■ SYSTEMATIC REVIEW

Clinical efficacy of multiple intra-articular injection for hip osteoarthritis

A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Aims

Intra-articular (IA) injection may be used when treating hip osteoarthritis (OA). Common injections include steroids, hyaluronic acid (HA), local anaesthetic, and platelet-rich plasma (PRP). Network meta-analysis allows for comparisons between two or more treatment groups and uses direct and indirect comparisons between interventions. This network meta-analysis aims to compare the efficacy of various IA injections used in the management of hip OA with a follow-up of up to six months.

Methods

This systematic review and network meta-analysis used a Bayesian random-effects model to evaluate the direct and indirect comparisons among all treatment options. PubMed, Web of Science, Clinicaltrial.gov, EMBASE, MEDLINE, and the Cochrane Library were searched from inception to February 2023. Randomized controlled trials (RCTs) which evaluate the efficacy of HA, PRP, local anaesthetic, steroid, steroid+anaesthetic, HA+PRP, and physiological saline injection as a placebo, for patients with hip OA were included.

Results

In this meta-analysis of 16 RCTs with a total of 1,735 participants, steroid injection was found to be significantly more effective than placebo injection on reported pain at three months, but no significant difference was observed at six months. Furthermore, steroid injection was considerably more effective than placebo injection for functional outcomes at three months, while the combination of HA+PRP injection was substantially more effective at six months.

Conclusion

Evidence suggests that steroid injection is more effective than saline injection for the treatment of hip joint pain, and restoration of functional outcomes.

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Introduction

Hip osteoarthritis (OA) is a degenerative disease associated with deteriorationof the hyaline cartilage, leading to pain, stiffness, and reduced mobility.[1,2] It is common in older adults, but can also affect younger individuals who have experienced hip injuries or abnormal loading across the joint.[3] Hip OA has no cure, but medications, physiotherapy, exercise, and weight loss can help manage symptoms. If severe arthroplasty may be necessary.[4] Targeted anti-inflammatory treatment may be useful in managing the condition.[5,6] In early stages, intra-articular (IA) injection has been offered with many clinical randomized controlled trials (RCTs) conducted. Commonly injected drugs include hyaluronic acid (HA), local anaesthetic, platelet-rich plasma (PRP), and steroids, which can relieve hip pain symptoms and have some anti-inflammatory effect.[2]

There is some controversy whether HA is beneficial in hip OA.[7-9] IA injection of local anaesthetics, such as mepivacaine, has potential therapeutic properties compared with HA.[7] Its primary function is to dilute and reduce inflammatory factors in the joint cavity and inhibit neuropeptides from reducing neurally mediated inflammatory responses.[7] Local anaesthetics appear to have an extended analgesic effect on hip OA.[7] Steroid

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injections have been shown to be helpful in hip OA, but there is debate whether the combination with local anaesthetic is preferable, and the extent to which benefit of IA can been prolonged and adverse reactions reduced.[10–13] PRP has an advantage of being generated from the patient's own cells.[14] However, it is controversial whether it has superior therapeutic value over other IA injections.[15,16] Some studies have proposed that treating hip OA with combinations of IA injections offers better results. Nouri et al[17] found that composite injection of PRP+HA showed improvement in pain and function sustained for more than six months. However, Dallari et al[15] reported that PRP+HA did not significantly improve pain symptoms at 12 months' follow-up. Two recent meta-analyses have analyzed the benefits and drawbacks of IA injection therapy with substances such as PRP, HA, and steroids for hip OA. However, the studies included in those meta-analyses did not include local anaesthetics or mixed-drug injections.[18,19]

This systematic review and network meta-analysis investigates the clinical outcomes of seven treatment options for hip OA, including HA, steroid, PRP, local anaesthetic, steroid+local anaesthetic, and PRP+HA. Building upon previous research, this study aimed to optimize treatment selection for hip OA patients.

Methods

Protocol and registration. This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations.[20] Before its commencement, the meta-analysis was also registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY; registration number: INPLASY202320092).

Search strategy. We searched PubMed, Web of Science, Clinicaltrial.gov, EMBASE, MEDLINE, and the Cochrane Library databases from inception to February 2023. The search strategy terms were: (("Osteoarthritis, Hip") OR (Hip Osteoarthritis) OR (Osteoarthritis Of Hip) OR (Osteoarthritis Of Hips) OR Coxarthrosis OR Coxarthroses OR (Osteoarthritis of the Hip)) AND (("Injections, Intra-Articular") OR (Injection, Intra-Articular) OR (Intra-Articular Injection) OR (Intraarticular Injection) OR (Injection, Intraarticular) OR (Intraarticular Injections) OR (Intra-Articular Injections) OR (Injections, Intraarticular) OR (Intra Articular Injection) OR (Articular Injection, Intra) OR (Articular Injections, Intra) OR (Injection, Intra Articular) OR (Injections, Intra Articular) OR (Intra Articular Injections)) AND ("Randomized Controlled Trial" [Publication Type]). The flowchart is shown in Figure 1.

Inclusion criteria. All the investigations included in this study were RCTs involving adult patients with hip OA. The studies mentioned a comparison of at least two of the seven intervention measures (HA, PRP, steroid, local anaesthesia, HA+PRP, steroid+local anaesthesia, and placebo). Clinical outcomes of retrospective studies included one of the following results: visual analogue scale (VAS) scores for pain at three and six months, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[21] scores at three and six months

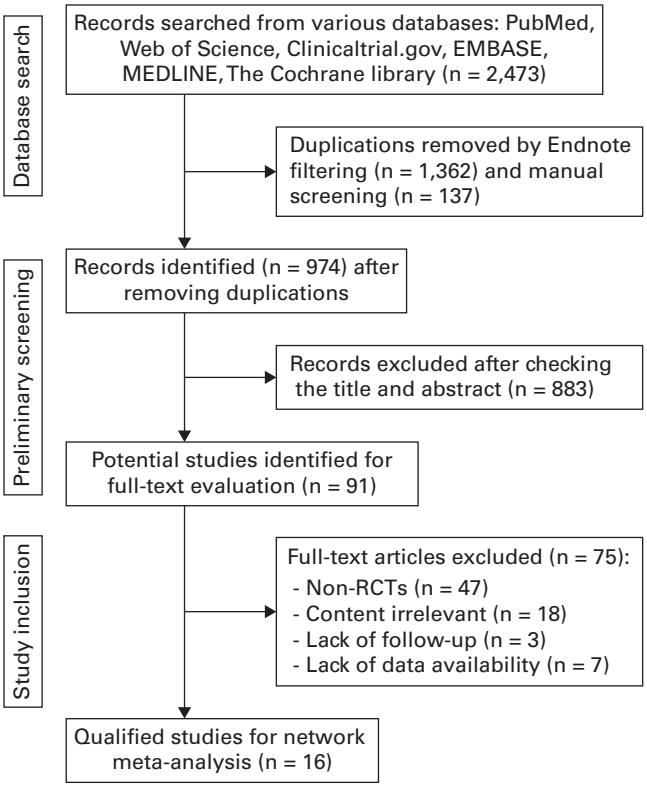

Fig. 1

The flow diagram of study screening process. RCT, randomized controlled trial.

(with a maximum score of 100, lower scores indicating less severe OA). The original studies had to include sufficient data to summarize the final results.

Ethical approval. Ethical approval was not required for this literature review. All the included studies had themselves been subject to ethical approval.

Quality assessment and publication bias. According to the Cochrane Collaboration guidelines,[22] two evaluators (TL, ML) assessed the quality of the included studies. The policies cover several items, including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. Each item is categorized as low risk of bias, unclear risk of bias, or high risk of bias. In addition, the consistency of different evaluation results was explored using the kappa statistic.

Study selection and data extraction. Two evaluators (TL, ML) used two standardized data collection forms to extract data independently for inclusion in the study. Any disagreements were resolved through discussion; otherwise, a third reviewer (LH) evaluated the data and provided a majority decision. We also contacted the authors of relevant studies for additional information when needed. Important information extracted from the original literature included the first author's name, year of publication, country, study design, intervention, sample size, sex, mean age, and clinical outcomes (VAS and WOMAC scores at three and six months). If there were no scores at three

Table I. Baseline characteristics of the randomized controlled trials included.

Studies	Year	Country	Intervention (n)	Sample size	Female, %	Mean age, yrs
Migliore et al[7]	2009	Italy	HA (17), anaesthetic (17)	34	47.6	67.5
Spitzer et al[11]	2010	USA	Steroid (156), HA (156)	312	51.5	59
Kullenberg et al[24]	2004	Sweden	Steroid (40), anaesthetic (40)	80	N/A	N/A
Dallari et al[15]	2016	Italy	PRP (36), HA (44), PRP/HA (31)	111	47.7	N/A
Qvistgaard et al[12]	2006	Denmark	Steroid (26), HA (29), placebo (33)	88	64.5	65.9
Nouri et al[17]	2022	Iran	PRP (34), HA (33), PRP/HA (33)	100	72.8	59.8
Atchia et al[25]	2011	UK	Placebo (19), steroid (19), HA (19)	76	55.1	69
Kraeutler et al[26]	2021	USA	PRP (19), HA (14)	33	41.9	53.4
Villanova-López et al[27]	2020	Spain	PRP (36), HA (38)	74	55.4	61.2
Battaglia et al[16]	2013	Italy	PRP (48), HA (48)	96	37	53.5
Richette et al[8]	2009	France	Placebo (43), HA (42)	85	58.4	60.1
Lambert et al[13]	2007	Canada	Placebo (21), Steroid (31)	52	59.9	62.1
Brander et al[9]	2019	Canada	Placebo (175), HA (182)	357	59.1	60.3
Di Sante et al[28]	2016	Italy	PRP (21), HA (22)	43	53.4	71.5
Kubo et al[29]	2022	Japan	Placebo (44), HA (46)	90	88.9	59.9
Paskins et al[10]	2022	UK	Anaesthetic (62), steroid+anaesthetic (61)	178	57	62.8

HA, hyaluronic acid; N/A, not available; OA, osteoarthritis; PRP, platelet-rich plasma; RCT, randomized controlled trial.

Table II. Surface under the cumulative ranking curve values of eight treatments under four endpoint outcomes.

Treatment	SUCRA value			
	VAS (3 mths)	VAS (6 mths)	WOMAC (3 mths)	WOMAC (6 mths)
Anaesthetic	35.7	37.1	N/A	N/A
HA	94.5	55.4	74.6	46.8
PRP	37.1	37.4	54	42.1
PRP+HA	49.3	61.9	85.3	76.1
Placebo	51.1	46.6	31.2	31.7
Steroid	0.1	54.2	4.8	53.2
Steroid+anaesthetic	82.2	57.5	N/A	N/A

HA, hyaluronic acid; N/A, not available; PRP, platelet-rich plasma; SUCRA, surface under the cumulative ranking curve; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

or six months, then score evaluated close to three or six months were identified as being at three or six months.

Network meta-analysis. To evaluate the direct and indirect evidence of all hip joint injection treatments for hip OA strategies, a network meta-analysis was conducted to compare the two outcomes of all treatments: pain and function scores, respectively, at three and six months. The results were evaluated using the weighted mean difference (WMD) and its 95% confidence interval (CI). Inconsistency analysis was conducted to assess the consistency of the results. A league table was used to describe the effects of pairwise comparisons. Ranking diagrams and bar graphs were generated for each treatment outcome. The surface under the cumulative ranking curve (SUCRA) values were reported. ADDIS software v. 1.16.8; (Erasmus, Netherlands) and STATA softwarev. 15 (StataCorp, USA) were used for the meta-analysis. A p-value < 0.05 in the Bayesian network meta-analysis was considered statistically significant.

Assessment of heterogeneity, inconsistency, and transitivity. We compared the distribution of baseline participant characteristics across different studies to evaluate the potential effect-modifying factors between various trials. The control group was given saline, which did not affect the outcome. Therefore, the results were transferable. We evaluated the evidence of network consistency in two ways: we used the node-splitting approach to identify inconsistencies in the model, using its Bayesian p-value ($p > 0.05$ for consistency). We used the loop-specific method to study the consistency within each closed triangle or quadratic loop in each network as the difference between the direct and indirect estimates (inconsistency factors) of a specific treatment comparison in the loop. We identified inconsistent loops with 95% CIs, not including zero. We also classified the studied interventions based on the ranking probability of each outcome.

Dealing with missing data. If the mean or standard deviation (SD) was missing, the mean score for each timepoint was calculated by subtracting the mean difference from the baseline score. According to the Cochrane Handbook, the SD is calculated according to the method introduced in previous studies.[23]

Results

The literature search process is shown in Figure 1. We identified 1,735 relevant studies from the databases mentioned above. With selective screening 16 RCTs were included, involving 1,809 patients (HA, 690; PRP, 194; HA+PRP, 64; steroid, 272; anaesthetic, 119; steroid+anaesthetic, 61; placebo, 335) were included in the meta-analysis.

A list of included studies and patient baseline data is provided in Tables I and II. There were four three-group evaluations compared steroid, HA, and placebo; PRP, HA, PRP+HA; HA, steroid, and placebo. A total of 12 studies with two arms compared placebo, steroid; placebo, HA; HA, anaesthetic; HA, RPR; steroid, anaesthetic; steroid, HA; and anaesthetic, steroid+anaesthetic. Four studies were from Italy, two from the UK, one from Sweden, two from Canada, one from Denmark, two from the US, one from France, one from Iran, one from Japan, and one from Spain. The control group included in the study was given normal saline. Network plots between all direct and indirect comparisons are shown in Figure 2 and Supplementary Figure a.

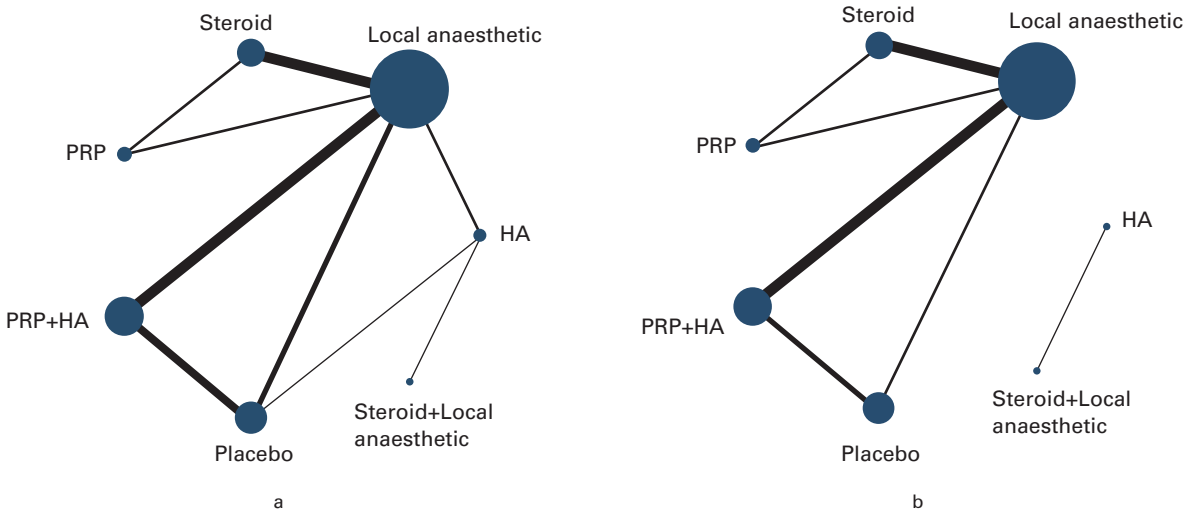

Fig. 2

Network diagram of a) visual analogue scale score and b) Western Ontario and McMaster Universities Osteoarthritis Index score at three months. HA, hyaluronic acid; PRP, platelet-rich plasma.

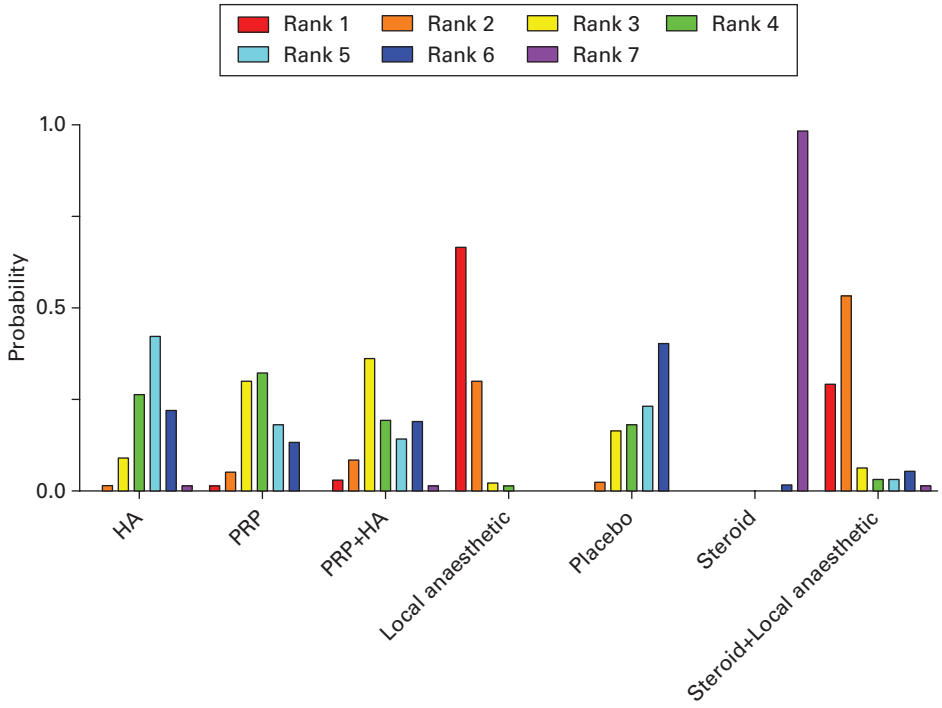

Fig. 3

Rank probability of visual analogue scale score at three months, with Rank 1 as the worst. HA, hyaluronic acid; PRP, platelet-rich plasma.

Quality assessment. Two of the 16 studies were at high risk of bias, and the remaining 14 were at low risk. The overall K-value of the included RCTs' bias risk was 0.872, and the consistency between the two reviewers was excellent. A summary and plot of the bias risk are shown in Supplementary Figures b and c.

VAS. The network meta-analysis showed that steroids reduced VAS scores at three months (WMD -1.64 (95% CI -2.79 to -0.62)) compared with the placebo group. However, at six months, no reduced effection were observed in any of the treatments compared with the control placebo in the Bayesian network meta-analysis (Supplementary Table i).

WOMAC. For the network meta-analysis of WOMAC scores at three months, compared with placebo, the HA reduced the WOMAC score (WMD -1.85 (95% CI -7.78 to 3.77)), PRP

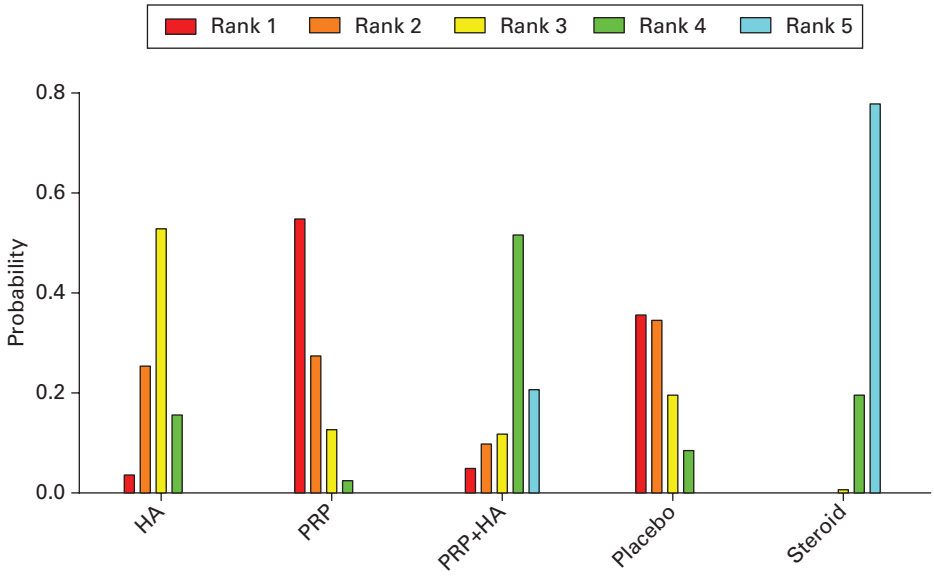

Fig. 4

Rank probability of Western Ontario and McMaster Universities Osteoarthritis Index score at three months. HA, hyaluronic acid; PRP, platelet-rich plasma.

Study	Mean difference (95% CI)	p-value
HA, Local anaesthetic		
Direct effect	0.23 (-1.86 to 2.40)	0.03
Indirect effect	3.51 (1.65 to 5.12)	0.03
Overall	2.18 (0.37 to 3.68)	0.03
HA, Placebo		
Direct effect	-0.14 (-0.96 to 0.68)	0.16
Indirect effect	1.56 (-0.81 to 3.70)	0.16
Overall	-0.05 (-0.91 to 0.81)	0.16
HA, Steroid		
Direct effect	-1.03 (-1.81 to -0.34)	0.00
Indirect effect	-3.64 (-5.06 to -2.28)	0.00
Overall	-1.67 (-2.77 to -0.76)	0.00
Local anaesthetic, Steroid		
Direct effect	-4.79 (-6.31 to -3.37)	0.03
Indirect effect	-1.51 (-3.85 to -0.80)	0.03
Overall	-3.88 (-5.28 to -2.24)	0.03
Placebo, Steroid		
Direct effect	-1.66 (-3.00 to -0.44)	0.90
Indirect effect	-1.79 (-3.75 to -0.06)	0.90
Overall	-1.63 (-2.78 to -0.64)	0.90

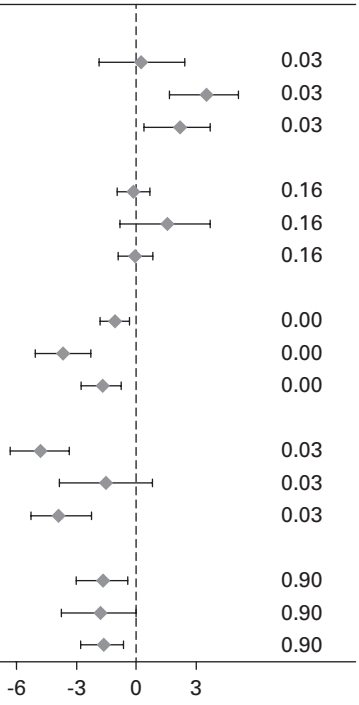

Fig. 5

Forest plot of the mean difference of visual analogue scale score at three months. CI, confidence interval; HA, hyaluronic acid.

improved it (WMD 1.04 (95% CI -7.58 to 9.76)), PRP+HA reduced it (WMD -5.21 (95% CI -16.60 to 5.92)), and steroid reduced it (WMD -9.70 (95% CI -16.87 to -3.23)), respectively. At six months, compared with placebo, the HA reduced the WOMAC score (WMD -0.31 (95% CI -27.56 to 26.86)), PRP improved it (WMD 4.92 (95% CI -24.72 to 35.02)), PRP+HA reduced it (WMD -3.04 (95% CI -35.52 to 30.68)), and steroid improved it (WMD 1.35 (95% CI -36.20 to 39.36)), respectively.

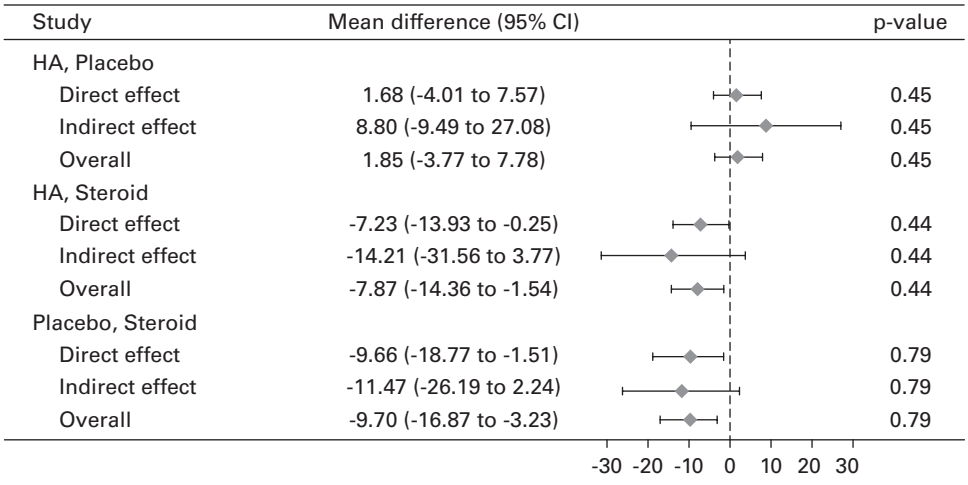

Fig. 6

Forest plot of the mean difference of Western Ontario and McMaster Universities Osteoarthritis Index score at three months. CI, confidence interval; HA, hyaluronic acid.

Cumulative probability of improved VAS. As shown in Figure 3, Supplementary Figure d, and Table II, the SUCRA values of the seven interventions showed that steroids had the lowest SUCRA value (0.1), indicating that steroids had the lowest pain intensity in the VAS score at three months. The results showed that steroids were the most effective drugs for reducing VAS scores at three months. For VAS scores at six months, there was little difference in SUCRA values among the seven interventions, meaning there was no difference in VAS scores among the seven interventions at six months.

Cumulative probability of WOMAC improvement. As shown in Figure 4, Supplementary Figure e, and Table II, the SUCRA values of the five interventions showed that steroids had the lowest SUCRA value (4.8) in the WOMAC score at three months. In addition, HA (74.6), PRP+HA (85.3), PRP (54), and placebo (31.2) were higher than steroids. This means that steroids had the lowest pain intensity in WOMAC scores at three months. Therefore, the steroid was the most effective drug in lowering WOMAC scores at three months.

For the WOMAC score at six months, the SUCRA value showed that HA (46.8), PRP (42.1), PRP+HA (76.1), and steroid (53.2) were all higher than placebo (31.7), which means that HA, PRP, PRP+HA, and steroid were no better at reducing WOMAC at six months than placebo, and placebo is the most effective drug in lowering WOMAC score at six months.

Comparisons between direct and indirect evidence. The node-splitting method was used to determine the consistency of the results. In this network meta-analysis, only three-month VAS and WOMAC scores could be included in node-splitting. The results are shown in Figure 5 and Figure 6. The 95% CIs of WOMAC direct and indirect evidence were generally consistent, with no significant statistical difference ($p > 0.05$), which means that there was no inconsistency between the included studies. However, the inconsistent factor values of VAS scores at three months for HA and anaesthetic, HA and steroid, and anaesthetic and steroid showed p-values < 0.05, which indicates that VAS scores at three months may not be consistent.

Discussion

Hip OA is a common degenerative joint disorder that compromises hip functionality and overall quality of life.[30,31] As the condition advances, hip arthroplasty often emerges as the sole effective intervention for alleviating persistent pain and restoring function.[32]

Prior to arthroplasty, in the earlier stages of OA a layered treatment strategy aimed at slowing the progression of the disease can be adopted.[33] IA injections offer a role in providing pain relief and functional improvement as part of the staged approach. A network meta-analysis by Zhao et al[19] compared the effectiveness of injecting PRP, HA, steroids, and a combination of PRP+HA. Their findings indicated that steroid injections were superior in alleviating pain within the first three months, whereas PRP injections were more effective over six months. However, the study's methodology, which used local anaesthetic and saline injection as control groups, may compromise the accuracy of their conclusions, especially as the impact on joint functionality was not assessed. Another network meta-analysis by Gazendam et al[18] found that saline injections were as effective as PRP, HA, and steroid injections in pain relief and hip function restoration. However, neither of the preceding RCTs used combined drug injections. Paskins et al[10] had highlighted the significant pain relief and functional restoration achieved through ultrasound-guided intra-articular corticosteroid and local anaesthetic injections compared to patients did not manage that drugs.

We have extended previous RCTs by examining the clinical efficacy of HA, PRP, PRP+HA, steroids, local anaesthetics, steroid+local anaesthetic combinations, and placebos on hip OA, through a networked meta-analysis. The main findings revealed that steroid injections offered the most significant pain relief and functional improvement within the initial three months compared to the other treatments. Interestingly, placebo

injections appeared to provide better pain relief over six months, while PRP+HA injections provided functional improvement. Despite some inconsistencies in the analysis, especially within the first three months, our findings underscore the potential of steroid injections for short-term benefits, and highlight the intriguing efficacy of placebo and PRP+HA injections over longer periods. The mechanisms behind the effectiveness of these treatments requires further clarification.

As the predominant symptom of OA, pain results in psychological distress, which leads to the avoidance of activities and subsequent impaired joint function.[34] The early pain of OA occurs with frequent use of the joint, abating after rest, but ultimately occurring more frequently and worsening as the disease progresses. Weak evidence has been published demonstrating an association between pain severity and structural joint abnormalities.[35] Pain can be stimulated by various physical and chemical signals,[36] with inflammatory mediators implicated in the occurrence of pain in OA.[37] It has been reported that steroids injected into the joint reduce the inflammatory reaction by blocking the release of arachidonic acid, which is essential in the formation of inflammatory endoperoxides and thromboxanes.[38] The short-term pain relief of steroid injection may be attributable to its anti-inflammatory effect. However, over the six-month follow-up, the pain relief decreased, and PRP+HA showed the best efficacy in function restoration.

This study comprehensively compared the clinical efficacy of different IA injections for treating hip OA by extrapolating from 16 RCTs (1,735 patients), by network meta-analysis. Nevertheless, some limitations should be considered when generalizing our conclusions. First, several types of HA used in these included studies, with different molecular weights. Similarly, the dosage and brand of the other injected drugs varied. In addition, the follow-up data at three and six months were used in this study, but if these points were not included in the contributing studies, then follow-up data within three months or over six months were identified as three or six months results, respectively. Overall, more clinical studies with longer follow-up should be carried out to further detect the clinical efficacy of these treatments.

In this study, we compared the clinical efficacy of eight treatments (HA, PRP, PRP+HA, local anaesthetic, steroid, placebo, and steroid+local anaesthetic) for hip OA. The network meta-analysis indicated that the steroid injection showed best pain relief and function restoration within three months, while the placebo injection showed best pain relief, and PRP/HA injection showed best function restoration when the follow-up time reached six months. In general, weak evidence has been provided that steroid injection outperformed the other treatment choices in terms of pain relief and function, while this clinical efficacy decreased with the extension of follow-up.

Take home message

- Patients receiving intra-articular injection of steroids showed better pain relief and function restoration of the hip joint within three months, compared with the other six treatments.
- Patients receiving intra-articular injection of placebo seemed to have better pain relief than the other drugs over six months.
- The platelet-rich plasma and hyaluronic acid group showed better function performance compared with the other six treatments over six months.

Supplementary material

Network diagram of visual analogue scale (VAS) score and Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index score at six months; the quality evaluation of included studies; rank probability of VAS score at six months; rank probability of part of WOMAC score at six months; weighted mean difference and 95% confidence intervals for VAS scores at three and six months, and WOMAC scores at three and six months.

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