2019

Is Hyaluronic Acid Intra-Articular Injection Better Than Corticosteroid Intra Articular Injection At Reducing Pain In Patients With Knee Osteoarthritis?

Madison Cohen
Philadelphia College of Osteopathic Medicine

Is Hyaluronic Acid Intra-Articular Injection Better Than Corticosteroid Intra Articular Injection At Reducing Pain In Patients With Knee Osteoarthritis?

Madison Cohen, PA-S

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

December 14, 2018

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Hyaluronic Acid intra articular injection is better than Corticosteroid intra articular injection at reducing pain in patients with knee osteoarthritis."

STUDY DESIGN: Review of three double-blind, randomized control trials published between 2014 and 2016. All studies were published in English language in peer reviewed journals.

DATA SOURCES: All three randomized control trials were found via PubMed.

OUTCOMES MEASURED: The primary outcomes measured by the patient and investigator being improvement of knee pain severity, knee function, and range of motion after hyaluronic acid intra articular (IA) injection versus corticosteroid intra articular injection.

RESULTS: Leighton et al demonstrated that NASHA hyaluronic acid as a single injection intra-articular treatment is a valuable treatment for knee osteoarthritis (OA), providing effectiveness that was non-inferior to methylprednisolone. It also indicated that the effect of NASHA hyaluronic acid as a single injection intra-articular treatment is longer lasting, with significantly improved pain response at 26 weeks compared to methylprednisolone with a p value of <0.05. Tammachote et al demonstrated that patients who took triamcinolone acetonide had similar improvement in knee pain. Both hylan G-F 20 and triamcinolone acetonide are both effective at reducing pain from knee OA and there is not a significant difference in pain reduction between the two groups with a p value >0.05. Bisicchia et al demonstrated that HYADD is effective at reducing pain from knee OA and more effective than corticosteroids with a p value <0.0001.

CONCLUSIONS: It can be concluded there is conflicting evidence whether or not hyaluronic acid intra-articular injection is better than corticosteroid intra articular injection at reducing pain in patients with knee OA. Based upon this evidence, both corticosteroids and hyaluronic acid intra articular injections are effective at reducing pain in patients with knee OA with no clear-cut answer if one is superior to the other. It was shown, however, that hyaluronic acid intra articular injections are possibly better long term in that they are longer lasting than corticosteroid intra articular injections.

KEY WORDS: Osteoarthritis, Hyaluronic Acid, Corticosteroid

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease in which all of the structures of the joint have undergone pathological changes. It is the most common form of joint disease as well as the leading cause of disability in the elderly. By 2013, knee OA contributed more than $27 billion in health care expenditures annually.[1] A study in 2012 demonstrated that OA cost the U.S. economy more than $100 billion annually.[1] In 2010, there were more than 100 million outpatient visits due to arthritis and OA accounts for more than 25 percent of all arthritis-related health care visits.[1]

The exact cause of OA is unknown but is thought to be caused by a combination of systemic, intrinsic, and loading factors such as: age, gender, race, obesity, repetitive use, and previous damage. The presentation of OA is described as a gradual onset of joint pain that increases with activity and is relieved with rest. There is morning stiffness usually not lasting longer than 30 minutes as well as a feeling of joint instability.

Treating OA varies from person to person mainly relying on reducing the pain caused by the pathological changes occurring within the joint structures. Unfortunately, there is not any treatment to prevent OA from occurring or slowing down the progression of it. Nonpharmacological treatment includes avoiding weight bearing exercises causing pain, physical therapy, using braces, heat and cold compresses, as well as weight loss. Pharmacological treatment involves Acetaminophen, NSAIDs, Capsaicin topical cream, topical NSAIDs, Opioids, and Intra-articular injections (Glucocorticoids and Hyaluronic acid). The only cure for OA is a joint replacement surgery.

Though surgery is the only cure for OA, it is a highly invasive and aggressive treatment that patients prefer to keep as their last resort. Also, there are risks to constant NSAID use like

peptic ulcer disease, cardiovascular complications, and gastric ulcers. In addition, long term corticosteroid use carries complications such as osteoporosis, cataracts, glaucoma, thinning of the skin, hypertension, diabetes, and weight gain. Considering that OA is a chronic, degenerative joint disease, it is pivotal to find a way to treat it in a safer, long term approach. Reducing pain in patients with OA, allowing them to live without constant discomfort, and doing so without invasive and side effect filled treatments is an attainable goal. According to Bowman et al, there are multiple hyaluronic acid products approved by the FDA currently and hyaluronic acid treatment shows great potential in lubrication, anti-inflammatory, and chondroprotective.[6]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Hyaluronic Acid intra articular injection is better than Corticosteroid intra articular injection at reducing pain in patients with knee osteoarthritis."

METHODS

Three randomized controlled trials were used in this review. The selected population of interest were patients greater than 30 years of age with diagnosed and symptomatic knee pain. The intervention in the three randomized controlled trials was hyaluronic acid intra articular injection. The treatment group receiving hyaluronic acid intra articular injection was compared to the experimental group receiving corticosteroid intra articular injection. The primary outcomes measured by the patient and investigator were improvement of knee pain severity, knee function, and range of motion after hyaluronic acid intra articular injection versus corticosteroid intra articular injection. The types of studies used were three randomized controlled trials comparing

hyaluronic acid intra articular injection to corticosteroid intra articular injection at reducing pain in patients with knee OA.

The keywords Hyaluronic acid intra articular injection and corticosteroid intra articular injection and OA were searched on PubMed and selected based upon the relevance to my clinical question and if they had patient oriented outcomes (POEMS: Patient Orientated Evidence that Matters). All of the articles were published in English and published in peer reviewed journals. The inclusion criteria were studies that were RCTs published after 2008 and exclusion criteria was age less than 30 years old and Intra-articular injections in the last 12 months or surgery in either knee within the preceding 12 months. The statistics used and reported in this selective based medicine review were p- values, mean change from baseline, and number needed to treat (NNT).

Table 1- Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Leighton[3] (2014)	RCT	442	35–80	Men and women aged 35-80 with BMI of ≤40 kg/m^2, ability to walk 50 m unaided, Unilateral knee pain meeting, WOMAC pain score of 7-17, Radio-graphically verified OA.	Participants with clinically detectable knee effusion, clinically significant contralateral knee OA (WOMAC pain score >3), clinically significant pain in joints other than the knee, IA steroid injection into the study knee within the preceding 3 months, IA HA injection into the study knee within the preceding 9 months, use of systemic glucocorticosteroids within the preceding 3 months, Arthroscopy or other surgical procedure in the study knee within the preceding 12 months.	10	NASHA hyaluronic acid gel as single-injection intra-articular methylprednisolone acetate intra-articular injection
Tammachote [4] (2016)	RCT	110	The mean age of the patient s in the	Symptomatic knee OA, dissatisfaction with conservative treatment, no lumbar spondylosis with radiculopathy, good cognition, ability to	Participants with an allergy to any of the medications used, bone-on-bone arthritis on any radiograph, varus or valgus deformity of >5 degrees, previous fracture or surgical	11	Hyaluronic acid (hylan G-F 20) intra articular injection and triamcinolone

			hylan G-F 20 group was 63 years (range, 46 to 77 years). The mean age of the patients in the triamcinolone acetonide group was 61 years (range, 47 to 81 years),	understand the study protocol, agreement to participate.	procedure of knee, previous intra-articular injection in the ipsilateral knee in the past 6 months, current infection in the affected limb.		acetonide intra-articular injection
Bisicchia[5] (2016)	RCT	150	HYADD 4 group (mean age 71.5±10.6 years), CS group (mean age 68.6±9.9 years)	Male and female walking patients older than 45, single symptomatic knee, Kellgren-Lawrence (29) grade 2–3 knee osteoarthritis and a VAS for pain ≥3.	Participants with grade 1 or 4 OA, according to Kellgren-Lawrence (29), symptoms in both knees, a varus or valgus deformity greater than 10 degrees, flexion contracture greater that 15 degrees, ligamentous instability or meniscal tears, NSAIDSs used in the last 30 days, Intra-articular injections in the last 12 months; septic, inflammatory or crystal arthritis, previous surgeries in the last 6 months, physical therapy in the last 30 days.	0	HYADD 4 intra articular injection and methylprednisolone intra articular injection

OUTCOMES MEASURED

The primary outcomes measured were knee pain severity, knee function, and range of motion after using of hyaluronic acid intra articular injection versus corticosteroid intra articular injection. This was done via the visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

RESULTS

This selective evidence based medicine review evaluates hyaluronic acid (HA) intra articular (IA) injections for the treatment of OA in comparison to corticosteroid intra articular injections. All three of these studies were randomized controlled trials. Leighton et al and Tammachote et al were both double blind clinical trials. Bisicchia et al was a single center, single blind, clinical trial.

Leighton et al is an active-controlled, double-blind, non-inferiority clinical trial that evaluates NASHA HA for the treatment of OA in order to prove that it is not inferior at treating pain in comparison to methylprednisolone (MPA). In total, 442 patients with unilateral pain in their knee from OA entered this clinical trial.[3] The patients were randomized 1:1 to receive either hyaluronic acid or MPA intra articular injection. All of the patients were followed and evaluated for 26 weeks. At that time, the patients returned to the clinic and were given NASHA hyaluronic acid and then reevaluated in an additional 26 weeks. The initial 26-week period was a completely blinded study. The following 26-week period was an unblinded study with NASHA hyaluronic acid treatment only.[3] Only the first 26-week period will be discussed throughout this review. There were 15 sites in Canada, 4 in the UK, and 5 in Sweden. The follow up consisted of a screening visit, a baseline visit at which the IA injections were administered, telephone calls at 2 and 4 weeks to evaluate safety and concomitant medication use, and clinic visits at 6, 12, 18 and 26 weeks to determine effectiveness or any safety issues. Rescue medication with acetaminophen was allowed at up to 3 g per day.[3] Arthralgia was the most common treatment-related complaint in both study groups. Most of the patients receiving the injections had side effects within the first 3 days with them being resolved in 2-3 weeks. Primary

effectiveness analysis was measured using the WOMAC pain scale. At 26-weeks the data portrayed a responder rate of NASHA at 54% and MPA at 44% with a p-value of 0.043 which is a significant p value being <.05. This data shows that NASHA is non-inferior to MPA and that NASHA has more long-term effects whereas MPA declined throughout the study. Number needed to treat (NNT) was calculated as 10 which is a large treatment effect. This value means that for every 10 participants who took NASHA hyaluronic acid as a single injection intra-articular treatment, there was one more person who had a pain reduction than in the group taking methylprednisolone. In conclusion, this study showed that NASHA hyaluronic acid IA is an effective and safe treatment for OA and is non-inferior to MPA.[3]

Table 2: Patient Outcomes as Evaluated by Responder Rate in WOMAC pain scale Leighton et al[3]

	RESPONDER RATE AT 12 WEEKS	RESPONDER RATE AT 26 WEEKS
NASHA	44.6%	54%
MPA	46.2%	44%
P-VALUE		0.043

Tammachote et al is a prospective, randomized, double-blind clinical trial that compares of hyaluronic acid (hylan G-F 20) with triamcinolone acetonide as a single intra-articular (IA) injection for knee OA. The purpose of this clinical trial was to prove which treatment had a better outcome in knee pain, range of motion, and knee function. Knee pain and range of motion will be the two outcomes discussed throughout this review. In total, 110 patients entered the clinical trial and were put into two separate groups to receive the injection; 55 in each group. The patients were then followed for six months. All of the injections were given in an outpatient clinic and the patients and evaluators were kept blinded.[4] Knee pain was measured using the

VAS pain scale and knee function was measured using the WOMAC index. The VAS pain scale was completed at baseline; at days 1, 2, and 3; at weeks 1 and 2; and at months 1, 2, 3, 4, 5, and 6. The WOMAC index was completed at baseline, week 2, and months 1, 2, 3, 4, 5, and 6. At the end of the clinical trial, 49 patients remained in the triamcinolone acetonide group and 50 remained in the hyaluronic acid group. The author did not report why the 11 patients withdrew from the trial.[4] In reference to knee pain, the triamcinolone acetonide group had significantly better pain relief especially in the first week with a p value of 0.02. Right after the injection, the VAS score for pain was evaluated. The mean difference between groups was 11 with a p value of < 0.05. As time went on, the mean difference was small and not significant.[4] Even though the triamcinolone acetonide group showed more overall pain relief in the first week, both groups showed significant pain relief after injection ($p < 0.0001$). Both groups had similar improvement in knee function with a p value > 0.05. At the end of 6 months, the mean modified WOMAC scores had significantly improved ($p < 0.0001$ for both) from 43 to 21 points (95% CI, 16.7 to 29.2 points) in the hylan G-F 20 group and from 39 to 21 points (95% CI, 11.0 to 24.3 points) in the triamcinolone acetonide group. At the end of the 6 months, the mean change in VAS scores was almost 30 points in both groups: 29 points (95% CI, 236.4 to 222.7 points) in the hylan G-F 20 group and 30 points (95% CI, 236.0 to 222.8 points) in the triamcinolone acetonide group ($p < 0.0001$).[4] This is a large mean change from baseline. According to Tammachote et al there were no serious adverse effects reported throughout this clinical trial from both groups. Knee pain and swelling were reported by one patient in the hylan G-F 20 group which was relieved with the post injection pain medication. In conclusion, hyaluronic acid and triamcinolone acetonide as a single IA injection for knee OA have similar outcomes in knee pain relief and functional improvement at 6 months with a p-value = 0.81 for the WOMAC pain scale and a p-

value of 0.60 for the VAS pain scale. Both of these p values are not statistically significant p values. However, it was seen that triamcinolone acetonide has a quicker response on pain relief within the first two weeks.[4]

Table 3: Differences in Mean Outcome Scores Between Groups[4]

	VAS PAIN SCALE AT 6 MONTHS	WOMAC PAIN SCALE AT 6 MONTHS	P-VALUE AT 6 MONTHS
Hylan G-F 20 Group	24±22	21±15	0.60 (VAS PAIN SCALE)
Triamcinolone Acetonide Group	21±22	21±19	0.81 (WOMAC)

Bisicchia et al is a single-center, single blind prospective randomized controlled clinical study that compares HA (HYADD 4) with corticosteroid (CS). All of the patients who entered this trial were randomly assigned and either received two injections of HA or two injections of CS. There were 53 females and 22 males in the HYADD 4 group and 50 females and 25 males in the CS group. The patients were followed throughout an entire year and evaluated using the WOMAC pain index and VAS pain scale. The two most common side effects reported were discomfort during the injection and joint discomfort for about 2–3 days after the injection being almost equal between both groups with a p value >0.05.[5] All of the patients completed the evaluation at 6 and 12 weeks. Between 12 and 26 weeks and between 26 and 52 weeks, some patients returned back to the clinic for a new injection cycle due to a significant reduction in the treatment effect. All of the patients that returned back were considered treatment failures and excluded from the trial. With the exclusion of those patients, there were 72 patients in HYADD 4 group and 64 in the CS group at the 26-week evaluation. At the 26-week follow up, the HYADD 4 group reported significantly better results compared to the CS group with a p value of <0.0001 on the WOMAC pain index. At any point in time on the WOMAC pain index, patients significantly improved compared to baseline in both groups. In reference to the VAS pain scale, at week 26, patients in the HYADD 4 group obtained significantly better results with a p value of

0.0004 at 26 weeks.[5] At 26 weeks, the mean change from baseline for HYADD 4 was 14.1 and the mean change from baseline for corticosteroids was 9. This is a large mean change from baseline for both groups, however, HYADD had a larger mean change from baseline at 26 weeks. At the one year mark, both groups returned back to baseline on the WOMAC pain index and VAS pain scale. In conclusion, HYADD 4 provided better pain relief than the Corticosteroid group in short term, but neither had long term control of the symptoms.[5]

DISCUSSION

Osteoarthritis is a chronic, degenerative disease in which patients need long term pain control. This makes treating patients safely and adequately with OA difficult. The three randomized controlled trials discussed in this review suggest that hyaluronic acid intra articular injection is an effective treatment for knee OA with conflicting evidence whether it is superior or inferior to corticosteroid intra articular injection. In Leighton et al, they considered the absence of a saline control arm being a limitation, but to add such a thing was medically unethical.[3] In Bisicchia et al was a single blind study towards the observers so the patients were informed which treatment they would be receiving. This might have cause a bias limiting the efficacy of the clinical trial. An additional limitation in Bisicchia et al clinical trial includes that the evaluators did not record the BMI of the patients. Patients with higher BMIs could have had a higher pain levels and higher failure rates due to the excess weight they have.[5]

CONCLUSION

In conclusion, there is conflicting evidence whether hyaluronic acid IA injection is superior to corticosteroid IA injection for unilateral knee pain from OA. According to Leighton et al, HA is non-inferior to corticosteroid and has a longer effect on pain relief. However,

according to Tammachote et al, both have similar effects, with corticosteroids having a quicker onset. According to Bisicchia et al, hyaluronic acid provides better short-term control of symptoms and neither has more side effects than the other. All three of these trials have some opposing results about which treatment is superior, but all three clinical trials show that both have similar effects on knee OA at reducing pain and improving function.

Further studies are warranted to evaluate HA in the treatment of knee OA with a larger sample size and longer follow up. It is important to factor in the amount and type of physical activity each patient is participating in throughout the follow up period. Also, separating the groups based upon sex could give more insight as to which population has greater benefit with hyaluronic acid IA injection as opposed to corticosteroid IA injection.

References

1. Arthritis By The Numbers - Arthritis Foundation. https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf. Accessed October 1, 2018.

2. What is Osteoarthritis? www.arthritis.org. https://www.arthritis.org/about-arthritis/types/osteoarthritis/what-is-osteoarthritis.php. Accessed October 8, 2018.

3. Leighton R, Akermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: A prospective, multi-centre, randomized, non-inferiority trial. *Osteoarthritis Cartilage*. 2014;22(1):17-25. doi: 10.1016/j.joca.2013.10.009 [doi].

4. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-articular, single-shot hylan G-F 20 hyaluronic acid injection compared with corticosteroid in knee osteoarthritis: A double-blind, randomized controlled trial. *J Bone Joint Surg Am*. 2016;98(11):885-892. doi: 10.2106/JBJS.15.00544 [doi].

5. Bisicchia S, Bernardi G, Tudisco C. HYADD 4 versus methylprednisolone acetate in symptomatic knee osteoarthritis: A single-centre single blind prospective randomised controlled clinical study with 1-year follow-up. *Clin Exp Rheumatol*. 2016;34(5):857-863. doi: 10105 [pii].

6. Bowman S, Awad ME, Hamrick MW, Hunter M, Fulzele S. Recent advances in hyaluronic acid based therapy for osteoarthritis. *Clin Transl Med*. 2018;7(1):6. Published 2018 Feb 16. doi:10.1186/s40169-017-0180-3

7. Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: A key molecule in skin aging. *Dermatoendocrinol*. 2012;4(3):253-8.

8. Tamura T, Higuchi Y, Kitamura H, et al. Novel hyaluronic acid–methotrexate conjugate suppresses joint inflammation in the rat knee: efficacy and safety evaluation in two rat arthritis models. *Arthritis Research & Therapy*. 2016;18(1). doi:10.1186/s13075-016-0971-8.