

Intravenous glucocorticoid for pain control after spinal fusion

A meta-analysis of randomized controlled trials

Feng Wang, MD, Keqin Shi, MD, Yu Jiang, MD, Zhengjie Yang, MD, Gang Chen, MD, Kerong Song, MD*

Abstract

Objective: Postoperative pain was a common symptom after spinal surgery. This meta-analysis aimed to assess whether intravenous glucocorticoids has a beneficial role in reducing pain in patients following spinal fusion.

Methods: We systematically searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and Google databases, from inception to March 2, 2018. Randomized controlled trials (RCTs) that comparing intravenous glucocorticoids with control treatment for spinal fusion were included. A meta-analysis was performed to generate pooled risk ratio (RR) and weighted mean difference with corresponding 95% confidence interval (CI) for discontinuous outcomes (the occurrence of nausea and infection) and continuous outcomes (visual analog scale [VAS] at 12, 24, and 48 h; total morphine consumption; and the length of hospital stay), respectively.

Results: Eight clinical trials involving 918 patients (glucocorticoid group=449, control group=469) were finally included in this meta-analysis. Compared with control, intravenous glucocorticoids had significantly reduced VAS at 12, 24, and 48 hours with statistically significance ($P < .05$). Intravenous glucocorticoids can decrease the occurrence of nausea (RR=0.42, 95% CI 0.29–0.62, $P=.000$; $I^2=0.0\%$) and the length of hospital stay. No difference was noticed in the occurrence of infection between glucocorticoids intravenous and control ($P > .05$).

Conclusion: Existing evidence indicated that intravenous glucocorticoids have a beneficial role in decreasing early pain and the occurrence of nausea after spinal fusion surgery. In consideration of the limitation in current meta-analysis, more high-quality RCTs were needed to identify the optimal dose of glucocorticoids in spinal fusion patients.

Abbreviations: 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, RCT = randomized controlled trial, RR = risk ratio, TJA = total joint arthroplasty, VAS = visual analog scale, WMD = weighted mean difference.

Keywords: glucocorticoids, meta-analysis, pain control, spinal fusion surgery

1. Introduction

Spinal interbody fusion has become a widely accepted technique for addressing pathology in spine.^[1,2] However, several patients will underwent acute pain and chronic pain after surgery.^[3] This resulting in a major challenging to manage. Adequate pain control after a spinal surgery is a prerequisite to enable early mobilization, which leads to improved functional recovery and

enhance patient satisfaction.^[4] Multiple pain control was usual in modern surgical spine care.^[5]

Glucocorticoids have attracted increasing attention as possible analgesic adjuvants in the treatment of acute postoperative pain.^[6,7] However, the benefit versus harm of intravenous glucocorticoids in spinal infusion patients is still undetermined. Thus, we conducted a meta-analysis from randomized controlled trials (RCTs) to conclude whether intravenous glucocorticoids was associated with a reduction of pain intensity and postoperative nausea and vomiting (PONV) after spinal fusion.

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Orthopedics Department, Nanjing Medical University Affiliated Wuxi Second Hospital, Wuxi, China.

* Correspondence: Kerong Song, Orthopedics Department, Nanjing Medical University Affiliated Wuxi Second Hospital, No. 68 Zhongshan Road, Wuxi, 214002, China (e-mail: chunfengburu@163.com).

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2. Materials and methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions^[8] and was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.^[9]

2.1. Search strategy and study selection

Electronic databases (PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and Google database) were searched from their inception until October 29, 2017. Free text and MeSH terms “dexamethasone,” “betamethasone,”

“triamcinolone,” “prednisone,” “pain,” “postoperative,” “preoperative,” “analgesia,” and “opioid” were used individually and in various combinations with AND or OR. No language restriction was used. An attempt to identify additional studies not found by the primary search methods was made by reviewing the reference lists from identified studies. Meta-analysis was collected from published data and thus ethical review or approved was not necessary.

2.2. Eligibility criteria

1. Participants: Patients undergoing spinal fusion.
2. Interventions: The comparison group was with an intravenous administration of glucocorticoids.
3. Comparisons: The comparison group was with saline or nothing.
4. Outcomes: Visual analog scale (VAS) at 12, 24, and 48 hours after spinal fusion, the occurrence of nausea, the incidence of infection, and length of hospital stay after spinal fusion.
5. Study design: Only RCTs were included.

2.3. Data extraction and outcome measures

Two authors (FQ and KQS) 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 discussion. Different types of glucocorticoids were converted to equivalence to dexamethasone: 0.75 mg dexamethasone = 4 mg methylprednisolone = 5 mg prednisolone = 20 mg hydrocortisone.^[10] The outcomes were VAS at 12, 24, and 48 hours; the occurrence of nausea; the length of hospital stay; and the occurrence of infection after spinal fusion surgery. If the data were presented in figures or other forms, we used GetData Graph Digitizer software to extract relevant data.^[8]

2.4. Risk of bias assessment and quality of evidence assessment

Two authors (YJ and ZJY) independently evaluated the risk of bias of included RCTs and written in Reviewer Manager 5.3.0.^[8] The assessment criteria included the following 7 domains: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. All domains were evaluated as “low,” “high,” or “unclear” according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.3.0)^[8] and the risks of bias were drawn by the Review Manager 5.3.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Kappa values were used to measure the degree of agreement between the 2 reviewers.^[11] Two reviewers (GC and KRS) independently evaluated the quality of evidence assessment in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).^[12] Each item was classified as high, moderate, low, or very low.^[12,13]

2.5. Statistical analysis

For VAS at 12, 24, and 48 hours; the length of hospital stay; and the length of hospital stay after spinal fusion surgery, the

weighted mean difference (WMD); and 95% confidence interval (CI) were calculated. For dichotomous outcomes (the occurrence of nausea and infection), we calculated the risk ratio (RR) and 95% CI. Heterogeneity was considered to be statistically significant if the I^2 value was >50%. A fixed-effects model was applied if the I^2 value was <50%. All statistical analyses were conducted using Stata 12.0 (Stata Corp, College Station, TX). The subgroup analysis was conducted based on the dose of glucocorticoids (≥ 10 mg [high dose] or <10 mg [low dose]) and total knee arthroplasty (TKA) or total hip arthroplasty. The relationship between glucocorticoid dosage and the occurrence of PONV was explored using SPSS software (SPSS Corp, Los Angeles). The correlation coefficient (r) was used to assess the relationship between glucocorticoid dosage and the occurrence of PONV. A P value <.05 was considered statistically significant.

3. Results

3.1. Search results and quality assessment

In the initial search, 356 articles were selected for full-text screening. Then, we used Endnote X7 (Thomson Reuters Corp, Los Angeles) software to remove the duplicate articles (48 articles were removed). Next, Then, according to the inclusion criteria, 209 articles were removed after reading the titles and abstracts. Finally, we included 8 RCTs^[14–21] with 918 patients (glucocorticoid group = 449, control group = 469, Fig. 1) in this meta-analysis. The general characteristic of the included RCTs can be seen in Table 1. The sample ranged from 19 to 146. The mean age ranged from 36.8 to 55.2. We converted glucocorticoid equivalent to the dose of dexamethasone and the dose ranged from 3 to 80 mg. Risk of bias summary and risk of bias graph can be seen in Figures 2 and 3, respectively.

3.2. Results of the meta-analysis

3.2.1. Visual analog scale at 12, 24, and 48 hours. There were 8 studies with a total of 374 patients taking intravenous glucocorticoid and 433 patients on the control treatment in this group. Intravenous glucocorticoid can decrease VAS scores at 12 hours (WMD = -8.41, 95% CI -13.59, -3.23, $P = .001$, $I^2 = 94.4\%$, Fig. 4, GRADE: very low).

Compared with control treatment, intravenous glucocorticoid can reduce VAS scores at 24 hours (WMD = -7.46, 95% CI -11.17, -3.74, $P = .000$, $I^2 = 83.7\%$, Fig. 4, GRADE: very low) after spinal fusion surgery.

Four studies with 448 patients (glucocorticoid group = 201, control group = 247) included VAS scores at 48 hours. Intravenous glucocorticoid was associated with fewer VAS scores at 48 hours than control treatment (WMD = -13.99, 95% CI -20.28, -7.71, $P = .000$, $I^2 = 90.0\%$, GRADE: very low Fig. 4).

3.2.2. Total morphine consumption. Six studies (523 participants) reported data on the total morphine consumption. Compared with placebo treatment, intravenous glucocorticoids significantly decreased the total morphine consumption by 5.53 mg (WMD = -5.53, 95% CI -8.02 to -3.04, $P = .000$; $I^2 = 73.4\%$, GRADE: very low; Fig. 5).

3.2.3. Length of hospital stay. A total of 3 studies (307 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 = -0.95, 95% CI -1.47 to -0.43, $P = .000$; $I^2 = 44.4\%$, GRADE: very low; Fig. 6).

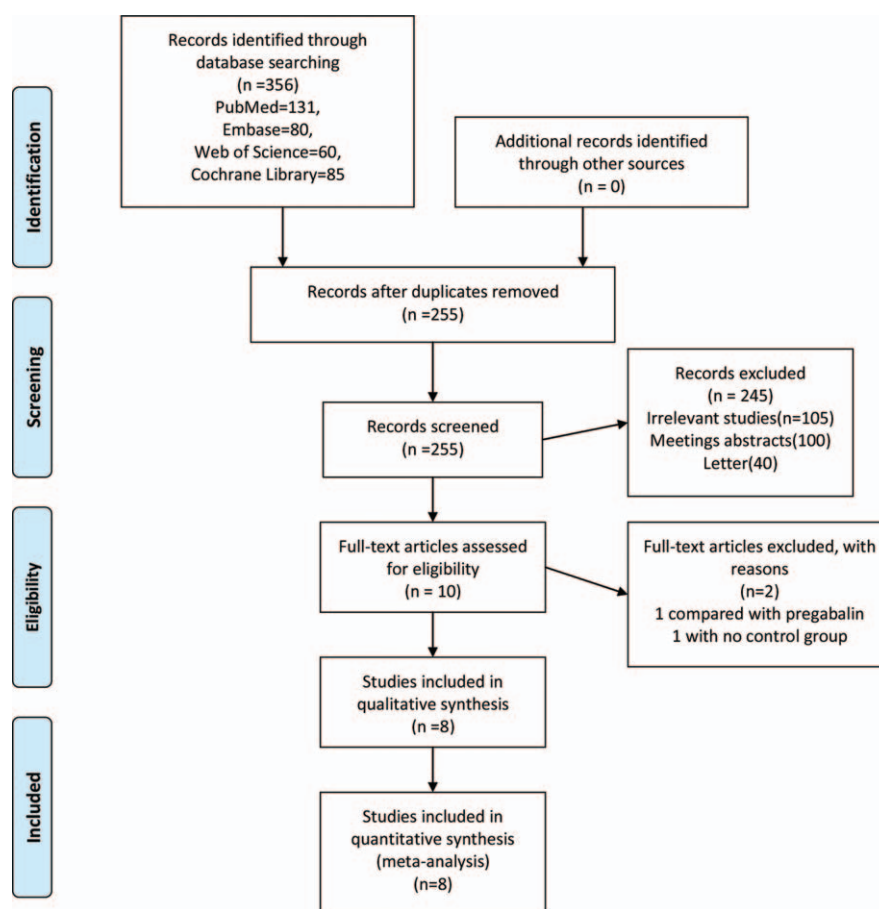


Figure 1. Flowchart of the study search and inclusion criteria.

3.2.4. The occurrence of nausea. Five studies (523 participants) reported data on the occurrence of nausea. Compared with placebo, intravenous glucocorticoids significantly decreased the occurrence of nausea (RR=0.42, 95% CI 0.29–0.62, $P=.000$; $I^2=0.0\%$, GRADE: very low; Fig. 7).

3.2.5. The occurrence of infection. Six studies (495 participants) reported data on the occurrence of infection. There was no significant difference between the glucocorticoid group and

control group in the occurrence of infection (RR=0.91, 95% CI 0.34–2.38, $P=.841$; $I^2=0.0\%$, GRADE: very low; Fig. 8).

4. Discussion

This is the first meta-analysis that comparing intravenous glucocorticoid for pain control after spinal fusion. After strictly search, we finally included 8 RCTs and final results indicated that intravenous glucocorticoid has positive role in reducing pain

Table 1
The general characteristic of the included studies.

Author	Country	No of patients (S)	Control group (n)	Age (S:C)	Sex (% male)	Equivalency to dexamethasone, mg	Interval of S	Control	Postoperative anesthesia
Aminmansour, 2006	Iran	Arm 1=19 Arm 2=20	22	36.8 39.3	52 49	40 80	Single dose	Saline Placebo	LIA and FNB ECA
Bednar, 2015	Canada	132	146	55.2/54.0	31	16	Single dose	Saline	CFNB
Choi, 2013	Korea	36	36	54/53	59	20	Two doses	Saline	FNB and ECA
Jeyamohan, 2015	USA	56	56	55/54	48.2	20	Three doses	Saline	NS
Lundin, 2003	Sweden	38	42	40.0/42.1	38.5	15	Three doses	Saline	ECA
Nielsen, 2015	Denmark	77	76	45/45	39.1	40	Three doses	Saline	PCA
Watters, 1989	USA	31	29	53.4/50.6	55.4	6	Three doses	Saline	ECA
Wittayapairoj, 2017	Thailand	40	40	58.8/57.7	82.2	12	Single dose	Placebo	PCA

C= control group, CFNB=continuous femoral nerve block, EA=epidural anesthesia, ECA=epidural controlled anesthesia, FNB=femoral nerve block, LIA=local infiltration anesthesia, NS=not stated, S, steroid group; SA, spinal anesthesia.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aminmansour 2006	+	?	?	?	+	+	+
Bednar 2015	+	+	+	+	+	+	+
Choi 2013	?	?	?	?	+	+	+
Jeyamohan 2015	+	+	+	+	+	+	+
Lundin 2003	?	?	+	+	+	+	?
Nielsen 2015	+	+	+	+	+	+	+
Watters 1989	?	?	?	?	?	?	-
Wittayapairoj 2017	+	+	+	+	+	+	+

Figure 2. The risk of bias graph. +, no bias; -, bias; ?, bias unknown.

intravenous glucocorticoid, it will not increase the occurrence of infection.

There were a total of 3 major strength in current meta-analysis: we performed a comprehensively search of the electronic databases; we calculated the final outcomes rigorously (use random-effect model of fixed-effect model according to the heterogeneity); this meta-analysis was compliance with the PRISMA guidelines and the recommendations of the Cochrane Collaboration. Final results indicated that intravenous glucocorticoid can decrease the VAS at 12 and 24 hours and by 8.41 points, 7.46 points, and 13.99 points, respectively, with clinical significance. Liu et al^[22] identified that intravenous glucocorticoids may be as an effective and safe method to reduce postoperative pain in patients following TKA. Meng and Li^[23] found that intravenous dexamethasone could significantly reduce postoperative pain scores following total joint arthroplasty (TJA).

Current meta-analysis indicated that intravenous glucocorticoid has a positive role in reducing pain intensity and postoperative nausea in spinal infusion. Lee et al^[24] revealed that dexamethasone 8 mg may be valuable for preventing patient-controlled analgesia-related nausea in patients undergoing major orthopedic surgery. However, Liu et al^[25] reported that 10 mg dexamethasone given intravenously during induction in major gynecological surgery provided only minimal pain reduction. Wittayapairoj et al^[21] hypothesized that dexamethasone might only be beneficial for less extensive procedures and have a relatively small influence on extensive and invasive procedures.

Current meta-analysis revealed that intravenous glucocorticoid will not increase the occurrence of infection when compared with control group ($P > .05$). Richardson et al^[26] 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^[27] 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^[28] revealed that blood glucose levels in the glucocorticoid group were higher at 24 hours than saline group with statistically significance. In the present study, results shown that intravenous

intensity and morphine consumption. What's more, intravenous glucocorticoid was associated with a reduction of the length of hospital stay and the occurrence of nausea. For the safety of

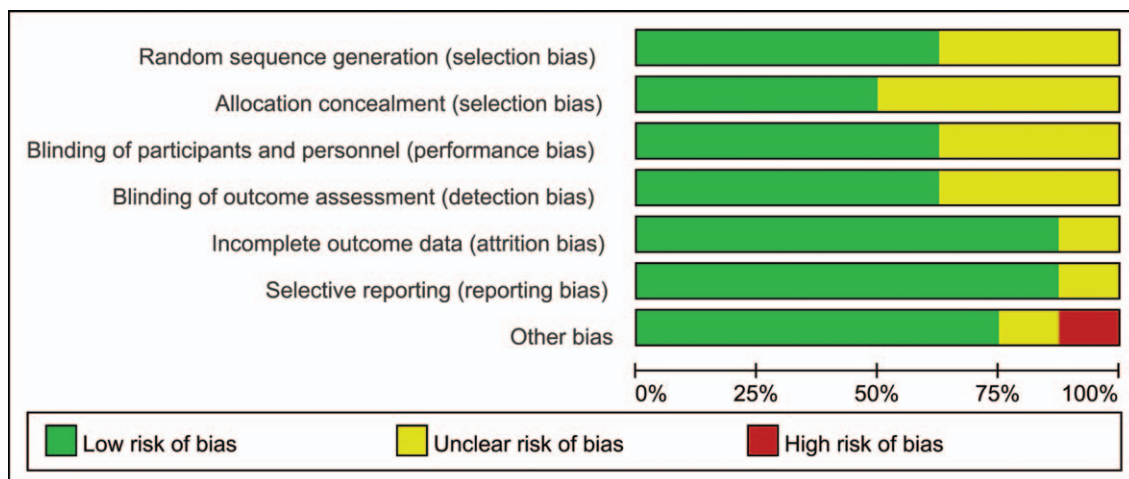


Figure 3. Risk of bias summary of included in randomized controlled trials.

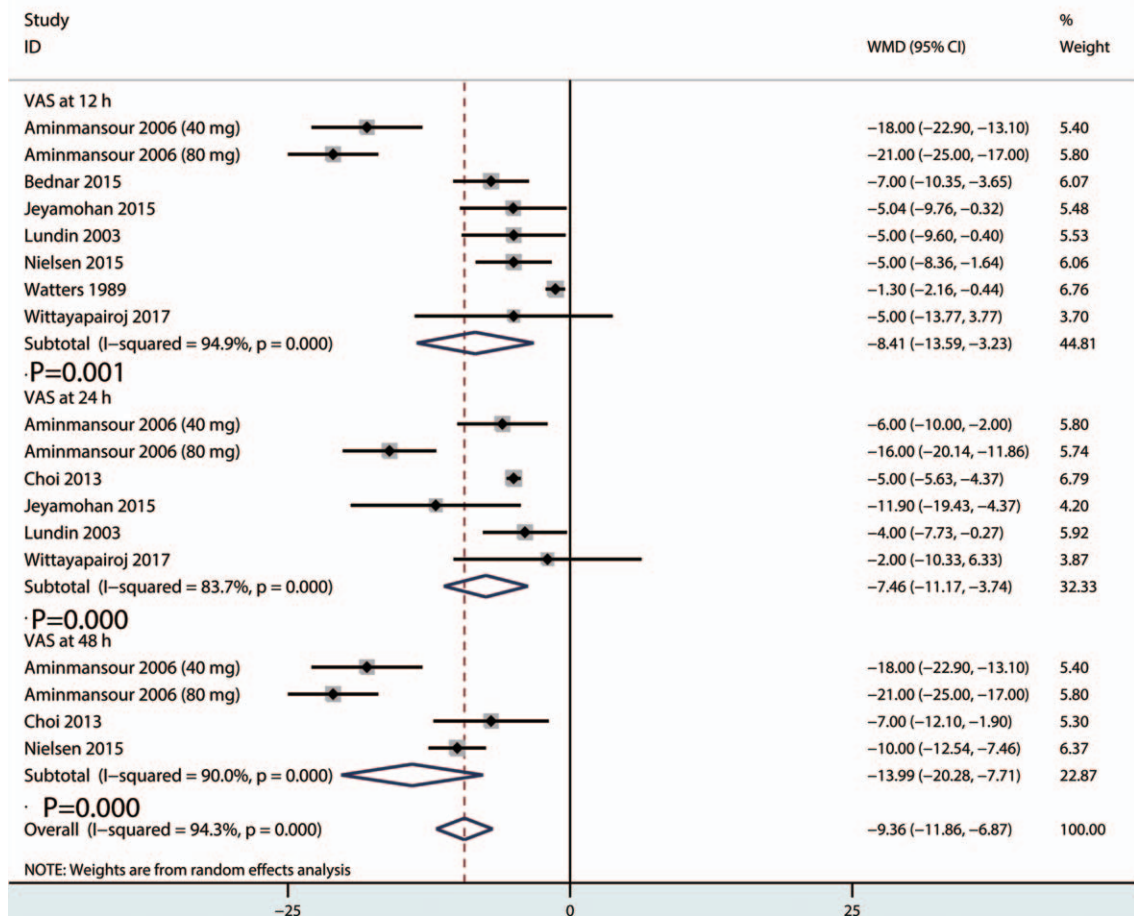


Figure 4. Forest plots of the included studies comparing the VAS at 12, 24, and 48 hours. VAS=visual analog scale.

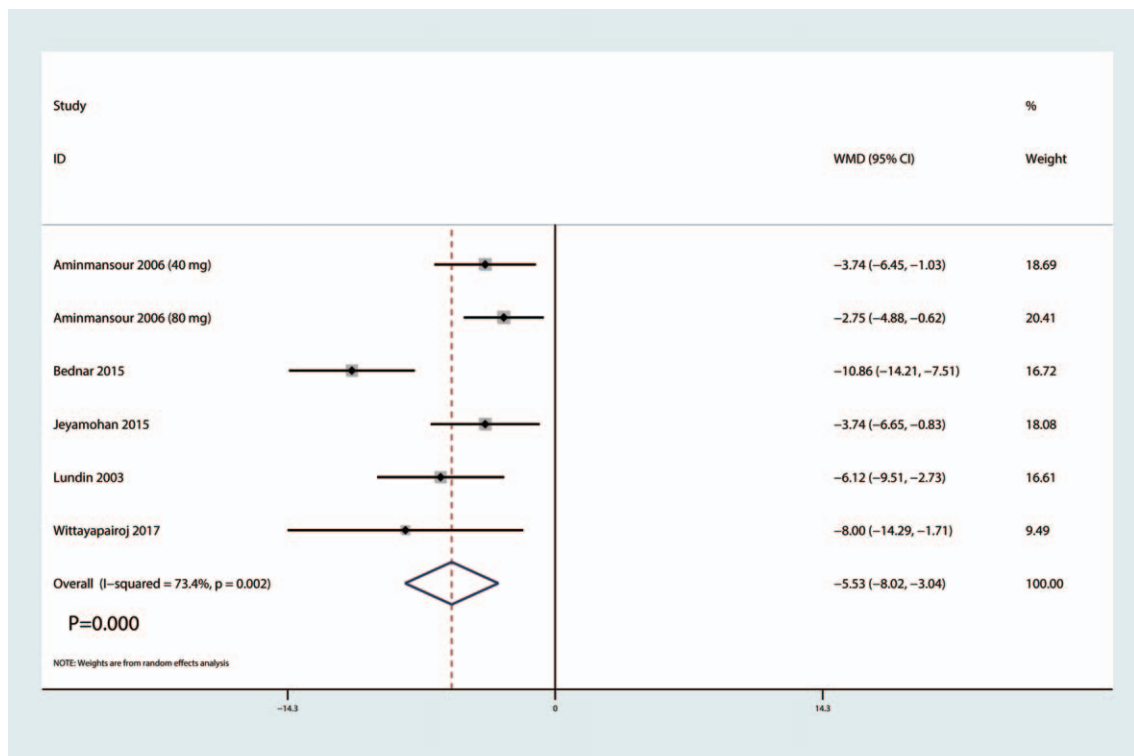


Figure 5. Forest plots of the included studies comparing the total morphine consumption between the 2 groups.

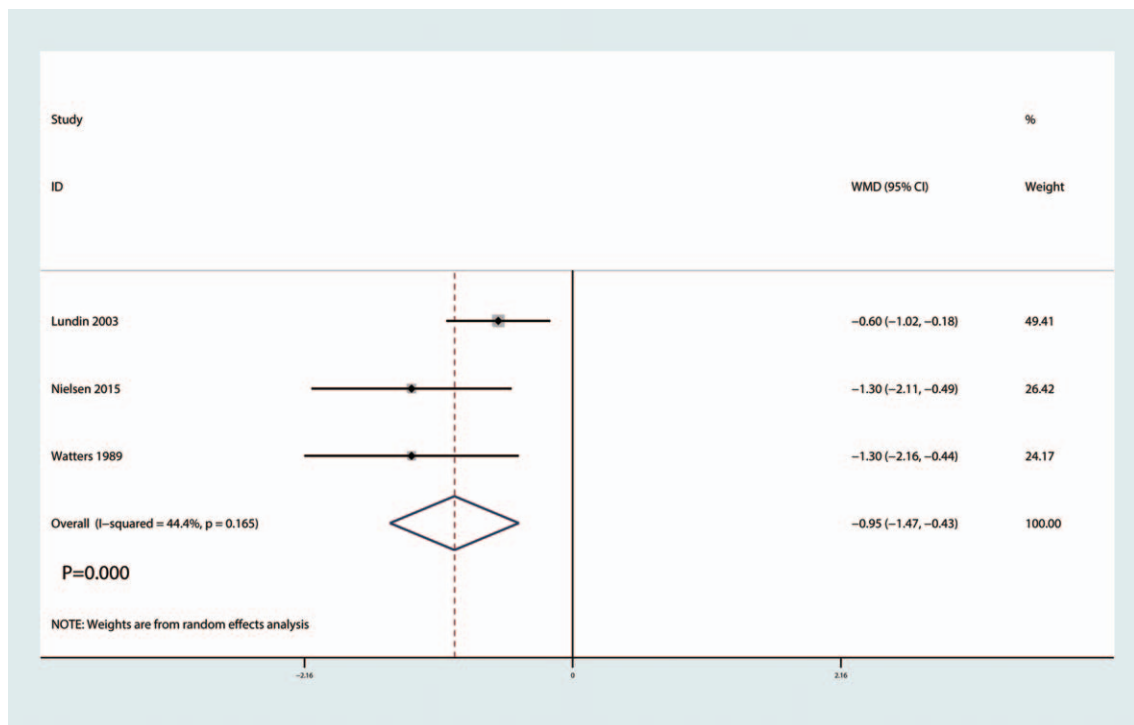


Figure 6. Forest plots of the included studies comparing the length of hospital stay between the 2 groups.

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 review and meta-analysis has several limitations. Included studies with patients were treated with different types of glucocorticoids and thus have a large heterogeneity for the outcomes. Final outcomes were with large heterogeneity and

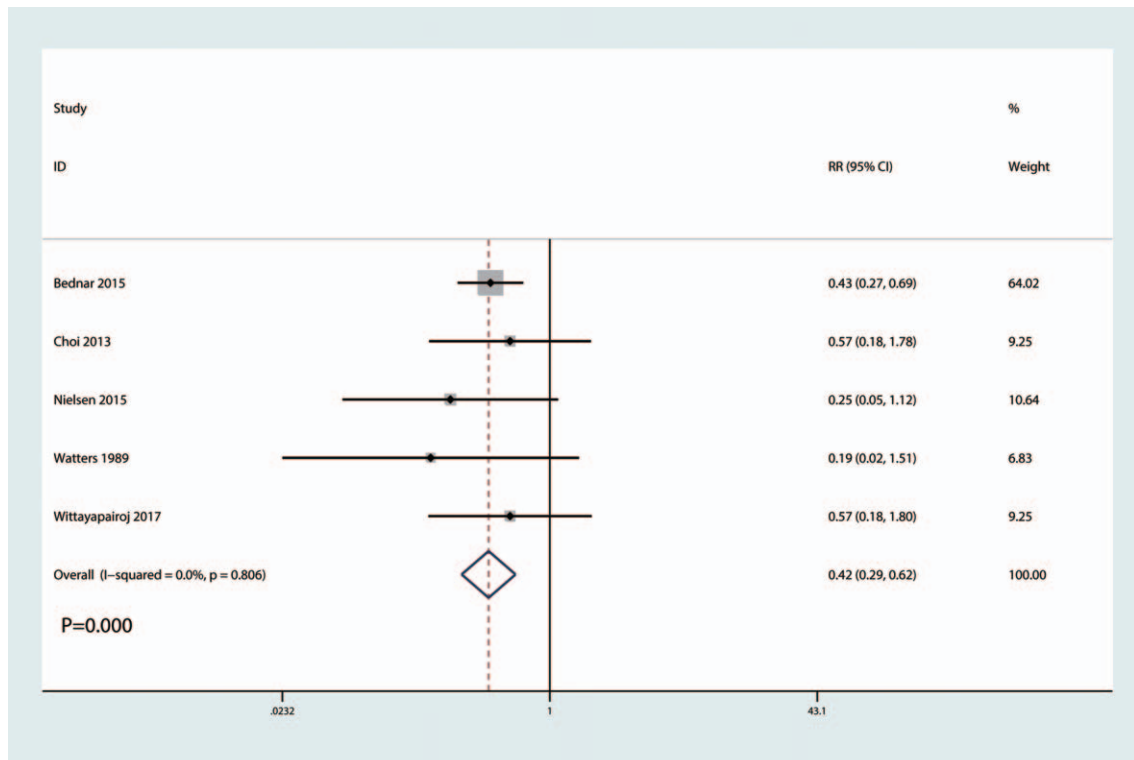


Figure 7. Forest plots of the included studies comparing the occurrence of nausea.

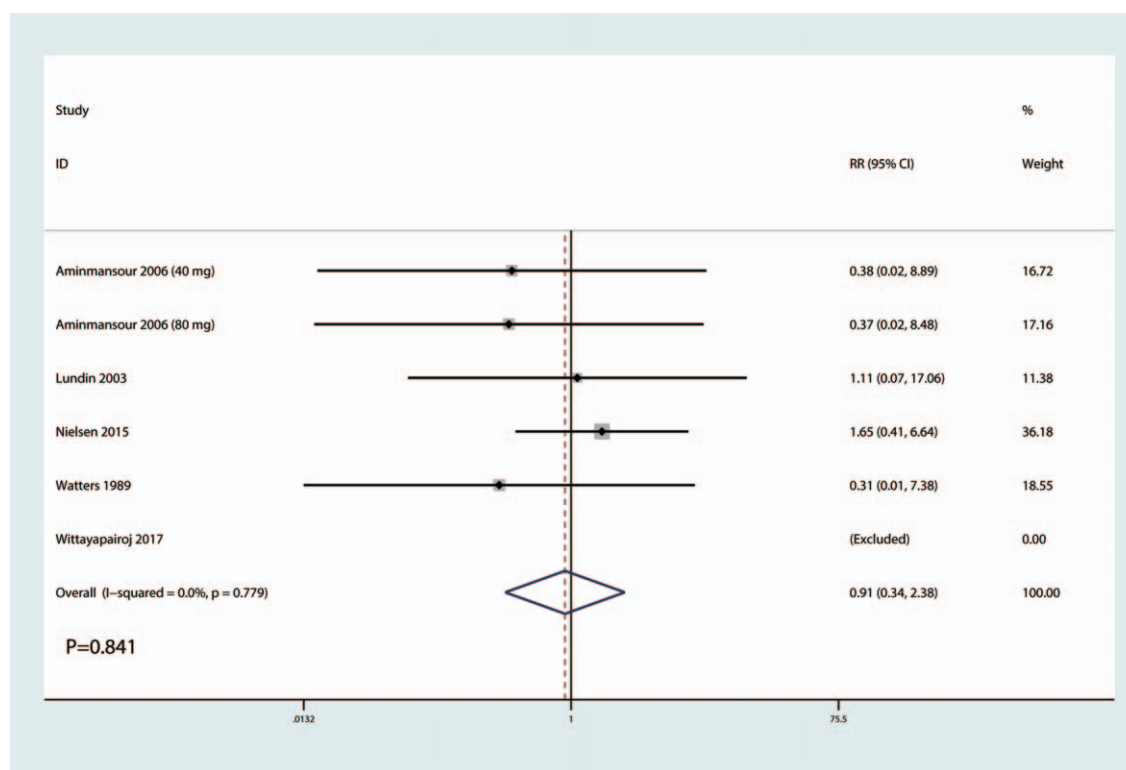


Figure 8. Forest plots of the included studies comparing the occurrence of infection.

these results reflect the inconsistent benefit patients acquired from intravenous glucocorticoids. Postoperative pain management and follow-up duration were different in the included studies and thus may cause the clinical heterogeneity. The qualitative outcomes (the occurrence of infection and nausea) lacked uniformity of definition.

5. Conclusions

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

Author contributions

Conceptualization: Keqin Shi, Yu Jiang, Gang Chen.

Data curation: Feng Wang, Yu Jiang.

Formal analysis: Zhengjie Yang.

Funding acquisition: Keqin Shi.

Software: Zhengjie Yang.

Supervision: Zhengjie Yang.

Validation: Zhengjie Yang, Gang Chen.

Writing – review and editing: Kerong Song.

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