REVIEW ARTICLE

Efficacy and Safety of Hyaluronic Acid Intra-articular Injection after Arthroscopic Knee Surgery: A Systematic Review and Meta-analysis

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Objective: Hyaluronic acid (HA) intra-articular injection after arthroscopic knee surgery has been widely applied but its efficacy and safety remain controversial. The aim of this systematic review is to analyze the efficacy and safety of HA intra-articular injection after arthroscopic knee surgery, and to compare the efficacy of HA with different molecular weights.

Methods: We conducted a systematic literature search in PubMed, Embase, Google scholar and the Cochrane library from inception to 16 September 2022 for English-written articles, in order to identify randomized controlled trials that evaluated the clinical efficacy and/or safety of HA intra-articular injection after arthroscopic knee surgery. Then we meta-analyzed the outcomes of patients given intra-articular HA injections postoperatively and control patients. We also evaluated the influence of HA with different molecular weights. In every calculation, sensitive analysis was performed. The visual analogue scale (VAS) for pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and adverse events were selected as the primary outcome measurements, while Lysholm, International Knee Documentation Committee (IKDC) and Tegner score were selected as the secondary outcome measurements. Publication bias of every outcome was evaluated using egger test.

Results: Fifteen studies involving 951 knees were included and 12 of them were used to performed the meta-analysis. The results showed no significant difference between the HA group and control group according to VAS, whether assessed at less ($P = 0.90$) or more than 6 months ($P = 0.55$). Besides, there were no statistical differences between the HA group and control group according to subgroup analysis (*P*s = 0.77, 0.91 and 0.81 in anterior cruciate ligament reconstruction, meniscectomy and overall groups, respectively). Compared to control group, the overall effect of WOMAC score showed no significant differences ($P = 0.25$), nor did in two subgroups ($P = 0.37$ and $P = 0.22$). Outcomes measured by Lysholm ($P = 0.13$), IKDC ($P = 0.86$) and Tegner ($P = 0.42$) scores showed no significant differences, either. The analysis of the risk of adverse events indicated no increase in HA groups ($P = 0.06$). We found no significant differences between high- and low-molecular-weight HA at 6 ($P = 0.96$) or 12 months ($P = 0.93$) postoperatively. Two studies failed to pass the sensitive analysis and the reasons were discussed detailly and acceptable publication bias was observed.

Conclusions: Although HA injection after arthroscopic knee surgery is safe, the available evidence does not support its efficacy in pain relief and functional recovery. Therefore, the application of HA injection after arthroscopic knee surgery is not recommended.

Key words: Arthroscopy; Hyaluronic acid; Meta-analysis; Viscosupplementation

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Introduction

Viscosupplementation is an intra-articular injection technique applied globally in orthopedic practice to manage osteoarthritis (OA) in joints.[1,2] Hyaluronic acid (HA) exerts a mechanical effect by providing lubrication of the joint, protecting against loads and impacts, and restoring the rheological properties of the synovial fluid.[3] Furthermore, it also interacts with mediators of inflammation, inhibits nociceptors of pain, stimulates chondrocyte growth, facilitates synthesis of extracellular matrix proteins, and reduces apoptosis in osteoarthritic cartilage.[4–7] These benefits have made HA a commonly adopted bioactive molecule for intra-articular therapy.[8–10]

Intra-articular HA injections are typically administrated simultaneously in combination with other treatments, including nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors, analgesics, physical therapy, intra-articular steroids, and surgery.[11] Despite the large amount of data investigating the role of HA intra-articular injection after arthroscopic knee surgery, different studies have displayed conflicting results. Although the effect of HA has been investigated in a single previous meta-analysis,[12] its searching strategy has omitted some randomized controlled trial (RCT)[13–16] and its analysis of the included studies has mistaken the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score as WOMAC total score, which may lead to an unreliable conclusion. In addition, the authors did not evaluate the safety of this method. Therefore, we decided to perform the present meta-analysis to evaluate the efficacy and safety of HA intra-articular injection after arthroscopic knee surgery, and to compare the efficacy of HA with different molecular weights.

Methods

This work was reported in line with preferred reporting items for systematic reviews and meta-analyses (PRISMA) and assessing the methodological quality of systematic reviews (AMSTAR) guidelines.[17] The review protocol was registered at Research Registry (UIN: Review Registry 1248).

Search Strategy

We systematically searched the literature in PubMed, Embase, Google scholar and the Cochrane database from inception to 16 Sep 2022, in order to identify relevant studies published in English. Electronic searches using medical subject headings (MeSH) terms and/or corresponding keywords included, arthroscopy, knee arthroscopy, viscosupplementation, hyaluronic acid, hyaluronan and hyaluronate. The search strategy in PubMed, for instance, was ("Arthroscopy") AND ("Viscosupplementation" [MeSH] OR "Hyaluronic Acid" [MeSH] OR Hyaluronan OR Hyaluronate). Besides, we reviewed the references of the qualified articles in sequence to identify potentially eligible literature.

Selection Criteria

Two reviewers independently selected the initial articles. After removing duplicate records, articles were screened by titles and abstracts. In case of uncertainty, we read the full-text article carefully to identify whether it was eligible. Discrepancies between two reviewers were resolved by discussion or consulting a senior doctor.

For a purpose of obtaining enhanced data reliability, only studies with high level of evidence were included. The detailed inclusion criteria were: (i) RCTs; (ii) the study populations were patients who had symptomatic knee problems and were diagnosed as knee OA, meniscus injury or anterior cruciate ligament (ACL) injury; (iii) arthroscopy surgery were performed in both groups, including debridement, meniscectomy or anterior cruciate ligament reconstruction (ACLR); and (iv) the intervention was intra-articular injection of HA immediately following surgery while the controls were saline, analgesic or nothing. Studies were excluded if: (i) other knee diseases were combined, such as rheumatoid arthritis, even though arthroscopy was performed; and (ii) duplicate data was published in another article with more complete data.

Data Extraction

Data were extracted independently by two reviewers using a standardized electronic form. A third reviewer confirmed the data and disagreements were resolved by discussion. The following data were extracted: first author, year of publication, country of origin, number of participants, age, sex, body

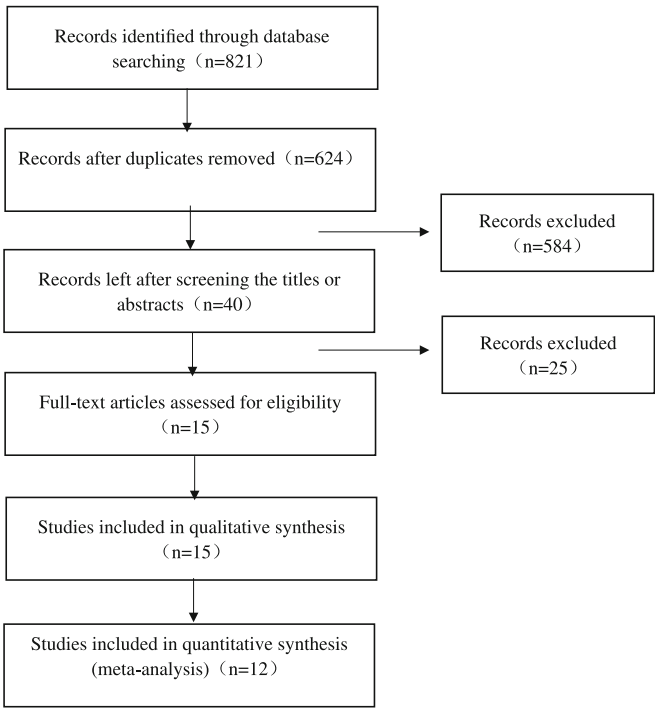

Fig. 1 Flowchart of study selection

TABLE 1 The characteristics of included studies

First author, year	No. of Patients		Age		Sex (Male: Female)		BMI (kg/m^2)		Total follow-ups (months)	Diagnosis	Operation	Primary outcomes
	HA	Control	HA	Control	HA	Control	HA	Control				
Dahlberg, 1994	28	24	46 ± 8	44 ± 9					12	ACL injury	ACL reconstruction	VAS for pain, Lysholm score, range of motion
Mathies, 2006	20	20	47.4 ± 8.9	46.4 ± 8.6	16:4	16:4			1	Meniscal pathology	Meniscectomy	VAS for pain, Joint swelling, Lysholm Score, MODEMS
Hempfling, 2007	40	40	60.9 ± 8.1		39: 41				24	Knee pain	Debridement	CGI, restricted ability to walk, pain on walking, night pain
Atay, 2008	30	15	53.2 ± 5.6	53.1 ± 6.9	19:26		30.1 ± 5.3	27.5 ± 5.3	12	OA	Debridement	WOMAC total
Westrich, 2009	23	20	59.3, range 42–81				29.0 range 19.8–38.2		6	OA, meniscal tears	Debridement, meniscectomy	VAS, timed 50-foot walk test
Baker, 2012	49	49	46.5	44.1	34:15	36:13			1.5	Meniscal tears	Debridement, meniscectomy	VAS for pain, WOMAC total, Lysholm Score
Chau, 2012	16	16			13:3	15:1			3	ACL injury	ACL reconstruction	KOOS, knee swelling, range of movement, knee circumference, analgesic use
De Paula, 2014	49	49	36 ± 11.3	33 ± 12.1	34:15	31:18			2	Meniscal tears	Meniscectomy	VAS for pain, Lysholm Score
Anand, 2016	24	24	43.5 ± 12.2	43.3 ± 11.7	14:10	16:8			1.5	OA, meniscal tears	Meniscectomy	VAS for pain, WOMAC total
Di Martino, 2016	30	30			25:5	23:7	24.3 ± 2.9	24.0 ± 2.5	12	ACL injury	ACL reconstruction	VAS for pain, SF-36, IKDC, Tegner score
Filardo, 2016	45	45	39.0 ± 10.4	40.8 ± 9.6	37:8	33:12	26.2 ± 3.7	24.1 ± 3.2	6	Meniscal tears	Meniscectomy	IKDC, VAS for pain, KOOS, Tegner score, VAS for general health status
Vasavilbaso, 2017	30	10	66.3 ± 8.7	67.5 ± 7.8	17:13	5:5	27.7 ± 3.0	28.1 ± 3.2	18	Meniscal tears	Meniscectomy	WOMAC total, MCII
Lin, 2020	54	54	50.1 ± 2.2	50.3 ± 2.4	25:29	26:28			6	Meniscal tears	Meniscectomy	VAS for pain, SF-36, Lysholm Score
Basar, 2021			49.3 ± 38	48.4 ± 5.3	11:18	15:26	28.3 ± 2.8	27.5 ± 2.7	6	Meniscal tears	Meniscectomy	VAS for pain, WOMAC total, range of motion
Yoon, 2022	23	24	47.7 ± 13.2	46.7 ± 14.3	15:8	17:7	27.0 ± 3.6	26.2 ± 4.9	3	Meniscal tears	Meniscectomy	IKDC, VAS for pain, Tegner score, WOMAC total

mass index, diagnosis, intervention, and outcome data. Predefined primary outcomes were visual analogue scale (VAS) for pain, WOMAC total score and adverse events. Secondary outcomes were Lyshom, International Knee Documentation Committee (IKDC) and Tegner scores.

Risk of Bias Assessment

Two reviewers independently used the Cochrane risk of bias tool to assess the risk of bias in the RCTs. Each study was reviewed and scored according to the following categories: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Based on these scores, risk of bias was deemed as high, low, or unclear. Discrepancies between the reviewers were resolved by discussion until consensus was reached.

Statistical Analysis

Treatment effect was measured by calculating differences in VAS for pain and WOMAC total score between pre- and post-intervention in the control and treatment groups. Given that some papers did not report standard deviation (SD), we calculated it using sample size and standard error or confidence intervals or interquartile ranges according to the method in the Cochrane handbook.[18] The safety of the treatment was evaluated by the ratio of adverse events between HA and control groups. Higher ratio in HA group indicated unsafety. Risk ratios (RR) with 95% confidence intervals (CIs) were calculated for dichotomous data. The mean differences (MDs) with 95% CIs were calculated for continuous outcomes. Since different studies used different full-mark VAS scoring, we converted all the data onto a full-mark scale of 10 and then calculated the standardized mean differences (SMDs) with 95% CIs. Heterogeneity across studies was tested using the I^2 statistic. I^2 of 25% was defined as low heterogeneity; while 50% and 75%, indicated moderate and high heterogeneity.[19] A fixed-effects model was used if $I^2 < 50\%$; otherwise, a random-effects model was used.

Sensitivity analysis was performed in every analysis, by excluding each study and defining the extent of influence on overall results. Once a study led to an inconsistency result, it was excluded in statistical analysis.

Meta-analyses were performed using RevMan 5.3 software (the Cochrane Collaboration, London, UK), while sensitivity analysis and publication bias were analyzed using Stata15 (Stata Corp, College Station, TX, USA). The 2-tailed $P < 0.05$ was considered significant. Due to a variation in follow-up times and operation types across studies, subgroup analyses were performed. The efficacy of HA with different molecular-weight was also evaluated using WOMAC total score.

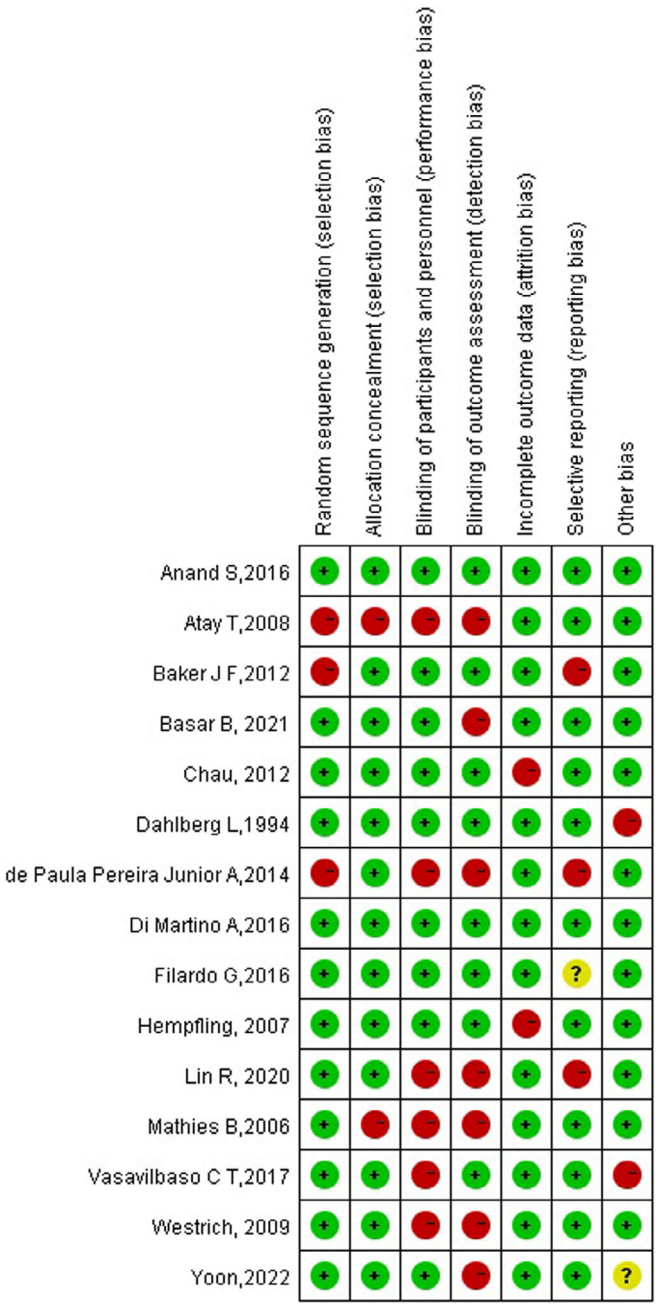

Fig. 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (+ low risk of bias; − high risk of bias; ? unclear risk of bias)

Results

Literature Search

The flowchart of study selection is shown in Fig. 1. In the initial search, we identified 821 relevant records. After removal of duplicate studies, 624 records were left. Scanning of titles and abstracts deemed 40 studies potentially eligible. After reading the full texts, 15 studies met our inclusion

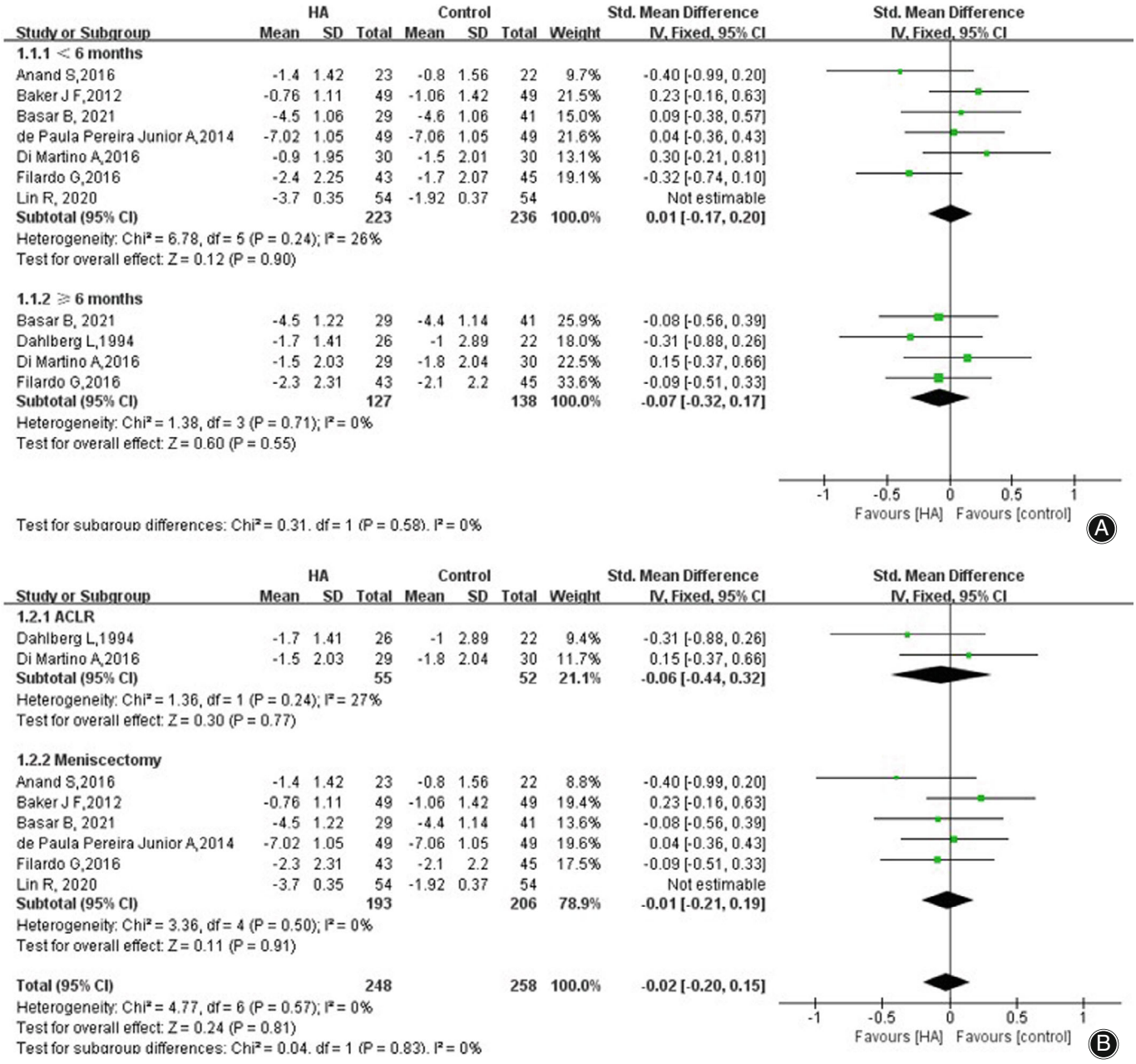

Fig. 3 Subgroup analysis for VAS. (A) VAS grouped by follow-up time. (B) VAS grouped by operations

criteria and 12 of them were used to perform this meta-analysis.[13–16,20–30]

Study Characteristics

Fifteen qualified articles were published from 1994 to 2022 including original studies from Sweden, Switzerland, Turkey, Ireland, Brazil, USA, Italy, Germany, Mexico and China.[13–16,20–30] Sample sizes ranged from 40 to 108 patients involving 951 knees. One study[27] had a follow-up time of 24 months, which was the longest, and four studies[14,22,26,29] had a follow-up time of over 12 months, and the remaining studies[13,15,16,20,21,23–25,28,30] had a follow-up time of 6 months and less. Three studies[14,23,29] enrolled patients with ACL injury, while the others[13,15,16,20–22,24–28,30] involved mainly patients with meniscus tears and/or OA. The study characteristics are shown in Table 1.

Risk of Bias

Risk of bias assessment indicated that three studies[13–15] were low risk, and 12 studies[16,20–30] were high risk (Fig. 2). The

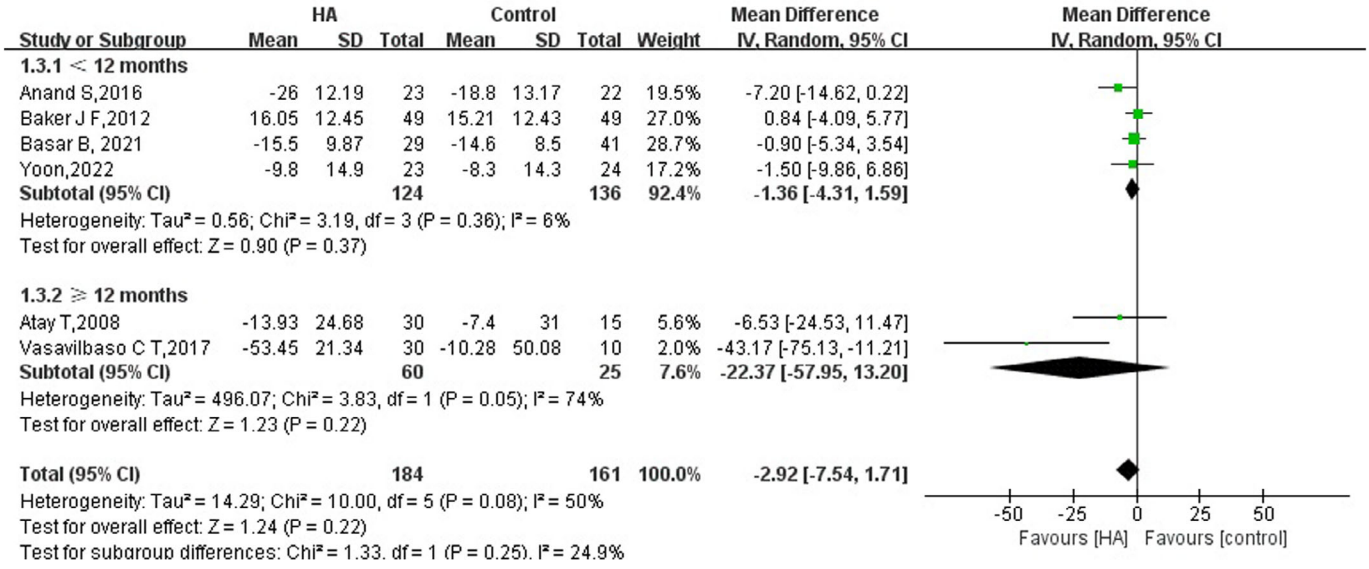

Fig. 4 Forest plot for WOMAC total score

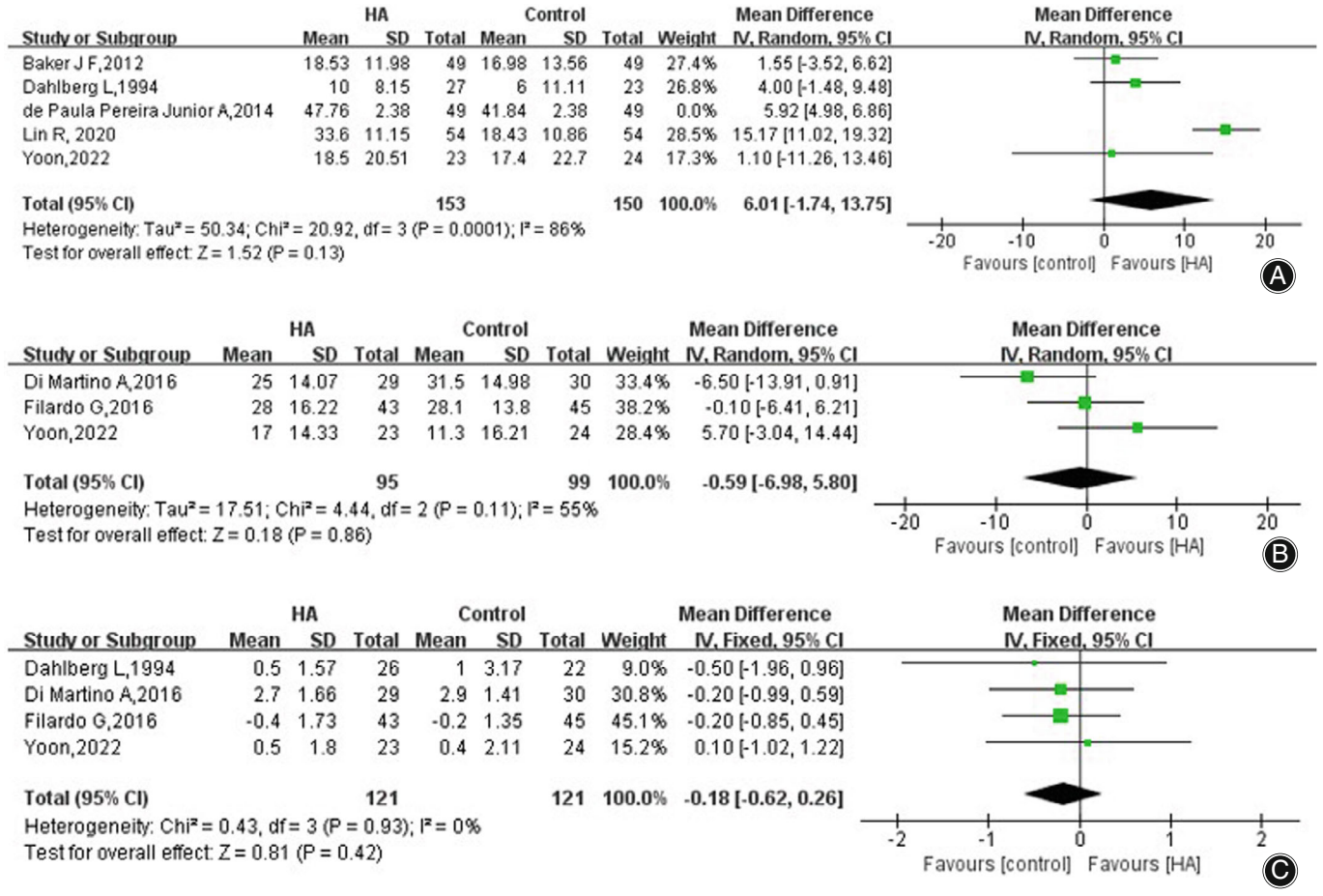

Fig. 5 Forest plot for other functional scales. (A) Lysholm score. (B) IKDC. (C) Tegner

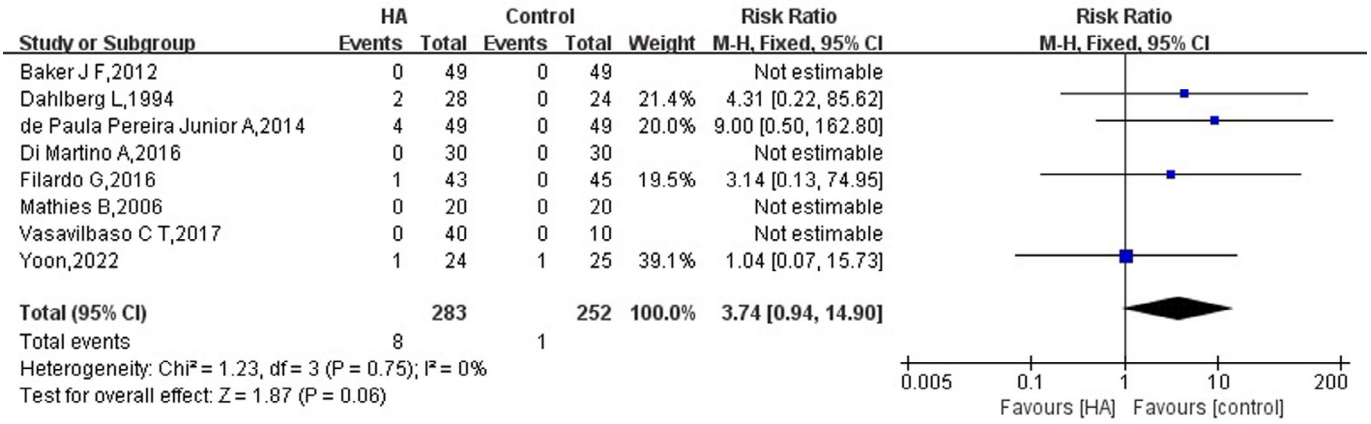

Fig. 6 Forest plot for adverse events

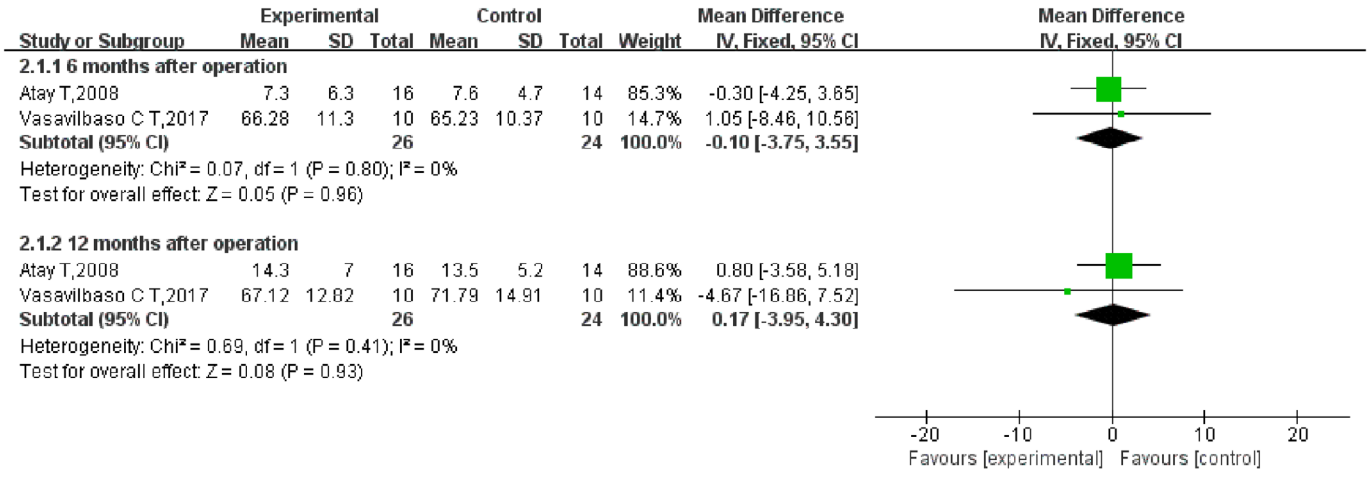

Fig. 7 Comparison of WOMAC total score between HMW and LMW grouped by time

studies were divided among the following risk of bias characteristics: 12 studies carried out adequate randomized sequencing, 13 studies implemented an appropriate allocation concealment, nine studies clearly described blinding of participants, eight studies described blinding of personnel during outcome assessments, and three studies showed risk of selective reporting. And two studies failed to report complete outcome data.

Pain Assessment

Scores on VAS for pain were reported in eight studies.[14–16,20,21,24,28,29] Considering that the follow-up time and the operations varied in different studies, subgroup analysis was performed. The analysis showed no significant difference between the HA and control groups within postoperative 6-month timepoint (SMD 0.01; 95%CI −0.17 to 0.20; $P = 0.90$) and over the postoperative 6-month timepoint (SMD −0.07; 95%CI −0.32 to 0.17; $P = 0.55$). Moderate heterogeneity was found in less than 6 months subgroup ($I^2 = 26\%$), and no heterogeneity was found in the data for over 6 months subgroup($I^2 = 0\%$).

There was no significant difference between the HA and control groups neither in ACL reconstruction (SMD −0.06; 95%CI −0.44 to 0.32; $P = 0.77$) nor in meniscectomy subgroup (SMD 0.01; 95%CI −0.21 to 0.19; $P = 0.91$). Similarly, overall effect failed to show significant difference (SMD −0.02; 95%CI −0.20 to 0.15; $P = 0.81$). The heterogeneity was 27%, 0% and 0% for ACL reconstruction, meniscectomy subgroup and both, respectively. The heterogeneity between subgroups was 0%. The results were shown in Fig. 3.

WOMAC Total Score

Six studies mentioned results on the total WOMAC scale.[15,20,22,24,26,30] Subgroup analysis detected no significant difference between the HA and control groups at the timepoint less than 12-month follow-up (MD −1.36; 95%CI −4.31 to 1.59; $P = 0.37$) and the timepoint longer than 12-month follow-up (MD −22.37; 95%CI −57.95 to 13.20;

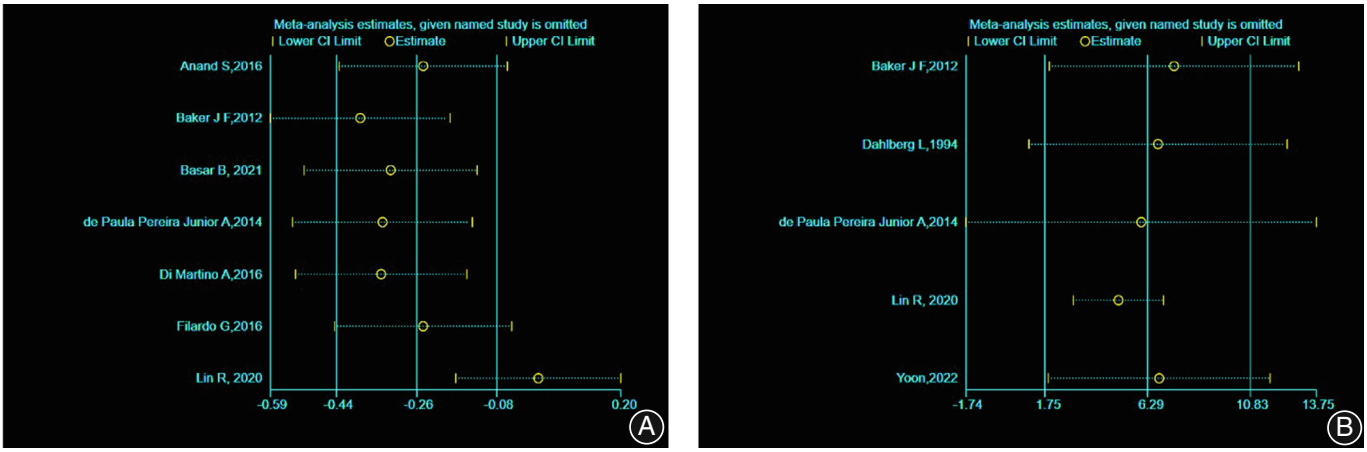

Fig. 8 Sensitivity analysis. (A) VAS less than 6 months subgroup. (B) Lysholm

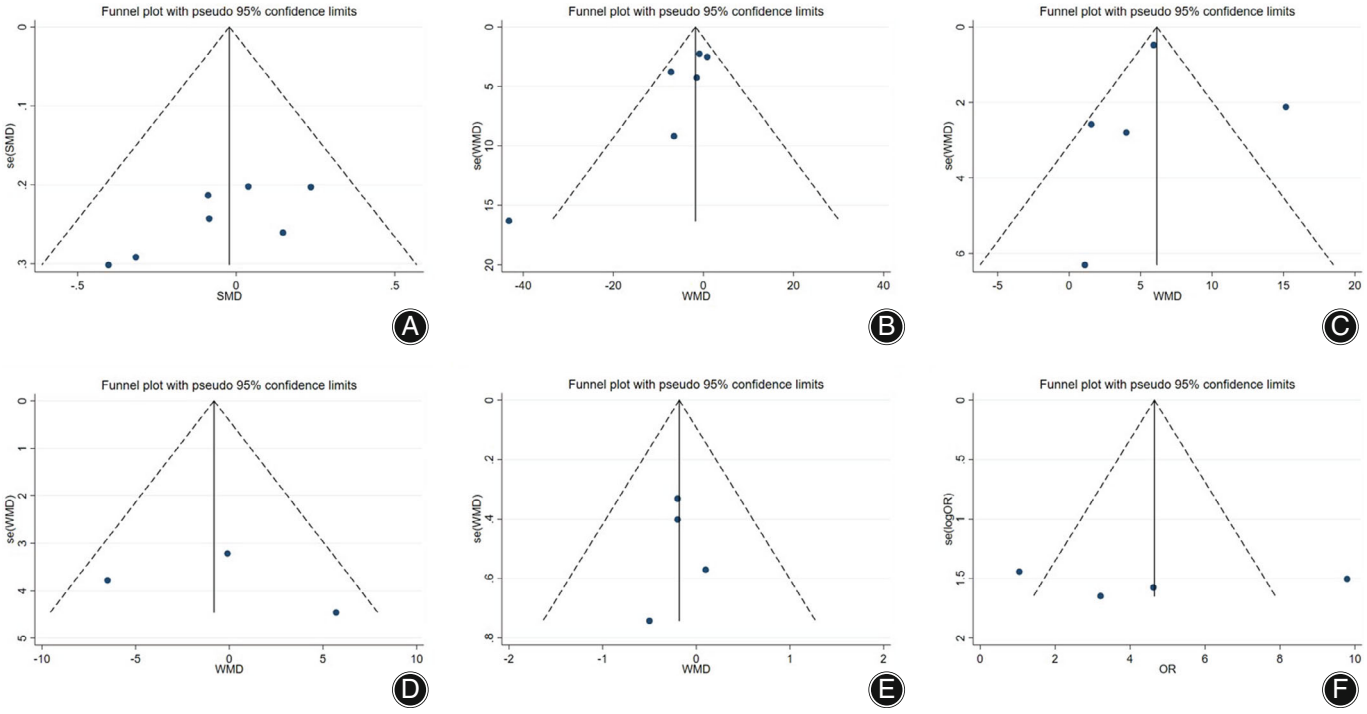

Fig. 9 Funnel plot of analyzed outcomes. (A) VAS; (B) WOMACA; (C) Lysholm; (D). IKDC; (E). Tegner; (F) adverse events

$P = 0.22$). And the overall showed no difference, either (MD −2.92; 95%CI −7.54 to 1.71; $P = 0.25$). Heterogeneities were $I^2 = 6\%$, $I^2 = 74\%$ and $I^2 = 50\%$, respectively. The results were shown in Fig. 4.

Other Functional Scales

Five studies displayed results on Lysholm score,[16,21,24,29,30] while one of them failed to pass the sensitive analysis, and the exhibited results was the corrected data. The pooled results showed a trend favoring the HA group, but did not show any differences (MD 6.01; 95%CI −1.74 to 13.75; $P = 0.13$). The heterogeneity was 86%. The results were shown in Fig. 5A.

Interestingly, the pooled data of IKDC (MD −0.59; 95%CI –6.98 to 5.80; $P = 0.86$) and Tegner (MD −0.18; 95% CI –0.62 to 0.26; $P = 0.42$) both showed a opposite trend from Lysholm score, tend to control group, with even lower statistical heterogeneity ($I^2 = 55\%$ and 0%, respectively),

though significant difference was also not detected. The results were shown in Fig. 5.

Adverse Events

Seven of the included studies did not investigate adverse events.[15,20,21,23,25–27] Meta-analysis of the remaining eight studies concerning odds ratio of adverse events showed no significant difference between HA and control groups ($P = 0.06$). The results were shown in Fig. 6.

High- *vs* Low-molecular-weight HA

Two studies reported the comparation concerning molecular weights of HA in 6 months and 12 months. We found no significant difference in WOMAC total score between patients receiving high- molecular-weight (HMW) or low-molecular-weight (LMW) HA at 6 months ($P = 0.96$) or 12 months post-operation ($P = 0.93$). Neither of the subsets of studies showed heterogeneity (both $I^2 = 0$). The results were shown in Fig. 7.

Sensitivity Analysis

Sensitivity analysis was performed in every data merging, and most of them withstood this test, except for two analyses. In the less than 6 months subgroup of VAS analysis, removal of one study[21] changed the overall effect. And in analysis of the Lysholm scores, removal of one study[16] changed the overall effect, too. And both of their pooled results before sensitivity analysis showed that HA had a significantly better effect than the control group. However, after carefully reviewing the related studies and analyzing the reasons, we believed that the modified results were more reliable. Hence, the results reported above were based on the corrected data synthesis. The results of sensitivity analysis were shown in Fig. 8.

Risk of Publication Bias

A serious risk of publication bias was observed in Lysholm, and a slight risk of publication bias was observed in WOMAC, according to dissymmetry of the funnel plot. The results were shown in Fig. 9.

Discussion

Objectives and Brief Results

HA is a long-chain biopolymer molecular exiting in the joint. It plays a particular role in shock absorption and viscoelastic property.[31] The efficacy of HA in the management of OA has been confirmed by many studies[32,33] but whether it can be used as an adjunctive therapy after arthroscopic knee surgery is still in dispute.[13,15,22,27,34] And high-quality meta-analysis about this issue still lacks. Therefore, the aim of the present study was to evaluate the efficacy and safety of HA intra-articular injection after arthroscopic knee surgery, as well as the performance of HA with different molecular weights.

The present study did not find that HA injection after knee arthroscopic surgery contribute to improvements in pain relief, based on the pooled results in VAS. And the results were consistent with the following subgroup analysis. Data analysis of WOMAC score, IKDC, Tegner and Lysholm scores reached similar results that HA injection was ineffective. And no significant difference was observed between HA with high- and low- molecular weight, based on the assessment of WOMAC. Among these analyses, only a slight publication bias was found.

Pain Management

The current meta-analysis demonstrated that HA injection after arthroscopic knee surgery failed to provide additional pain control with regards to the control group. Furthermore, we performed a subgroup analysis regarding different time points or different operations to explore a specific impact of HA, and reached the same results. It is worth mentioning that the pooled data of VAS short term subgroup showed a superior in HA in the initial analysis. However, in sensitive analysis, Lin *et al.*'s study was found to have too much influence on the results. Lin *et al.*'s study did not carry out a blind method. Patients in the control group were instructed to carry out functional exercises themselves while patients in the treatment group was given intra-articular HA injections weekly additionally. Because they were not blind, investigators and patients in the treatment group were likely to exaggerate the effects. Besides, patients in the experimental group went to hospital and received intervention weekly after operation, which meant they met doctors and had more opportunity to get instructions in their functional exercises.[21] These reasons all led to a bias to HA. In addition, by removal of this study the statistical heterogeneity changed from 96% to 26%. The huge heterogeneity caused by the single study also proved the heterogeneity in methodology. Given these reasons, Lin *et al.*'s study data was excluded in the analysis of VAS. Thus, the results of VAS regarding various time and operation reached consistent results. HA was regarded as an effective treatment on pain relieving for its lubricity and anti-inflammatory. Chau *et al.* conducted a RCT on 36 patients underwent ACLR combined with HA, and found a decreased VAS score after intervention.[23] Nevertheless, Baker *et al.* regarded HA as not more effective in pain management after arthroscopy than traditional methods.[24] The authors believed the good analgesic effect of bupivacaine used in control groups might be the reason why the HA group did not show a bias. In fact, the short-term analgesic effect of intra-articular HA was also proved not to be superior to some other analgesic drugs.[35] Shen *et al.*'s meta-analysis also reached the conclusion that HA injection after arthroscopy did not provide extra analgesia in rest.[12] Our results confirmed his conclusion in pain management, with a larger sample size. In addition, we found the ineffectiveness had no relation to assessing time or operation.

WOMAC Score

For the WOMAC total score, the current meta-analysis showed no significant difference between the HA and control groups at any timepoint. The WOMAC total was a functional scale made up by WOMAC pain and WOMAC function subscales.[36] Shen *et al.*[12] used a similar meta-analysis using WOMAC total score, and their conclusion was that HA was associated with significantly increased physical function, as evidenced by the improved WOMAC scores, which was not proved by us. The differences between the present meta-analysis and the previous one might be caused by differences in inclusion criteria and sample size. We analyzed six studies of 345 knees, rather than their two studies of 96 knees. The limited sample sizes made their results not so reliable. Also, we found that one RCT[34] included in their analysis did not actually report the total WOMAC score as they reported, but rather a subscale score of WOMAC. This error might also influence their results.

Other Functional Scales

Although the results of IKDC and Tegner score reached similar results as the VAS and WOMAC total scores, the initial results of the Lysholm score indicated that the HA injection group had a better outcome than the control group. This result was corrected by excluding de Paula *et al.*'s study, since it did not pass the sensitive analysis. Interestingly, we found that the data in this single study did not seriously influence the overall effect, only the CI. The overly concentrated data in this study made it more weighted in the analysis, thus decreasing the contributions of the other four studies, and led a concentration of CI. In addition, the study failed to perform blind experiments as well, at least in the Lysholm assessment. It was reported that patients in the HA group received injections weekly while patients in control group did not. It could be speculated that patients in both groups knew their allocations as Lysholm is a subjective scale which is answered by patients,[36–39] the assessment was judged not blind, although the authors reported "all evaluations were performed by the same examiner who did not know at which group the patient belonged". The scales mentioned above focused on different fields. Compared to the WOMAC and Tegner scores, the Lysholm score emphasized more on ligaments, and the difference between IKDC and Lysholm was that Lysholm focused more on motion while IKDC underlined symptoms and functions.[36–39] The combined performance of these scales suggested that postoperative use of HA was ineffective.

Safety

As for safety, our results showed HA injection was not related to the increase of adverse events, compared to the control group. In de Paula *et al.*'s study, four patients appeared in severe pain and need intervention more than once.[16] One patient from the HA group in Filardo's study had a marked swelling after the procedure, which required aspiration at 1 and 7 days postoperatively.[9] In Dahlberg's study, one patient acquired candida arthritis and one patient felt intolerable pain.[29] However, the pooled data did not provide evidence that injection of HA after arthroscopic knee surgery was associated with any risk of side effects. HA is a major natural component of cartilage and synovial fluid, which is produced by chondrocytes and synoviocytes.[40] Some previous animal study and clinical studies also proved its safety.[18,41,42] The present study confirmed the conclusion with a higher evidence level.

High- *vs* Low-molecular-weight HA

We also explored the influence of different molecular weight. HA products differed in many characteristics, including origin (animal *vs* biofermentation), molecular weight (high *vs* intermediate *vs*. low), structure (linear, crosslinked, or mixed), volume of injection, and dosage. Some evidence suggested that efficacy and safety of HA depended on its molecular weight.[8,43–45] One meta-analysis[46] concluded that HA with molecular weight of 3000 kDa consistently demonstrated better efficacy and safety than HA with lower molecular weights in patients with knee OA. In contrast to that meta-analysis, we included patients with ACL or meniscus injury besides, and we considered only patients undergoing arthroscopic knee surgery. We found no significant difference in WOMAC total score between patients receiving HA of 500–1200 kDa or HA of 6000–7000 kDa.

Risk of Publication Bias

As for publication bias, the studies were symmetrically distributed in most funnel plots, except for funnel plots of Lysholm and WOMAC, which indicated publication bias in these two results and decreased the reliability of them. However, considering the consistent of the results in pain control, function recovery and scale assessment, the comprehensive results should be considered reliable.

Comparison with Previous Studies

A previous RCT[47] investigated the benefits of HA in 120 patients undergoing ACLR *via* arthroscopy. The experimental groups received 2 mL of hylan G-F 20 at weeks 4, 8, or 12 post-operatively, whereas the control group received saline solution. The authors concluded that intra-articular injection of HA resulted in better functional recovery. In fact, the group receiving HA injection at week 8 post-operation showed the greatest improvement in clinical results, which remained significant at 1 year after surgery. However, the group receiving HA at the earliest time point showed no significant improvement over the control group, similarly to our study. These results suggested that the timing of injection after arthroscopic knee surgery may be important and further research efforts in this area could be beneficial.

Another meta-analysis on this issue came out with a conclusion that was consistent with ours. They used an evidence-based method to confirm that HA injection after arthroscopic ACLR surgery had no effect.[48] The present study should be considered higher level of evidence though

both studies reached the same results, since the previous one included observational study as well.

A recently published meta-analysis explored the efficacy of arthroscopy combined with intra-articular injection of HA in the treatment of knee OA. They concluded that arthroscopy combined with intra-articular injection of sodium hyaluronate demonstrates significant clinical effects in the treatment of knee OA.[49] Differences between the present meta-analysis and previous meta-analyses should be noted. First, the previous one included too many retrospective case–control literatures, which might decrease the reliability of their results, while we included RCTs only. Second, we evaluated the efficacy of intervention in pain relief and functional recovery, as well as safety, while they used the Lysholm score as the only outcome measurement, which might lead to bias. Third, their control group consisted of patients undergoing arthroscopy or not. Finally, they included OA patients only while we included patients with knee OA, meniscus injury or ACL injury, and performed subgroup analysis to ensure a comprehensive and reliable conclusion.

Limitations and Strengths

Some limitations of the present study need to be mentioned. First, the RCTs included in this study were heterogeneous in terms of varied control groups (placebo, blank and analgesic), which might affect the results. Second, 15 studies recruited patients with different diagnoses and conducted different kinds of arthroscopic knee operations. We performed subgroup analysis to observe the influence from the heterogeneity. Finally, we included only studies published in English, which might lead to a language or cultural bias.

Despite these limitations, the present study carried out the most extensive literature search and reached the most credible conclusions through quantitative analysis, compared to similar studies. In addition, the present study demonstrated the ineffectiveness of HA injection after arthroscopic knee surgery through reliable means, thus had great clinical significance.

Conclusions

In conclusion, despite HA injection being safe, our review of available evidence suggests that HA intra-articular injection after knee arthroscopic surgery does not contribute to improvements in pain relief and functional recovery, compared to other management approaches after knee arthroscopic surgery. And there was no difference between the effect of high- and low- molecular HA applied following knee arthroscopic surgery. Based on the available evidence, the application of HA injection after arthroscopic knee surgery is not recommended.

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Author Contributions

The corresponding author had full access to the data in the study and would take responsibility for the integrity of the data and the accuracy of the data analysis. Mao and Fu conceived the study and its design. Pan and Zhang conducted the database searching and data extraction. Mao and Pan analyzed the data and Li was responsible to explain the results. Mao drafted the initial manuscript while Yu revised it. All authors read and approved the final manuscript.

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