



## ■ INFECTION

# Do preoperative intra-articular injections of corticosteroids or hyaluronic acid increase the risk of infection after total knee arthroplasty? A meta-analysis

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## Aims

There is conflicting evidence on the safety of intra-articular injections of hyaluronic acid (HA) or corticosteroids (CSs) before total knee arthroplasty (TKA). We performed a meta-analysis of the relationship between intra-articular injections and subsequent infection rates after TKA.

## Methods

We searched PubMed, EMBASE, and the Cochrane Library for cohort studies that assessed the effect of preoperative injection of drugs into the joint cavity on the infection rate after TKA. The outcomes analyzed included the total infection rate, as well as those for different preoperative injection time periods and different drugs.

## Results

Eight studies, including 73,880 in the injection group and 126,187 in the control group, met the inclusion criteria. The injection group had a significantly higher postoperative infection rate than the control group (risk ratio (RR) 1.16; 95% confidence interval (CI) 1.07 to 1.27;  $p < 0.001$ ;  $I^2 = 32\%$ ). For patients who received injections up to three months preoperatively, the postoperative infection risk was significantly higher than that in the control group (RR 1.26; 95% CI 1.18 to 1.35;  $p < 0.001$ ;  $I^2 = 0\%$ ). There was no significant difference in the infection rates between the four-to-six-month injection and control groups (RR 1.12; 95% CI 0.93 to 1.35;  $p = 0.240$ ;  $I^2 = 75\%$ ) or between the seven-to-12-month injection and control groups (RR 1.02; 95% CI 0.94 to 1.12;  $p = 0.600$ ;  $I^2 = 0\%$ ).

## Conclusion

Current evidence suggests that intra-articular injections of CSs or HA before TKA increase the risk of postoperative infection. Injections administered more than three months before TKA do not significantly increase the risk of infection.

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## Article focus

■ This study evaluated the relationship between preoperative intra-articular injections and infection after total knee arthroplasty (TKA).

infection. This increased risk decreases in direct proportion to the interval between the injection and TKA; injections more than three months before TKA do not cause a significant increase in the risk of infection.

## Key messages

■ Current evidence suggests that intra-articular injections of corticosteroids (CSs) or hyaluronic acid (HA) before TKA increase the risk of postoperative

## Strengths and limitations

■ The advantage of this study is that it is the first meta-analysis of the relationship

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between preoperative knee cavity injection and postoperative TKA infection.

- Some articles included in this study were from large cohort studies with a large sample size, which can maximize the detection of the relationship between injection and infection.
- Eight articles were finally included, all of which were retrospective cohort studies; therefore, confounding factors, such as the injection schedule and patient characteristics, could not be well controlled for.
- The definition of infection in each study was unclear or unexplained.
- The surgeons, the time interval between the injections and surgery, and the total number of injections administered before surgery varied across studies, so the results were prone to bias.
- Other risk factors for infection, such as diabetes, malnutrition, and immune deficiencies, may increase the infection risk.

## Introduction

Osteoarthritis (OA) is the most common chronic bone and joint disorder and one of the main causes of disability.<sup>1-3</sup> Management strategies include pharmacological and non-pharmacological options. Intra-articular therapies include injections of hyaluronic acid (HA), corticosteroids (CSs), and mesenchymal stem cells.<sup>4-6</sup> Intra-articular CS and HA injection therapies are the two main treatments for knee OA. The purpose of these injection therapies is to control the patient's symptoms in the early stage, and total knee arthroplasty (TKA) is usually required in the late stage.<sup>7-9</sup> There is considerable evidence suggesting that joint injections can effectively relieve pain in the short term. In fact, the American College of Rheumatology has the conditions to promote the use of CS injections for the management of OA.<sup>4</sup> Pharmacological methods are conditionally recommended for the initial management of patients with knee OA; intra-articular CS injections and intra-articular hyaluronate injections are conditionally recommended for patients who have an inadequate response to initial therapy.<sup>5</sup> There have been clinical concerns that such injections may predispose patients to infection if TKA is to be subsequently performed at the injected joint. Other studies have shown no evidence that intra-articular injections increase the incidence of infection after TKA. It is still controversial whether intra-articular injections before TKA increase the risk of periprosthetic joint infection (PJI).<sup>10-18</sup> Some meta-analyses of PJI were conducted after TKA or total hip arthroplasty (THA),<sup>19-21</sup> however, the results were contradictory, emphasizing the lack of evidence in existing studies.

There is conflicting evidence regarding the safety of intra-articular injections during the perioperative period. Therefore, this review aimed to assess the impact of preoperative intra-articular injections on the risk of

postoperative infection in patients with TKA, focusing on the timing of injection before surgery.

## Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)<sup>22</sup> guidelines (PROSPERO number CRD42021268042).

**Literature search and selection of studies.** We systematically searched PubMed, EMBASE, and the Cochrane Library for relevant studies published in English prior to 3 March 2021. The reference lists of original and review articles were searched manually to identify more relevant studies. The search conditions were set according to the participants and interventions. The following search terms were combined using the Boolean operators AND/OR: injections, arthroplasty, replacement, knee, and infections. Subject words and free words were combined, the appropriate cut-off characters and Boolean logic operators were used, and the search strategies were formulated in accordance with the search requirements of each electronic database. The retrieval strategy is shown in the Supplementary Material.

**Acceptance criteria.** Relevant data were extracted from all included studies using standard data extraction forms. Studies were included for analysis if they met the following criteria: 1) Participants (patients who received intra-knee injections before TKA); 2) Intervention (intra-articular knee injections of CSs or HA before TKA); 3) Comparison (no drugs were injected into the knee joint cavity before TKA); and 4) Outcomes (the primary outcome was the infection rate after TKA during a follow-up period of at least six months).

The exclusion criteria were as follows: 1) unicompartmental knee arthroplasty after the injection of drugs into the knee joint; 2) comparison of infection and noninfection after TKA; 3) no data on the incidence of infection; 4) no comparison of outcomes with a control group; and 5) overlapping samples and results.

**Data extraction.** Data were extracted from the included studies by two authors (XY and LL). Any disagreements between the two authors were resolved through consensus or through consultation with the senior author (LX). From each report, relevant information was extracted, including the name of the first author, journal, country of origin, year of publication, study population, patient registration procedures, sample size, study design, patient age, patient sex, which drugs were injected in the joint cavity, the time of injection, and outcomes (infection rate).

**Risk of bias.** Methodological quality was assessed by two reviewers (XY and LL) using the Newcastle-Ottawa Quality Assessment Scale independent assessment, and some changes were made to meet the needs of this study. Study quality was assessed regarding the following three aspects: selection, comparability, and exposure outcome conditions. The maximum total score for the three items

was nine points, and a study with a score of  $\geq$  seven points was considered a high-quality study. We used a standardized data table to extract all the data to be evaluated.

**Statistical analysis.** All analyses were performed using Review Manager, version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration), and  $p < 0.05$  was considered statistically significant. Dichotomy data analysis was used to determine the risk ratio (RR) and 95% confidence interval (CI). Individual relative risk estimates and summary estimates were displayed graphically in forest plots. The heterogeneity between the studies was tested using  $I^2$ . A  $p$ -value  $> 0.1$  and an  $I^2$  value of  $< 50\%$  indicated that there was no obvious heterogeneity;  $p < 0.05$  and an  $I^2$  value of  $> 50\%$  were considered to be suggestive of statistical heterogeneity. If there was heterogeneity among studies in the results, possible sources of heterogeneity were identified through subgroup analysis. The data for each study were pooled by random-effects models based on the degree of heterogeneity. Subgroup analyses included different injection time periods and drug types. A funnel chart was used to assess publication bias.

## Results

**Literature search results.** The preliminary search of each database resulted in a total of 1,277 articles. A total of 405 duplicate articles were excluded, and 858 articles were excluded after reading the titles and abstracts. We read the full text of the remaining 14 documents, and six articles were excluded because they did not meet the inclusion criteria, as follows: one paper lacked the comparison group; four papers had incomplete data; and one paper was a review. Eight articles met the inclusion criteria. The literature selection process is shown in Figure 1.

**Characteristics of the studies.** The eight studies included 200,067 participants, including 73,880 in the injection group and 126,187 in the control group; all participants were from the USA and UK. All included studies were retrospective cohort studies published between 2005 and 2020. In the included studies, the proportions of females were 60% to 72.8%. Four studies used CS injections, and four studies used CS or HA injections. The definition of infection was not universally reported and was variable across studies. The follow-up period ranged from six to 72 months (Table I).

**Risk of bias assessment.** All eight included articles were retrospective studies. The quality of the eight articles was analyzed according to the Newcastle-Ottawa Scale (NOS)<sup>23</sup> scoring method; three articles scored six points, three articles scored seven points, one article scored eight points, and one article scored nine points. The included articles were of moderate quality (Table II).

**Total infection rate.** The eight studies reported the infection rates at the final follow-up for 73,880 and 126,187 participants in the injection and control groups, respectively. Compared with the control group, the injection group had a significantly higher infection rate (RR 1.16;

95% CI 1.07 to 1.27;  $p < 0.001$ ). The heterogeneity analysis showed that the  $I^2$  value was 32% (Figure 2).

**Infection rates in patients who received injections preoperatively.** Four studies reported infection rates in patients who received injections zero to three, four to six, and seven to 12 months preoperatively. One study reported infection rates in patients who received injections up to three months preoperatively. The patients who received injections up to three months had a significantly higher infection rate than those in the control group (RR 1.26; 95% CI 1.18 to 1.35;  $p < 0.001$ ;  $I^2 = 0\%$ ). Compared with the control group, the four-to-six-month injection group did not show a significantly different infection rate (RR 1.12; 95% CI 0.93 to 1.35;  $p = 0.240$ ;  $I^2 = 75\%$ ). Compared with the control group, the seven-to-12-month injection group did not show a significantly different infection rate (RR 1.02; 95% CI 0.94 to 1.12;  $p = 0.600$ ;  $I^2 = 0\%$ ) (Figure 3).

**Infection rates in the HA group versus the CS group.** Two studies reported 3,672 patients injected with HA and 17,016 patients injected with CSs. There was no significant difference between the HA and CS groups (RR 0.84; 95% CI 0.67 to 1.05;  $p = 0.130$ ;  $I^2 = 0\%$ ) (Figure 4).

**Superficial infection and deep infection.** Two studies included 350 patients in the injection group and 386 patients in the control group, and there was no significant difference in the superficial infection rates between these groups (RR 1.73; 95% CI 0.93 to 3.23;  $p = 0.090$ ;  $I^2 = 0\%$ ). Two studies reported that there was no significant difference in the deep infection rates between the injection group and control group of 337 and 376 participants, respectively (RR 1.99; 95% CI 0.08 to 50.96;  $p = 0.680$ ;  $I^2 = 76\%$ ). Without the time node, we performed no further subgroup analysis (Figure 5).

**Analysis of publication bias.** In this study, one comparison group included more than eight articles, and therefore publication bias analysis was required. The scatter diagram method was used to draw comparison indicators into scatter plots. The eight included articles were all based on the total infection rate as an outcome indicator. RevMan 5.4 software was used to draw an asymmetric funnel chart, and there was publication bias (Figure 6).

## Discussion

Meta-analysis has been recognized as an effective method to answer a wide variety of clinical questions by summarizing and reviewing previously published quantitative research. This study compared the total infection rates with and without intra-articular injection before TKA, providing comprehensive evidence for cohort studies. The results of the analysis showed that the total infection rate in the injection group was significantly higher than that in the control group. Some studies have also indicated that preoperative joint cavity injection may increase the postoperative infection rate.<sup>12,15,24,25</sup> The exact mechanism by which these drugs increase the risk of infection is unclear. Infection may be due to contamination

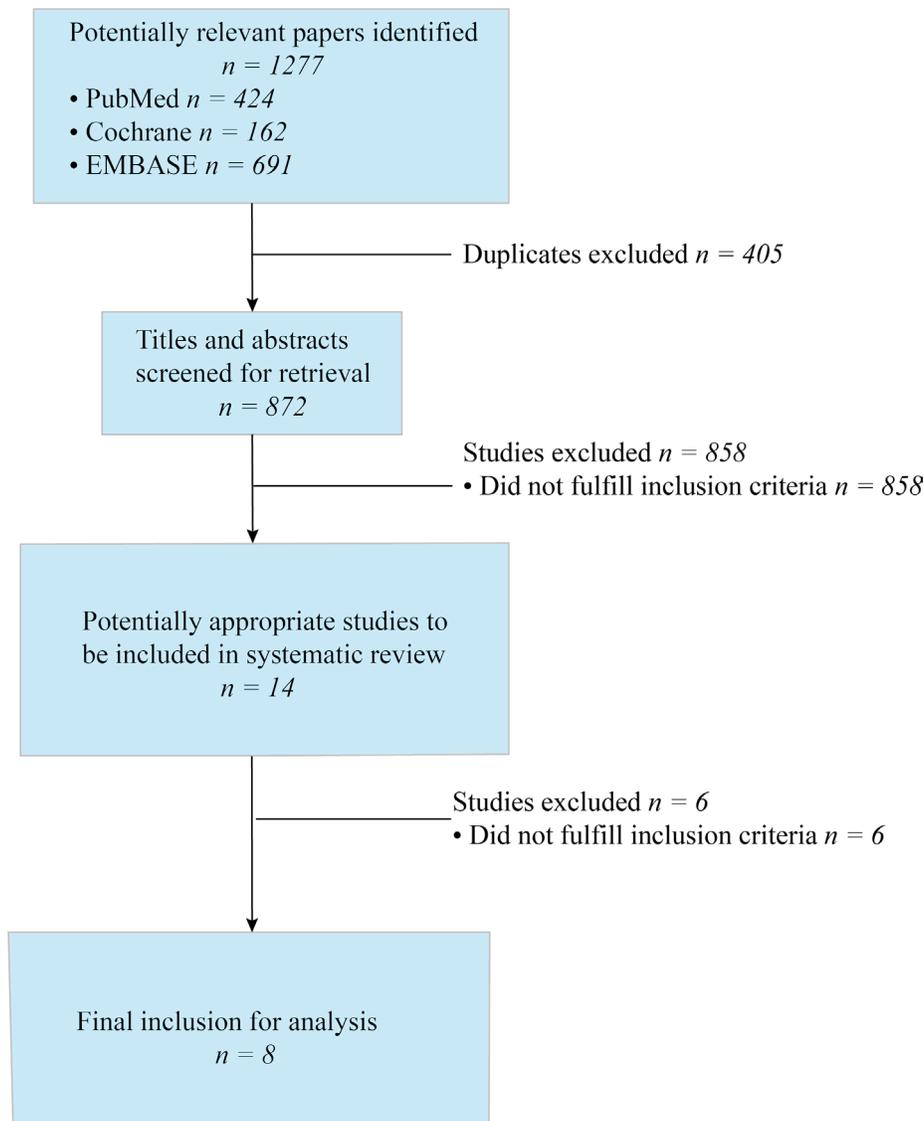


Fig. 1

Flow chart showing the selection process of studies for analysis with specifications of reasons.

of the joint during injection. Even if an aseptic technique is used, the injection may still bring a small number of bacteria into the joint cavity. If these bacteria persist, they may colonize the prosthesis and cause periprosthetic joint infection. CSs are well-known immunosuppressants used to treat a variety of systemic immune diseases. Intra-articular injections may result in dissolution failure of drugs, which may persist in the joint cavity and cause local immunosuppression after joint arthroplasty.<sup>25</sup> These immunosuppressive agents can also cause a decrease in the systemic immune response and increase the infection rate. Studies on the mechanism of action of HA in joints have indicated that HA may reduce immune function by altering the production of immunomodulatory factors in the synovium, cartilage, and subchondral bone.<sup>26–29</sup> The combination of direct injections and local

immunosuppression may lead to an increased chance of infection around the prosthesis, which is associated with the two injection types. Previous meta-analyses of patients with hip and knee surgery showed no significant differences between these groups in the infection rates, which was potentially due to the small sample size and low confidence level.<sup>19,30</sup>

We grouped the injection times into the following categories: zero to three, four to six, and seven to 12 months. The zero-to-three-month injection group had a significantly higher postoperative infection risk than the control group. Compared with the control group, the four-to-six-month injection group did not show a significant difference in the infection rate. Compared with the control group, the seven-to-12-month injection group did not show a significant difference in the infection rate.

Table 1. Characteristics of studies.

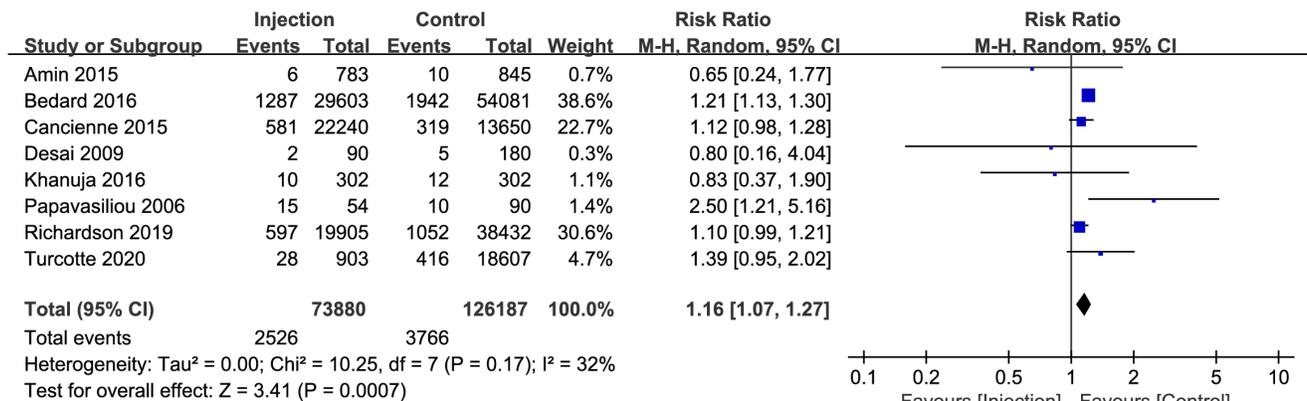
Study	Country	Design	Year	Injection group			No injection group			Outcome	Mean follow-up, mths			
				Sample size	Mean patient age	Female (%)	Injection drug (product information)	Injection dosage	Sample size			Mean patient age, yrs	Female (%)	
Papavasiliou et al <sup>10</sup>	UK	Retrospective cohort	2006	54	NR	NR	CS (NR)	NR	90	NR	NR	Purulent drainage; culture from aseptically aspirated fluid, swab/tissue biopsy from the deep-tissue layers, or pus cells on microscopy; deep incision that spontaneously dehiscenced or was explored for a temperature of > 38°C, localized pain or tenderness; an abscess or other evidence of infection involving the deep incision; diagnosis of a deep infection by clinician	Deep infection rate; superficial infection rate	12
Desai et al <sup>11</sup>	UK	Matched cohort study	2009	90	68 (49 to 87)	60	CS (Depomedrone)	Depomedrone 2 ml (Depomedrone 40 mg/ml; Pharmacia, UK) and Chirocaine (5 mg/ml; Abbott, UK)	180	72 (51 to 88)	53	Positive swab cultures; wound with positive culture; revision surgery for infection	Deep infection rate; superficial infection rate	33 (12 to 72)
Cancienne et al <sup>12</sup>	USA	Matched cohort study	2015	22,240	< 65 yrs: 1,909; 65 to 69 yrs: 5,320; 70 to 74 yrs: 5,811; 75 to 79 yrs: 3,298; 80 to 84 yrs: 3,072; ≥ 85 yrs: 1,201	68.5	CS (NR)	NR	13,650	< 65 yrs: 1,243; 65 to 69 yrs: 3,267; 70 to 74 yrs: 3,545; 75 to 79 yrs: 2,993; 80 to 84 yrs: 1,862; ≥ 85 yrs: 739	68.4	PJI was characterized by either a diagnosis or procedure for wound or deep infection after TKA using CPT and ICD-9 codes	Wound infection rate; deep infection rate	6
Khanuja et al <sup>13</sup>	USA	Matched cohort study	2016	302	66 (49 to 92)	72.8	CS (triamcinolone acetate)	Kanalog 40 mg/ml; Bristol Myers Squibb; USA) combined with xylocaine 1% (4 ml)	302	65 (47 to 94)	72.8	CDC and Prevention/National Healthcare Safety Network definitions: superficial surgical site infection; deep PJI	Superficial surgical site infection rates; deep PJI rate	42 (17 to 69)
Amin et al <sup>14</sup>	USA	Matched cohort study	2015	783	63.82 (36 to 89)	NR	CS or HA (NR)	NR	845	64.14 (32 to 91)	NR	Definition from the Workgroup of the Musculoskeletal Infection Society	Deep infection rate	8.67 (1 to 14)
Bedard et al <sup>15</sup>	USA	Retrospective cohort	2016	29,603	NR	66.7	CS or HA (NR)	NR	54,081	NR	62.5	Infection requiring surgical intervention	Infection rate	6
Richardson et al <sup>16</sup>	USA	Matched cohort study	2019	19,905	NR	63	CS or HA (NR)	NR	38,432	NR	61.7	Infection was defined via appropriate ICD-9, ICD-10, and CPT diagnosis	Infection rate	6
Turcotte et al <sup>17</sup>	USA	Matched cohort study	2020	903	66.5	NR	CS or HA (NR)	NR	18,607	65.6	NR	Infection was identified by the ICD-10 code for infection due to internal knee prosthesis or the CPT codes for treatment of infection	Infection rate	12

CDC, Centers for Disease Control and Prevention; CPT, current procedural terminology; CS, corticosteroid; HA, hyaluronic acid; ICD, International Classification of Diseases; NR, not reported; PJI, periprosthetic joint infection; TKA, total knee arthroplasty.

**Table II.** Newcastle-Ottawa Scale quality evaluation form.

Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Papavasiliou et al <sup>10</sup>	*	*	*	*		*	*		6
Desai et al <sup>11</sup>	*	*	*	*		*	*	*	7
Cancienne et al <sup>12</sup>	*	*	*	*	**	*	*		8
Khanuja et al <sup>13</sup>	*	*	*	*	**	*	*	*	9
Amin et al <sup>14</sup>	*	*	*	*		*	*		6
Bedard et al <sup>15</sup>	*	*	*	*		*	*	*	7
Richardson et al <sup>16</sup>	*	*	*	*		*	*		6
Turcotte et al <sup>17</sup>	*	*	*	*		*	*	*	7

A study could be awarded a maximum of one star for each item except for the item "Control for important factor or additional factor".

**Fig. 2**

Results of meta-analysis for total infection rate. CI, confidence interval; M-H, Mantel-Haenszel.

At all levels that could be analyzed, injections before TKA were associated with a higher risk of postoperative infection. The risk of infection significantly increased up to three months after surgery, and significantly decreased after three months. This result is consistent with those of many other large retrospective database studies that examined injections administered prior to TKA<sup>12,15,16</sup> and THA.<sup>24,31</sup>

This analysis showed that in two studies, there were no significant differences in the infection rates between the HA and CS groups. In a national medical insurance-based database study,<sup>16</sup> there was no significant difference in the risk of infection between patients injected with different types of drugs. Amin et al<sup>14</sup> also compared a CS group and HA group and found no significant difference between the two groups ( $p = 0.4226$ ). In addition to these two studies, separate data for CSs and HA are provided. To date, few studies have compared the risk of infection according to a history of HA and CS injection. The two groups had similar infection rates, and possible reasons are as follows: 1) injection contamination may occur during the injection of HA and CSs; and 2) both HA and CSs have pharmacological mechanisms leading to low local immunity.<sup>25–29</sup> However, further studies

comparing the two drugs for the risk of subsequent infection are needed to derive stronger conclusions.

This analysis showed that two studies reported no significant difference in the superficial infection rate between the injection group and the deep infection group. There was no significant difference in the rate of deep infection compared with the control group. Khanuja et al<sup>13</sup> reported that during a mean follow-up period of 3.5 years after TKA, there were no significant differences in the prevalence of superficial infection (7 cases vs 6 cases), periprosthetic deep infection (3 cases vs 6 cases), or global infection (10 cases vs 12 cases) between the two groups. Similarly, Papavasiliou et al<sup>10</sup> showed that the difference in the incidence of superficial infections between the two groups was not statistically significant ( $p > 0.05$ ). Studies that have shown that the risk of infection does not increase with preoperative injections typically have smaller sample sizes, so they may have insufficient power to detect differences in rare outcomes.

Another factor not considered in our results is the number of injections before surgery. However, a few studies have analyzed this issue. Richardson et al<sup>16</sup> compared the risk of infection after TKA between multiple versus a single intra-articular injection before surgery, and

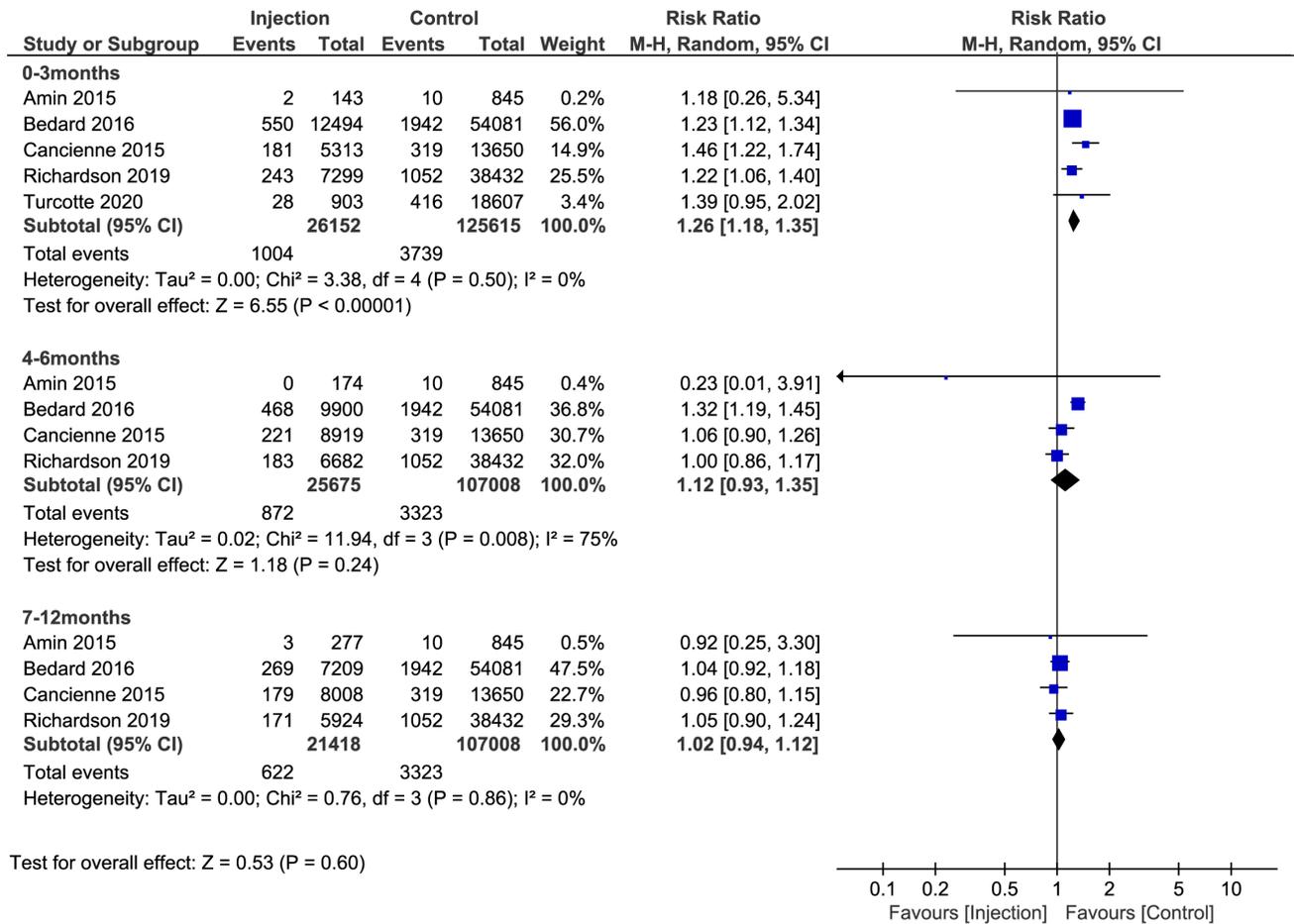


Fig. 3

Results of meta-analysis for different preoperative injection time periods. CI, confidence interval; M-H, Mantel-Haenszel.

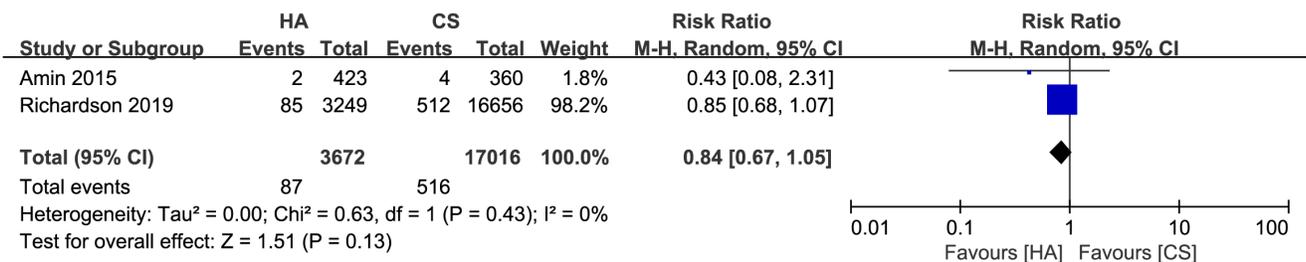


Fig. 4

Results of meta-analysis for hyaluronic acid (HA) group versus the corticosteroid (CS) group. CI, confidence interval; M-H, Mantel-Haenszel.

found that there was no difference in the risk of infection. However, the exact relationship between the number of injections and the risk of infection requires more research for verification.

This study has several limitations: eight articles were finally included, all of which were retrospective cohort studies, and therefore confounding factors, such as the injection schedule and patient characteristics, could not

be well controlled. Furthermore, the definition of infection in each study was unclear or unexplained. The lack of standardized definitions may overestimate or underestimate the incidence of infection in the included studies. Part of our research is derived from administrative databases, and those data are collected using current procedural terminology codes; however, such databases are prone to coding errors. The surgeons, the time interval

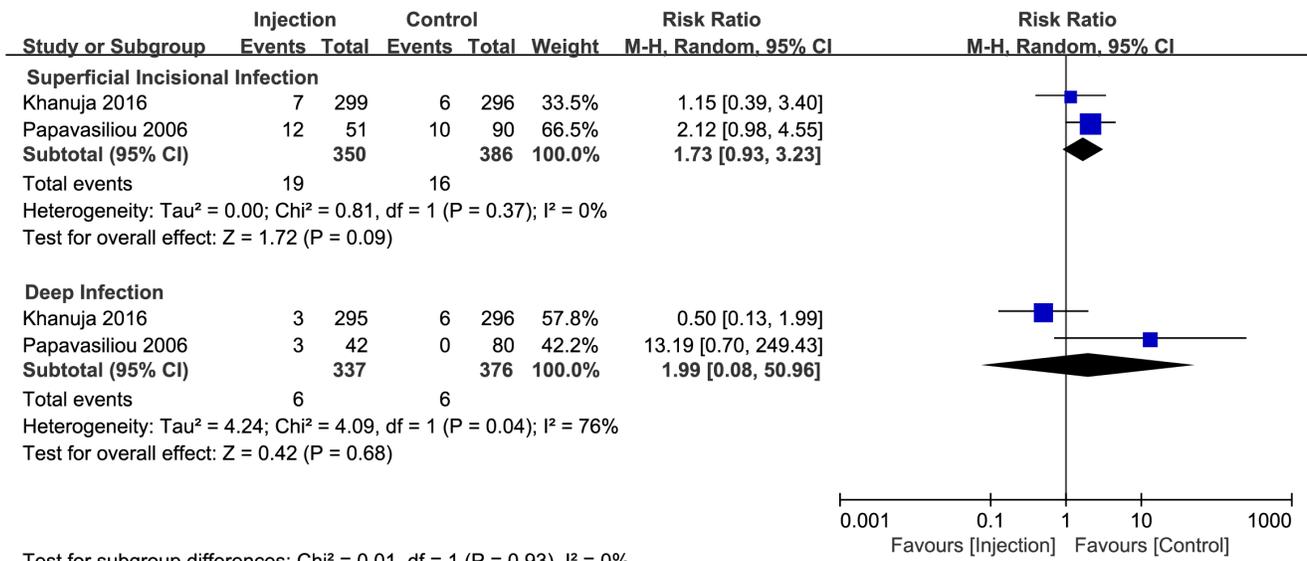


Fig. 5

Results of meta-analysis for superficial infection and deep infection rates. CI, confidence interval; M-H, Mantel-Haenszel.

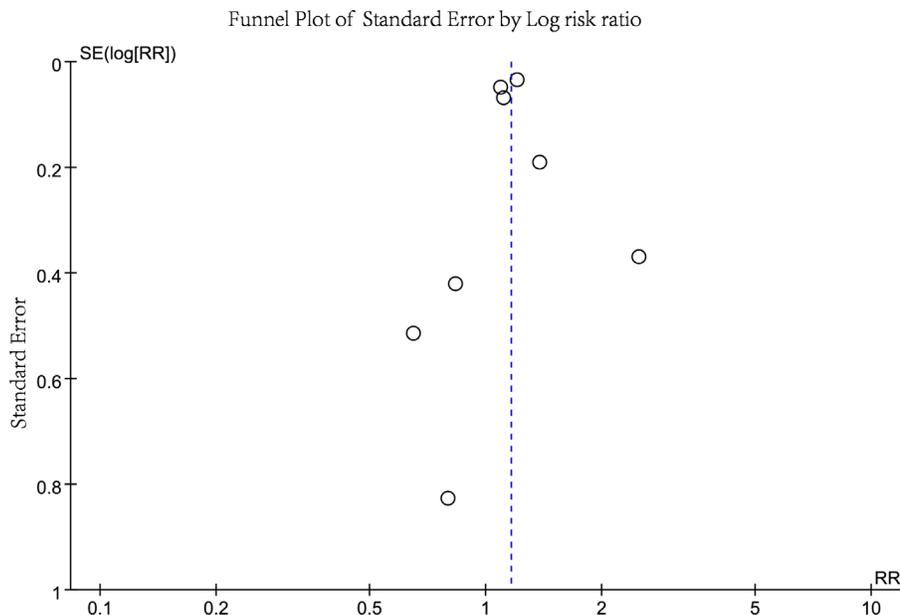


Fig. 6

Funnel plot of studies meta-analyzed for infection rates. RR, risk ratio; SE, standard error.

between the injections and surgery, and the total number of injections administered before surgery varied across studies, so the results are prone to bias. Additionally, other risk factors for infection, such as diabetes, malnutrition, and immune deficiencies, may increase the infection rate. Finally, some of the included studies had a follow-up time of six months, and there was a lack of long-term follow-up studies.

In conclusion, current evidence suggests that intra-articular injections of CSs or HA before TKA increase the risk of infection. Injections administered more than three

months before TKA do not significantly increase the risk of infection. Multicentre prospective studies are needed to further study this issue.

**Supplementary material**

Retrieval strategy and the PRISMA 2009 Checklist.

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