REVIEW ARTICLE

CLINICAL OUTCOMES OF INTRA-ARTICULAR HIGH MOLECULAR WEIGHT HYALURONIC ACID INJECTION FOR HIP OSTEOARTHRITIS- A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Osteoarthritis is the most common degenerative disease of the synovial joints in the elderly population with hip osteoarthritis as the second most commonly affected joint. A multitude of conservative treatments is used for pain relief and functional improvement including acetaminophen, NSAID, intra-articular corticosteroid, and viscosupplementation (VS). Different preparations of VS based on different molecular weights are commercially available. No systematic review or meta-analysis regarding the use of intra-articular high molecular weight hyaluronic acid (HMWHA) injection for the hip joint was published before. This review analyzes the efficacy of intra-articular HMWHA for hip osteoarthritis. **Methods:** PubMed, Google Scholar, Cochrane Library for randomized trials describing the efficacy of HMWHA for hip osteoarthritis was searched. The search terms were osteoarthritis, hip joint, outcomes, viscosupplementation, and high molecular weight hyaluronic acid in different combinations. Standardized mean difference (SMD) in VAS for pain relief and Lequesne index for functional outcomes while risk ratio (RR) for complications was used for data pooling. **Result:** Four studies comprising 185 and 189 patients in HMWHA and control groups were included, respectively. SMD for VAS and Lequesne index was -0.056 and -0.114, respectively while RR for complication was 0.879. **Conclusion:** Intra-articular HMWHA injection provided pain relief, functional improvement, and no severe complications on immediate short term basis. However, the results do not favor treatment with HMWHA over other treatment methods. Randomized trials are further necessary to provide data regarding comparisons between HMWHA for hip osteoarthritis concerning clinicians' convenience, compliance, duration of relief, and cost-effectiveness.

Keywords: High molecular weight hyaluronic acid; arthritis; Hip osteoarthritis; Viscosupplementation; Orthopedic procedures; Rheumatology

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INTRODUCTION

Osteoarthritis is one of the most common types of arthritis that millions of people are affected around the world. The most common joints targeted by osteoarthritis include hands, knees, hips, and spine. Hip osteoarthritis is the second most commonly affected joint affecting about 6.4% of the population.[1] The prevalence of hip osteoarthritis (OA) among adults aged ≥45 is estimated to range from 6.7% to 9.2% and increases with age.[2,3] Hip osteoarthritis is treated conservatively, if not effective then surgical interventions are planned accordingly. Among the currently available conservative treatment options for hip osteoarthritis, weight loss,[4] exercise,[5,6] walking aids,[7] topical agents,[8] analgesics such as NSAIDs, COX 2 inhibitors are commonly prescribed[9,10]. In 2012, Snijders, van den Ende[11] published the results of their clinical trials where only 25% of osteoarthritis patients showed pain improvement with medication while 46% of the were non-compliant with dosing regimens.

Due to poor patient compliance and gastrointestinal problems, the administration of intra-articular injections replaced oral and topical analgesics for hip osteoarthritis. Intra-articular corticosteroid was the first prescribed intra-articular treatment and it was found to be beneficial; however, the stated outcomes varied massively. Short term pain alleviation for one to three months,[12–14] worsening of pain after 3 months,[12], and increased cartilage degeneration were the most common adverse effects. Hence, most clinicians are cautious regarding the frequency of intra-articular corticosteroid injections.[15]

Viscosupplementation came forward as a novel approach to treat hip osteoarthritis. The technique was based upon the injection of intra-articular hyaluronic acid (HA) which is considered as the major structural and biochemical molecule of cartilage.[16] Exogenous HA serves to replace the

reduced intra-articular HA in the joint to reduce pain and functional disability. Commercially-available HA products are based upon the different sources of HA, structure, molecular weight, concentration, volume per injection, and the number of injections per course of therapy.[17,18] HA are available commercially in three categories based upon the molecular weights:

- Low molecular weight hyaluronic acid (LMWHA) (MW: 0.5–1.5 million Dalton)[19]
- Medium molecular weight hyaluronic acid (MMWHA) (MW: 1.5–6 million Dalton)[19]
- High molecular weight hyaluronic acid (HMWHA) (MW: 6–7 million Dalton)[19]

HMWHA results in a better increase in fluid retention into the joint and possibly present with stronger anti-inflammatory effect compared to other HA preparations.[20] Many animal model studies regarded HMWHA as a chondroprotective agent with better lubrication.[21–23] Clinical trials evaluated the efficacy of different molecular weight HA products on different joints including the knee, hip, temporomandibular, and shoulder joint.[24] Literature reviews by Pai, Allgar[25], Colen, Geervliet[26], and Colen, Geervliet[26] have summarized HMWHA as an effective management option for knee and shoulder joint, respectively but no systematic review has reported the outcomes after administration of HMWHA for hip osteoarthritis. The major objective of this article is to report the role of HMWHA in improving the clinical outcomes for hip osteoarthritis and pave the way for clinicians to use HMWHA as a treatment modality in hip osteoarthritis.

MATERIAL AND METHODS

"Preferred reporting items for systematic reviews and meta-analysis (PRISMA)" was used to obtain researches regarding outcomes of HMWHA. The literature available was assessed by its title, abstract, and finally full texts for applying quality assessment scores.

PubMed/Medline, Google Scholar, and Cochrane library were systematically searched with the keywords high molecular weight hyaluronic acid, HMWHA, outcomes of, and hip osteoarthritis in different combinations for clinical trials in English on the human specimen. References of included trials were also checked for eligible studies.

Two authors (S.M.E.A and B.S) scored the researches independently with the quality assessment checklist for methodological quality by the "Oxford quality scoring system"[27] for randomized trials. For the Oxford quality scoring system, a score of 5 or 4 suggests a good quality trial; 3 or 2 suggests a fair quality trial while 1 or 0 signifies a poor-quality study. Any disagreements were resolved through internal discussion among all the authors. An expert from our institute was involved if disagreements could not be resolved after discussions among authors.

An inclusion criterion was set after discussion among the authors. All randomized trials that involved outcomes of HMWHA for hip osteoarthritis were included. The studies were read deeply to search for any subgroup included in trials that received HMWHA with any one or more of the given outcomes. The participants included in trials should have hip osteoarthritis and no other arthritis associated such as septic, autoimmune, crystal-induced, hyper coagulopathy, and vasculitis with pre-intervention VAS score above 5 or above and/or Lequesne index 7 or above with at least 3 months follow-up. The intervention should be intra-articular high molecular weight hyaluronic acid for hip osteoarthritis with no adjuvant surgical or intra-articular pharmacological therapy that may influence the overall results such as corticosteroid, hormonal therapy, low molecular weight hyaluronic acid (LMWHA), medium molecular weight hyaluronic acid (MMWHA). Poor methodology trials, letters, short communications, commentaries, editorials, case reports, conference papers, proceedings, and personal communications were excluded. The trials were excluded if concomitant use of NSAIDs, opioids, or any other analgesics was employed with HMWHA. The corresponding author of this article contacts the authors of trials to sort out the ambiguities within the trials before exclusion.

The outcomes measured are pain relief in terms of change in Visual Analogue Score (VAS) which is an 11 point score starting from 0–10 where 0 means no pain while 10 means worse pain and functional disability measured by Lequesne index of Severity for Osteoarthritis of the Hip in index score from score 0–24 which is based upon three-section questionnaire with a zero to eight score for each section. The Lequesne index Score less than 4 means mild disability, 5–7 means moderate disability, 8–10 means severe disability, 11–13 means very severe disability while above 14 means extremely severe disability. The complications of the procedure were site-infections, systemic complications, post-operative pain, avascular necrosis, effusion, local skin reaction, femoral head collapse, and septic arthritis.

OpenMetaAnalyst Software was used. The authors used means±SD for continuous variables and the number of patients (n) for dichotomous

variables during data extraction. VAS and Lequesne index were continuous outcomes while complication was the dichotomous outcomes. The pooling of data was performed by using the standardized mean difference (SMD) and risk ratio (RR) for continuous and dichotomous variables, respectively regarding the outcomes by a random-effects, generic inverse variance method of DerSimonian and Laird.[28] The inclusion of SMD was considered due to the expected high dropouts in longer follow-up trials.[29] The heterogeneity was tested by I^2 Statistics. Heterogeneity was considered negligible when I^2 of less than 25%, low when I^2 of 26–50%, moderate when I^2 of 51–75%, and high when I^2 above 75%.[30]

In case of significantly moderate to high heterogeneity, a random-effect meta-regression model was used for weighing the studies by their within-study variance and the degree of heterogeneity to assess the covariates predicting the treatment effect of HMWHA.[31] The heterogeneity between the studies was explored with differences in the characteristics of the trials as shown in Table-1 on the x-axis of meta-regression plots. The statistical significance of each variable was examined using the intercept coefficient (IE) and slope coefficient (SE) with their respective *p*-value.

Table-1: Characteristics of trials included

Clinical Trial	Year of study[a]	Country	Design[b]	Quality	Number of patients	Number of HMWHA injections	Last follow up (months)	Age[c]	Gen der[d]	Body Mass Index (BMI)[c]	Laterality[d]
Spitzer, A.I., *et al.*[32]	2010	USA	RCT	Fair	102/94	2	6.5	59±12	48:52	29.3±5.5	88/12
Tikiz, C., *et al.*[33]	2005	Turkey	RCT	Fair	18/25	3	6	60.4±9.6	22:78	29.8±3.9	66.7/33.3
Clementi, D., *et al.*[34]	2018	Italy	RCT	Good	23/27	1	12	65.9±10.02	34.8:65.2	27.2±2.38	100/0
Richette, P., *et al.*[35]	2009	France	RCT	Good	42/43	1	3	60.8±10.2	36:64	26.7±4.2	100/0

[a]Year of publication of the study. [b]Study design of included trials; RCT, Randomized Controlled Trial; OS, Observational study. [c]Scores are reported as a mean±SD representing age and BMI. [d]Reported as a percentage of patients representing gender (male/female) and laterality (unilateral/bilateral) N/A Not available

Table-2: Characteristics of trials included

Clinical Trial	Intervention	VAS score pre-treatment[(a)]	VAS score post-treatment[(a)]	Change in VAS score	Lequesne index pre-treatment[(a)]	Lequesne index post-treatment[(a)]	Change in Lequesne index	Adverse effects[(b)]
Spitzer, A.I., *et al.*[32]	HMWHA	N/A	N/A	N/A	N/A	N/A	N/A	16
	Control	N/A	N/A	N/A	N/A	N/A	N/A	21
Tikiz, C., *et al.*[33]	HMWHA	6.7 ± 1.7	3.4 ± 3.00	-3.3 ± 3.4	11.8 ± 3.3	5.9 ± 5.4	-5.9 ± 6.3	3
	Control	7.2 ± 1.5	4.6 ± 2.5	-2.6 ± 2.9	11.4 ± 4.6	6.2 ± 5.8	-5.2 ± 7.4	3
Clementi, D., *et al.*[34]	HMWHA	6.4 ± 1.7	4.8 ± 1.6	-1.6 ± 2.3	12.5 ± 4.1	9.8 ± 3.3	-2.7 ± 5.3	0
	Control	6.3 ± 2.1	4.9 ± 1.6	-1.4 ± 2.6	11.5 ± 4.4	9.5 ± 3.3	-2 ± 5.5	0
Richette, P., *et al.*[35]	HMWHA	5.8 ± 1.2	5.1 ± 2.8	-0.8 ± 2.5	N/A	N/A	N/A	5
	Control	6.0 ± 1.0	5.1 ± 2.9	-0.9 ± 2.7	N/A	N/A	N/A	2

[(a)] Scores are reported as a mean ± SD at last follow-up; VAS, visual analog score. [(b)]Number of patients reporting complications. N/A, Not available

RESULT

After an initial review of 77 articles, four studies comprising 185 and 189 patients in HMWHA and control groups were included summarized in Table-1. The studies were based in Italy (n=1), United States (n=1), France (n=1), and Turkey (n=1). The reviewed publications included four randomized controlled trials published from 2005 to 2018. Two studies were of good quality, while two studies were of fair quality. A median follow-up of 6.25 (3–12) months was calculated from the included studies. Three of the four trials measured subjective pain using the VAS score on a scale of either 0–10. The overall SMD for VAS score was statistically non-significant (SMD -0.056; 95% CI; -0.351, 0.239; *p*=0.709). The I^2 value for heterogeneity was negligible and non-significant (I^2=0%, *p*=0.788) (Figure-1).

Two of the four trials measured functional disability using the Lequesne index. The overall SMD for Lequesne index was statistically non-significant (SMD -0.114; 95% CI; -0.524, 0.296; *p*=0.585). The I^2 value for heterogeneity was negligible and non-significant (I^2=0%, *p*=0.945) (Figure-2). All four trials compared the incidence of treatment-associated adverse effects. The overall risk ratio of complications was statistically non-significant (Risk ratio 0.879; 95% CI; 0.527, 1.466; *p*=0.622). The I^2 value for heterogeneity was negligible and non-significant (I^2=0%, *p*=0.44) (Figure-3).

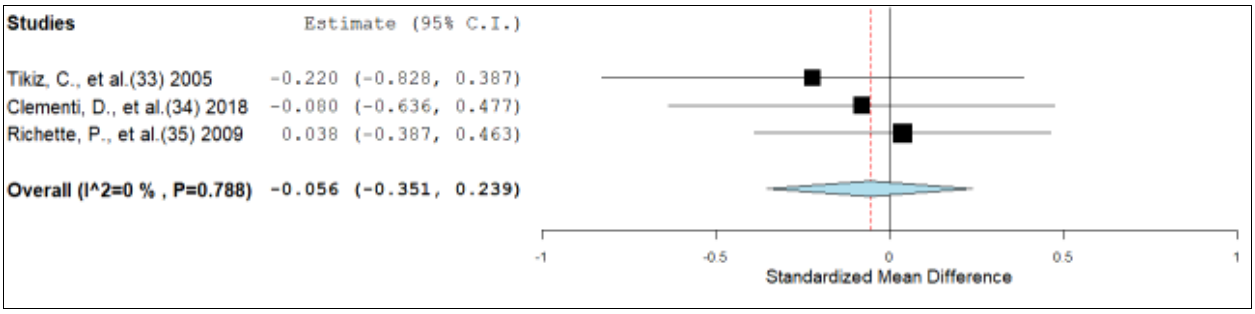

Figure-1: Forest plot comparison where square boxes representing effect sizes and diamond shape represents overall treatment: Standardized mean difference between post-intervention and pre-intervention Visual Analogue Score (VAS)

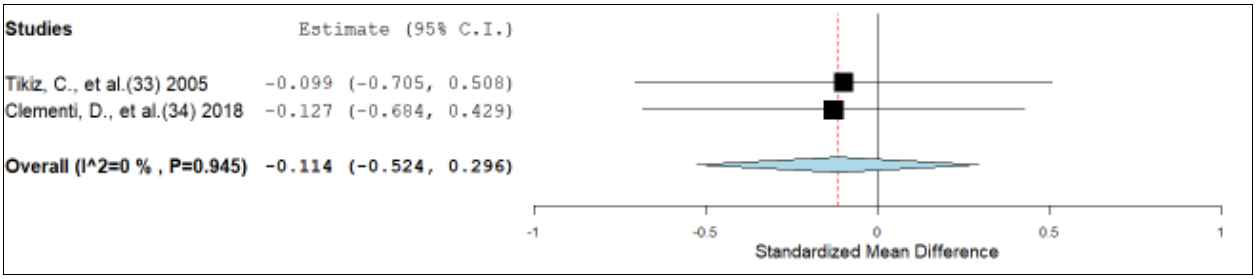

Figure-2: Forest plot comparison where square boxes representing effect sizes and diamond shape represents overall treatment: Standardized Mean Difference between post-intervention and pre-intervention Lequesne index for severity

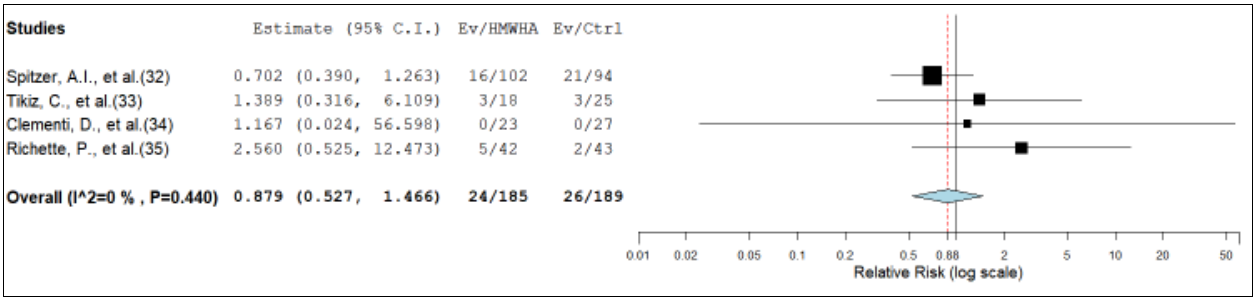

Figure-3: Forest plot comparison where square boxes representing effect sizes and diamond shape represents overall treatment: Risk ratio for post-therapeutic complications

DISCUSSION

The present systematic review included four randomized trials that investigated the clinical outcomes of HMWHA. Our analysis was based upon three outcomes which were mainly related to pain relief, functional relief, and complications after the intra-articular HMWHA injection. The review included randomized controlled trials where HMWHA was compared to a control group. The control groups were given steroid, LMWHA, MMWHA, and placebo, respectively. During our literature reviews, we found no published systematic review or meta-analysis regarding the clinical outcomes of intra-articular HMWHA injection for hip osteoarthritis. Osteoarthritis manifests most commonly as a chronic painful condition of synovial joint among senile patients.[36,37] Pain is usually the first symptom before any other signs and symptoms develop. The pain increases with activity and decreases after rest which leads the patients opting a sedentary lifestyle. Studies have reported higher risks of obesity, metabolic syndromes, depression, and anxiety among osteoarthritis patients.[38–40] Hence, most therapeutic options target pain relief as a primary target to enhance the daily activity of patients. HMWHA was also investigated for its pain-relieving efficacy. We reported pain relief in terms of change in the VAS score by SMD. A negative value concluded betterment in pain while a positive value showed worsening of pain. Our study reported equivocal betterment in pain as shown in forest plot in Figure-1 (SMD -0.056; 95% CI; -0.351, 0.239; p=0.709).

This review also focused on the functional outcomes of hip osteoarthritis. A severity index proposed by Lequesne, Mery[41] for knee and hip was chosen as a tool to assess the treatment effect of HMWHA. The Lequesne index has the advantage of collective measurement of three outcomes which were pain or discomfort, maximum distance walked, and activities of daily living. The index was designed as a questionnaire with a 0–2 scale rating of each question. Lecorney, Verhoeven[42] showed a significant relationship between the radiographical scale and the Lequesne index (r=0.3. *p*-value= 0.006). A negative value of the Lequesne index favored the treatment effect of HMWHA while a positive value favored the control group. The results of our review showed equivocal functional outcomes after intra-articular HMWHA injection compared to the control group (SMD -0.114; 95% CI; -0.524, 0.296; *p*=0.585).

The negligible and non-significant heterogeneity in our statistical analysis might be against certain concepts that were published previously. Previous articles have proven the better effects of HMWHA in younger candidates for knee osteoarthritis as cartilage degeneration accelerates with increasing age.[43–45] Our systematic review proved that age may not be the predictor in treatment effect as the trials included in our article showed candidates from age 59±12 years to 65.9±10.02 years. The results thus negate the principles of variable outcomes related to age. During our literature search, we also found that trials with longer follow-ups reported lesser change in functional outcomes while studies with shorter follow-ups showed better functional outcomes on the last follow-up. This phenomenon was explained by the degradation of hyaluronic acid with the time to lower weight hyaluronans by enzymatic activity.[46,47] We included trials with different follow-ups ranging from 3 months to 12 months but no significant differences were observed in terms of outcomes. Pochon, Peterson[48] mentioned in their results that females were 2.80 and 2.90 times more likely to report clinically relevant improvement at 1 day (*p*=.049) and 1 month (*p*=.045), respectively while Zarringam, Saris[49] concluded the male gender as a significant prognostic predictor after hip arthroplasty. Whereas in our review, we did not find any heterogeneity to prove the gender-related differences in outcomes.

Complications that were most commonly seen after intra-articular HMWHA injection were site infections, post-therapeutic pain, mild effusion, and local skin reactions. None of the trials reported systemic complications, septic arthritis, femoral head collapse, or severe effusion. Our forest plot found the risk of postoperative complications (Risk ratio 0.879; 95% CI; 0.527, 1.466; *p*=0.622) similar in both groups as the results are statistically non-significant. Cassuto, Delledonne[50] compiled post-marketing data of adverse effects of HMWHA on 40,000 patients and our results regarding no major adverse effects in HMWHA are similar to theirs. Similar results were reported by Rivera.[51]

There were certain limitations in the present review. Firstly, the article includes only four randomized studies which qualified the inclusion criteria. Secondly, the results of the review represent the mid-term duration success rate of the intra-articular HMWHA injection for hip osteoarthritis with a follow-up duration of 3–12 months, and greater follow-up is needed to support the use of HMWHA for hip osteoarthritis.

CONCLUSION

Intra-articular HMWHA injection provided pain relief, functional improvement, and no severe complications on an immediate short term basis. However, the results do not favor treatment with HMWHA over other treatment methods based on outcomes in this review. Randomized trials are further necessary to provide data regarding comparisons between HMWHA for hip osteoarthritis concerning clinicians' convenience, compliance, duration of relief, and cost-effectiveness.

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