

Perioperative intravenous glucocorticoids can decrease postoperative nausea and vomiting and pain in total joint arthroplasty

A meta-analysis and trial sequence analysis

Ping Chen, MM^a, Xiwen Li, MM^b, Lili Sang, MM^c, Jiangfa Huang, MM^{a,*}

Abstract

Background: This meta-analysis aimed to demonstrate the efficacy and safety of intravenous glucocorticoids for reducing pain intensity and postoperative nausea and vomiting (PONV) in patients undergoing total joint arthroplasty (TJA).

Methods: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Google databases were searched for randomized controlled trials (RCTs) comparing intravenous glucocorticoids versus no intravenous glucocorticoids or sham for patients undergoing TJA. Outcomes included visual analogue scale (VAS) pain at 12, 24, and 48 hours; the occurrence of PONV; length of hospital stay; the occurrence of infection; and blood glucose levels after surgery. We calculated risk ratios (RR) with a 95% confidence interval (CI) for dichotomous outcomes and the weighted mean difference (WMD) with a 95% CI for continuous outcomes. Trial sequential analysis was also used to verify the pooled results.

Results: Thirteen clinical trials involving 821 patients were ultimately included in this meta-analysis. The pooled results indicated that intravenous steroids can decrease VAS at 12 hours (WMD = -8.54, 95% CI -11.55 to -5.53, $P=0.000$; $I^2=35.1\%$), 24 hours (WMD = -7.48, 95% CI -13.38 to -1.59, $P=0.013$; $I^2=91.8\%$), and 48 hours (WMD = -1.90, 95% CI -3.75 to -0.05, $P=0.044$; $I^2=84.5\%$). Intravenous steroids can decrease the occurrence of PONV (RR = 0.56, 95% CI 0.44–0.73, $P=0.000$; $I^2=33.1\%$). There was no significant difference in the length of hospital stay, occurrence of infection, and blood glucose levels after surgery.

Conclusion: Intravenous glucocorticoids not only alleviate early pain intensity but also decrease PONV after TJA. More high-quality RCTs are required to determine the safety of glucocorticoids before making final recommendations.

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, PONV = postoperative nausea and vomiting, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCTs = randomized controlled trials, RR = risk ratios, THA = total hip arthroplasty, TJA = total joint arthroplasty, TKA = total knee arthroplasty, TSA = trial sequence analysis, VAS = visual analogue scale, WMD = weighted mean difference.

Keywords: glucocorticoids, meta-analysis, pain control, total joint arthroplasty

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^a Department of Orthopedics, The 2nd Affiliated Hospital of Guangzhou University of Chinese Medicine, ^b Guangzhou University of Chinese Medicine, Guangzhou,

^c Department of Orthopedic, Traditional Chinese Medicine Hospital of Zhongshan, Zhongshan, Guangdong, China.

* Correspondence: Jiangfa Huang, Department of Orthopedics, The 2nd Affiliated Hospital of Guangzhou University of Chinese Medicine, No. 261 Datong Road, 510000, Yuexiu district, Guangzhou, Guangdong, China (e-mail: hetianxia001@qq.com).

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1. Introduction

Postoperative nausea and vomiting (PONV) is often cited as the most common complication after anesthesia, with a reported incidence of 20% to 38% after major orthopedic surgery.^[1–3] Despite an increased emphasis on postoperative pain control, several recent studies have indicated that 30% to 77% of patients experience moderate-to-severe pain postoperatively.^[4] Many multimodal analgesic regimens have become the standard protocol to minimize postoperative pain and nausea and improve functional recovery following total joint arthroplasty (TJA, including total knee arthroplasty (TKA) and total hip arthroplasty (THA)).^[5] Intravenous glucocorticoids have been shown to reduce the postoperative rise of serum markers of systemic inflammation and lung injury in patients undergoing TKA and THA.^[6] A single preoperative dose of glucocorticoids may be a prophylactic agent for decreasing PONV. However, concerns regarding their effects and potential side effects have prevented glucocorticoids from being regularly included in perioperative protocols for TJA despite randomized trials indicating short-dose glucocorticoids to be safe and effective for reducing PONV.^[6]

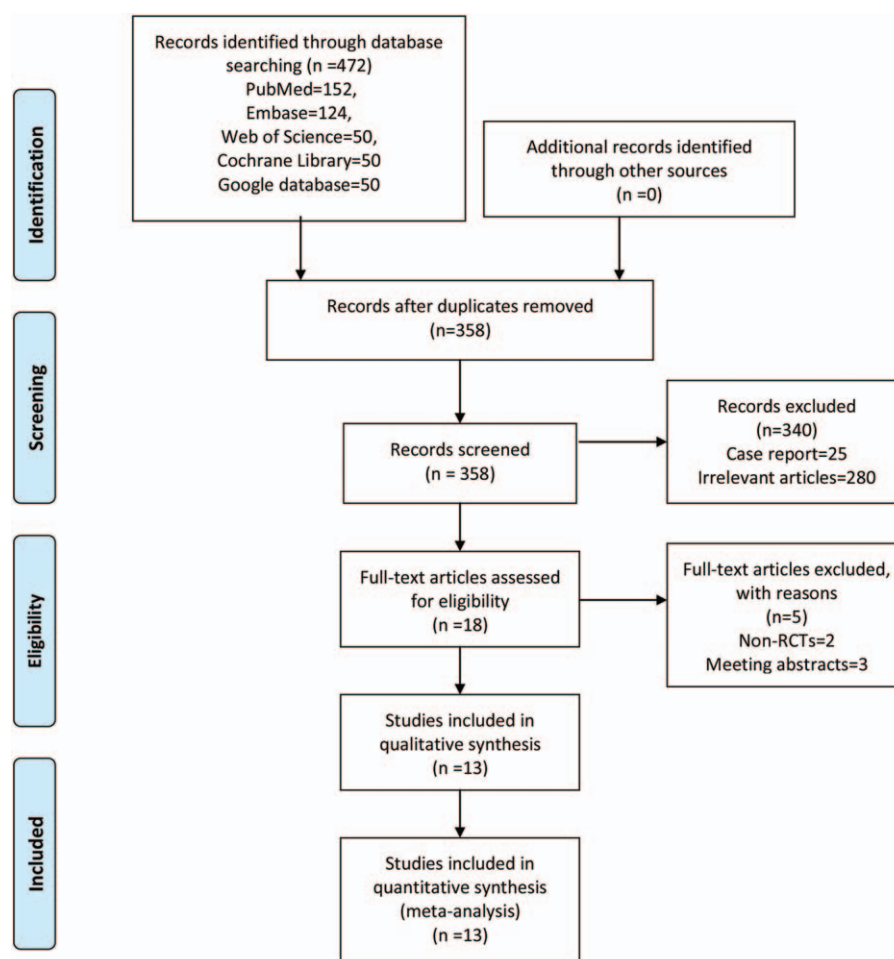


Figure 1. Flowchart of the study search and inclusion criteria.

Moreover, there has been no meta-analysis comparing the effects and safety of glucocorticoids for TJA. Thus, we performed a meta-analysis and trial sequence analysis (TSA) to summarize the existing evidence from randomized controlled trials (RCTs) to determine the effectiveness and safety of glucocorticoids for TJA.

2. Materials and methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions^[7] and was written in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist.^[8]

2.1. Search strategy and study selection

The electronic databases PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Google database were systematically searched from inception to December 31, 2016. The detailed PubMed search strategy was as follows: (((((((("Arthroplasty, Replacement, Knee"[Mesh]) OR TKR) OR TKA) OR total knee replacement) OR total knee arthroplasty) OR "Arthroplasty, Replacement, Hip"[Mesh]) OR THR) OR THA) OR total hip arthroplasty) OR total hip replacement)) AND (glucocorticoid OR steroid OR corticosteroid

OR hydrocortisone OR cortisone OR prednisone OR methylprednisone OR triamcinolone OR dexamethasone OR betamethasone). Meta-analysis was collected from published data and thus ethical review or approved was not necessary.

2.2. Eligibility criteria

1. Participants: Patients undergoing primary TJA.
2. Interventions: The comparison group was a preoperative intravenous administration of glucocorticoids.
3. Comparisons: The comparison group was with no intravenous glucocorticoids or sham group.
4. Outcomes: Visual analogue scale (VAS) at 12, 24, and 48 hours after TJA, the occurrence of PONV, the incidence of infection, length of hospital stay and blood glucose level after surgery.
5. Study design: Only RCTs were included.

2.3. Data extraction and outcome measures

Two authors (PC and XL) independently extracted the author, publication year, the number of patients in intervention and control groups, the proportion of male patients and the mean age of the patients, the dose of glucocorticoids and comparison, outcomes and duration of follow-up. Any disagreement was resolved by

Table 1
The general characteristic of the included studies.

Reference	No. of patients		Male, %	Mean age, y	Anesthesia	Intervention		Outcomes	Study design	Follow-up	Surgery
	Intervention	Control				Equivalency to dexamethasone	Control				
Sculco 2016	14	13	44	66	SA/EA	7.5 mg	Placebo	1, 2, 3, 4, 5, 6, 7	RCTs	3 mo	THA
Kardash 2008	25	25	50	68	SA	40 mg	Saline	1, 2, 3, 4, 7	RCTs	1 mo	THA
Bergeron 2009	25	25	NS	NS	SA	40 mg	Saline	7	RCTs	1 y	THA
Mathiesen 2008	40	40	50	67	SA	8 mg	Placebo	1, 2, 4, 7, 7	RCTs	24 h	THA
Lunn 2013	24	24	44	66	SA	23.43 mg	Saline	1, 4, 7	RCTs	30 d	THA
Lunn 2011	24	24	NS	66	SA	25 mg	Saline	2, 3, 4,	RCTs	1 mo	TKA
Fujii 2005	20	10	53	58	EA	4, 8 and 16 mg	Saline	4	RCTs	1 d	TKA
Koh 2013	135	134	51	72	SA	10 mg	Placebo	2, 3, 4, 7	RCTs	3 d	TKA
Jules-Elysee 2011	15	15	62	68	SA/EA	11.3 mg	Saline	1, 2, 3, 4, 5, 6, 7	RCTs	2 d	TKA
Jules- Elysee 2012	17	17	48	68	SA/EA	11.3 mg	Saline	1, 2, 3, 4, 5, 6, 7	RCTs	3 d	TKA
McLawhorn 2016	11	12	51	67	SA/EA	11.3 mg	Placebo	2, 6	RCTs	2 d	TKA
Morales-Munoz 2016	27	27	50	68.8	SA	8 mg	Saline	3, 4, 7	RCTs	2 d	TKA
Backes 2013	41	37	56.8	66	SA	10 mg	Placebo	1, 2, 3, 4, 5, 7	RCTs	3 d	TJA

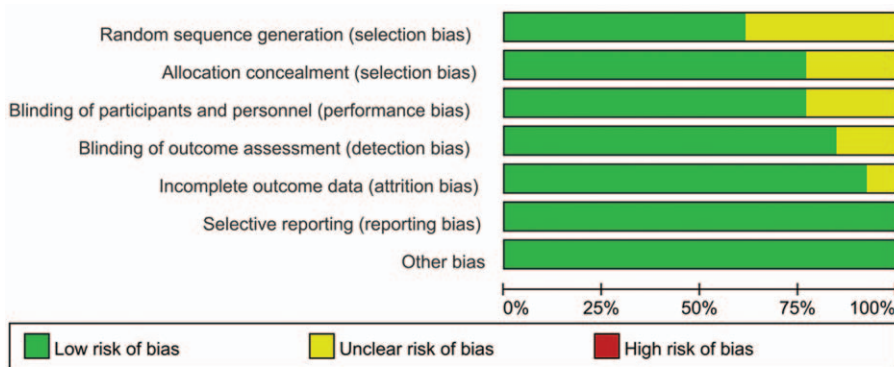
1 = VAS at 12 h, 2 = VAS at 24 h, 3 = VAS at 48 h, 4 = the occurrence of nausea and vomiting, 5 = length of hospital stay, 6 = the blood glucose, 7 = the occurrence of infection, EA = epidural anesthesia, NS = not stated, RCTs = randomized controlled trials, SA = spinal anesthesia, THA = total hip arthroplasty, TJA = total joint arthroplasty, TKA = total knee arthroplasty.

discussion. Different types of glucocorticoids were converted to equivalence to dexamethasone: 0.75 mg dexamethasone=4 mg methylprednisolone=5 mg prednisolone=20 mg hydrocortisone.^[9] The outcomes were VAS at 12, 24, and 48 hours; the occurrence of PONV; the length of hospital stay; the occurrence of infection; and blood glucose level after surgery. If the data were not reported numerically, we extracted mean and standard deviation

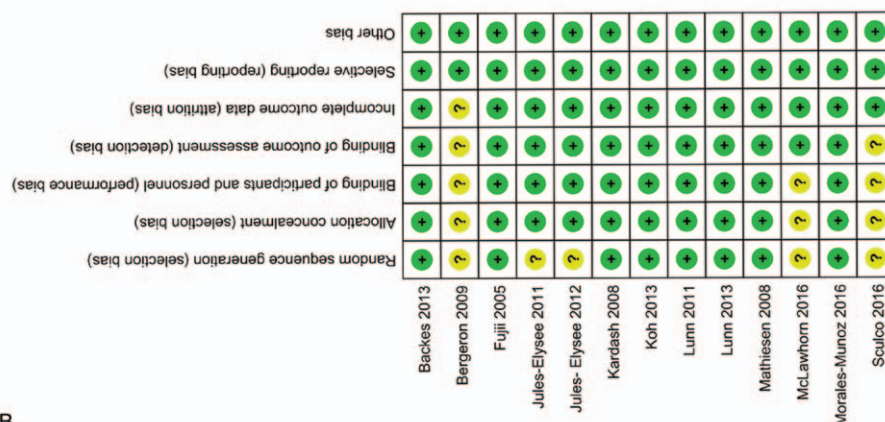
values from the published papers using GetData Graph Digitizer software as needed.^[7]

2.4. Risk of bias assessment

Two authors (LS and JH) independently evaluated the risk of bias of included RCTs according to the recommendations of the



A



B

Figure 2. A, The risk of bias graph. BA=risk of bias of included in randomized controlled trials. +=no bias, -=bias, ?=bias unknown. B, The risk of bias summary of the included studies.

occurrence of PONV. A *P* value less than 0.05 was considered statistically significant. Kappa values were used to measure the degree of agreement between the 2 reviewers and were rated as follows: fair, 0.40 to 0.59; good, 0.60 to 0.74; and excellent, 0.75 or more.^[12] To test the robustness of the pooled results and avoid a type I error,^[13–16] TSA was conducted (TSA software, version 0.9.5.5 beta; Copenhagen Trial Unit) for the primary outcome.

3. Results

3.1. Search results

The literature search and selection process are illustrated in Fig. 1. The initial search yielded 472 articles; 358 papers were read after excluding the duplicates. Next, 340 papers were excluded based on the inclusion criteria. Five papers were then excluded as 2 were non-RCTs and 3 were meeting abstracts. Finally, we included 13 clinical studies with 821 patients for this meta-analysis.^[6,9,17–27]

3.2. Study characteristics

The detailed baseline characteristics of the included studies are presented in Table 1. Five studies were included in the meta-analysis. All articles were published in English between the years of 2008 and 2016. The sample sizes ranged from 13 to 40 (total = 821) and the mean age ranged from 58 to 72. The follow-up ranged from 1 day to 1 year. The glucocorticoid dose equivalency

to dexamethasone ranged from 4 to 40 mg. Detailed information on the included patients is presented in Table 1.

3.3. Risk of bias among the included studies

Figure 2 presents the details of the risk of bias assessment for all of the included studies. Randomized sequence generation was implemented adequately in 8 studies;^[6,9,18,20–23,27] the other 5 studies had an unclear risk of bias. Allocation concealment was implemented adequately in all included studies.^[6,9,18,20–23,27] All studies reported blinding of the participants, personnel, and outcome assessors.^[6,9,17–27] The overall kappa value regarding the evaluation of risk of bias of included RCTs was 0.913, indicating an excellent degree of agreement between the 2 authors.

3.4. Quality of evidence assessment

A summary of the quality of the evidence based on the GRADE approach is shown in Supplement S1, <http://links.lww.com/MD/B608>. The GRADE level of evidence was high for VAS at 12 hours, the occurrence of PONV and the occurrence of infection, low for VAS at 24 hours, and the blood glucose level after surgery and very low for VAS at 24 hours.

3.5. VAS at 12, 24, and 48 hours

Six studies including 269 patients tested the effect of intravenous glucocorticoids on the VAS at 12 hours. Compared

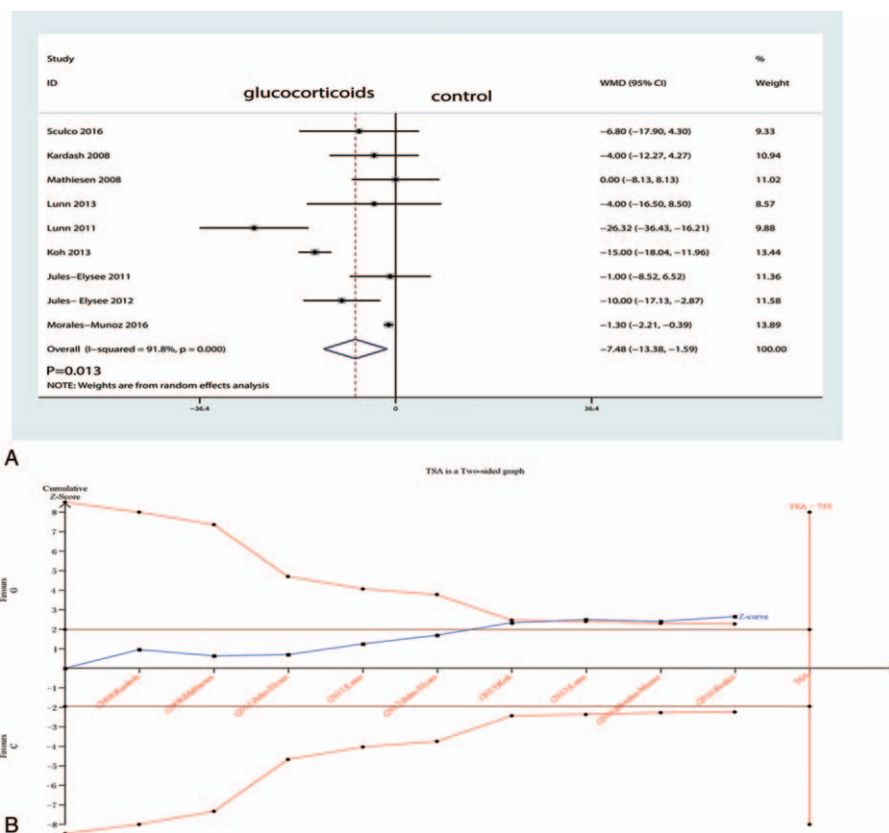


Figure 4. A, Forest plots of the included studies comparing the VAS at 24 h. B, Z curve crossed the trial sequential monitoring boundary for benefit (red curve) but did not reach the required sample size based on TSA (n = 735), entering the area of benefit (above the upper red line). TSA = trial sequence analysis, VAS = visual analogue scale.

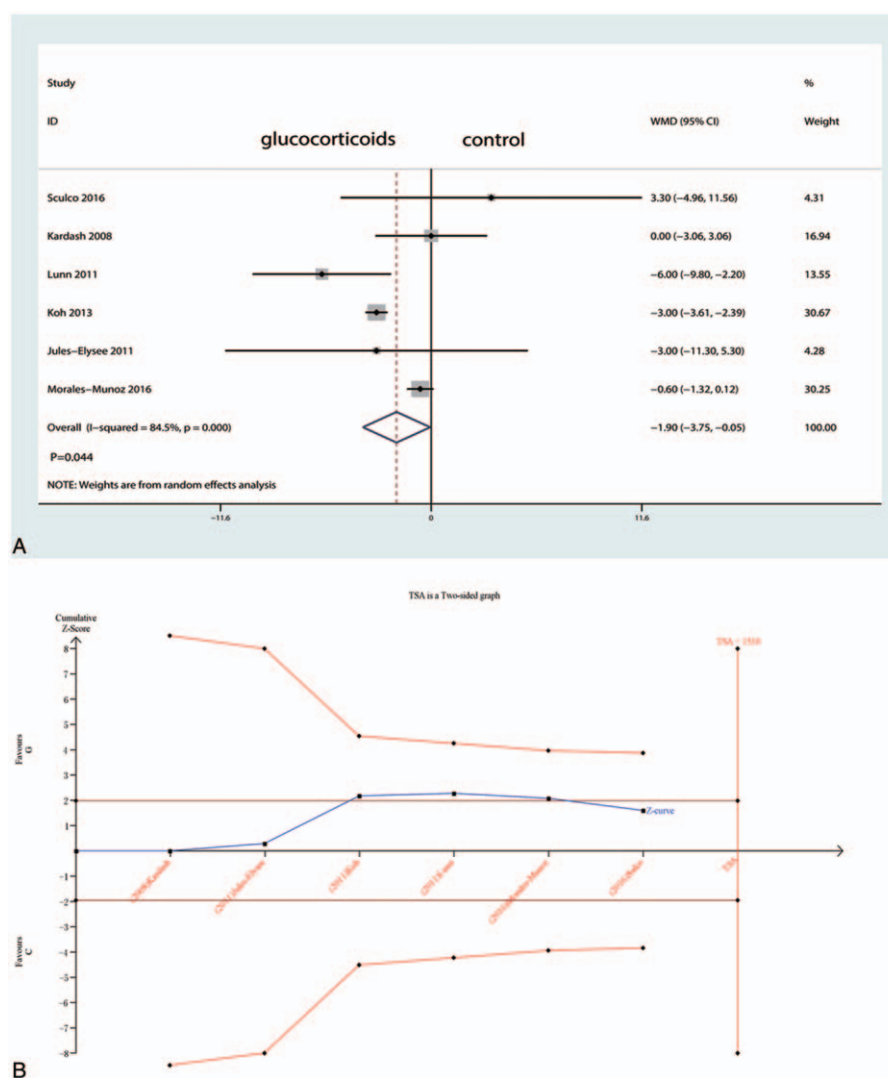


Figure 5. A, Forest plots of the included studies comparing the VAS at 48h. B, Z curve crossed the trial sequential monitoring boundary for benefit (red curve) but did not reach the required sample size based on TSA ($n = 1510$), entering the area of benefit (above the upper red line).

with the placebo, intravenous glucocorticoids were associated with a significant reduction in the VAS at 12 hours (WMD = -8.54 , 95% CI -11.55 to -5.53 , $P = 0.000$; $I^2 = 35.1\%$) (Fig. 3A). A TSA confirmed the pooled results at 12 hours (Fig. 3B). Nine studies reported data from 640 participants with TJA and were included in this meta-analysis to estimate the effect of intravenous glucocorticoids on the VAS at 24 hours. Compared with placebo, intravenous glucocorticoids were associated with a significant reduction in the VAS at 12 hours (WMD = -7.48 , 95% CI -13.38 to -1.59 , $P = 0.013$; $I^2 = 91.8\%$) (Fig. 4A). A TSA did not confirm the pooled results (Fig. 4B). Six trials (478 participants) were pooled to evaluate the efficacy of intravenous glucocorticoids on the VAS at 48 hours. Pooled data demonstrated that intravenous glucocorticoids significantly decreased the VAS at 48 hours (WMD = -1.90 , 95% CI -3.75 to -0.05 , $P = 0.044$; $I^2 = 84.5\%$) (Fig. 5A). A TSA did not confirm the pooled results (Fig. 5B).

Subgroup analysis results are shown in Table 2. The results indicated that high-dose glucocorticoids (equivalency to dexamethasone >10 mg) are more effective than low-dose glucocorti-

coids (equivalency to dexamethasone <10 mg). There was no significant difference between TKA and THA.

3.6. The occurrence of PONV

Four studies (501 participants) reported data on the occurrence of PONV. Compared with placebo, intravenous glucocorticoids significantly decreased the occurrence of PONV (RR = 0.56 , 95% CI 0.44 – 0.73 , $P = 0.000$; $I^2 = 33.1\%$) (Fig. 6A). A TSA did not confirm the pooled results (Fig. 6B).

We plotted the glucocorticoid dose on the abscissa and the corresponding occurrence of PONV to generate a scatterplot. In addition, the linear correlation coefficient (r) was also calculated. A significantly positive correlation between the dosage of glucocorticoids and the occurrence of PONV was found ($r = -0.835$, $P = 0.003$; Fig. 7). The occurrence of PONV tended to decrease as the glucocorticoid dose increased.

3.7. The occurrence of infection

Nine studies (460 participants) reported data on the occurrence of infection. Compared with placebo, intravenous glucocorti-

Table 2

Subgroup analysis of the VAS at 12, 24, and 48 h.

Subgroup	Mean difference		Heterogeneity		Subgroup difference, P value
	Mean (95% CI)	P value	I ² , %	P value	
VAS at 12 h					
Low dose	-7.96 (-8.76, -5.37)	<0.0001	33.5	0.684	0.69
High dose	-12.38 (-13.16, 7.66)	0.016	52.4	0.023	
TKA	-6.59 (-15.23, 2.05)	0.135	58.4	0.135	
THA	-10.40 (-14.18, 6.62)	<0.0001	0.0	0.789	
VAS at 24 h					
Low dose	-2.86 (-6.69, -3.23)	0.005	33.6	0.216	0.02
High dose	-7.31 (-9.32, 2.05)	0.001	58.4	0.108	
TKA	-10.21 (-18.80, 1.63)	0.020	95.9	0.000	
THA	0.40 (-2.47, 3.27)	0.194	0.0	0.164	
VAS at 48 h					
Low dose	-1.10 (-2.04, 1.06)	0.596	76.5	0.031	0.13
High dose	-1.36 (-1.86, 0.96)	0.037	56.4	0.006	
TKA	-2.60 (-4.70, 0.50)	0.015	89.6	0.000	
THA	0.40 (-2.47, 3.27)	0.786	0.0	0.463	

THA = total hip arthroplasty, TKA = total knee arthroplasty, VAS = visual analogue scale.

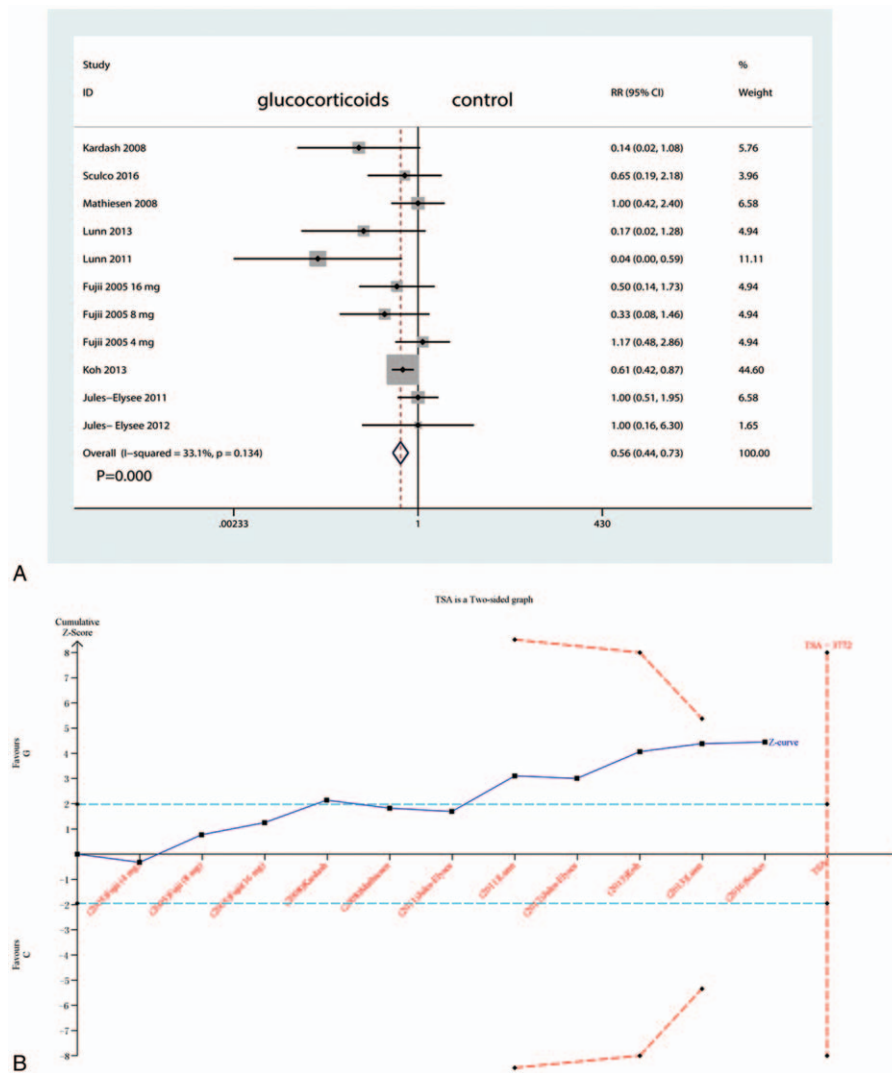


Figure 6. A, Forest plots of the included studies comparing the occurrence of PONV. PONV=postoperative nausea and vomiting; B, Z curve crossed the trial sequential monitoring boundary for benefit (red curve) but did not reach the required sample size based on TSA (n= 1510), entering the area of benefit (above the upper red line).

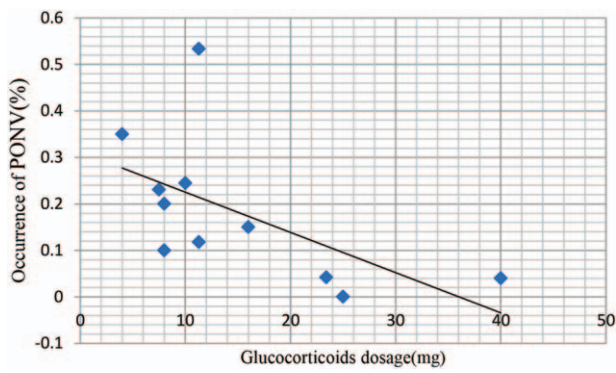


Figure 7. Scatter plot showing the relationship between the changing of glucocorticoid dose and the occurrence of PONV.

coids significantly decreased the occurrence of PONV (RR = 0.71, 95% CI 0.23–2.19, $P = 0.106$; $I^2 = 0.0\%$) (Fig. 8).

3.8. Length of hospital stay

A total of 6 studies (282 patients) were included in the meta-analysis of length of hospital stay. Compared with placebo, intravenous glucocorticoids were associated with a significantly decreased length of hospital stay (WMD = -0.45, 95% CI -1.00 to 0.10, $P = 0.106$; $I^2 = 84.1\%$) (Fig. 9).

3.9. Blood glucose levels after surgery

A total of 4 studies (114 patients) were included in the meta-analysis of blood glucose levels after TJA. There was no significant difference between the blood glucose after TJA

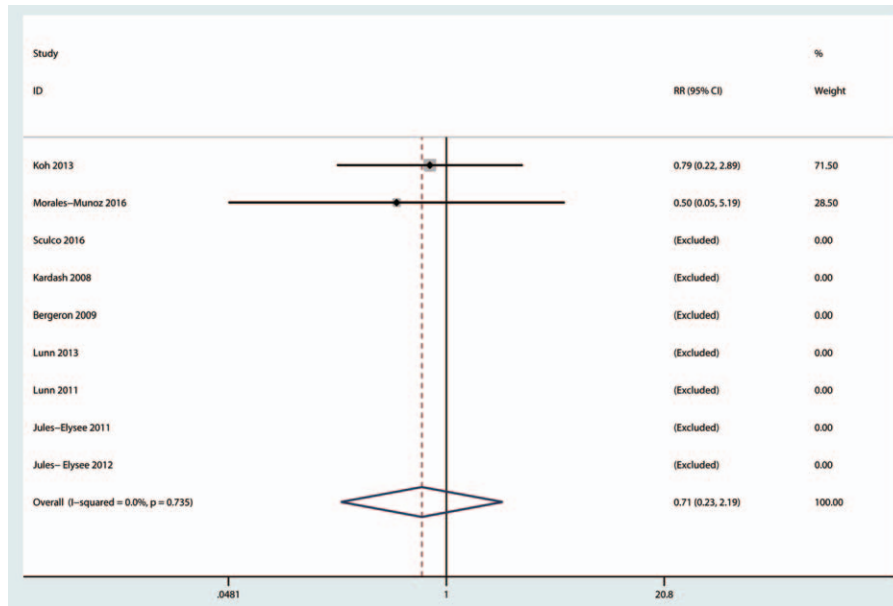


Figure 8. Forest plots of the included studies comparing the occurrence of infection.

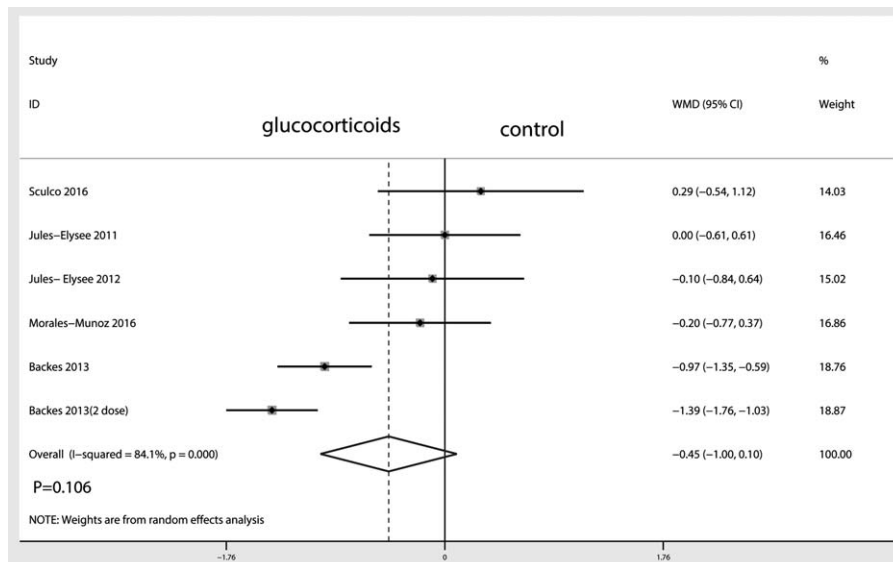


Figure 9. Forest plots of the included studies comparing the length of hospital stay.

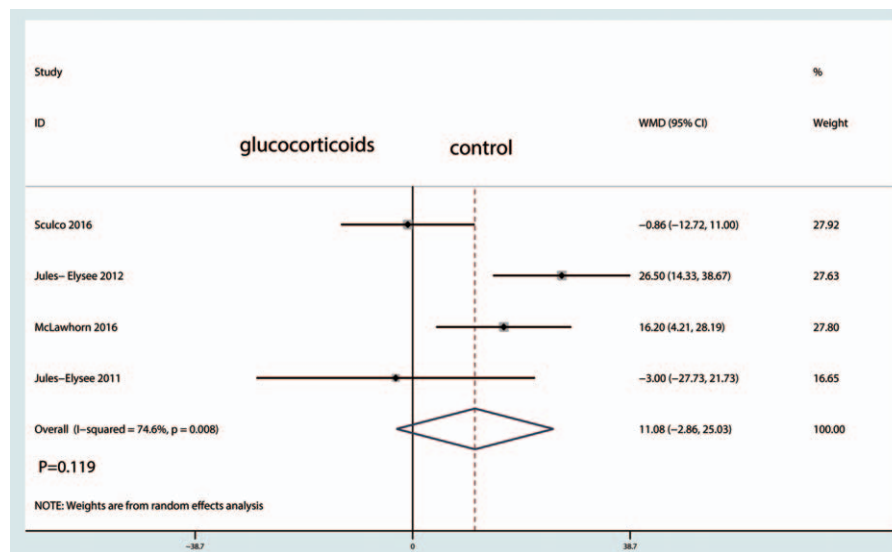


Figure 10. Forest plots of the included studies comparing the blood glucose levels.

(WMD=11.08, 95% CI -2.86 to 25.03, $P=0.119$; $I^2=74.6\%$) (Fig. 10).

4. Discussion

To our knowledge, this is the first meta-analysis and TSA on the effect of intravenous glucocorticoids for TJA. The pooled results showed that intravenous glucocorticoids are effective and safe for the short-term treatment of PONV and pain. Furthermore, there was no significant difference between the length of hospital stay and the occurrence of infection. The TSA results showed that the pooled evidence was robust for VAS at 12 hours follow-up, but requires confirmation for VAS at 24 and 48 hours follow-up. The level of evidence, which was undermined by heterogeneity and/or study design limitations, was moderate or low, indicating that the degree of benefit must be studied, although the benefit is conclusive.

A major strength of the current analysis is the comprehensive search with strict statistical calculations. A previous review found that perioperative administration of glucocorticoids can decrease PONV after knee and hip surgeries.^[28] However, a combined statistical analysis was not conducted. Moreover, studies with intra-articular glucocorticoids were also included and we did not acknowledge whether intravenous glucocorticoids can benefit TJA. Another meta-analysis indicated that perioperative doses of dexamethasone had small but statistically significant analgesic benefits.^[29] The current meta-analysis included all available RCTs that included comparisons of efficacy and safety. A TSA was also performed to consolidate the results, overcoming the shortcomings of conventional meta-analyses. Results indicated that perioperative intravenous glucocorticoids in addition to multimodal anesthesia can decrease pain intensity and PONV after TJA. TSA results indicated that there is no need for further studies to determine the effects of glucocorticoids on VAS at 12 hours. Dexamethasone is commonly given intraoperatively at the time of anesthesia induction to reduce PONV.^[30] De Oliveira Jr et al^[31] revealed that dexamethasone at doses higher than 0.1 mg/kg is an effective adjunct in multimodal strategies to reduce

postoperative pain and opioid consumption after surgery. For VAS at 24 and 48 hours, more trials will be necessary to determine the effects of intravenous glucocorticoids for reducing pain intensity and PONV.

For infection, there was no significant difference between the glucocorticoid and control groups (RR=0.71, 95% CI 0.23–2.19, $P=0.106$). Richardson et al^[32] conducted a retrospective analysis of 6294 patients who underwent TJA and found that a single intravenous dexamethasone dose resulted in no statistically significant difference in the rate of infection after TJA. Toner et al^[33] conducted a meta-analysis of 56 clinical trials, and the evidence did not find any safety concerns with respect to the use of perioperative glucocorticoids and subsequent infection, hyperglycemia, or other adverse outcomes. Waldron et al^[29] revealed that blood glucose levels were higher at 24 hours in the glucocorticoid group than in the control group, with statistical significance. The present meta-analysis results indicated that intravenous glucocorticoids will not increase the blood glucose level compared with the control group. However, blood glucose alterations were specifically mentioned in only 4 trials; more trials should focus on this important side effect.

Our meta-analysis also has several potential limitations: patient treatment with different types and doses of glucocorticoids; marked heterogeneity among the included studies in VAS at 24 and 48 hours, reflecting the inconsistent benefit patients acquired from intravenous glucocorticoids, although these analyses were performed using a random effects model; and the follow-up in the included studies ranging from 1 day to 1 month after surgery. Thus, some adverse events may be underestimated. Finally, some data for comparisons were not originally available but were calculated by estimation, potentially leading to other bias.

5. Conclusions

In conclusion, the present meta-analysis demonstrated that intravenous glucocorticoids can alleviate pain and reduce the incidence of PONV without sacrificing safety. Furthermore, the

anti-emesis effects were dose-dependent. Considering the limitations of the current meta-analysis, the conclusions regarding infection and blood glucose levels should be interpreted cautiously; more RCTs are warranted before making final recommendations.

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