physical activity, weight management, and the use of assisted devices.¹ Initial pharmacologic treatment includes acetaminophen, COX-2 inhibitors, nonsteroidal anti-inflammatories, capsaicin cream, and diclofenac gels.¹ Intraarticular joint injections of glucocorticoid as well as viscosupplementation injections such as hylan and hyaluronic acid are recommended after failing primary treatment options. Hylan and hyaluronic acid injections have been proposed for treatment of osteoarthritis based on the restoration of lubrication from the injection.⁵ Total joint replacement, the most invasive treatment option is reserved for severe knee osteoarthritis. Hyaluronic acid naturally occurs in the synovial fluid around the knee joint and absorbs shock.⁵ Patients with osteoarthritis have a decreased amount of hyaluronic acid found in their joints.⁵ Viscosupplementation augments hyaluronic acid to the joint in efforts to increase lubrication and decrease joint pain and stiffness. This paper evaluates three randomized controlled studies comparing the safety and efficacy of hylan and hyaluronic acid derivative injections for reducing stiffness in patients with primary knee osteoarthritis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not hylan injections are more effective in reducing stiffness in primary knee osteoarthritis compared to hyaluronic acid derivative injections.

METHODS

This review consists of three randomized controlled trials which were selected based on relevance and patient oriented evidence that matters (POEMS). Although each of the trials had specific criteria, the mutual criteria for the studies included men and non-pregnant females with radiologically confirmed knee osteoarthritis aged 18 or older. All studies included intra-articular hylan injections once weekly for three consecutive weeks as the intervention therapy. The intervention therapy was compared to intra-articular hyaluronic acid injections. The outcomes measured were the efficacy and tolerability of hylan injections for the treatment of stiffness in patients with knee osteoarthritis. The incidence of serious adverse events included septic arthritis, anaphylactic shock, pain, effusion, erythema and injection site hematoma.

Key words include knee osteoarthritis, hylan, hyaluronic acid were used to generate the articles. Once these articles were generated, only randomized control trials published after 2006 were used and selected based on the relevance and the importance of outcome to the patient. The articles chosen were published in English and published in peer-reviewed journals. The performed searches included the use of PubMed database. Inclusion criteria included randomized controlled trial prospective studies and included patients who were 18 years and older with primary knee osteoarthritis. Exclusion criteria included patients who received previous intra-articular treatment with corticosteroids, local anesthetic agents or viscosupplementation agents in the past 3 months to the study. Statistics used in this review and

calculated by the author using dichotomous data included relative risk increase (RRI), absolute risk increase (ARI), numbers needed to harm (NNH) and p-values. Table 1 displays the characteristics of the included studies.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Juni ⁸ (2007)	Patient blind RCT	660	63.3 ± 12.3	Men and non-pregnant women with radiographically confirmed knee osteoarthritis with symptoms for at least 6 months and reported pain on most days for the previous 3 months; Did not respond to acetaminophen or nonsteroidal anti-inflammatory drugs	Inflammatory joint disease; Previous viscosupplementation treatment within 6 months; Previous replacement surgery in the affected knee; Chondrocalcinosis with evidence from radiographs or synovial fluid analysis; Infection in or around affected knee or relevant skin disease surrounding injection site	8	A high molecular weight cross-linked hylan derived from rooster combs (Synvisc; Genzyme, Cambridge, MA) Administered as a series of 3 weekly injections
Raman ⁹ (2008)	Double blind RCT	392	42-82	Minimum pain score of 6 on a visual analogue scale (0-10, 10 as worst pain) in the study knee; Patients with primary osteoarthritis of the study knee affecting the tibio-femoral +/- the patello-femoral compartment	Previous surgery to study knee; Previous intra-articular treatment with corticosteroids, local anesthetic agents or viscosupplementation agents to the study knee; Bilateral knee osteoarthritis which warranted treatment	32	Hylan G-F 20 with average molecular weight of 6 million Daltons administered as a series of 3 weekly injections

Pavelka ¹⁰	Double blind RCT	381	40-81	Radiologically confirmed diagnosis of osteoarthritis of the affected and clinically diagnosed by an American Colleague of Rheumatology	Body Mass Index ≥ 32 kg/m ² ; Viscosupplementation to knee within the past year or initiation of physical therapy in the past 3 months;	27	Once weekly for 3 weeks 16mg/2ml (0.8%) of intra-articular hylan A
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OUTCOMES MEASURED

All studies measured the efficacy outcome of improvement of stiffness using the Western Ontario McMaster University Index (WOMAC) stiffness subscale. In the study by Juni (2007)⁸, the WOMAC stiffness subscale was measured at baseline and 6 months post injection. In the study by Raman (2008)⁹, the WOMAC stiffness subscale was measured at 3, 6 and 12 months following treatment. In the study by Pavelka (2011)¹⁰, the WOMAC stiffness subscale was measured at baseline and 26 weeks post treatment. The safety outcome was measured by self-reported adverse events at each follow up visit with investigator documentation of adverse events including septic arthritis, anaphylactic shock, pain, effusion, erythema and injection site hematoma. Safety outcomes were also assessed using patient-administered questionnaires.

RESULTS

This review assesses three randomized controlled trials to evaluate the efficacy of intra-articular hylan injections in reducing stiffness in primary knee osteoarthritis compared to hyaluronic acid derivative intra-articular injections. In the study by Juni⁸, 660 patients with symptomatic knee osteoarthritis were enrolled in the study. Patients were randomly divided into three groups by a computer-generated program: first group of 222 patients were treated using intra-articular hylan injections; the second group of 219 patients were treated using intra-articular

avian hyaluronic acid injections and the third group of 219 patients were treated using intra-articular bacterial hyaluronic acid injections (third group will not be discussed in this review). The patients in each group received one cycle of three intra-articular injections of 2ml per knee treated at weekly intervals. All injections were performed per the Swiss Association of Rheumatologists guidelines. Data were collected at baseline and 6 months after the last intra-articular injection was performed. At baseline, all three groups had similar clinical characteristics with no statistical differences regarding the WOMAC stiffness subscale. WOMAC scores were analyzed using analysis of covariance adjusted for baseline values. The results determined that there was a 0.1 (95% CI -0.3, 0.4) change for the WOMAC stiffness score from baseline between the hylan and hyaluronic acid derivative injections.

Local adverse events including effusion and flare were obtained during the first 6 months of the study. During the first 6 months of the study, 9.5% of patients receiving the hylan injection experienced local adverse events and 7.3% of patients receiving the hyaluronic acid injection experienced local adverse events with a difference of 2.2% (95% CI 2.4, 6.7). The trend toward an increase in local adverse events in the hylan receiving group increased in the second cycle resulting in a difference of 6.4% (95% CI 0.6, 12.2). During the first 6 months of the study, 15 of 222 patients receiving hylan and 25 of 438 patients receiving hyaluronic acid experienced serious adverse events. Serious adverse events are characterized as neoplasms, endocrine and metabolic disorders, mental and behavior disorders, disorders of the nervous system, disorders of the circulatory system, disorders of connective tissues, disorder of genitourinary system, septic arthritis and anaphylactic shock (which only occurred after injection of hylan). To measure safety of hylan and hyaluronic acid derivative, the NNH was calculated and resulted as -76.

Table 3: Safety and adverse events (calculated data for treatment using dichotomous data)

CER (Proportion of patients having adverse events with hylan)	EER (Proportion of patients having adverse events with hyaluronic acid derivative)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Numbers needed to harm (NNH)	95% CI
6.8%	5.5%	-19.1%	-1.3%	-76	-2.4, 6.7

In the prospective randomized study completed by Raman⁹, 392 patients who met criteria of having primary knee osteoarthritis participated in this study. There were no substantial differences in the age or sex between the two groups. There were 199 patients who received hylan intra-articular injections and 193 patients received hyaluronic acid intra-articular injections. All patients were randomly allocated to receive either hylan or hyaluronic acid injections by computer generator. Hylan was administered in a series of 3 weekly injections and hyaluronic acid was administered in a series of 5 weekly injections per the manufacturer's recommendations. All injections were performed by the same surgeon using a default blind technique. Patients were informed to be 24 hours analgesia free before baseline measurement and were told to avoid non-steroidal anti-inflammatories for 6 months. Data were collected using the WOMAC stiffness subscale at 3 months, 6 months and 12 months post treatment. There was improvement in the WOMAC stiffness subscale at 3,6 and 12 months post treatment and no statistical difference observed between the two groups at any follow up visit.

Figure 1: WOMAC improvement at 6 months

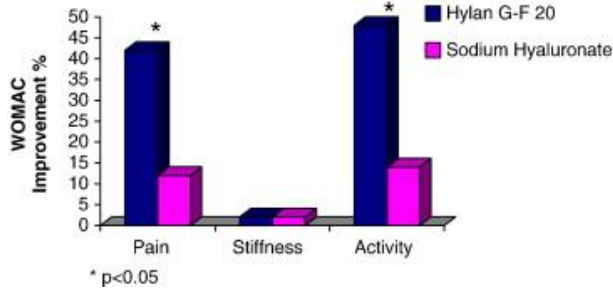


Figure 1: Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV. Efficacy of hylan G-F 20 and sodium hyaluronate in the treatment of osteoarthritis of the knee -- a prospective randomized clinical trial.

Safety and adverse events were evaluated at each patient visit throughout the study.

There were 39 patients who reported treatment related adverse events in the hylan injection group while 30 patients reported adverse events in the hyaluronate group. There was 1 severe adverse event reported within the hylan group in which the patient was admitted to the hospital and diagnosed with “pseudo-sepsis” in the knee. All other reports were characterized as minor adverse events which mostly included injection site pain. 32 of the patient reported adverse events in the hylan group occurred within 48 hours of the injection. Of note, there were no systemic adverse events reported in either the hylan or hyaluronic acid injection groups. To measure safety of hylan and hyaluronic acid derivative, the NNH was calculated and resulted as - 25.

Table 5: Safety and adverse events (calculated data for treatment using dichotomous data)

CER	EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Numbers needed to harm (NNH)
20%	16%	-20%	-4%	-25

In the double-blind randomized controlled trial by Pavelka¹⁰, 381 patients who were diagnosed with primary knee osteoarthritis and aged between 40 and 81 years. 189 patients

received hylan 16 mg/2 ml intra-articular injections while 192 patients received hyaluronic acid derivative 16 mg/2ml intra-articular injections. Patients were randomized to receive once weekly injections in a three-week interval for both groups. Patients were given a one month supply of rescue medication however patients were informed to not consume this within 24 hours prior to study visits. Use of rescue medications and adverse events were recorded in a patient journal. The WOMAC stiffness subscale was measured at baseline and 26 weeks post treatment. At baseline, there were no statistical differences between the groups. The results determined that the WOMAC stiffness score from baseline to 26 weeks did not differ significantly between treatment groups.

Table 6: WOMAC stiffness score at baseline and 26 month follow up

	Baseline		26 month follow up	
	Hylan	Hyaluronic Acid	Hylan	Hyaluronic Acid
WOMAC stiffness score	50.1 ± 19.1	50.1 ± 19.4	25.8	25.7

Adverse reactions were assessed and reported throughout the 26 weeks. Adverse reactions were characterized as injection site hematoma, injection site pain, arthralgia and joint swelling. 5 adverse events were reported within the hylan injection group and 1 adverse event was reported within the hyaluronic acid injection group. There was a total of 7 severe adverse events reported: 6 events reported in the hylan injection group and 1 event reported in the hyaluronic acid group. To measure safety of hylan and hyaluronic acid derivative, the NNH was calculated and resulted as -41.

Table 7: Safety and adverse events (calculated data for treatment using dichotomous data)

CER	EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Numbers needed to harm (NNH)
2.9%	0.54%	-82.8%	-2.4%	-41

DISCUSSION

This systematic review of three randomized controlled trials evaluated the efficacy of hylan compared to hyaluronic acid derivatives regarding improving stiffness in patients with knee osteoarthritis. Unfortunately, there is not a cure for osteoarthritis or the process of a degenerating joint. While viscosupplementation will not cure osteoarthritis, it has been used as a therapeutic modality of knee osteoarthritis for several years. Viscosupplements including hylan and hyaluronic acid derivative injections have been approved by the FDA for the treatment of primary knee osteoarthritis. Viscosupplements are available in the United States however the wholesale price is approximately \$1,500 per knee for a treatment series.⁶ Most insurance companies require failing conservative treatment options such as analgesics, physical therapy and possibly receiving an intra-articular glucocorticoid injection before approving viscosupplementation treatments.

There were notable limitations within the three randomized control trial studies. The first limitation included the lack of a placebo control in all three trials. While all three trials used the same hylan injection (Synvisc), there were three different hyaluronic acid derivative injections used. In the study by Juni⁸, a non-cross linked medium molecular weight hyaluronic acid derivative known as Orthovisc was used. In the study by Raman⁹, Hyalgan was used as the hyaluronate viscous solution. A chemically non-modified sodium hyaluronate known as

Sinovial was used in the study by Pavelka¹⁰. Secondly, the studies by Juni⁸ and Pavelka¹⁰ involved different physicians performing the viscosupplementation injections which can be considered a limitation due to the variety of injection techniques. Viscosupplementation injections require a precise technique to work effectively and limit adverse side effects.⁷

In the study by Raman⁹, the hyaluronic acid derivative injection required 5 injections compared to the 3 injections required with the hylan creating a treatment bias. However, the manufacturer of the hyaluronic acid injection recommended to follow their guidelines. Finally, stiffness was assessed during the 6 month and 12 month follow up visits in the studies by Juni⁸ and Raman⁹. Extending the follow up time would allow for a better understanding of efficacy and the hylan injection's full effects in regards to improving stiffness.

CONCLUSION

Based on this systemic review of the three randomized controlled studies, hylan injections do not prove to be more effective in reducing stiffness in primary knee osteoarthritis compared to hyaluronic acid derivative injections. The WOMAC stiffness score used in all three studies was assessed via questionnaire format. Future studies may benefit from an objective form of measuring stiffness such as range of motion measurements performed at follow up visits. The actual effectiveness of hylan or hyaluronic acid derivatives reducing stiffness in primary knee osteoarthritis could not be proved in any three trials due to the lack of a placebo control group. Although both viscosupplements were statistically equivalent in reducing stiffness, data from all three studies displayed an increase number in local and severe adverse events within the hylan injection groups. Future studies are warranted to evaluate the length of the effects of the viscosupplements and how often injections series are recommended for patients with primary knee osteoarthritis.

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