 Acta Chir Orthop Traumatol Cech., 91, 2024, No. 2, p. 109–119
DOI: 10.55095/ACHOT2024/009

ORIGINAL PAPER
PŮVODNÍ PRÁCE

Viscosupplementation with High Molecular Weight Hyaluronic Acid for Hip Osteoarthritis: a Systematic Review and Meta-Analysis of Randomised Control Trials of the Efficacy on Pain, Functional Disability, and the Occurrence of Adverse Events

Viskosuplementace vysokomolekulární kyselinou hyaluronovou pro kyčelní osteoartrózu: systematický přehled a metaanalýza randomizovaných kontrolních studií účinnosti na bolest, funkční postižení a výskyt nežádoucích účinků

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ABSTRACT

PURPOSE OF THE STUDY

Hip osteoarthritis (OA) has a prevalence of around 6.4% and is the second most commonly affected joint. This review aims to assess the clinical outcomes of intra-articular high molecular weight hyaluronic acid (HMWHA) in the management of hip osteoarthritis.

MATERIAL AND METHODS

We conducted a comprehensive search across PubMed, Google Scholar, and the Cochrane Library for randomised trials investigating the effectiveness of high molecular weight hyaluronic acid (HMWHA) in the treatment of hip osteoarthritis. Quality and risk of bias assessments were performed using the Cochrane RoB2 tool. To synthesise the data, we utilised the Standardised Mean Difference (SMD) for assessing pain relief through the Visual Analogue Scale (VAS) and the Lequesne index (LI) for evaluating functional outcomes. Risk Ratio (RR) was calculated to assess the occurrence of complications.

RESULTS

A total of four studies involving HMWHA and control groups were included. The standardised mean difference (SMD) for the Visual Analogue Scale (VAS) (SMD -0.056; 95% CI; -0.351, 0.239; p = 0.709) and the Lequesne index (SMD -0.114; 95% CI; -0.524, 0.296; p = 0.585) were not statistically significant. Analysis for complications demonstrated an overall relative risk ratio (RR) of 0.879 (95% CI; 0.527, 1.466; p = 0.622), and was not statistically significant.

DISCUSSION & CONCLUSIONS

Intra-articular HMWHA in hip OA can significantly reduce pain and improve functional recovery when compared with the condition before treatment. However, there is no significant difference between HMWHA, or saline, or other therapeutic treatments. Currently, available evidence indicates that intra-articular HMWHA in hip OA would not increase the risk of adverse events.

Key words: hip osteoarthritis, hyaluronic acid, intra-articular, molecular weight, viscosupplementation.

INTRODUCTION

Osteoarthritis (OA) is acknowledged as a significant condition due to its progressive disability. An estimated 240 million people worldwide are affected by OA, and its prevalence is anticipated to grow as the population ages and obesity rates rise (Lawrence et al., 1998, Thomas et al., 2004)(19,36). This increase in the disease burden is evident in the years of disability attributed to OA, which rose by 31.4% from 2007 to 2022 (Felson, 1988, Solignac et al., 2004) (13,31). Despite a growing number of individuals experiencing symptomatic OA, there is still no known curative approach to halt, prevent, or mitigate its progression. Current pharmaceutical treatments for OA primarily focus on symptom management. These include the use of paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), Platelet-rich Plasma (PRP) and intraarticular (IA) injections of hyaluronic acid (HA) or steroids. NSAIDs are frequently prescribed to alleviate joint pain and inflammation, but they are associated with an elevated risk of gastrointestinal and cardiovascular side effects (Zhang et al., 2005, Zhang et al., 2010) (39,40).

In contrast, IA-HA injections can alleviate joint pain with minimal systemic side effects, and they have been developed and widely adopted over the past two decades (Sperati et al., 2008) (32). The chronic inflammatory process seen in OA leads to a reduction in the molecular weight (MW) and concentration of HA, impairing the lubricating and protective properties of synovial fluid (Ling et al., 1998, Lo et al., 2003) (22,23). Physically, viscosupplementation with IA-HA injections can directly restore the rheological properties of synovial fluid and reduce joint friction to prevent cartilage degradation. The MW is positively linked to rheological properties and residence time. Accordingly, the effectiveness of different HA products has been found to vary with MW, supported by accumulating evidence (Moreland, 2003, Goldberg et al. 2005) (27,15). Besides improving the viscosity and fluid dynamics of synovial fluid, IA-HA may also exert additional cellular modification effects, including antioxidative, anti-inflammatory, and analgesic properties (Arrich et al., 2005, Bannuru et al., 2006) (3,6). The biological effects of HA also vary significantly with its MW. An in vitro study revealed a correlation between MW and macrophage activation: HA with an MW less than 5 kDa induced macrophage changes that facilitated pro-inflammatory responses, while HA with an MW exceeding 800 kDa promoted changes leading to pro-resolving responses. HA with an MW of 2000 to 4000 kDa was observed to inhibit interleukin-6 (IL-6)-induced matrix metalloproteinase production from human chondrocytes, thus impeding proteoglycan degradation in articular cartilage (Gigis et al., 2016, Chang et al. 2013) (14, 9).

From a clinical perspective, the influence of MW on the effects of HA treatment has been extensively investigated for knee OA. A recent meta-analysis that assessed the efficacy and safety of currently used IA treatments, comparing HAs, platelet-rich plasma, and extended-release or standard release corticosteroids, demonstrated that HA with a higher MW had more comprehensive therapeutic effects on both pain and function, surpassing other IA treatments (Chang et al., 2013, Higgins et al., 2003) (9,16). Another meta-analysis evaluating the efficacy and safety of different HA products for knee OA suggested that HA with an MW exceeding 3000 kDa resulted in a lower rate of discontinuation due to treatment-related adverse effects (0.77%), compared to 2.20% for HA with an MW less than 1500 kDa. Based on knee OA studies, it appears that HAs of different MWs exhibit distinct features, and they should not be grouped into a single category (Kendzerska et al., 2018, Qvistgaard et al., 2006) (18,29).

Viscosupplementation has emerged as an innovative approach for addressing hip osteoarthritis, involving the injection of intraarticular hyaluronic acid (HA), a key structural and biochemical component of cartilage. Exogenous HA is used to replace the diminished intra-articular HA in the joint, aiming to alleviate pain and enhance functional capacity by joint expansion (Atchia et al., 2011, Di Sante et al., 2016) (4,12).

Commercially available HA products vary in their sources, structure, molecular weight, concentration, injection volume, and the number of injections in a treatment course. These HA products are categorised into three groups based on their molecular weights (**Table 1**) (McCabe et al., 2016) (25):

1. Low molecular weight hyaluronic acid (LMWHA) (MW: 0.5–1.5 million Dalton)
2. Medium molecular weight hyaluronic acid (MMWHA) (MW: 1.5–6 million Dalton)
3. High molecular weight hyaluronic acid (HMWHA) (MW: 6–7 million Dalton)

HMWHA is known to enhance fluid retention within the joint and may potentially offer more robust anti-inflammatory effects compared to other HA preparations. Numerous animal studies have recognised HMWHA as a chondroprotective agent with superior lubrication. Clinical trials have examined the effectiveness of HA products with different molecular weights on various joints, including the knee, hip, temporomandibular, and shoulder joint (McAlindon et al., 2017, Brandt et al., 2000, Lindqvist et al., 2002, Dahl et al. 1985) (24,8,21,11).

While literature reviews have summarised the effectiveness of HMWHA in managing knee and shoulder joint OA, there is a notable absence of systematic reviews addressing the outcomes of HMWHA administration in hip osteoarthritis (Arden et al., 2014, Altman et al.

Table 1. Hyaluronic acid classification based on molecular weight (McCabe et al., 2016) (25)

Classification	Grouping Standard (kDa)	Bank of HA	Molecular Weight (kDa)	Crosslinking
LMW HA	< 1,200	Hyalgan	500–730	
		Adant	600–1,200	
MMW HA	1,200–3,600	Ostenil	1,200–1,400	
		Hyalubrix	1,500–3,200	
		Hyalubrix 60	1,300–3,600	
		Synocrom	Averaging 1,600	
HMW HA	3,600–10,000	Hylan G-F 20	Averaging 6,000–7,000	v
UHMW HA	> 10,000	Durolane	Averaging > 10,000	v
		Fermathron S	Not quantifiable	v

HA = hyaluronic acid; LMW = low-molecular-weight; MMW = moderate-molecular-weight; HMW = high-molecular-weight; UHMW = ultra-high-molecular-weight.

Level 1 Study Proves Efficacy of ACP in Early Stage Osteoarthritis of the Knee

Randomized, Double-Blind, Placebo-Controlled Clinical Trial

FDA-Sanctioned, Randomized Control Trial[1]

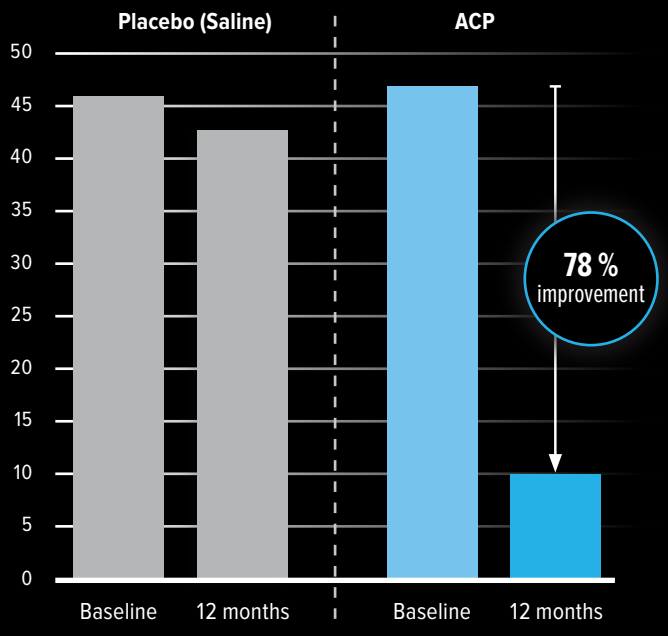
- ACP is safe and provides quantifiable benefits for pain relief and functional improvement with regard to knee OA
- ACP improved WOMAC scores by 78 % versus only 7 % for the placebo control group after one year
- No adverse events for ACP treatment were reported

Double Syringe (ACP) System

- Closed system
- Safe and rapid preparation
- Ability to mix with autograft and allograft products

Overall WOMAC OA Index Score

Baseline versus 12 months



For more information about ACP for osteoarthritis and other sports related injury treatments, please visit:
arthrex.com/orthobiologics/autologous-conditioned-plasma

Reference

1. Smith PA. Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis: An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial. Am J Sports Med. 2016 Apr;44(4):884-91.

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2004, Bagga et al., 2006) (2,1,5). This article's primary aim is to evaluate the clinical outcomes of intra-articular injection with high molecular weight hyaluronic acid in the management of hip osteoarthritis and provide healthcare practitioners with valuable insights into the use of HMWHA as a treatment option for this condition.

MATERIAL AND METHODS

Literature Search and Search Strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocols (Moher et al., 2010) (26). Three electronic databases were adopted to comprehensively screen relevant articles from inception to November 2023, including PubMed/Medline, Google Scholar, and Cochrane library. The following key terms with Boolean operators were used to search articles: high molecular weight hyaluronic acid, HMWHA, outcomes of, and hip osteoarthritis in different combinations for randomised control trials in English on human patients. Boolean operators were utilised in the database searches: ("high molecular weight hyaluronic acid" AND "hip osteoarthritis"). References of the included trials were also checked for eligible studies (PROSPERO International Prospective Register of Systematic Reviews) (28)

Study Selection

For the searching procedure, duplicates in the identified articles were removed. Then, titles and abstracts of the remaining articles were screened for potential studies. Finally, full texts of the potential studies were further examined. The searching procedure was performed independently by 2 reviewers. Any discrepancy was resolved after discussion by the 2 reviewers until a consensus was reached. We also manually searched the reference lists of related reviews and the included articles to include additional relevant studies.

Eligibility Criteria: Inclusion and Exclusion Criteria

The authors arrived at specific inclusion and exclusion criteria for the review through discussion. Searches on all databases were restricted to the English language, but date restrictions were not applied. All randomised trials investigating the effects of high molecular weight hyaluronic acid (HMWHA) on hip osteoarthritis outcomes were considered for inclusion. The selected studies underwent a thorough examination to identify any subgroups within the trials that received HMWHA and exhibited one or more of the specified outcomes. The trial participants had to be diagnosed with hip osteoarthritis confirmed by clinical or radiographical assessment, and they did not have any other types of arthritis such as septic, autoimmune, crystal-induced, hyper-coagulopathy, or vasculitis. Additionally, participants needed to have a pre-intervention Visual Analogue Scale (VAS) score of 5 or higher and/or a Lequesne index of 7 or higher, with a minimum follow-up duration of 3 months.

The intervention of interest was the intra-articular administration of high molecular weight hyaluronic acid for hip osteoarthritis, and trials involving adjuvant surgical or intra-articular pharmacological treatments that could potentially affect the overall results (e.g., corticosteroids, Platelet-rich plasma (PRP) injections, hormonal therapy, low molecular weight hyaluronic acid, or medium molecular weight hyaluronic acid) were excluded. Trials with inadequate methodologies, as well as those categorised as letters, short communications, commentaries, editorials, case reports, conference papers, proceedings, and personal communications, were not considered.

Trials were also excluded if they involved the concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, or any other pain-relief medications alongside HMWHA.

Type of Outcome

For evaluating the therapeutic effect on hip OA, several scales or indices were commonly used, including VAS, Lequesne index, Western Ontario, and McMaster Universities Osteoarthritis Index (WOMAC) score, and Harris hip score. After collecting data from potential studies, we decided to adopt VAS and Lequesne index due to well-documented records for most included studies.

VAS is a tool for the measurement of pain level, which contains a line with a fixed length of 10 cm or 100 mm. The left end anchored with 0 cm represents "no pain," and the right end anchored with 10 cm for "the worst pain." It is a continuous scale, and any point on the line between the ends can be selected. To standardise VAS among included studies, we used the unit of cm. We retrieved VAS data at the last follow-up time after initial injection, and we adopted the VAS while walking or in activity.

Lequesne index consists of 3 components, including evaluating discomforts, maximal walking distance and ability for daily activity. Scoring of each part ranges from 0 to 8, and the maximum total score is 24. 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 (reference). Data of Lequesne index were retrieved at follow-up time after the initial injection.

The complications of the procedure noted numerically were injection site infections, systemic complications, post-operative pain, avascular necrosis, effusion, local skin reaction, femoral head collapse, and septic arthritis.

Data Extraction

A data extraction Microsoft Excel spreadsheet was completed by two authors. and any disagreements were

resolved by collaboration with the senior author. The main characteristics of included studies were extracted, including the first author's name, publication year, study design, study location of publication, treatment implementation (type of HA used, and the number of injections), last follow-up, demographics of enrolled patients (sample size, male-to-female ratio, mean age, BMI, and laterality), VAS score pre-treatment, VAS score post-treatment, Lequesne index pre-treatment, Lequesne index post-treatment and the number of adverse effects.

Risk of Bias Assessment

The Cochrane RoB2 tool was used to undertake a risk of bias assessment in the RCTs using the templates provided by the Cochrane Group. Two researchers completed the template assessing the risk of bias over the five domains: D1, Risk of bias arising from the randomisation process; D2, Risk of bias due to deviations from the intended interventions; D3, Missing outcome data; D4, Risk of bias in measurement of the outcome; and D5, Risk of bias in the selection of the reported result. For the different domains, a score of low, moderate, or high risk of bias was given. Following this, an overall score was applied to each article included in this study. The overall risk of bias was judged by each individual researcher and any discrepancies were resolved by discussion with the senior author. Data were extracted into Microsoft Excel and a summary diagram and risk of bias in individual studies were compiled (Sterne et al., 2019) (34).

Quality Assessment

Two authors scored the researches independently with the quality assessment checklist for methodological quality by the "Oxford Quality Scoring System" for randomised trials. For the Oxford quality scoring system, a score of 5 or 4 suggests a good quality trial; 3 or

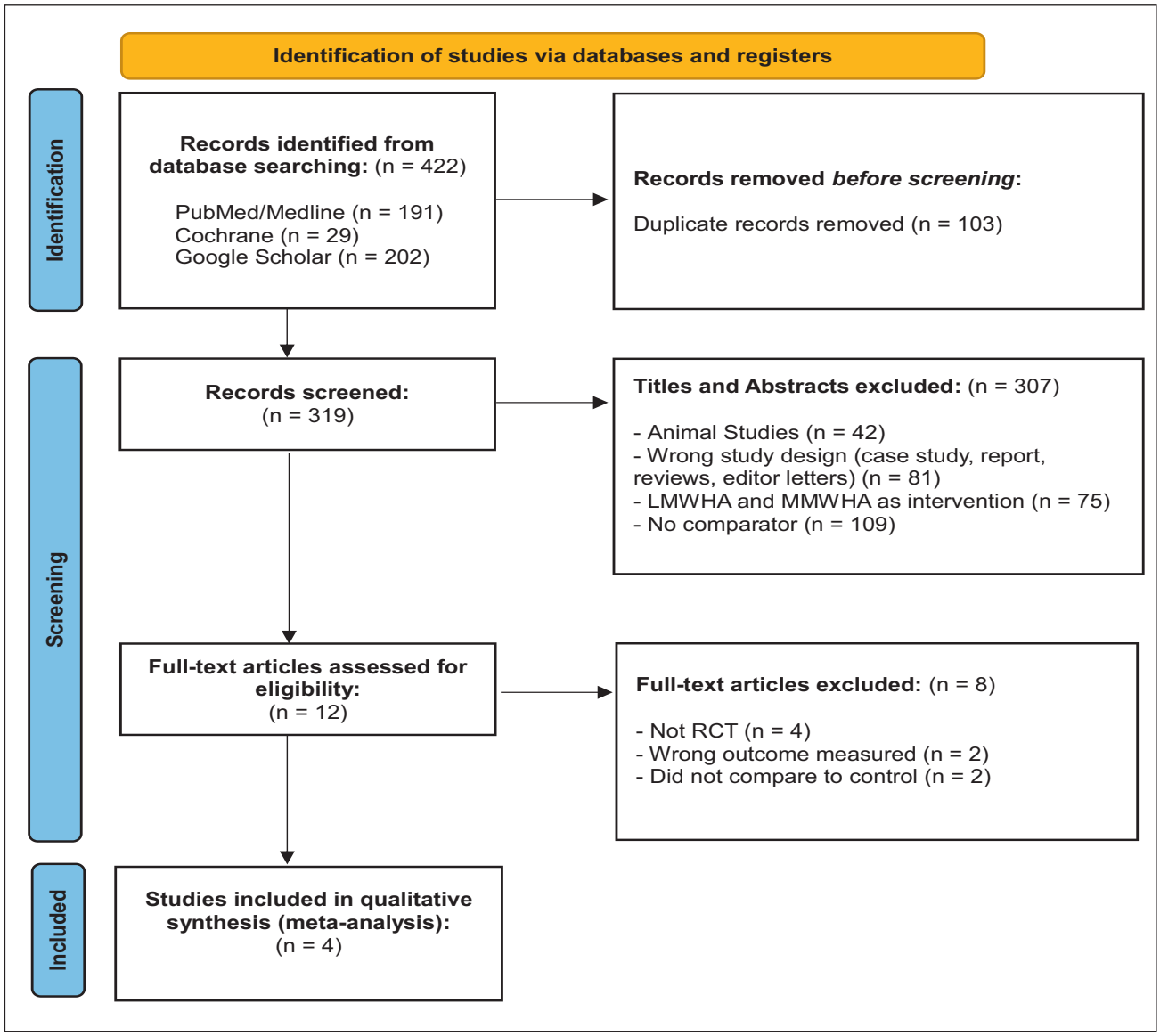

Fig. 1. PRISMA chart showing the selection of included studies.

2 suggests a fair quality trial while 1 or 0 signifies a poor-quality study.

Data Synthesis and Statistical Analysis

All statistical analyses were conducted by Review Manager (RevMan 5.3, Cochrane Informatics & Technology, London, UK). Two authors synthesised the results by random effects model (I^2 more than 50%) or fixed model (I^2 less than 50%), and the results were presented in the form of a forest plot. The authors used Mean ± 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 standardised mean difference (SMD) and risk ratio (RR) for continuous and dichotomous variables, respectively regarding the outcomes by a random effect, generic inverse variance method of Der Simonian and Laird. A meta-analysis was conducted in RevMan 5.3 (Cochrane Informatics & Technology, London, UK), using the dichotomous data function employing a random effects model.

The inclusion of SMD was considered due to the expected high dropouts in longer follow-up trials. 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%. 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. The statistical significance of each variable was examined using the intercept coefficient (IE) and slope coefficient (SE) with their respective p-value.

RESULTS

Study Selection

Initially, 422 relevant articles were identified from the three electronic databases. Following the removal of duplicates, 319 studies were extracted and imported into the Covidence database for screening. At this stage, 307 studies were excluded based on the inclusion and exclusion criteria, resulting in 12 for full text assessment. A further 8 studies were then excluded following full-text analysis and 4 randomised control trials met our inclusion criteria and were included for this meta-analysis. The flow diagram of the selecting process is shown in PRISMA flowchart is provided in Figure 1.

Study Characteristics

The studies included in this systematic review were published between 2005 and January 2018 and were conducted in four countries: USA, Turkey, Italy, and France. All four studies were of an RCT design, with a total of 374 patients randomised to either the HMWHA group or control group (Spitzer et al., 2010, Tikiz et al., 2005, Clementi et al., 2018, Richette et al., 2009) (33,37,10,30). There was minimal variation in patient population characteristics, such as age, gender, and body mass index. Two of the studies gave patients one HMWHA IA injection, one study gave two HMWHA IA injections and one study gave three HMWHA IA injections. A median follow-up time of 6.25 (3–12) months was calculated from the included studies. All the studies HMWHA was the intervention, and the control (Placebo) was denoted as normal saline. All four RCT reported on our primary outcome measure of VAS or Lequesne pre and post treatment. Three of the four trials measured subjective pain using the VAS score and Two of the four trials measured functional disability using the Lequesne index. All four studies reported our secondary outcome measure of complications noted post-treatment. The main characteristics of the included studies are presented in Table 2.

Results of Meta-Analysis – Clinical Outcomes

After an initial review of 442 articles, four studies comprising 185 and 189 patients in HMWHA, and control groups were included summarised 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 randomised controlled trials published from 2005 to 2018. Two studies were of good quality, while two studies were of fair quality based on the Oxford Quality Scoring System. A median follow-up of 6.25 (3–12) months was calculated from the included studies.

VAS

Three of the four trials measured subjective pain using the VAS score on a scale of 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) (Fig. 2). Therefore, it cannot be concluded with any reasonable certainty that this result is not due to chance.

Lequesne Index

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 nonsignificant (I^2 = 0%, p = 0.945) (Fig. 3). Therefore, it cannot be concluded with any reasonable certainty that this result is not due to chance.

Adverse effects

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 4). Therefore, it cannot

Table 2. Main characteristics of the included studies

Study / Reference	Year of study	Country	Design	Quality	Number of patients	Number of HMWHA Injections	Last follow- up (months)	Age	Gender M : F	Body Mass Index (BMI)	Laterality R : L
Spitzer AI, *et al.* [33]	2010	USA	RCT	Fair	102/94	2	6.5	59±12	48:52	29.3±5.5	88/12
Tikiz C, *et al.*[37]	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.*[10]	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.*[30]	2009	France	RCT	Good	42/43	1	3	60.8±10.2	36:64	26.7±4.2	100/0

Table 2. Main characteristics of the included studies (continued)

Study / Reference	Intervention	VAS score pretreatment	VAS score posttreatment	Change in VAS score	Lequesne index pretreatment	Lequesne index posttreatment	Change in Lequesne index	Adverse effects
Spitzer AI, et al.[33]	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. [37]	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. [10]	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.[30]	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

be concluded with any reasonable certainty that this result is not due to chance.

Risk of Bias in Studies

All four studies were assessed across five domains, using the RoB-2 tool, to evaluate the potential for risk of bias in methodology and outcomes. Individual study scores are shown in Figure 5 and Figure 6.

DISCUSSION

As the incidence of hip osteoarthritis (OA) continues to increase, there is a pressing need to establish effective conservative treatment approaches. While the utilisation of intra-articular hyaluronic acid (IA-HA) for hip OA is on the rise, questions persist regarding the effectiveness of HA with high molecular weights.

Viscosupplementation as therapy for knee OA has been the focus of numerous controlled trials and the subject of meta-analyses. In a recent review, (Bellamy et al., 2006) (7) concluded that viscosupplementation is effective for knee OA and has beneficial effects on pain and function. However, this efficacy is controversial, and some authors do not recommend the use of IA injections of HA for the treatment of knee OA. Data on the efficacy of viscosupplementation for hip OA is scarce, and there is even less evidence supporting the use of IA injections of HA for the treatment of hip OA (Keizer et al., 2018) (17). Results of several open-label trials have suggested that HA treatment could improve pain and function, although no definitive conclusions can be drawn from these studies due to their lack of a placebo group (Wooley et al., 2012, Leighton et al., 2018) (20, 38).

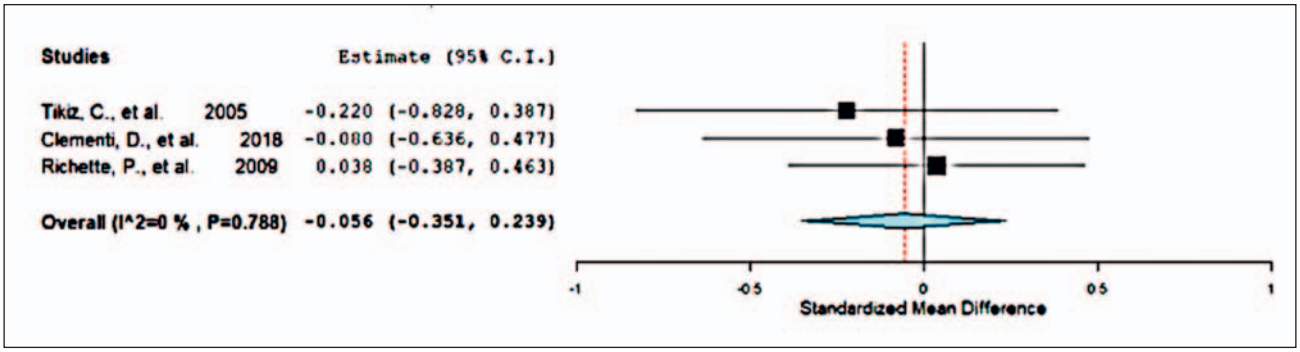

Fig. 2. Forest plot of meta-analysis of comparison for the standardised mean difference (SMD) between post-intervention and pre-intervention Visual Analogue Score (VAS). Black square boxes representing effect sizes and blue diamond shape represents overall treatment SMD.

This meta-analysis included four RCTs aimed to investigate the effectiveness of intra-articular HMWHA for hip OA treatment and make any definitive conclusions about improvement scores of pain reduction, functional disability and adverse events comparing baseline and control groups. The findings of our studies suggest an improvement in clinical outcome scores from baseline. However, the standardised mean difference (SMD) for the Visual Analogue Scale (VAS) and the Lequesne index was not statistically significant (SMD -0.056; 95% CI; -0.351, 0.239; p = 0.709) and (SMD -0.114; 95% CI; -0.524, 0.296; p = 0.585). We also indicate that there are no high risks of inducing adverse events by intra-articular HMWHA for hip OA treatment. Analysis for complications demonstrated an overall relative risk ratio (RR) of Risk ratio (0.879;

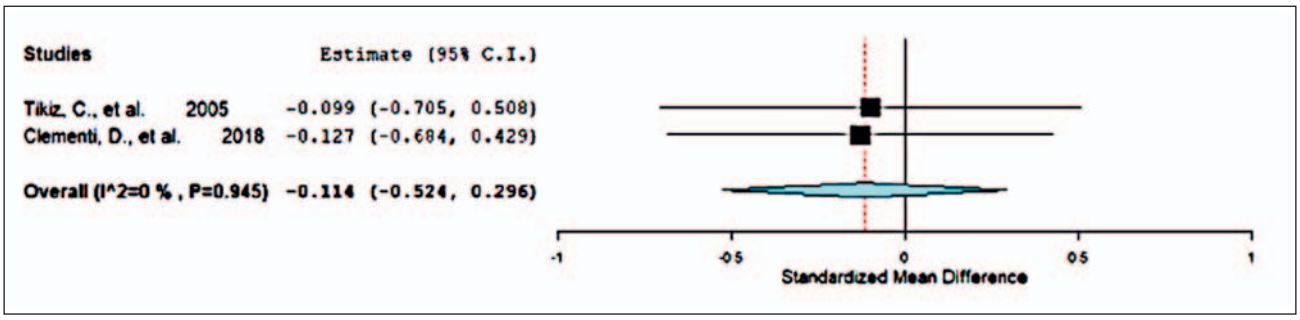

Fig. 3. Forest plot of meta-analysis of comparison for the standardised mean difference (SMD) between post-intervention and pre-intervention Lequesne index for severity. Black square boxes representing effect sizes and blue diamond shape represents overall treatment SMD.

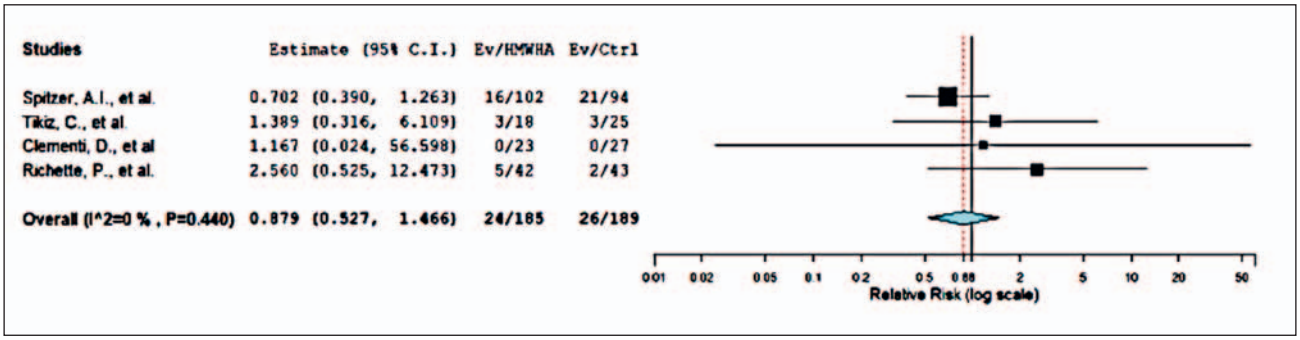

Fig. 4. Forest plot of meta-analysis of comparison for the risk ratio (RR) for post-therapeutic complications. Black square boxes representing effect sizes and blue diamond shape represents overall treatment RR.

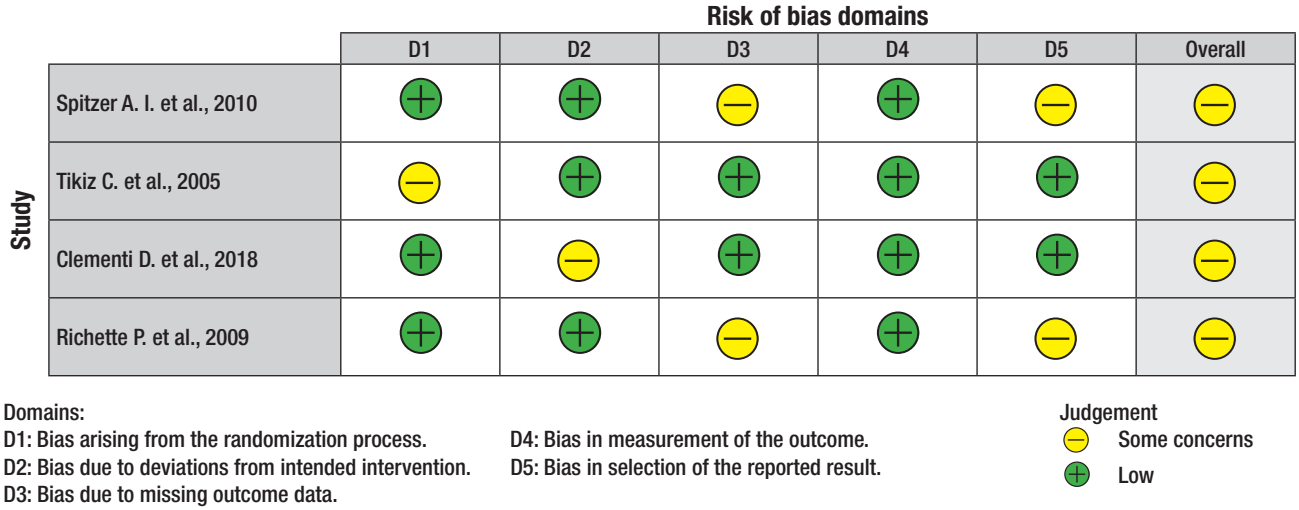

Fig. 5. Risk of bias assessment summary for each included study according to the Cochrane RoB-2 Traffic Light Plot tool. Green – Low Risk of Bias, Amber – Some concern of Bias, Red – High Risk of Bias.

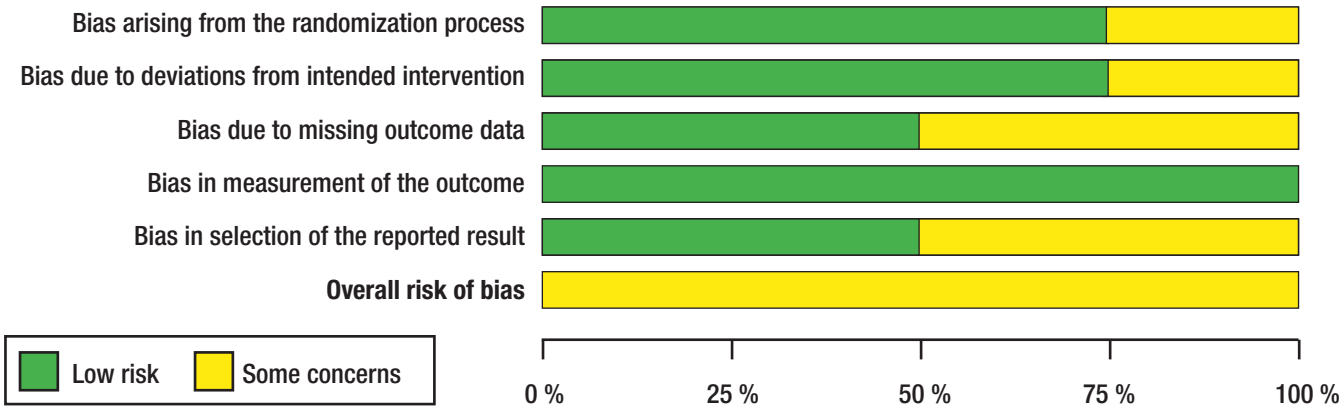

Fig. 6. Risk of bias assessment summary for each included study according to the Cochrane RoB-2 Summary Plot tool. Green – Low Risk of Bias, Amber – Some concern of Bias, Red – High Risk of Bias.

95% CI; 0.527, 1.466; p = 0.622), and not statistically significant.

The methodological quality assessment identified some limitations to the current evidence bases. The four RCTs satisfied the defined eligibility criteria, however, the size of the comparative groups was small. One study reported the specific methods of randomisation without referring to random sequence generation and allocation concealment, arguably allowing for selection bias. Two studies possess a lack of information regarding blinding of assessors, which brings concern of expectation bias and the potential for type II statistical errors in measurements of these clinical outcomes. One study reported a follow-up rate of only 25%, thus compromising its validity due to incomplete outcome data. No studies noted were considered to have performed an intent-to treat analysis. Heterogeneity may have been caused as a result of the high risk of all types of biases caused by variations in patient characteristics, different therapeutic strategies, and different strategies for measuring outcomes. Although we performed subgroup analyses stratified by follow-up time, it is unlikely that this resolved the heterogeneity. None of the trials reported independent funding from any governmental or not-for-profit organisation.

Hip Pain

We assessed pain relief by measuring the alleviation of pain through changes in the VAS score, utilising the Standardised Mean Difference (SMD) as the metric. A negative SMD value signified an improvement in pain relief, whereas a positive value indicated a decline in pain relief. Our study revealed a slight improvement in pain, as illustrated in the forest plot in Figure-1 (SMD -0.056; 95% CI; -0.351, 0.239; p=0.709).

Hip Dysfunction

Our review findings indicated inconclusive results in functional outcomes following intra-articular HMWHA injection in comparison to the control group (SMD -0.114; 95% CI; -0.524, 0.296; p=0.585).

Adverse Events

The most frequently encountered complications following intra-articular HMWHA injections encompassed site infections, post-treatment discomfort, minor effusion, and localised skin reactions. It is noteworthy that none of the trials reported systemic complications, septic arthritis, femoral head collapse, or substantial effusion. Our forest plot analysis indicated that the risk of postoperative complications (Risk ratio 0.879; 95% CI; 0.527, 1.466; p=0.622) was not statistically significant.

Limitations

The limitation in the number of published trials available on databases was a significant hindrance in formulating this systematic review; with many of the included studies being of low-quality evidence not in accordance with the Consolidated Standards of Reporting of Trials (CONSORT) (The CONSORT Statement, 2022) (35). This meant that certain studies had inadequate reporting of numerical data and therefore were not included in the subsequent meta-analysis despite the best efforts in contacting the relevant authors. In addition, articles not written in the English language were excluded from this review which meant some studies may have been missed out during our literature search.

There were further limitations in the designs of the randomised trials. Some of the studies were open trials which meant that there was no concealment for both the researchers or patients in the randomisation process and for which patients received the intervention or control. Subsequently, this is likely to impact the effect the of response to treatment due to performance bias. Future studies should incorporate blinding of both patients and assessors.

CONCLUSIONS

The outcomes derived from this meta-analysis suggest that the utilisation of intra-articular HMWHA in the context of hip osteoarthritis confers a notable reduction in pain and a corresponding enhancement in func-

tional recovery, relative to the baseline pre-injection condition. Nevertheless, the analysis does not reveal any statistically significant benefit of the effects of HWHA over saline. Furthermore, the available evidence from the literature demonstrates that the administration of intra-articular HMWHA in hip osteoarthritis is not associated with an elevated risk of adverse events. Due to the high heterogeneity, low level of evidence and medium to high risk of bias in the current available literature, the strength of our conclusions is limited.

Consequently, for forthcoming research studies, it is imperative to undertake robust, large-scale randomised controlled trials (RCTs) characterised by sound methodological design. These trials should specifically address the assessment of both the potential risks and benefits inherent to HMWHA therapy for hip osteoarthritis, particularly in comparison to various other intra-articular agents. Future RCTs should establish more rigorous methodological criteria and reporting, following CONSORT guidelines. Baseline values such as the mean and standard deviation must be reported to ensure that future meta-analysis can provide more precise effect sizes.

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