Systematic Review and Meta-Analysis

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A systematic review and meta-analysis of intravenous glucocorticoids for acute pain following total hip arthroplasty

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Abstract

Background: Glucocorticoids are increasingly used perioperatively, principally to prevent postoperative nausea and vomiting (PONV), and acute postoperative pain following total hip arthroplasty (THA). The authors hypothesized that preoperative intravenous glucocorticoids is associated with less pain scores and PONV without increasing the complications after THA.

Methods: Four databases (PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science) were searched with the limitations of randomized controlled trials (RCTs). The search cutoff date was set at November 6, 2016. Participants were patients who were prepared for primary THA. Intervention was preoperative intravenous glucocorticoids for postoperative pain control. Outcomes including the visual analog scale (VAS) scores at the postanesthesia care unit (PACU) and at 24 and 48 hours post operation, the occurrence of PONV and total morphine consumption were recorded. We calculated risk ratio (RR) with a 95% confidence interval (CI) for dichotomous outcomes, and the weighted mean difference (WMD) with a 95% CI for continuous outcomes.

Results: A total of 6 studies were evaluated, which included 297 patients who underwent hip surgery with intravenous glucocorticoid treatment and control patients who underwent hip surgery without glucocorticoid treatment. Pooled results indicated that intravenous glucocorticoid treatment was associated with a reduction of VAS scores at the PACU (WMD = −9.06, 95% CI −12.67 to −5.45, $P = .000$) and total morphine consumption by 15.68 mg (WMD = −15.68, 95% CI −24.60 to −6.75, $P = .001$). No significant difference was observed in the VAS scores at 24 and 48 hours between the intravenous glucocorticoid and placebo treatments. Intravenous steroids can decrease the occurrence of PONV (RR = 0.46, 95% CI 0.26–0.82, $P = .029$).

Conclusion: Intravenous glucocorticoid treatment can decrease early pain intensity and PONV after THA. However, the evidence for the use of glucocorticoids is limited by the low number of studies and variation in dosing regimens. Thus, additional high-quality RCTs are needed to identify the optimal drug protocol and determine the safety of intravenous glucocorticoids.

Abbreviations: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, PACU = postanesthesia care unit, PONV = postoperative nausea and vomiting, RCT = randomized controlled trial, RR = risk ratio, THA = total hip arthroplasty, VAS = visual analog scale, WMD = weighted mean difference.

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

1. Introduction

In recent years, total hip arthroplasty (THA) has been used as an effective measure for the treatment of elderly patients with end-stage hip osteoarthritis. The incidence of postoperative nausea and vomiting (PONV) is significantly higher than that of postoperative pain and anemia.[1] Several studies have shown that the incidence of PONV in major orthopedic surgeries was between the range of 20% to 83%, and appropriately 85.9% of PONV occurred within 6 hours after surgery.[2–4] PONV seriously affects the subjective feelings of patients after surgery, reduces postoperative satisfaction, prolongs the length of hospital stay, and increases the psychological and economic burden of patients.[5–7] The use of opioids is classically used as the first alternative to control acute pain after THA; however, opioids will increase the occurrence of PONV and other intolerable complications.[8,9]

Glucocorticoids have potent anti-inflammatory, analgesic, and antiemetic effects. Glucocorticoids inhibit inflammatory gene expression and enhance oxidation activity to exert an analgesic effect.[10] These results indicate that intravenous glucocorticoids are potentially effective agents for reducing acute pain and PONV after THA. However, inconsistencies have been identified regarding pain relief and the morphine-sparing effects after intravenous glucocorticoids for THA.[11–13] Considering all of these issues, it is impossible to give clear advice regarding whether to adopt preoperative intravenous glucocorticoids as adjunct treatment to multimodal anesthetic management. In this study,

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we aimed to summarize the existing evidence from randomized controlled trials (RCTs) to determine whether preoperative intravenous glucocorticoid treatment was superior than control treatment with respect to pain scores, total morphine consumption, and PONV and additional postoperative complications. We hypothesized that preoperative intravenous glucocorticoid treatment results in lower pain scores, total morphine consumption, and PONV than controls.

2. Materials and methods

2.1. Search strategy and study selection

Four databases (PubMed, Embase, the Cochrane Central Register of Controlled Trials [CENTRAL], and Web of Science) were searched from inception to November 6, 2016 with the limitations of human subjects and RCTs. The details of the search strategy are shown in Supplement S1, http://links.lww.com/MD/B695. There were no restrictions on language and publication status. Relevant review studies and reference lists were also manually searched for additional relevant missing studies. Gray academic studies are also identified from the reference of included studies. A meta-analysis was performed to collect relevant data from published articles, and thus no ethics committee was needed for approval.

2.2. Eligibility criteria

According to the PICOS rule, the eligible criteria were as follows:

(i) Participants: Patients were prepared for primary THA.
(ii) Interventions: The experimental group received preoperative intravenous administration of glucocorticoids. Dosage and time of intravenous glucocorticoids were not limited in our search process.
(iii) Comparisons: The comparison group received a placebo or no intravenous treatment.
(iv) Outcomes: The visual analog scale (VAS) scores were recorded at the postanesthesia care unit (PACU) and at 24 and 48 hours after the THA, and total morphine consumption and the occurrence of PONV were recorded.
(v) Study design: Only RCTs were included. Any non-RCTs, quasi-RCTs, retrospective studies, reviews, and protocols were excluded. Disagreements were resolved by consensus.

2.3. Data extraction and outcome measures

Two authors (XL and ZS) independently extracted the first author name, publication year, the number of patients in intervention groups and control group, the proportion of male patients, and the mean age of the patients in the 2 groups, the anesthesia methods, the dose of glucocorticoids and equivalence to dexamethasone and controls, study type and duration of follow-up. The outcomes were assessed for the VAS scores at the PACU and at 24 and 48 hours post operation, the occurrence of PONV and total morphine consumption. Where papers only provide median (range) data, we convert these to mean (standard deviation) data following an established protocol.[14]

2.4. Methodological quality appraisal

Study methodological assessment was conducted by the 2 authors (BW and LH) using the modified Jadad scale following an established protocol.[15] There were a total of 8 items described: randomization, method of randomization, blinded analysis, blinding analysis methodology, withdrawal or dropouts, inclusion/exclusion criteria, adverse effects, and statistical analysis. The score for each item ranged from 0 to 1. In addition, total score ranges from 0 to 3 were identified as poor or low quality. Scores of 4 to 8 denoted high quality.

2.5. Quality of evidence assessment

Two reviewers (CH and LH) independently evaluated the quality of evidence assessment in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[16] The assessment items included the risk of bias, inconsistency, indirectness, imprecision, and publication bias.[16,17] Each result was classified as high, moderate, low, or very low. GRADE Pro software (GRADEpro, version 3.6) was used to construct summary tables for the included studies.

2.6. Statistical analysis

Weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for continuous variables. Risk ratio (RR) and the corresponding 95% CI were calculated for discontinuous variables. Heterogeneity was divided into 3 grading categories (0%–30% = low heterogeneity, 30%–60% = middle heterogeneity, and 60%–100% = high heterogeneity). A random-effects model was applied to all of the results due to the heterogeneity between the studies. Funnel plots and Egger linear regression test was performed to test the publication bias. All statistical analyses were conducted using Stata 12.0 (Stata Corp., College Station, TX). Different types of glucocorticoid treatments were converted to equal dexamethasone dosage (0.75 mg dexamethasone = 4 mg methylprednisolone = 5 mg prednisolone = 20 mg hydrocortisone).[11] $P < .05$ was used to denote statistical significance.

3. Results

3.1. Search results

The literature search and selection processes are shown in Fig. 1. In the initial search, a total of 585 relevant studies were identified, of which 256 studies were from PubMed, 129 from Embase, 99 from CENTRAL, and 101 from Web of Science. All of the included studies were imported into the Endnote Software (Version X7; Thompson Reuters, Sunnyvale, CA) to remove duplicates. The titles and abstracts of a total of 462 papers were read, and 401 papers were excluded as they did not fulfill the inclusion criteria. Full-text studies were then obtained, and 55 papers were excluded. One study only compared the incidence of deep venous thrombosis between a glucocorticoid-treated group and a nonglucocorticoid-treated group and was thus excluded.[18] Finally, we included 6[12,19–23] RCTs (total = 297 patients, glucocorticoid treatment group = 152, and controls = 145) for current meta-analysis.

3.2. General characteristic of the included studies

The detailed baseline characteristics of the included studies were presented in Table 1. Two studies were published in the year of 2008,[12,22] 1 study was published in the year of 2009,[21] 1 study was published in the year of 2010,[24] 1 study was published in the year of 2013,[23] and 1 was published in the year of 2016.[20]

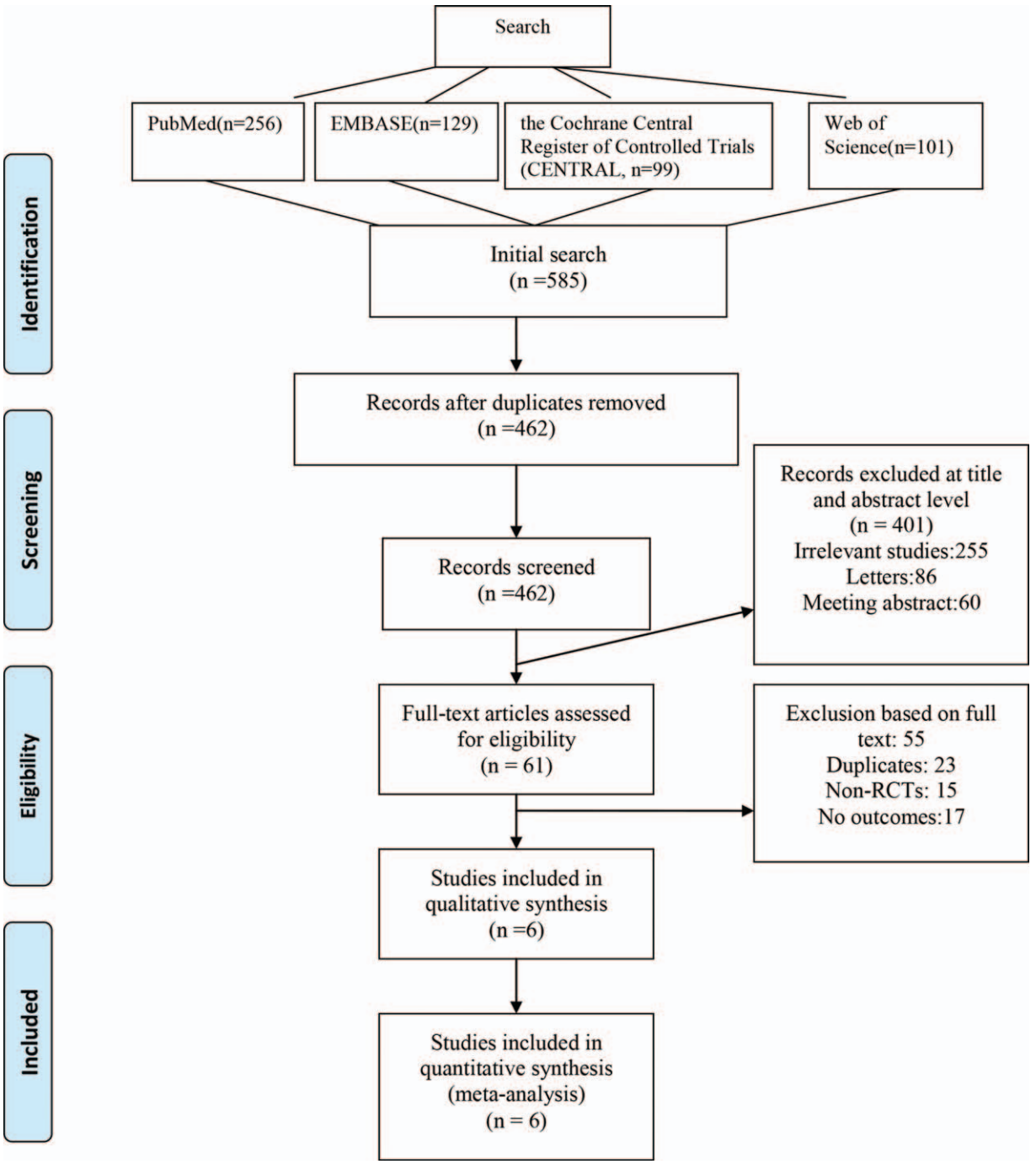

Figure 1. Flowchart of systematic database search and study selection.

The sample size in the glucocorticoid-treated group ranged from 14 to 40, and sample size in the control group ranged from 13 to 40. The doses of glucocorticoids that are equivalent to dexamethasone ranged from 7.5 to 40 mg.

3.3. Risk of bias

The details of the risk of bias assessment and the modified Jadad scores are shown in Table 2. The modified Jadad score for Sculco et al,[20] Rasmussen et al,[24] Kardash et al,[12] Bergeron et al,[21] Mathiesen et al,[22] and Lunn et al[23] was 6, 7, 6, 6, 7, and 8, respectively.

3.4. Quality of evidence assessment

A summary of the quality of the evidence according to the GRADE approach is shown in Supplement S2, http://links.lww.com/MD/B695. The GRADE level of evidence was low for the VAS scores at the PACU and at 24 hours and was very low for the VAS scores at 48 hours as well as for the occurrence of PONV and total morphine consumption.

3.5. Primary outcomes

3.5.1. VAS scores at the PACU. Five studies[12,20,22–24] (247 THAs) provided the data of preoperative intravenous glucocorti-

Table 1

The general characteristic of the included studies.

Author and year	No. of patients (n)		Male (%)		Mean age, y		Anesthesia	Drugs		Outcomes	Study design	Follow up	Jadad scale
	G	C	G	C	G	C		G (Equivalence to Dexa)	C				
Sculco (2016)	14	13	46.9	56.4	66		SA/EA	Hydr 200 mg (7.5 mg)	Placebo	1, 2, 3, 4, 5, 6, 7, 8	RCTs	3 mo	6
Rasmussen (2010)	24	18	57.1		68		SA	Dexa 8 mg (8 mg)	Saline	1, 2, 3, 4, 7, 8	RCTs	3 mo	7
Kardash (2008)	25	25	50.4		68		SA	Dexa 40 mg (40 mg)	Saline	1, 2, 3, 4, 7, 8	RCTs	1 mo	6
Bergeron (2009)	25	25	41.8		NS		SA	Dexa 40 mg (40 mg)	Saline	8	RCTs	6 mo	6
Mathiesen (2008)	40	40	50.7		67		SA	Dexa 8 mg (8 mg)	Placebo	1, 2, 4, 7, 8	RCTs	24 h	7
Lunn (2013)	24	24	44.2		66		SA	MP 125 mg (23.43 mg)	Saline	1, 4, 8	RCTs	30 d	8

C = control group, Dexa = dexamethasone, EA = epidural anesthesia, G = glucocorticoid treatment group, Hydr = hydrocortisone, P = methylprednisolone, SA = spinal anesthesia; 1, VAS scores at the PACU; 2, VAS scores at 24 hours; 3, VAS scores at 48 hours; 4, the occurrence of PONV; 5, length of hospital stay; 6, the blood glucose; 7, total morphine consumption; 8, the occurrence of infection.

coids on the VAS scores at the PACU. Compared with the placebo group, intravenous glucocorticoids treatment was associated with a significant reduction in the VAS scores at the PACU (WMD = −9.06, 95% CI −12.67 to −5.45, $P = .000$), with low heterogeneity between the included studies ($I^2 = 9.0\%$, $P = .355$) (Fig. 2).

3.5.2. VAS scores at 24 hours post operation. Five studies[12,20,22–24] (247 THAs) were included in this meta-analysis to estimate the effect of preoperative intravenous glucocorticoid treatment on the VAS at 24 hours. No statistically significant difference was observed in the VAS scores at 24 hours between the intravenous glucocorticoid-treated group and the placebo group (WMD = −3.59, 95% CI −7.34 to 0.55, $P = .089$), with no heterogeneity between the included studies ($I^2 = 0.0\%$, $P = .880$) (Fig. 3).

3.5.3. VAS scores at 48 hours post operation. Three trials[12,20,24] (247 THAs) were available to provide the data of preoperative intravenous glucocorticoids on the VAS scores at 48 hours. The final results indicated that no statistically significant difference was found between the glucocorticoid treatment group and the control group in terms of the VAS scores at 48 hours (WMD = −0.74, 95% CI −2.82 to 1.35, $P = .489$), with low heterogeneity ($I^2 = 0.0\%$, $P = .405$) (Fig. 4).

3.5.4. The occurrence of PONV. Five studies[12,20,22–24] (247 participants) reported data on the occurrence of PONV. Compared with the placebo, intravenous glucocorticoid treatment significantly decreased the occurrence of PONV by 10.9% (RR = 0.46, 95% CI 0.26–0.82, $P = .029$), with low heterogeneity ($I^2 = 36.0\%$, $P = .181$) (Fig. 5).

3.5.5. Total morphine consumption. A total of 4 studies[12,20,22] (199 THAs) were available in the meta-analysis. Compared with the placebo group, intravenous glucocorticoid treatment was associated with a significant decrease in total morphine consumption by 15.68 mg (WMD = −15.68, 95% CI −24.60 to −6.75, $P = .001$), with moderate heterogeneity ($I^2 = 61.6\%$, $P = .050$) (Fig. 6).

3.6. Other outcomes

Sculco et al[20] reported the blood glucose and the length of hospital and found no significant difference between the glucocorticoid treatment group and the control group. Bergeron et al[21] reported the Harris scores at 6 weeks and 1 year follow-up and found that no significant difference between the glucocorticoid treatment group and the control group.

4. Discussion

To our knowledge, this is the first meta-analysis including only RCTs that compares the efficacy and safety of intravenous glucocorticoid treatment as an adjunct with multimodal anesthesia for patients prepared for primary THA. Pooled results indicated that intravenous glucocorticoid treatment, compared with the placebo group, was associated with a significant reduction in the VAS scores at the PACU, the occurrence of PONV, and total morphine consumption. There were no significant differences between the VAS scores at 24 and 48 hours between the glucocorticoid treatment group and the control group after THA; however, the efficacy of preoperative intravenous glucocorticoid treatment was limited in the first 24 hours. The level of evidence, which was undermined by heterogeneity, was low or very low, indicating that the advantage exists but the degree to which it does must be further studied.

Intravenous glucocorticoid treatment had a beneficial role on the VAS score at the PACU. There were no significant differences

Table 2

Methodological assessment of eligible studies using the modified Jadad scale.

Item assessed	Sculco (2016)	Rasmussen (2010)	Kardash (2008)	Bergeron (2009)	Mathiesen (2008)	Lunn (2013)
Was the study described as randomized?	×	√	√	√	√	√
Was the method of randomization appropriate?	×	×	×	×	×	√
Was the study described as blinded?	√	√	√	√	√	√
Was the method of blinding appropriate?	√	√	×	×	√	√
Was there a description of withdrawals and dropouts?	√	√	?	√	√	√
Was there a clear description of the inclusion/exclusion criteria?	√	√	×	√	√	√
Was the method used to assess adverse effects described?	√	√	√	√	√	√
Was the method of statistical analysis described?	√	√	√	√	√	√
Total score	6	7	6	6	7	8

√ = yes, × = no, ? = not described.

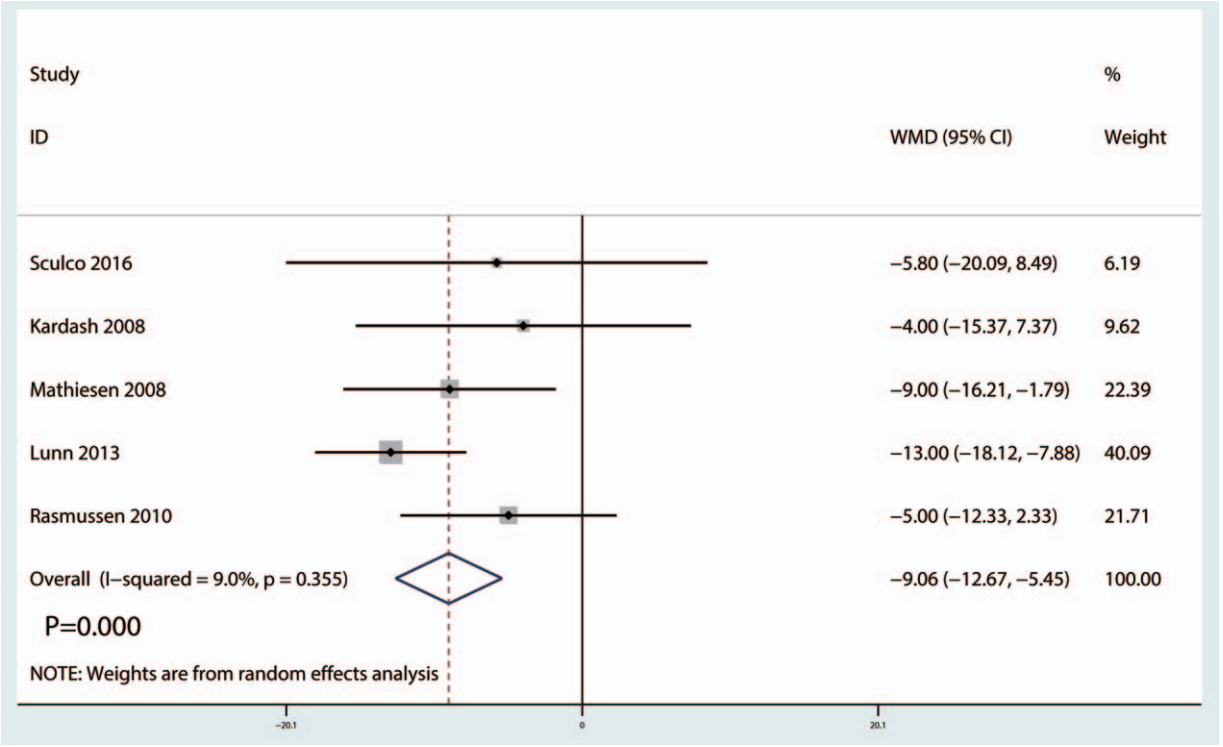

Figure 2. Forest plots of the included studies comparing the visual analog scale scores at the postanesthesia care unit.

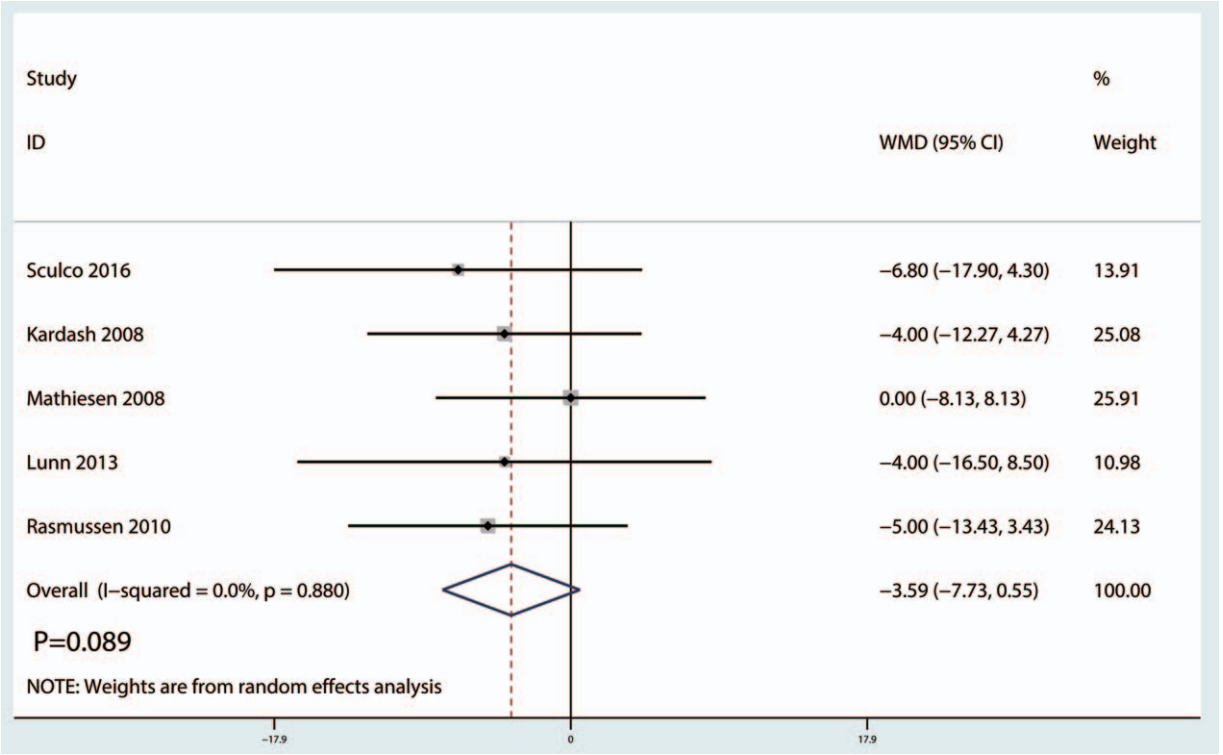

Figure 3. Forest plots of the included studies comparing the visual analog scale scores at 24-hour post operation.

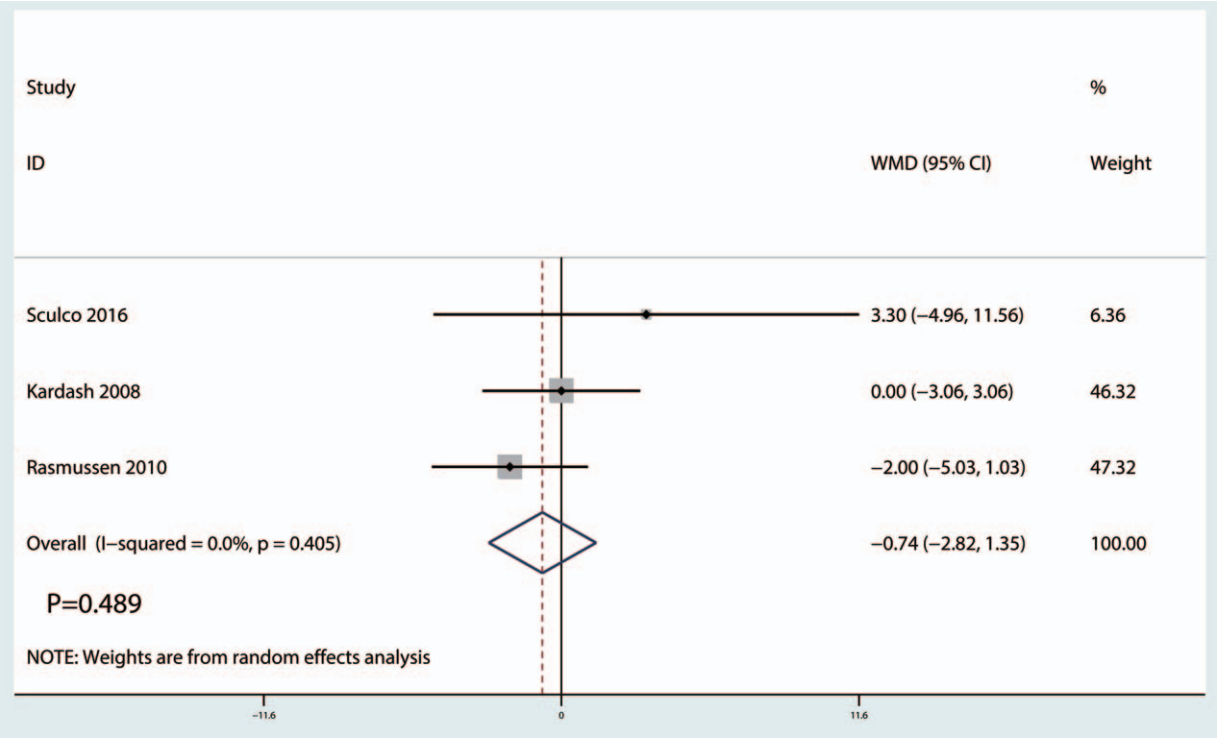

Figure 4. Forest plots of the included studies comparing the visual analog scale scores at 48-hour post operation.

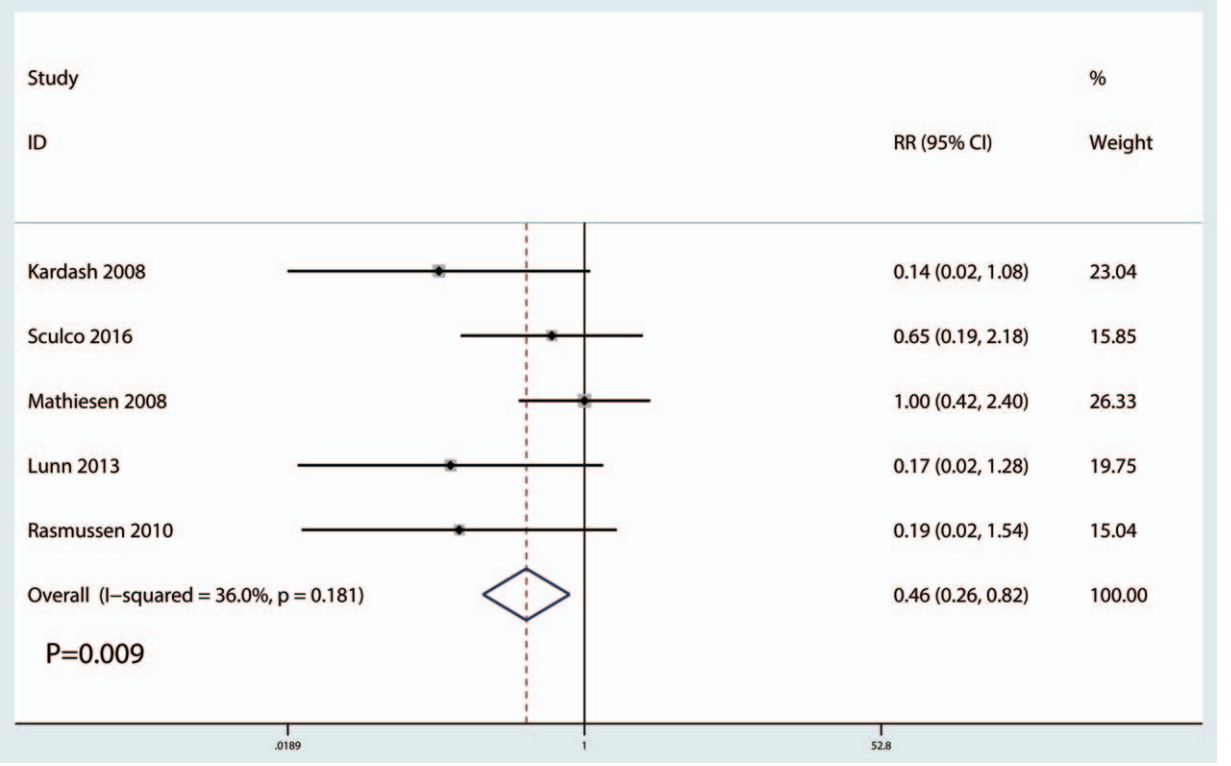

Figure 5. Forest plots of the included studies comparing the occurrence of postoperative nausea and vomiting.

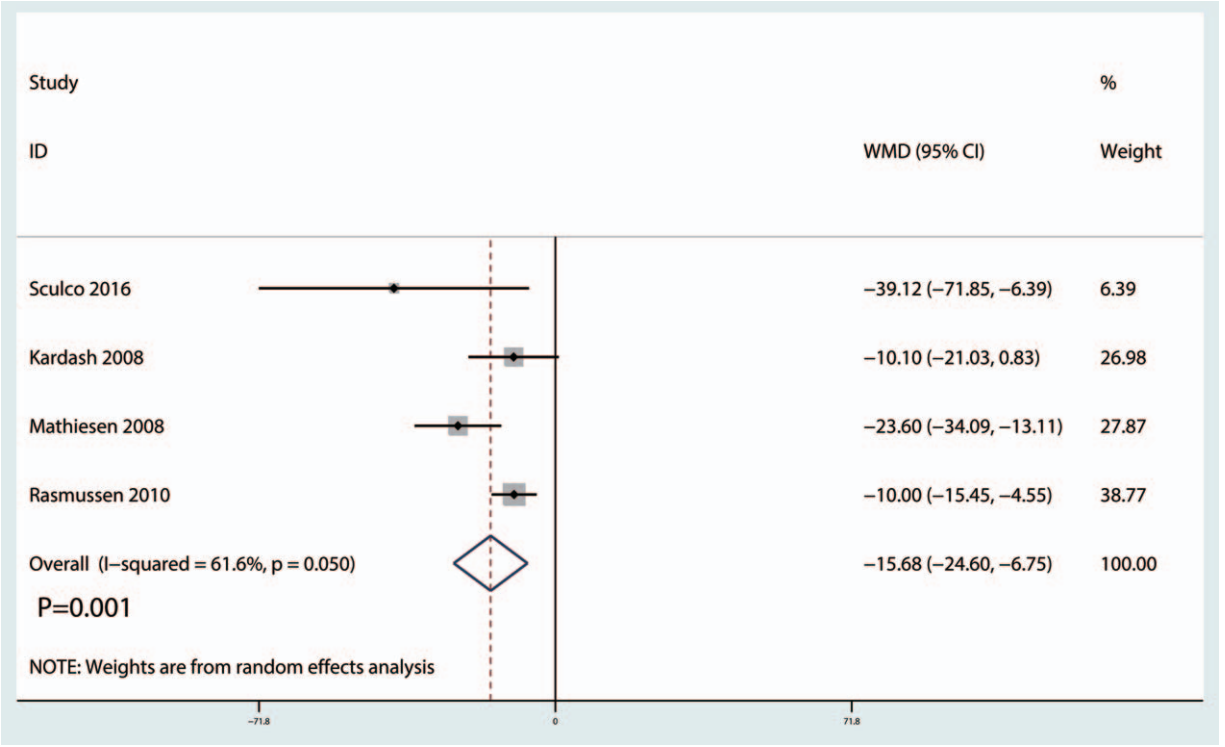

Figure 6. Forest plots of the included studies comparing the total morphine consumption.

between the VAS score at 24 and 48 hours after THA. De Oliveira et al[25] compared the efficacy of intravenous glucocorticoid treatment for patients with all types of surgeries and found that preoperative intravenous glucocorticoid treatment was effective in reducing postoperative pain. The limitation of the above meta-analysis was that the participants had undergone all types of surgeries; thus, a large degree of heterogeneity in the group existed. The strength of the current meta-analysis was that we only included THA patients. Moreover, we used a random-effect model to analyze the relevant data to avoid heterogeneity between the included samples.

Intravenous glucocorticoid treatment was associated with a significant reduction of PONV. Our findings have important clinical implications, as intravenous glucocorticoids are commonly given intraoperatively at the time of anesthesia induction to reduce PONV.[26] Previously, updated meta-analysis including 60 RCTs with 6696 subjects indicated that the 4-mg to 5-mg dose regimen of systemic dexamethasone is beneficial in reducing the occurrence of PONV.[27] Fujii and Nakayama[28] found that the rates of emesis-free effects were increased in dexamethasone groups treated with 8 and 16 mg compared with those treated with 4 mg of dexamethasone. Liu et al[29] found 2.5 mg to be the minimum effective dose for antiemesis without discernible side effects.

Glucocorticoids are not, however, without harm.[30] The long-term side effects of glucocorticoids involve most major organ systems. However, the relative short-term use of glucocorticoids has mainly been focused on blood glucose, wound healing and wound superficial, and deep infection. Postoperative infections are important as they prolong hospital stay, increase costs, and impact postoperative mortality, which extends to at least to 30 days.[31] The outcomes did not include blood glucose levels, as there were no sufficient data to comprise for meta-analysis. Sculco et al[20] revealed that blood glucose levels were elevated in the glucocorticoid treatment group, with statistically significant differences at the PACU after THA. Many studies have shown that a single dose of dexamethasone (less than 20 mg) does not cause increased incidence of adverse reactions after surgery.[32,33] Among the included studies, there were no significant differences between blood glucose levels and the occurrence of infection. Waldron et al[34] found that intravenous glucocorticoids were not accompanied by an increased risk of infection or delayed wound healing. Toner et al[35] found that the use of perioperative glucocorticoid treatment was not associated with an increase of infection, hyperglycemia, or other adverse outcomes.

The limitations of this study were as follows: the relatively small sample size of each primary study, especially that of Sculco et al[20]; in some RCTs, the random sequence generation and allocation concealment methods were not described, which may influence the stability of our outcomes to some extent; differences in surgical time, technique, approaches, and postoperative pain protocols may have influenced the final results; the length of follow-up times differed and the complications were underestimated to some extent; and the dose and type of glucocorticoid used in each of the primary studies differed, though a subgroup analysis was performed. Additional RCTs are needed to identify the optimal dose and type of glucocorticoid treatment.

5. Conclusion

Current present meta-analysis favors intravenous glucocorticoid treatment for the alleviation of acute postoperative pain and the reduction of the occurrence of PONV in patients following THA. Another main finding was that the antiemesis effects were dose-dependent. However, the evidence for the use of glucocorticoid treatment is limited by the low quality of studies and variation

dosing regimens. Thus, more RCTs are required to verify the optimal dose and type of glucocorticoid treatment for THA.

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