

2016

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## Recommended Citation

Antonoplos, Amalia, "Is Viscosupplementation Effective in Reducing Osteoarthritis Knee Pain?" (2016). *PCOM Physician Assistant Studies Student Scholarship*. 262.

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# **Is viscosupplementation effective in reducing osteoarthritis knee pain?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In partial fulfillment of the requirement for

The Degree of Master of Science

In

Health Sciences- Physician Assistant

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

December 18, 2015

## Abstract

**Objective:** The objective of this selective EBM review is to determine whether or not viscosupplementation is effective in reducing osteoarthritis knee pain

**Study Design:** Review of three randomized, double blind, placebo control trials between 2009-2010

**Data Sources:** Three randomized, double blind, placebo control trials were found via PubMed and NCBI

**Outcomes Measured:** Each randomized control trial measured knee pain and/or patient satisfaction following their intervention (placebo or hyaluronic acid) in patients with knee osteoarthritis, which was measured via WOMAC pain scale and patient global assessment forms.

**Results:** All three randomized studies showed treatment with hyaluronic acid (hylan G-F 20) were statistically significant ( $P < 0.05$ ) for change in pain at 14-26 weeks after injection (NNT=6-8 for Chevalier et al and 4 for Kul-Panza & Berker). Patient satisfaction was higher in the experimental groups as compared to the control with conclusions of NNT between 11 and 20 for Chevalier et al and Kul-Panza & Berker respectively. Chavelier et al found adverse events such as arthralgias and joint effusion in  $< 10\%$  of their study population (NNH=39). No dichotomous data was presented in Diacoglu et al; however an ANOVA was deemed statistically significant ( $p < 0.01$ )

**Conclusions:** Review of these articles concludes that the use of hyaluronic acid is beneficial in reducing knee pain and exhibits patient satisfaction. The use of hyaluronic acid needs to be evaluated on a case-by-case basis and should not be used in every patient with osteoarthritis, particularly if other additional knee injuries or significant surgical history are present.

**Key Words:** hyaluronic acid, osteoarthritis, knee pain



## INTRODUCTION

Osteoarthritis (OA) is a joint disease characterized by degeneration of cartilage with damage to the collagen proteoglycan matrix.<sup>1</sup> This paper evaluates three double blind, placebo controlled, randomized controlled trials (RCTs) comparing the severity of knee pain and patient satisfaction in those with osteoarthritis who received viscosupplementation (Hylan G-F 20) versus placebo.

OA is the most common form of arthritis and is in the top 5 leading causes of disability in the US.<sup>2</sup> The number of adults with osteoarthritis is 51.8 million, 22.1% of the United States population.<sup>3</sup> In 2009, it was estimated that health care costs for total knee replacements was \$28.5 billion.<sup>2</sup> Furthermore, the cost per patient for OA is ~\$5,700 each year.<sup>2</sup> There are 11.3 million visits to physician offices, hospital outpatient facilities and emergency departments every year for OA, as reported in 2010.<sup>3</sup> The above statistics confirm the importance of providing pain relief to patients with OA in efforts to decrease the number of health care visits and expensive surgeries, in turn, decreasing health care costs.

The exact etiology of osteoarthritis is unknown, but it may be idiopathic or secondary to trauma and other medical conditions, such as diabetes, acromegaly, lyme disease, obesity, and peripheral neuropathies.<sup>1,2</sup> OA results in non-inflammatory pain with common sites being the hips, knees, hands, spine, particularly sparing the elbows, wrists and ankles.<sup>1,2</sup> The best way to evaluate the severity of OA is radiographs.<sup>1,2</sup> The radiographic pathology and hallmarks are osteophytes, eburnation, joint space narrowing and sclerosis.<sup>2</sup>

First line treatment for OA is acetaminophen with additional treatments including NSAIDS, and COX specific NSAIDS with physical therapy.<sup>1</sup> Patients also benefit from unloading braces for the knee to relieve pressure on the joint space suffering significant cartilage

breakdown. Other measures are the use of capsaicin cream, chondroitin and viscosupplementation.<sup>4</sup> Surgical treatment options include arthroscopy with the definitive treatment being a total joint replacement.<sup>1</sup>

Total joint replacement requires general anesthesia, immense rehabilitation, risk of infection and other post op complications. The use of viscosupplementation injection directly into the knee joint has shown to be effective in reducing pain symptoms of osteoarthritis and prolong the need for knee replacement.<sup>4-6</sup> Viscosupplementation allows for lubrication of the knee joint by replacing the degraded hyaluronic acid in synovial fluid.<sup>4-6</sup> Viscosupplementation allows the joint to move easily, relieving the pain from the joint grinding bone on bone from cartilage degeneration.

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not viscosupplementation is effective in reducing osteoarthritis knee pain.

## **METHODS**

Middle to older adult men and women with knee osteoarthritis were included in all three studies. The intervention was viscosupplementation (hylan G-F 20) with a visually matched placebo comparison (0.9% saline). The studies measured knee pain and/or patient satisfaction following their intervention, using WOMAC pain scale and patient global assessment forms. All studies were randomized, double blind, placebo control trials.

All articles are published in peer-reviewed journals between 2009 and 2010 and published in English. Key words used during research via Pubmed and NCBI were “viscosupplementation AND osteoarthritis”; “hylan AND patient satisfaction”. The articles chosen were based on relevance to the clinical question and presented outcomes as POEMs

(patient oriented evidence that matters). Inclusion criteria were RCTs published between 2009-2010 and exclusions were patients who had secondary arthropathies, trauma, surgeries or recent corticosteroid injections. Statistics reported were relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), relative risk increase (RRI), absolute risk increase (ARI), numbers needed to harm (NNH), p-value. Table 1 represents the demographics and characteristics of the included studies.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	#pts	Age	Inclusion Criteria	External Criteria	W/D	Intervention
Chevalier et al (2010) <sup>4</sup>	Double blind RCT	253	>40 y/o	-Patients >40 y/o with primary osteoarthritis knee pain criteria -OA with medial and or lateral tibiofemoral compartment -grade II or III OA	-secondary OA in target knee -clinically apparent effusion in affected knee -grade IV OA -OA of contralateral knee -systemic CS in any joint within 3 mo before screening	21	Single 6mL intra-articular injection of hylan G-F 20
Kul-Panza & Berker (2010) <sup>5</sup>	Double blind RCT	48	Treatment group age= $59.5 \pm 8.8$ years  Placebo group age= $62.8 \pm 7.8$ years	Men and women with diagnoses of U/L or B/L -grades 1-4 OA	No exclusion criteria reported	3	3 inj of 2 mL of 1.5% hyaluronate sodium intra-articular injection to knee with osteoarthritis (U/L or B/L)
Diracoglu et al (2009) <sup>6</sup>	Double blind RCT	63	Treatment group age= $59.4 \pm 9.9$ year  Placebo	-pts with B/L knee osteoarthritis -stage II or III -minimum 50	-pts with co arthropathies, -trauma or previous surgeries x1 yr -pts who	3	3 intrarticular Hylan G-F 20 (Synvisc®) injections, 1 week apart

			group age= 56.2 ± 7.2 years	points from VAS scale of 100mm during motion	received HA injections past 6 mo from screening -pregnancy		
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## OUTCOMES MEASURED

Outcomes measured included pain level and patient satisfaction following the intervention. Chevalier et al<sup>4</sup> used the WOMAC pain scale A1-pain while walking for evaluation of treatment at week 18 and week 26 following injection. This was measured on a scale of none, mild, moderate, severe, extreme<sup>4</sup>. Additionally, Chevalier et al<sup>4</sup> used a patient global assessment and patient pain assessment forms to determine patient satisfaction following treatment. These forms evaluated satisfaction on a scale of feeling “very well, well, fair, poor, very poor”.<sup>4</sup> Chevalier et al<sup>4</sup> provided adverse events as dichotomous data, reporting the number of individuals in both experimental and control groups who experienced arthralgias, joint effusion, arthritis, arthropathies, or injection site pain.

Kul-Panza & Berker<sup>5</sup> used a WOMAC scale evaluating pain on walking, climbing stairs, pain at night and on sitting, lying, and standing at 14 weeks after injection. Patient satisfaction 14 weeks after injection was determined via patient questionnaire by feeling “worse, no change, minimal improvement, moderate improvement, very effective”.<sup>5</sup> Lastly, Diracoglu et al<sup>6</sup> did not present dichotomous data, but ran an ANOVA and recorded a p-value for all WOMAC parameters as well as resting and activity VAS pain.

## RESULTS

Two of the randomized control trials reported dichotomous data, whereas, Diracoglu et al<sup>6</sup> reported data as continuous. All three studies used hylan GF-20 in the experimental group and saline 0.9% in the control group. Chevalier et al<sup>4</sup> used one injection of hylan GF-20 for

treatment, whereas Diracoglu et al<sup>6</sup> used three injections separated by one week and patients in Kul-Panza<sup>5</sup> received three injections in one week. Kul-Panza & Berker<sup>5</sup> reported that their study population came from patients who were attending the Physical Medicine and Rehabilitation Output Clinic at Marmara University School of Medicine in Istanbul and presented with knee pain and a diagnosis of OA. Chevalier et al<sup>4</sup> and Diracoglu et al<sup>6</sup> did not report the setting of the patient population, but noted that their patients required a diagnoses of OA. The number of patients who withdrew from the study were 21 in Chevalier et al<sup>4</sup> and 3 patients in both Kul-Panza & Berker<sup>5</sup> and Diracoglu et al<sup>6</sup>, from a total patient population of 253, 48, and 63 respectively (Table 1).

Chevalier et al<sup>4</sup> noted that they lost 9 patients from their treatment group and 12 patients from the placebo group due to failure to keep on study schedule. Additionally, 1 patient was randomly assigned to the treatment group but received the placebo by error and therefore was then counted in the placebo group for analysis.<sup>4</sup> Diracoglu et al<sup>6</sup> reported that 1 patient from the placebo group was lost in follow-up due to not benefitting from the treatment, while 2 patients from the treatment group were lost in follow-up due to difficulty attending the clinic for treatment injections. The 3 patients lost from Kul-Panza<sup>5</sup> were due to failure to attend follow-up visits. Furthermore, the inclusion and exclusion criteria for the patients in the study are noted in Table 1.

Table 2 demonstrates the efficacy of hylauronic acid on pain. Chevalier et al<sup>4</sup> analyzed the WOMAC scales from patients at 18 and 26 weeks after hylan G-F 20 injections. The NNT were calculated from the WOMAC criteria, “pain on walking”.<sup>4</sup> At 18 weeks, 71% of patients from the hylan G-F 20 group (treatment) and 53% of patients from the control group were responders.<sup>4</sup> Responders were interpreted as those patients reporting a decrease in pain level

while walking. This was calculated into a NNT of 6 (Table 2). At 26 weeks, 64% of the patients in the experimental group and 50% in the control group were responders, leading to a NNT of 8.<sup>4</sup> The difference between the control and treatment groups was deemed significant by a p-value of 0.003 at 18 weeks and 0.028 at 26 weeks.<sup>4</sup> This data concluded that 18 weeks would need to pass following the treatment of 6 individuals for 1 more patient to see results.<sup>4</sup> Furthermore, 26 weeks would need to pass following the treatment of 8 individuals for 1 more patient to see results.<sup>4</sup>

Kul-Panza & Berker<sup>5</sup> recorded WOMAC score of walking pain at 14 weeks after injections. The percentage of improvement in pain while walking was significantly higher in the experimental group (35.2%) compared to the control group (9.1). This was calculated into a NNT of 4, meaning that 4 patients would need to be treated with viscosupplementation for 1 more patient have a decrease in pain when compared to placebo (Table 2). The treatment at 14 weeks on walking pain was statistically significant in the treatment group over the placebo as noted by a p value 0.01 in ANOVA.<sup>5</sup> No dichotomous data was reported from Diacoglu et al<sup>6</sup> and no continuous data was able to be converted to dichotomous. An ANOVA was run and VAS pain values as well as all WOMAC parameters except stiffness were significantly lower in the treatment group, as noted by a p value of <0.01 (Table 2).<sup>6</sup>

Table 2. Efficacy of hyaluronic acid in the treatment of knee osteoarthritis

Study	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Numbers needed to treat (NNT)	P-value
Chevalier et al (2010) <sup>4</sup> -at 18 weeks	34%	18%	6	0.003
Chevalier et al (2010) <sup>4</sup> - at 26 weeks	28%	14%	8	0.028
Kul-Panza & Berker (2010) <sup>5</sup>	2.86%	26.1%	4	0.01

Diracoglu et al (2009) <sup>6</sup>	n/a	n/a	n/a	<0.01
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Two of the randomized control trials reported dichotomous data on patient satisfaction following their treatment intervention.<sup>4,5</sup> Chevalier et al<sup>4</sup> reported patient global assessment on the basis of feeling very well, well, fair, poor, very poor. To determine treatment success, the categories “very well, well and fair” were used to calculate NNT. Based on this determination of success, 74.2% of patients in the experimental group and 64.4% of patients in the control group reported the intervention successful.<sup>4</sup> The NNT for patient satisfaction was then calculated to be 11 (Table 3). Kul-Panza & Berker<sup>5</sup> reported patient satisfaction as either no change from baseline, minimal improvement, moderate improvement, or very effective. Included in the calculation for NNT were the categories “minimal improvement, moderate improvement, and very effective”. This correlated to a reported 87% patient satisfaction in the treatment group compared to an 82% in the control group.<sup>5</sup> The NNT was calculated to be 20 (Table 3). Of these results, it is concluded that for 1 more patient to find the treatment successful, between 11 and 20 patients would need to be treated.

Table 3. Efficacy of hylauronic acid on patient satisfaction of knee OA improvement

Study	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Numbers needed to treat (NNT)
Chevalier et al (2010) <sup>4</sup> at 26 weeks	15.2%	9.8%	11
Kul-Panza & Berker (2010) <sup>5</sup> - at 14weeks	6%	5%	20

Only one randomized trial provided dichotomous data to calculate NNH based on adverse events of the treatment. Chevalier et al<sup>4</sup> demonstrated that 5.7% of the patients in the experimental group experienced some adverse events while 3.1% in the control group. This correlates to a NNH of 39, concluding that for every 39 people treated with hylauronic acid, 1

more person will experience an adverse event when compared to control (Table 4). The most common adverse events were arthralgia, joint effusion, and arthritis with a maximum of 2 patients in each category reporting such events.<sup>4</sup> Adverse events were not reported in Diracoglu et al.<sup>6</sup> Only 1 patient in the treatment group and control group of Kul-Panza & Berker<sup>5</sup> reported an adverse, with this event being knee instability.

Table 4. Adverse events of hyaluronic acid <sup>4</sup>

Adverse reactions	Relative risk increase (RRI)	Absolute risk increase (ARI)	Numbers needed to harm (NNH)	P-value
Any treatment and/or procedure related target knee adverse events <sup>4</sup>	83.8%	2.6%	39	0.366

## DISCUSSION

The above results suggest a benefit to the use of hyaluronic acid in patients with osteoarthritis. The NNT for pain from all three studies are between 4-8 suggesting that you need to treat an average of 6 patients in order for 1 more patient to see benefits (Table 2). The NNT for patient satisfaction are fairly higher, ranging from 11-20, suggesting that around 15 people need to be treated in order to have 1 more patient satisfied with the outcome (Table 3). The NNH for Chevalier et al<sup>4</sup> was 39, ensuring that a larger number of people can be treated before an adverse event occurs (Table 4). Even so, the adverse events reported were not serious and consisted of temporary knee issues. <sup>4-6</sup>

There may be a variety of reasons why the NNT for patient satisfaction is higher. Many patients want to see immediate results from treatments, especially when pain is involved. Hyaluronic acid takes an average of 5 weeks for patients to see improvements in their OA.<sup>7,8</sup> The product provides relief of symptoms for on average, 6 months.<sup>7,8</sup> Even though these global assessment forms were given to the patient at least 3 months following the injections, patients

may have too high of expectations on joint improvements. Hyaluronic acid is not a definitive treatment for OA, and many physicians offering this treatment are prolonging the need for invasive options, such as arthroscopy and total joint replacement.<sup>1,7</sup>

Hyaluronic acid is only FDA approved for knee osteoarthritis, even though some physicians use the injection off label in hips and/or shoulders without insurance coverage to the patient.<sup>7</sup> Hyaluronic acid comes as brand names *Synvisc*®, *Orthovisc*®, *Hyalgan*®.<sup>7</sup> Medicare and most insurance companies cover the costs of hyaluronic acid products; however if the product is not covered through insurance or it is injected off label, the product can cost up to \$661 for 5 vials<sup>7,8,9</sup> There are no black box warnings for these products but should not be used in patients with joint or skin infections, venous stasis or leg edema.<sup>8</sup> Particularly for *Synvisc*®, allergy to feathers, eggs or poultry are a contraindication due to the use of chicken combs in the product.<sup>8</sup>

There are some limitations in the studies that should be discussed. There was a failure to analyze all drop outs, leading to a potential bias in the studies.<sup>4-6</sup> A limitation in the efficacy of hyaluronic acid is noted in Kul-Panza & Berker<sup>5</sup> because the study only lasted 3 months, therefore no long term effects could be evaluated. Additionally, there was no difference between the two group outcomes except at week 14 evaluation of walking pain.<sup>5</sup> There is a possible placebo effect in all the studies, where the improvement in symptoms may be psychological more so than the effect of the actual composition of the injections.<sup>4-6</sup> Kul-Panza & Berker<sup>5</sup> as well as Diracoglu et al<sup>6</sup> had relatively small sample sizes of 48 and 63 respectively, compared to Chevalier et al<sup>4</sup> sample of 253. Lastly, Chevalier et al<sup>4</sup> and Kul-Panza & Berker allowed the patients to use other analgesics and physical therapy exercise during the course of the study,

while Diracoglu et al<sup>6</sup> did not allow any exercise routine nor the use of analgesics. These discrepancies may have skewed the results provided in the articles.

### **CONCLUSION**

The results of this review suggest that hyaluronic acid is safe and effective for the use of knee osteoarthritis. Even though a NNT could not be calculated for Diracoglu et al<sup>6</sup>, an ANOVA was conducted and therefore a p-value was provided for interpretation of statistical significance. The articles showed little adverse events with an NNH of 39 from Chevalier et al<sup>4</sup>. Statistics further show that adverse events occur in <2% of patients who receive hyaluronic injections, those events being joint pain and effusion and edema.<sup>8</sup> Further research is needed to evaluate the efficacy of hyaluronic acid in all joints, with the hope to make the product FDA approved for shoulder and hip OA. Further studies should also evaluate patient's pain and satisfaction at multiple time frames, from 1 week after injection to greater than 6 months after injection, in efforts demonstrate bell curve in efficacy of the injections overtime.

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