Can Preoperative Intravenous Corticosteroids Administration Reduce Postoperative Pain Scores Following Spinal Fusion?: A Meta-Analysis

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ABSTRACT

Objective: This meta-analysis aimed to assess whether preoperative intravenous corticosteroids reduced postoperative pain in patients undergoing spinal fusion surgery. Methods: We systematically searched PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google databases, from inception to March 29, 2018. Randomized controlled trials (RCTs) that compared preoperative intravenous glucocorticoids against a control treatment for the effect on pain following spinal fusion surgery were included. A meta-analysis was performed to generate a pooled risk ratio (RR) and weighted mean difference (WMD) with corresponding 95% confidence interval (CI) for discontinuous outcomes (the occurrence of postoperative nausea and vomiting [PONV] as well as surgical-site infections) and continuous outcomes (visual analog scale [VAS] scores at 12 h, 24 h, 48 h, and 72 h; total morphine consumption and the length of hospital stay), respectively. Results: Ten RCTs that compared intravenous corticosteroids versus placebo were included in our final meta-analysis. Compared with controls, intravenous corticosteroids were associated with a statistically significant reduction in pain VAS scores at 12 h, 24 h, 48 h, and 72 h. Additionally, intravenous corticosteroids decreased total morphine consumption, PONV, and the length of hospital stay. There was no significant difference between intravenous corticosteroids and controls, regarding the occurrence of infection ($p > 0.05$). Conclusions: In summary, our results indicated that intravenous corticosteroids not only reduce pain but also have anti-emetic effects. More studies should focus on the adverse effects of administering intravenous corticosteroids.

Keywords: corticosteroid; spinal fusion surgery; pain control; meta-analysis; morphine consumption; visual analog scale

INTRODUCTION

Spinal fusion surgery is a major orthopedic procedure, often associated with severe acute postoperative pain [1–3]. Inadequate pain control can lead to several poor postoperative outcomes, including economic burden, poor functioning, and prolonged hospital stay. Improper acute pain management was also associated with the development of chronic pain and may erode quality of life [1]. Opioids are often used for postoperative pain management; however, various complications occur with high doses of opioids [4, 5].

There is currently no consensus regarding optimal pain management of postoperative pain after spinal fusion surgery. Several medications and methods have been tried, including the use of different corticosteroids [6–9].

Preoperative intravenous corticosteroids have attracted increasing attention as possible analgesic adjuvants in the treatment of acute postoperative pain [10, 11]. However, the benefit versus harm of...
intravenous glucocorticoids in spinal infusion patients is still undetermined. Bednar et al. [12] found that systemic dexamethasone administration had no pain relieving benefit following spinal fusion surgery. Another randomized controlled trial (RCT) conducted by Nielsen et al. [13] revealed that preoperative dexamethasone not only significantly reduced pain but also decreased postoperative vomiting following spinal fusion surgery. Moreover, there was no relevant meta-analysis addressing the use of preoperative intravenous corticosteroids for pain control in spinal fusion surgery patients.

Thus, we conducted a meta-analysis from RCTs to conclude whether intravenous corticosteroids were associated with a reduction of pain and postoperative nausea and vomiting following spinal fusion surgery.

MATERIALS AND METHODS

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [14] and was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [15].

SEARCH STRATEGY AND STUDY SELECTION

Electronic databases [PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Google database] were searched from their inception until March 29, 2018. A structured search in the PubMed database was as follows: “intravenous dexamethasone,” OR “intravenous betamethasone,” OR “intravenous triamcinolone,” OR “intravenous prednisone,” OR “intravenous corticosteroids,” OR “intravenous steroids,” AND “spine surgery,” OR “spinal surgery,” OR “spinal fusion.” An attempt to identify additional studies missed by the primary search was made by reviewing the reference lists from identified studies. Data for our meta-analysis were collected from previously published data, and thus, ethical review and approval were not necessary.

ELIGIBILITY CRITERIA

1. Participants: Patients undergoing spinal fusion.
2. Interventions: The comparison group was administered intravenous corticosteroids.
3. Comparisons: The comparison group received placebo.
4. Outcomes: Visual analog scale (VAS) scores at 12h, 24h, 48h, and 72h after spinal fusion, postoperative nausea occurrence, the incidence of infection, and length of hospital stay following spinal fusion.
5. Study design: Only RCTs were included.

DATA EXTRACTION AND OUTCOME MEASURES

Two reviewers independently extracted the relevant data, including general characteristics and potential outcomes from a predesigned table. Disagreements were resolved either by discussion or by consultation with a senior reviewer. Since different types of corticosteroids were administered in the studies, we converted all corticosteroids to their dexamethasone equivalence, according to published references [16]. If the data were presented in figures or other forms, we used GetData Graph Digitizer software (GetData Co, Beijing, China) to extract relevant data [14].

RISK OF BIAS ASSESSMENT AND QUALITY OF EVIDENCE ASSESSMENT

Two authors used the Cochrane risk-of-bias tool to assess the risk of bias and exported the graph by Reviewer Manager 5.3.0 (Nordic Cochrane Centre, Copenhagen, Denmark) [14]. The Cochrane risk-of-bias tool included seven items, and each item was assessed as high, low, or unclear risk of bias. Next, we used kappa values to measure the degree of agreement between the two reviewers [17]. Two reviewers (G.C and KR.S) independently evaluated the quality of evidence assessment in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [18]. Each item was classified as high, moderate, low, or very low [18, 19].

STATISTICAL ANALYSIS

All statistical analyses were conducted using RevMan 5.30 (Nordic Cochrane Centre, Copenhagen, Denmark). Treatment effects were calculated as the risk ratio (RR) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes with a 95% confidence interval (CI). The heterogeneity among studies was examined by the $I^2$ statistic and considered significant if the $p$ value $<0.05$ or $I^2 >50\%$. If no evident heterogeneity existed, the fixed effects model was selected to pool results. If present, a random effects model was utilized, and a Galbraith plot was performed to look for outliers in the effect sizes. The expectation
is that 95% of the studies are within the area defined by two CI lines. Afterwards, a sensitivity analysis was performed by eliminating one or more studies that were not within or far away from the area defined by two CI lines, until heterogeneity was not present and results compared [20]. Publication bias was formally assessed by a funnel plot and Egger test ($p > 0.05$ suggests no significant bias) [21]. The subgroup analysis was conducted based on the dose of corticosteroids ($\geq 10$ mg [high dose] or $< 10$ mg [low dose]) according to a published reference [5–22]. Kappa values were used to assess the degree of agreement between the two reviewers, and the acceptable threshold was set as 0.65.

RESULTS
Search Results and Quality Assessment

The PRISMA statement flowchart shows the process of literature screening, study selection, and reasons for exclusion (Figure 1). In the initial search, we identified 466 papers from electronic databases and six additional papers discovered from references. Afterward, 403 records remained after duplicates were removed. Lastly, we included 10 RCTs [12, 13, 23–30] in this meta-analysis. The general characteristics of the included studies can be seen in Table 1. The sample size ranged from 19 to 146. The mean age ranged from 36.8 to 55.2 years. We converted glucocorticoid dose to the equivalent dose of dexamethasone, and the dose ranged from 3 to 80 mg. The risk of bias summary and risk of bias graph can be seen in Figure 2. The overall kappa value, evaluating the risk of bias of included RCTs, was 0.714.

RESULTS OF THE META-ANALYSIS

VAS Scores at 12 h, 24 h, 48 h, and 72 h

Nine trials totaling 675 patients provided data on VAS scores at 12 h. Compared with placebo, intravenous corticosteroids significantly reduced postoperative VAS scores at 12 h ($-7.45$; 95% CI, $-9.08$ to $-5.82$; $p < 0.001$) (Figure 3), with significant heterogeneity ($I^2 = 49\%$).

Compared with placebo, intravenous corticosteroids further reduced VAS scores at 24 h (WMD, $-4.96$; 95% CI, $-6.72$ to $-3.20$; $p < 0.001$) (Figure 3), with significant heterogeneity ($I^2 = 49\%$).

Compared with placebo, intravenous corticosteroids further reduced VAS scores at 48 h (WMD, $-4.44$; 95% CI, $-6.24$ to $-2.65$; $p < 0.001$) (Figure 3), with significant heterogeneity ($I^2 = 49\%$).

Compared with placebo, intravenous corticosteroids further reduced VAS scores at 72 h (WMD, $-3.91$; 95% CI, $-5.66$ to $-2.15$; $p < 0.001$) (Figure 3), with significant heterogeneity ($I^2 = 49\%$).

FIGURE 1. Flowchart of the study search and inclusion criteria.
–10.97; 95% CI, –15.15 to –6.79; p < 0.00001) (Figure 3), VAS scores at 48 h (WMD, –9.60; 95% CI, –15.23 to –3.97; p = 0.0008) (Figure 3), and VAS scores at 72 h (WMD, –5.33; 95% CI, –6.95 to –3.71; p < 0.0001) (Figure 3).

### Total Morphine Consumption

Seven studies (523 participants) reported data on the total postoperative morphine consumption. Compared with placebo, preoperative intravenous corticosteroids significantly decreased the total postoperative morphine consumption by 5.24 mg (WMD = –5.24, 95% CI –6.53 to –3.95, p < 0.0001; I² = 68%, Figure 4).

### Length of Hospital Stay

A total of three studies (307 patients) were included in the meta-analysis of length of hospital stay. Compared with placebo, preoperative intravenous glucocorticoids were associated with a significantly decreased length of hospital stay following spinal fusion surgery (WMD = –0.86, 95% CI –1.15 to –0.57, p < 0.0001; I² = 20%, Figure 5).

### The Occurrence of Postoperative Nausea and Vomiting (PONV)

Five studies (523 participants) reported data on the occurrence of nausea and vomiting. Compared with placebo, preoperative intravenous glucocorticoids significantly decreased the occurrence of postoperative nausea and vomiting (RR = 0.44, 95% CI 0.31 to 0.62, p < 0.0001; I² = 0.0%, Figure 6).
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FIGURE 3. Forest plots of the included studies comparing the VAS at 12, 24, 48, and 72 h.

FIGURE 4. Forest plots of the included studies comparing the total morphine consumption between the two groups.
FIGURE 5. Forest plots of the included studies comparing the length of hospital stay between the two groups.

FIGURE 6. Forest plots of the included studies comparing the occurrence of PONV.

FIGURE 7. Forest plots of the included studies comparing the occurrence of infection.
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 = 0.78, 95% CI 0.32 to 1.86, p = 0.57; I² = 0.0%, Figure 7).

GRADE Profile Evidence, Publication Bias, and Sensitivity Analysis

GRADE evidence profiles for the primary and secondary outcomes are shown in Supplement S1. The GRADE Working Group grades level of evidence is low for total morphine consumption and VAS scores at 48 h; moderate for VAS scores at 12, 24, and 72 h; and high for length of hospital stay and the occurrence of PONV and infection.

For the meta-analysis of intravenous corticosteroids for VAS at 12 h, there was no evidence of publication bias by inspection of the funnel plot (Figure 8) and formal statistical tests (Egger test, p = 0.69; Begg test, p = 0.73) (Figures 9 and 10).

Subgroup Analysis and Sensitivity Analysis

Table 2 presents the results of subgroup analyses. The findings of decreased first-attempt failure were consistent in all subgroup analyses. Sensitivity analysis results can be seen in Figure 11. The results when omitting one study at a time on the overall estimated effect indicated that it was not changeable, and thus, the stability of the pooled results was high.

DISCUSSION

Our meta-analysis comprehensively and systematically reviewed the current available literature to evaluate the effect of preoperative intravenous corticosteroids, compared with placebo, on clinical outcomes in spinal fusion surgery patients. We found that (i) preoperative intravenous corticosteroids could significantly reduce the postoperative pain, the evidence level was moderate, and the result was consistent in most subgroup analyses; (ii) preoperative intravenous corticosteroids reduced the total postoperative morphine consumption, the occurrence of nausea and the length of hospital stay; (iii) sensitivity analysis was investigated by omitting one study at a time and examining the influence of each individual study on the overall risk estimate (i.e., the “leave one out” approach), and this further confirmed our final results.

This was the first meta-analysis that evaluated the effect of preoperative intravenous corticosteroids on postoperative pain control in patients undergoing spinal fusion surgery. Several other meta-analyses regarding other types of surgery (e.g., total hip arthroplasty, total knee arthroplasty, etc.) have been published [10, 11]. Although the major outcomes of our meta-analysis were consistent with previous reviews, differences should also be noted. First, our
present meta-analysis was the most comprehensive and focused on spinal fusion surgery patients, and thus, the heterogeneity was small. Second, we used sensitivity analysis to increase the robustness of our meta-analysis. Third, we applied subgroup analysis to investigate the influence of various factors (e.g., the dose of corticosteroids, etc.) on the robustness of the primary efficiency outcome.

We chose postoperative VAS scores as the primary outcome, and the final results indicated that, compared with placebo, intravenous corticosteroids were associated with decreased pain scores after spinal fusion. Schmidt et al. [31] found that plasma concentrations of interleukin-6 (IL-6), IL-8, and C-reactive protein (CRP) were significantly lower in the group administered intravenous corticosteroids relative to the control group. Patient-controlled analgesia (PCA) was used for postoperative pain control, and postoperative total morphine consumption was significantly decreased after receiving preoperative intravenous corticosteroids.

Our results indicate that preoperative intravenous corticosteroids reduce the length of hospital stay by 0.86 days. Other previous meta-analyses in non-cardiac surgery have also reported reductions in the length of hospital stay after glucocorticoid administration [32]. Toner et al. [33] found that the length of hospital stay was not different with administration of perioperative glucocorticoids (p = 0.65).

Postoperative infections, particularly surgical-site infections, are destructive for spinal fusion patients as they require reoperation, increase costs, and prolong the length of hospital stay [34, 35]. Several published meta-analyses indicated that intravenous corticosteroids may increase the occurrence of infection [36–38]. Our results do not suggest an effect of corticosteroids on surgical-site infection. Toner et al. [33] included 56 trials involving 5607

### TABLE 2. Subgroup analysis for VAS at 12 h

| Subgroup     | Number of trials | Weighted mean difference (95% CI) | p Value | I² | Test of interaction, p |
|--------------|------------------|----------------------------------|---------|---|------------------------|
| VAS at 12 h  |                  |                                  |         |   |                        |
| Dose         |                  |                                  |         |   |                        |
| High dose    | 4                | -8.29 (-10.08, -6.77)            | 0.001   | 52%| 0.105                  |
| Low dose     | 5                | -7.11 (-8.99, -9.31)             | 0.001   | 47%|                        |
| Risk of bias |                  |                                  |         |   |                        |
| Low          | 6                | -7.56 (-9.52, -6.14)             | 0.001   | 41%| 0.203                  |
| Unclear/high | 3                | -7.38 (-9.25, -5.43)             | 0.001   | 56%|                        |

![FIGURE 11. Sensitivity analysis for VAS at 12 h (A), 24 h (B), 48 h (C), and 72 h (D).](image-url)
elective non-cardiac surgery patients and found that intravenous corticosteroids had no effect on the rate of surgical-site infections.

Our meta-analysis also had several limitations: (i) The number and sample of included RCTs was limited, which may cause biases; (ii) the dose of corticosteroids was different in the included RCTs, and future studies should be focused on the effect of a single dose of corticosteroids for pain control in patients undergoing spinal fusion surgery; (iii) we only included RCTs in the Chinese and English languages, and thus, a selective bias may exist; and (iv) the follow-up duration in the included RCTs was limited, and long-term outcomes need to be further elucidated.

**CONCLUSIONS**

Our meta-analysis suggests that, relative to placebo, preoperative intravenous corticosteroids significantly reduce postoperative pain and morphine consumption in spinal fusion patients. The use of intravenous corticosteroids for spinal fusion patients decreases the length of hospital stay and the occurrence of PONV, all without increasing the risk of surgical-site infections. Preoperative intravenous corticosteroids are recommended as an adjunct to pain management for patients undergoing spinal fusion surgery.

**DECLARATION OF INTEREST**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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