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Systematic Review and Meta-Analysis

Prophylactic Dexamethasone Decreases the Incidence of Postoperative Sore Throat after Tracheal Extubation: A Meta-Analysis

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ABSTRACT

Background: Postoperative sore throat (POST) is an undesirable complaint from patients undergoing general anesthesia. Dexamethasone, with its potent immunomodulatory effects, is used to reduce inflammation and tissue damage in a variety of clinical settings. The present study aimed to evaluate the effect of dexamethasone on the incidence of POST systematically.

Methods: Two researchers searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Google scholar, World Health Organization International Clinical Trials Registry Platform, Chinese BioMedical Literature Database, and China National Knowledge Infrastructure for randomized controlled trials that compared dexamethasone in patients undergoing general anesthesia and reported the outcome of POST.

Results: Five studies with a total of 582 patients receiving dexamethasone or placebo were included. The pooled results revealed that patients receiving dexamethasone had a lower incidence of POST at 1 hour (relative risk [RR] = 0.63, 95% confidence interval [CI] 0.40-0.98, P < 0.05) and 24 hours (RR = 0.42, 95% CI 0.30-0.60, P < 0.001) after surgery.

Conclusions: Prophylactic dexamethasone is effective in decreasing the incidence of POST after surgery relative to placebo.

Postoperative sore throat (POST) is a common complication after general anesthesia, with its incidence ranging from 40 to 90% (1-3). It is important to prevent POST to decrease the patients' dissatisfaction. Many factors including gender, history of smoking or lung diseases, postoperative nausea, endotracheal tube size and cuff pressure, and duration of surgery (1, 2), contribute to the occurrence of POST. Despite efforts devoted to reduce its incidence and severity, effective therapies were rarely determined for the prevention of POST in patients.

Dexamethasone, with its potent immunomodulatory effects, has been used to reduce inflammation and tissue damage in a variety of clinical settings. Previous studies demonstrated that dexamethasone can be safely used for the prevention of postoperative nausea and vomiting (PONV) (4-6). The efficacy of dexamethasone in reducing pain and inflammation after surgery has also been explored (7-12). Dexamethasone is also widely applied in the therapy for sore throat resulting from tracheal mechanical irritation (13, 14). Recently, several studies have explored the efficacy of dexamethasone in reducing the incidence of POST (15-19). Thus, we per-

formed the current meta-analysis to determine whether a single prophylactic dose of dexamethasone could reduce the incidence of POST in adults undergoing surgery under general anesthesia.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations for reporting our results (20). The risk of bias was checked by appraising "random sequence generation", "allocation concealment", "blinding of participants and personnel", "blinding of outcome assessment", "incomplete outcome data", "selective reporting", and "other bias" via valuing "low risk", "high risk" and "unclear risk" by the software of RevMan. In addition, the publication bias was also assessed by funnel plot and Egger's test. The inclusion criteria were defined as follows: randomized, controlled trials (RCTs), general anesthesia, comparing dexamethasone with placebo, drugs were used prophylacticly, collecting data of the incidence of POST but not relative number or which can be calculated from the exact number; while exclusion criteria were defined as follows: conducted by Fujii et al., double-lumen tubes, laryngeal mask airway, and drugs not used in vein.

Literature Search

The databases of MEDLINE (updated to July 2013), EMBASE (updated to July 2013), Cochrane Central Register of Controlled Trials (updated to July 2013), Google scholar, World Health Organization International Clinical Trials Registry Platform (July 2013), Chinese Bio-Medical Literature Database (1978 to July 2013), and the China National Knowledge Infrastructure (1994 to July 2013) were searched. Full reports of RCTs in which a single dose of dexamethasone was given intravascularly preoperatively to adult patients undergoing surgery under general anesthesia and was compared with placebo were identified. The Medical Subject Heading and the appropriate corresponding keywords "dexamethasone", "steroids" AND "postoperative sore throat" were used. We restricted the findings of the above restrictions with a highly sensitive search strategy recommended by the Cochrane Collaboration for identifying RCTs (21). Considering the validity of the data, studies conducted by Fujii et al. (22) were not included in the present meta-analysis. We also checked the reference lists of RCTs and previous meta-analyses to include any further potential eligible trials.

Data Collection and Presentation

Two authors (Bao-Ji Hu and Lu-Long Bo) independently conducted a comprehensive literature search to identify relevant studies. The quality of the reviewed RCTs was assessed independently by two of the authors (Bao-Ji Hu and Lu-Long Bo). In addition, the quality of the articles was also assessed by Jadad Scale (23) with a total possible score of 5. While an article with the scale no less than 3 was defined as high quality and included, otherwise the article would be discarded. All authors examined each title and abstract to exclude clearly irrelevant articles. Two authors extracted data independently. Any disagreements were resolved by discussion between two reviewers or with a third reviewer (Jin-Bao Li) available for arbitration if necessary.

The extracted data were entered into a data collection form including the following items: i) type of surgery, ii) number of patients, iii) dose (s) of dexamethasone, iv) comparator(s), v) timing of administration, vi) primary outcome measure of the study (POST), and vii) side-effects related to dexamethasone administration, including wound infection, delayed wound healing, hyperglycemia, and perennial pruritus. Attempts were made to contact the authors of original papers when additional data were required. Data were extracted from figures as needed if not been displayed numerically and the authors did not respond to our request for numerical data. Dexamethasone dose was converted to units in mg/kg using the mean weight reported for the dexamethasone groups. When information about group weight was unavailable, 70 kg was selected to represent the weight of the patient. POST documented at the early (1 hour) and late (24 hours) postoperative periods was included for analysis.

Statistical Analysis

Analyses were performed using the Review Man-

ager (RevMan) Software (Version 5.1 Cochrane Library, Oxford, England). Differences were expressed as relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes. The fixed-effect model was used as the overall heterogeneity had no significant difference, while a random-effect model was employed in case of significant heterogeneity, i.e., P value of chi-square test was less than 0.10 and I^2 was greater than 50% (24). Potential sources of heterogeneity were identified by sensitivity analyses conducted by omitting one study in each turn and investigating the influence of a single study on the overall pooled estimate. Publication bias was assessed by visually inspecting funnel plot and Egger's test. P value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of Eligible Trials

Our comprehensive search yielded to 1,006 relevant publications. Of those, five studies were finally included in the current analysis with a total of 582 patients (353 received dexamethasone and 229 received placebo) (15-19). The PRISMA flow diagram detailing the disposition of retrieved publications was shown in figure 1, a template modified from the PRISMA checklist (20). The characteristics and outcomes found in each of the included studies were summarized in the table 1.

Doses of dexamethasone applied in the original studies ranged from 0.05 to 0.2 mg/kg. Multiple doses of dexamethasone were used in three studies (15-17). Studies with doses ≤0.1 mg/kg and >0.1 mg/kg were defined into two subgroups, and then were compared with placebo (saline were used in all trials), respectively. Of the five studies(15-19), two studies (18, 19) had only one subgroup receiving dexamethasone been compared with saline, while the others had two. Dexamethasone was given preoperatively in all included studies. The incidence of sore throat at 1 hour post-operation was reported in four studies (15-18), at 3 hours post-operation in one study (16), at 6 hours post-operation in one study (18) and at 24 hours post-operation in four included studies (15, 17-19). According to the outcomes summarized, we deter-

Table 1. Detail Characters of Included Trials and Incidence of POST Treated with Placebo, Low Dose of Dexamethasone (≤0.1 mg/kg) and High Dose of Dexamethasone (>0.1 mg/kg).

Author (year)	Trial source	Gender	Age (Year)	Dose of DEX (mg/kg)	Time of administration	Adverse events	Study groups (N) Placebo/DEX	Duration of surgery (minute)	Tube size	Anesthetics	Procedure	Jadad Score*
Bagchi (2012)	India	either	18-60	0.2	before anesthesia induction	None	47/48	111-117	7.0-8.5	N_2O, ISO	general	4
Oliveira (2011)	USA	female	25-50	0.05, 0.1	premedication	None	36†/36†	90-120	NG	RF, SEV	gynecological laparoscopy	4
Ruangsin (2012)	Thailand	either	29-53	0.06, 0.11	preoperative	None	35/70	NG	7.5-8.0	NG	general	3
Park (2008)	Korea	either	18-75	0.1, 0.2	before anesthesia induction	None	56/110	155-164	35-37	SEV	thoracic	4
Thomas (2007)	India	either	31-57	0.11	before anesthesia induction	None	55‡/55‡	129-135	7.0-8.5	N_2O, ISO, BUP	abdominal and lower limb	5

*Jadad scale for quality appraisal (total possible score = 5) (20). †Number of patients included for analysis. Number randomized was 40. ‡Number of patients included for analysis. Number randomized was 60.
DEX, dexamethasone; NO, nitrous oxide; O_2, oxygen; ISO, isoflurane; RF, remifentanil; SEV, sevoflurane; NG, not given; BUP, bupivacaine; POST, postoperative sore throat.

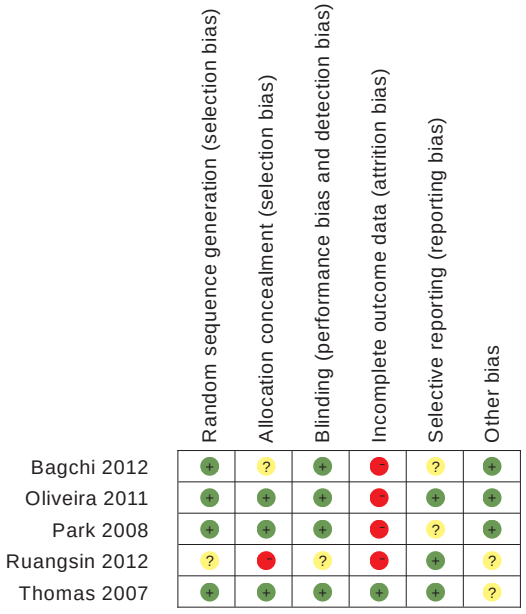

Figure 3. Risk of Bias Summary.

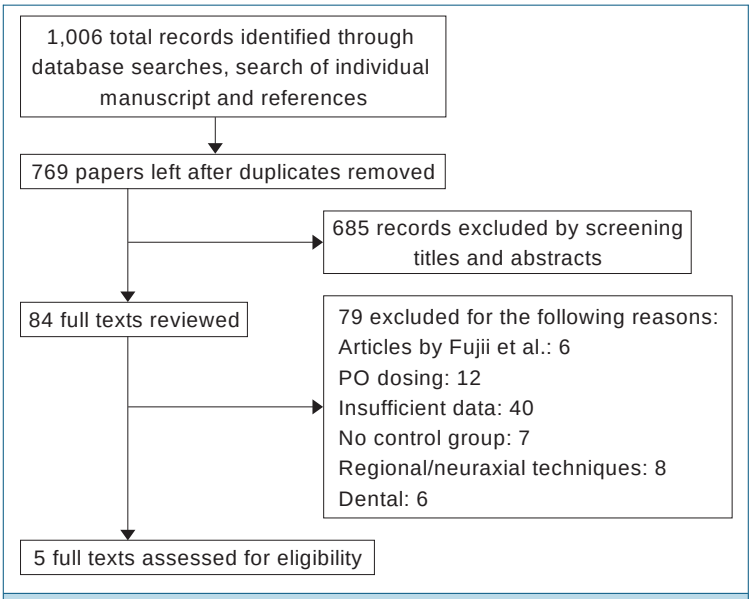

Figure 1. Flow Diagram Detailing the Disposition of Screened, Excluded, and Included Trials.

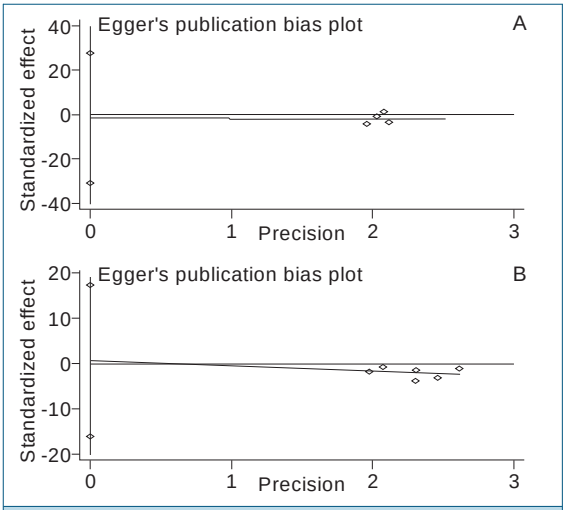

Figure 4. Egger's Test of Publication Bias at 1 Hour (A) and 24 Hours (B) after Surgery.

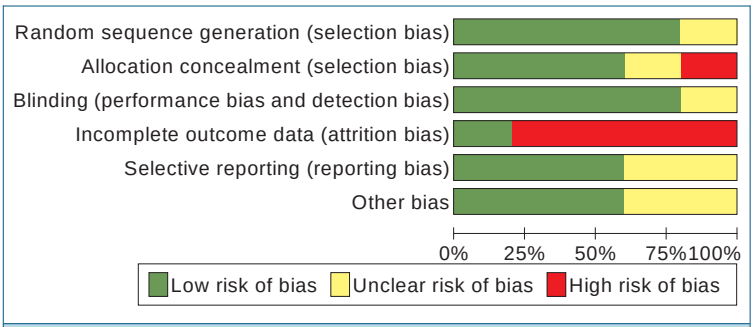

Figure 2. Risk of Bias Graph.

mined to compare the incidence of POST at 1 hour and 24 hours after surgery.

Risk of Bias

Among all selected trials, randomized sequence and allocation sequence concealment were adequately conducted. Blinded fashion was fully stated in all trials. The numbers of patients and reasons for withdrawal or dropout were reported in all trials. An overview of the risk of bias was shown in figure 2 and figure 3. The Cohen κ statistic for agreement on study inclusion was 0.89. Publication bias assessed by Egger's test at 1 hour and 24 hours after surgery was shown in figure 4.

Outcomes

Four studies (529 patients) recorded the occurrence of POST at 1 hour after surgery. Patients receiving dexamethasone had a significant lower incidence of POST (RR=0.63, 95% CI, 0.40-0.98, I^2=78%, P=0.04) (Figure 5). Tests for heterogeneity identified the trial by Oliveira et al. (16) for outlying results. Exclusion of this trial resolved the heterogeneity, which did not change the results of POST at 1 hour after surgery (RR=0.68, 95% CI, 0.5-0.84, I^2=9%, P<0.001). We performed a subgroup meta-analysis by the doses chosen in each trial. Dexamethasone ⩽ 0.1 mg/

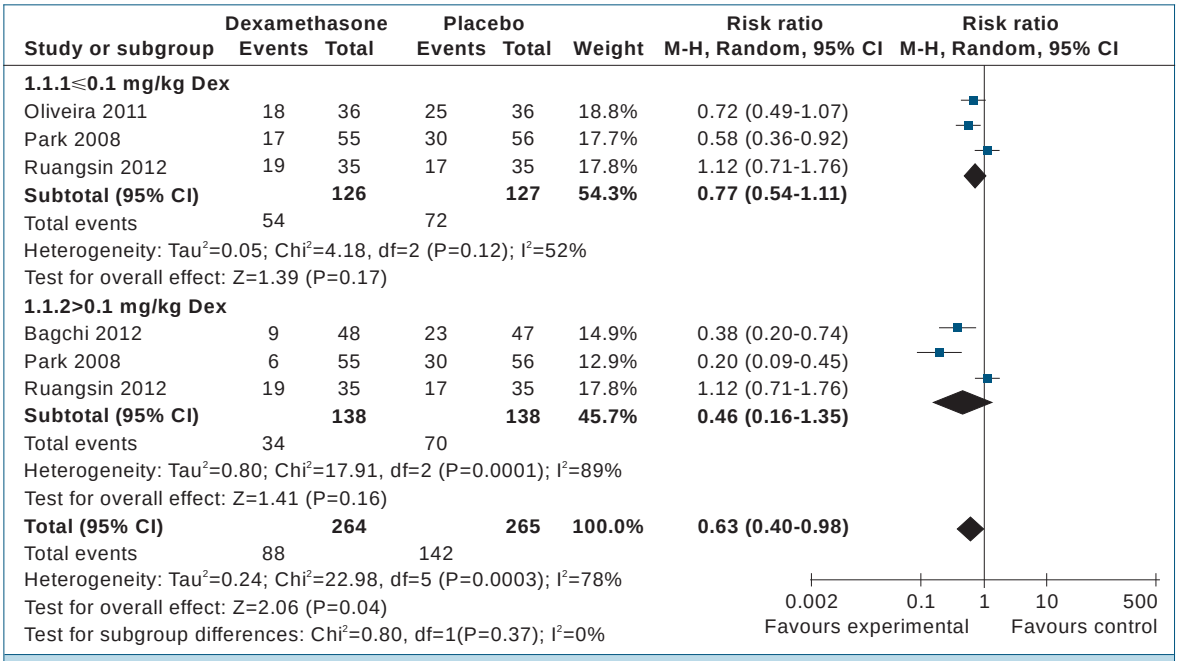

Figure 5. Forest Plot Showing the Effect of Dexamethasone on POST at 1 Hour after Surgery.

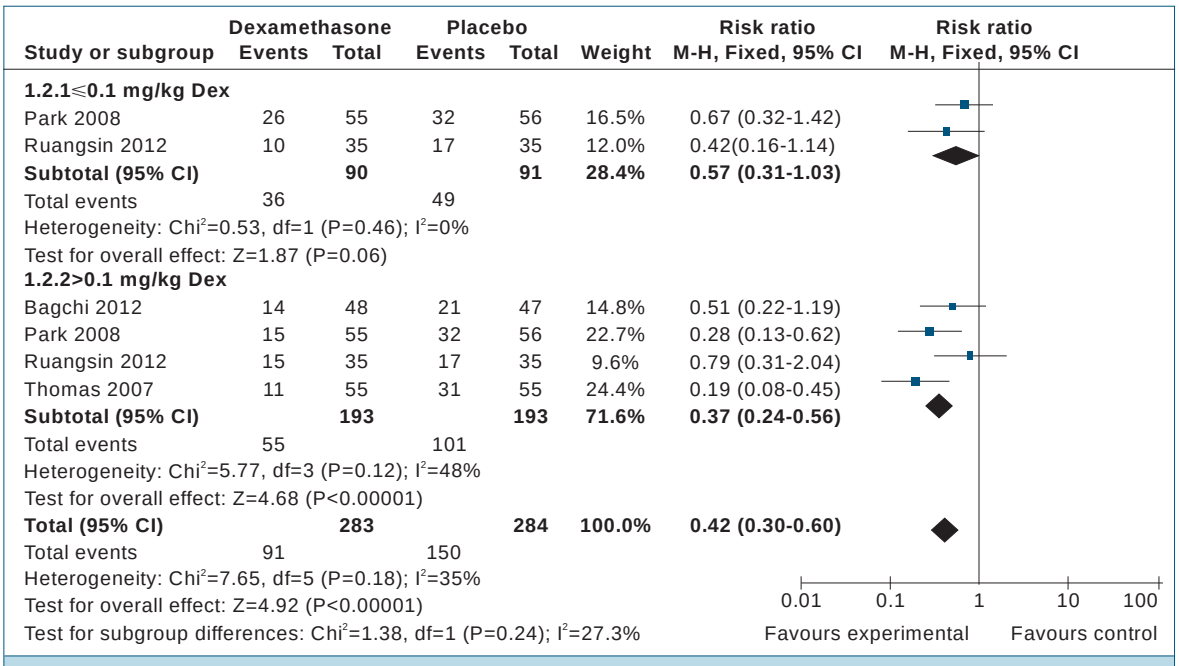

Figure 6. Forest Plot Showing the Effect of Dexamethasone on POST at 24 Hours after Surgery.

kg showed a trend toward a decreased (but not significant) incidence of POST (RR=0.77, 95% CI, 0.54- 1.11, I^2=52% , P=0.17), while dexamethasone > 0.1 mg/kg also showed a trend toward a decreased (but not significant) incidence of POST at 1 hour after surgery (RR=0.46, 95% CI, 0.16-1.35, I^2=89%, P=0.16).

Four studies (567 patients) recorded the occurrence of POST at 24 hours after operation. Patients receiving dexamethasone had a significant lower incidence of POST (RR=0.42, 95% CI, 0.30- 0.86, I^2=35%, P<0.01) (Figure 6). A subgroup meta-analysis was also done to examine the effect of different doses chosen on the in-

cidence of POST. Dexamethasone ⩽ 0.1 mg/kg showed a trend toward a decreased (but not significant) incidence of POST (RR=0.57, 95% CI, 0.31-1.03, I^2=0%, P=0.06), while dexamethasone > 0.1 mg/kg showed a significant decrease in incidence of POST at 24 hours after surgery (RR=0.37, 95% CI, 0.24-0.56, I^2=48%, P< 0.01). None of the studies recorded the side effects or adverse events of dexamethasone administration at 1 hour or 24 hours after surgery.

DISCUSSIONS

Our meta-analysis suggested that dexamethasone can lead to a statistically significant reduction in the incidence of POST at both 1 hour and 24 hours after surgery when administered to patients undergoing general anesthesia, compared with placebo.

Prophylactic administration of dexamethasone during the intra-operation was considered to be dramatically effective in reducing the incidence of POST by attenuating the occurrence of edema after extubation in patients under general anesthesia (25). The underlying mechanism of its effect was presumably based on its anti-inflammatory activity.

Multiple doses of dexamethasone were chosen in each trial. Although our pooled analysis of multiple doses of dexamethasone indicated that dexamethasone could lead to a decrease in incidence of POST at both 1 hour and 24 hours after surgery, the subgroup analysis exhibited conflicting results, especially at 1 hour after surgery. This could be explained by the relatively small number of patients included in each trial, which might be insufficient to define the effect of a relatively low or high dose of dexamethasone on POST after surgery.

Many factors can affect the incidence and severity of POST, such as the different types of surgical procedure, endotracheal tube size, intracuff pressure, gender, and anesthetic protocol, as well as the contributing factors, and the preventive measures. We had proven in a meta-analysis that a smaller size of endotracheal tube was associated with a lower incidence of POST after surgery (26).

Dexamethasone has several potential side-effects, such as hyperglycemia, wound healing, and susceptibility to infection. However, Oliveira et al. (16) demonstrated that a single dose of perioperative dexamethasone did not increase its dose-limiting complications such as wound infection and wound healing delay. All included studies reported no occurrence of any side effect of dexamethasone, which might be explained by its single dose use partly. Meanwhile, the follow-up time of included studies was within 24 hours, which was too short to identify the side effects of its use.

The results of our meta-analysis are subject to several limitations. Firstly, our present meta-analysis included only five RCTs. The sample size was relatively small, with multiple doses chosen in the original studies. Our combined results might be inconclusive because of wide CIs. Secondly, dexamethasone was administered preoperatively with a single dose, which limited our ability to investigate whether the timing of administration would influence the outcome measures. We could not assess the severity of POST, because the reports of the outcome differed among studies. Thirdly, a multivariable analysis, such as operation duration, gender, tube size and so on, has not been done on the source data allowing us to take into account some potential confounding factors. Another potential limitation is that the duration of most studies was limited to 24 hours with very few reporting beyond 24 hours after operation. Studies investigating dexamethasone in combination with other pharmacological analgesic and non-pharmacological methods for POST therapy are needed.

CONCLUSIONS

In summary, our current meta-analysis found that prophylactic intravenous administration of dexamethasone was associated with a statistically significant reduction in the incidence of POST after tracheal extubation. Further studies are warranted to determine the dose-ranging effect of dexamethasone and the effect in patients with high risk of POST.

All authors declare no conflict of interest.

Bao-Ji Hu and Lu-Long Bo defined inclusion and exclusion criteria, performed the electronic and manual search of the literature, and drafted and revised the

manuscript. Jin-Bao Li contributed to data analysis, manuscript revision and the interpretation of the data with his expertise. Xiao-Ming Deng had full access to all of the data in the study, contributed to the interpretation of the results, and took responsibility for the integrity of the data and the accuracy of the data analysis.

We acknowledge all authors whose publications were included in this study.

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