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Perioperative dexmedetomidine reduces emergence agitation without increasing the oculocardiac reflex in children

A systematic review and meta-analysis

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Abstract

Background: Intravenous dexmedetomidine (DEX) has been used to prevent emergence agitation (EA) in children. The aim of this meta-analysis was to evaluate whether DEX decreases EA incidence without augmenting oculocardiac reflex (OCR) in pediatric patients undergoing strabismus surgery.

Methods: We searched PubMed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wan Fang, and the Cochrane Library to collect the randomized controlled trials (RCTs) investigating the effects of intraoperative DEX in children undergoing strabismus surgery from inception to October 2019. Postoperative Pediatric Agitation and Emergence Delirium (PAED) score, postoperative EA, extubation or laryngeal mask airway (LMA) removal time, postanesthetic care unit (PACU) stay time, OCR, and postoperative vomiting (POV) were evaluated.

Results: 11 RCTs including 801 patients were included in this study. Compared with control group, intravenous DEX significantly reduced postoperative PAED score (WMD, 3.05; 95% CI: -3.82 to -2.27, $P=.017$) and incidences of postoperative EA 69% (RR, 0.31; 95% CI: 0.17 to 0.55, $P<.00$) and POV (RR, 0.28; 95% CI: 0.13 to 0.61, $P=.001$). Furthermore, the use of DEX significantly delayed extubation or LMA removal time (WMD, 2.11; 95% CI: 0.25 to 3.97, $P<.001$). No significant difference was found in the incidence of ORC and PACU stay time.

Conclusion: Intravenous DEX reduced the incidences of EA without increasing OCR in pediatric patients undergoing strabismus surgery. Meanwhile, DEX infusion decreased the incidence of POV in children.

Abbreviations: CI = confidence interval, EA = emergence agitation, LMA = laryngeal mask airway, OCR = oculocardiac reflex, PACU = postanesthesia care unit, POV = postoperative vomiting, RCTs = randomized controlled trials, RRs = risk ratios, WMDs = weighted mean differences.

Keywords: dexmedetomidine, emergence agitation, meta-analysis, oculocardiac reflex, strabismus surgery

1. Introduction

Emergence agitation (EA) is a complex of behavioral disturbances that occurs commonly in preschool age children in the early postanesthetic period.[1,2] Furthermore, it can increase the risks of self-injury, delayed discharge, extra nursing care, family dissatisfaction, and increased cost.[3,4] Strabismus surgery is one of the most common ophthalmologic procedures in children and it may be associated with high incidence of EA.[5,6] The oculocardiac reflex (OCR) is frequently encountered during pediatric strabismus surgery.[7,8] The incidence of the OCR during strabismus surgery has been variously reported between 32% and 90%, depending on the intensity of observation, anesthetic agent and the definition of OCR.[8]

Dexmedetomidine (DEX), an α2-adrenoceptor agonist with sedative, analgesic, and anxiolytic properties, has been used in pediatric and adult patients.[9] Several studies have demonstrated that DEX significantly reduces the incidence of EA after sevoflurane anesthesia.[2,10,11]

Recently, some clinical researches investigated the use of DEX in children undergoing strabismus surgery.[7,12–14] These studies showed that DEX reduced the incidence of EA without increasing intraoperative oculocardiac reflex.[7,12–14] However, the other

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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studies suggested that DEX and fast-acting opioids can produce more oculocardiac reflex during strabismus surgery.[15,16] Inorder to know whether there is enough evidence to support the use of DEX in strabismus surgery we performed a systematic review and meta-analysis to evaluate whether DEX in pediatric patients decreases ED incidence without augmenting oculocardiac reflex.

2. Methods

Studies were performed in accordance with the PRISMA protocol (Supplementary Table S1, http://links.lww.com/MD2/A100).[17]

2.1. Study search strategy

Two authors (QCS, SJY) independently searched the international databases (PubMed, EMBASE, Web of Science, and the Cochrane Library) and two Chinese databases (CNKI and WanFang database) from inception to October 2019. Medical subject headings and text words "dexmedetomidine or DEX" and "strabismus surgery or strabismus" were used to search for trials of interest. Details of the search strategies are summarized in Supplementary Table S2, http://links.lww.com/MD2/A101. No language restrictions were applied. In order to avoid omitting relevant clinical trials, we also searched conference summaries and references for potential eligible reports.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows:

1. studies designed as RCTs;
2. pediatric patients (aged less than 12) undergoing strabismus surgery;
3. under general anesthesia;
4. intravenous injection (IV) administration of DEX (DEX group) compared with placebo (control group).

Exclusion criteria were as follows:

1. non-RCTs;
2. nonpediatric patients (aged more than 12);
3. (3) DEX administered via a non-IV route;
4. no control group.

2.3. Data extraction and outcome measures

Two authors (QCS, SJY) independently extracted data from the selected studies. Disagreements were handled by discussion until a consensus was reached. The extracted date and information were as follows: first author, year of publication, country, number of patients, timing and dose of DEX, methods of delirium assessment. If data were presented as median and interquartile range (IQR), we contacted the corresponding author to obtain the necessary data. Failing that, the mean was considered to be equivalent to the median, and the standard deviation = IQR/1.35.[18] Primary outcomes are Postoperative Pediatric Agitation and Emergence Delirium (PAED) score and the incidences of postoperative EA and oculocardiac reflex. Secondary outcomes include extubation or laryngeal mask airway (LMA) removal time, postanesthetic care unit (PACU) stay time, and incidence of postoperative vomiting (POV).

2.4. Assessment of study quality

Two authors (QCS, SJY) independently assessed the risk of bias in the included studies. The following factors were assessed according to the Cochrane risk of bias tool for each study:[19]

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective reporting;
7. other bias.

Trials were classified as having low, unclear, or high risk of bias on each domain. Any disagreements were resolved by discussion.

For the assessment of publication bias of the studies included in the final analysis, both Begg's rank correlation and Egger's linear regression tests were performed.[20,21]

2.5. Statistical analysis

All statistical analyses were performed in Stata 15.0 (Stata Corp, College Station, TX, USA) and Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014). Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous data, and weighted mean differences (WMDs) with 95% CIs were calculated for continuous variables. Heterogeneity was measured by I^2, with $I^2 > 50\%$ indicating significant heterogeneity. If $I^2 \leq 50\%$, the fixed effects model was used; if $I^2 > 50\%$, a random effects model was used, and the heterogeneity was assessed.

Subgroup analysis and sensitivity analysis were performed on factors that may have contributed to the heterogeneity. Subgroup analysis was carried out according to timing of IV DEX. Sensitivity analyses were performed by removing one study at a time to evaluate the influence of a single study on the overall estimate.[22] This is a meta-analysis. Thus, ethical approval was not necessary and the informed consent was not given.

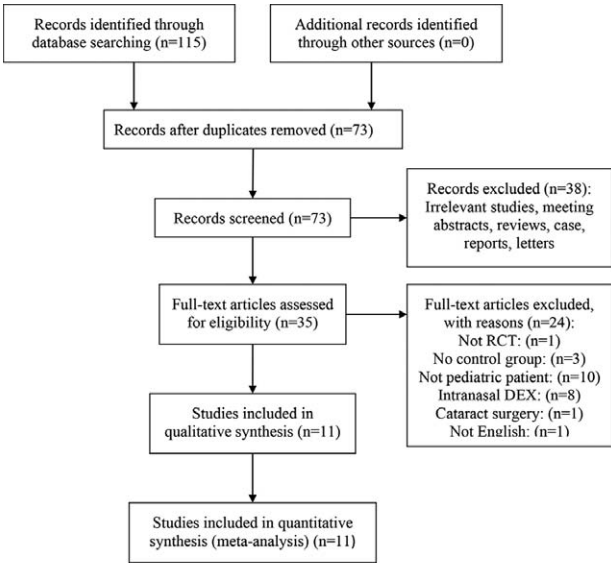

Figure 1. Flow chart summarizing the literature search.

Table 1

Characteristics of included studies.

Study	No. of patients DEX	No. of patients CTRL	Time of DEX administration	DEX infusion rate	Main outcomes
Fu 2018	45	45	20 min before the end of surgery	DEX 0.5 μg/kg	Time of extubation, PAED score, POV, analgesic requirement
Pei 2012	30	30	10 min before the end of surgery	DEX 0.3 μg/kg	PACU stay time, incidence of EA
Li 2016	30	30	Preoperative	DEX 0.5 μg/kg	PACU stay time, OCR, incidence of EA
Wu 2018	39	39	Preoperative	DEX 0.5 μg/kg	PACU stay time, PAED score, incidence of EA
Xiao 2015	20	20	After the induction	DEX 0.2 $\mu g/(kg{\cdot}h)^{-1}$	Time of extubation, PACU stay time, PAED score, incidence of EA
Li 2018	60	60	10 min before the induction	DEX 0.6 μg/kg	PAED score, incidence of EA, POV, glossoptosis
Xu 2014	20	20	10 min before the end of surgery	DEX 0.5 μg/kg	PAED score, time of extubation, PACU stay time
Chen 2013	27	24	Intraoperative	DEX 1 μg/kg given over 1 min	PAED score, OCR, LMA removal time, discharge from recovery room, POV score
Song 2016	78	28	Start of induction	DEX 0.25 to 1 μg/kg infused over 10 min	Time to LMA removal, PACU stay time, agitation score, PAED scale, OCR, postoperative vomiting
Mizrak 2011	30	30	Before the induction	Single dose of DEX 0.5 μg/kg given over 10 min	EA score, incidence of OCR, atropine requirement, analgesic requirement
Kim 2013	48	48	During surgery	DEX 0.2 $\mu g/(kg{\cdot}h)^{-1}$	PAED maximum score, incidence of severe EA, frequency of rescue fentanyl

DEX = dexmedetomidine, EA = emergence agitation score, LMA = laryngeal mask airway, OCR = oculocardiac reflex, PACU = postanesthetic care unit, PAED = Pediatric Agitation and Emergence Delirium, POV = postoperative vomiting.

3. Results

3.1. Study search

Figure 1 shows the summary of the study selection process. Hundred and fifteen potentially relevant articles were identified initially. After excluding duplicate references and reviewing titles and abstracts, we selected 35 studies for full-text evaluation. Of these, 24 trials did not meet the inclusion criteria. Reasons for exclusion included:

1. the study was not randomized (n = 1),
2. there were not pediatric patients (n = 11),
3. there was no control group (n = 3),
4. DEX was not given by IV route (n = 8),
5. there was not strabismus surgery (n = 1).

Ultimately, a total of 11 studies consisting 801 patients were included.[7,12–14,23–29]

3.2. Trial characteristics and study quality

Table 1 shows details of all the studies included in the meta-analysis. The 11 studies are published between 2011 and 2018, and sample sizes range from 40 to 120. DEX administration was started either preoperatively or intraoperatively. Two authors independently evaluated the quality of the RCTs. None of the 11 studies had a high risk of bias. The majority of trials demonstrated a low risk of bias, as well as several elements representing an unclear risk of bias. Risk assessment details are presented in Figure 2.

3.3. Outcomes of the meta-analysis

3.3.1. Postoperative Pediatric Agitation and Emergence Delirium score.

Data from seven studies involving 543 patients indicated that low-dose DEX significantly reduced postoperative PAED score by an estimate of 3.05 (RR, 0.31; 95% CI: -3.82 to -2.27, $P = .017$, $I^2 = 61.3\%$) (Fig. 3). Subgroup analyses of timing of IV DEX did not influence the pooled results (Fig. S1, http://links.lww.com/MD2/A97). Sensitivity analysis did not significantly alter the summarized results (Fig. S2, http://links.lww.com/

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Binding of participants and personnel (performance bias)	Binding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen 2013	+	+	+	+	+	+	+
Fu 2018	+	?	?	?	?	?	?
Kim 2013	+	+	+	+	+	+	+
Li 2016	?	?	?	?	?	?	?
Li 2018	+	?	?	?	?	?	?
Mizrak 2011	+	?	+	+	+	?	?
Pei 2012	?	?	?	?	?	?	?
Song 2016	+	+	+	+	+	+	+
Wu 2018	?	?	?	?	?	?	?
Xiao 2015	+	?	?	?	?	?	?
Xu 2014	+	?	?	?	?	?	?

Figure 2. Evaluation of risk of bias for each included study.

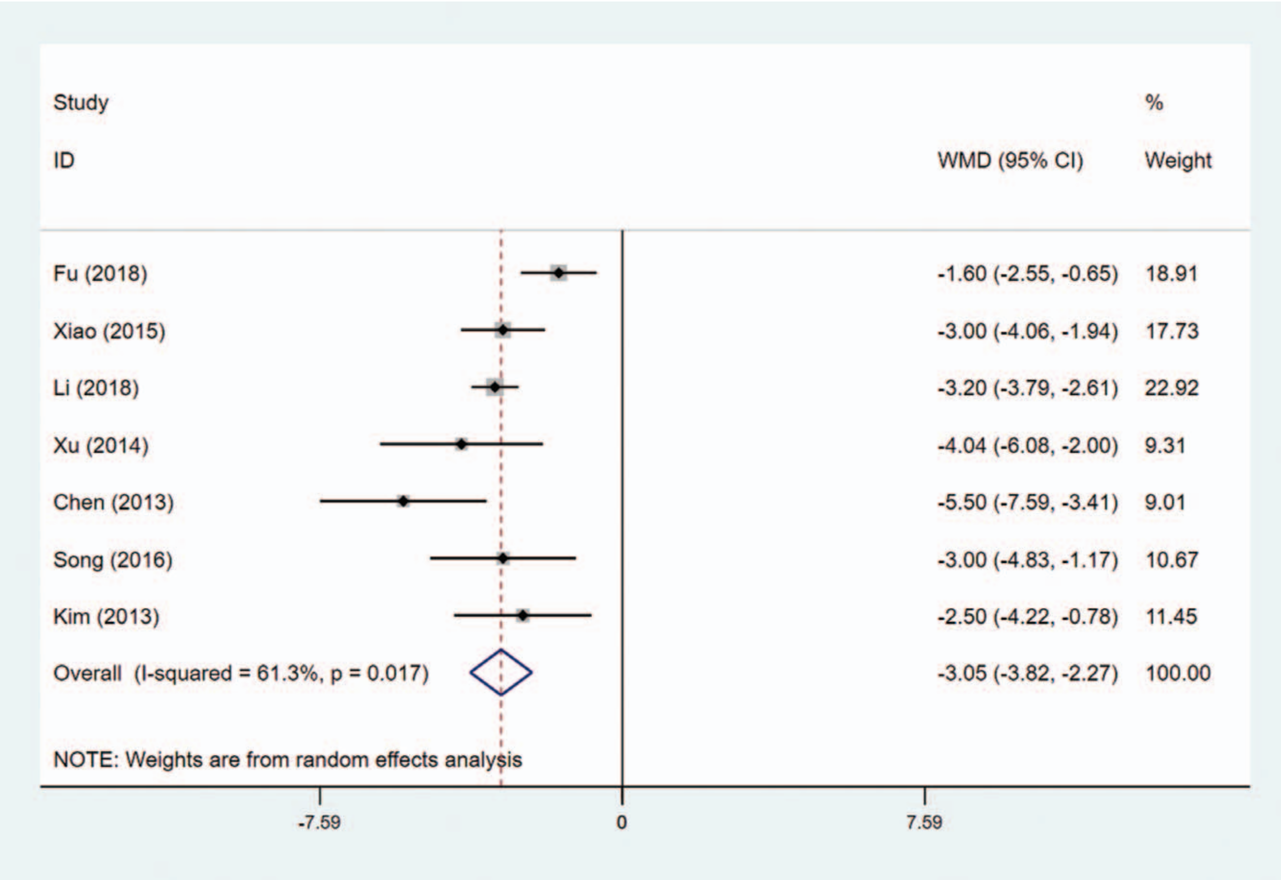

Figure 3. Forest plot depicting postoperative PAED score. CI = confidence interval, PAED = Pediatric Agitation and Emergence Delirium, WMD = weighted mean difference.

MD2/A98). No evidence of publication bias was observed on Begg's funnel plot ($P=.37$, Fig. S3, http://links.lww.com/MD2/A99) or Egger's test ($P=.59$).

3.3.2. Postoperative emergence agitation. Data from eight studies involving 565 participants showed that the addition of DEX significantly decreased the incidence of postoperative EA by 69% (95% CI: 0.17 to 0.55, $P<.001$, $I^2=79.2\%$) (Fig. 4). Subgroup analyses of timing of IV DEX did not influence the pooled results. Sensitivity analysis did not significantly alter the summarized results. Although Egger's test indicated publication bias ($P<.001$), Begg's test was not significant ($P=.39$).

3.4. Oculocardiac reflex

The incidence of OCR was described in four trials with 277 patients, but there were no differences between the 2 groups, with an estimate of 0.58 (95% CI: 0.20 to 1.67, $P=.066$, $I^2=58.3\%$) (Fig. 5). Subgroup analyses of timing of IV DEX did not influence the pooled results. Sensitivity analysis did not significantly alter the summarized results. Due to the small number of studies included, Begg's funnel plot or Egger's test could not be conducted for publication bias.

3.5. Extubation or laryngeal mask airway removal time

Extubation or LMA removal time was assessed in seven studies including 447 patients. The use of DEX delayed extubation or LMA removal time by an estimate of 2.11 min (95% CI: 0.25 to 3.97, $P<.001$, $I^2=93.7\%$) (Fig. 6) in children undergoing strabismus surgery. Subgroup analyses of timing of IV DEX did not influence the pooled results. Sensitivity analysis did not significantly alter the summarized results. No evidence of publication bias was observed on Begg's funnel plot ($P=.13$) or Egger's test ($P=.15$).

3.6. Postanesthesia care unit stay time

PACU stay time was assessed in nine studies with 615 patients. There was no differences between the 2 groups, with an estimate of 1.66 min (95% CI: -3.07 to 6.39, $P<.001$, $I^2=95.9\%$) (Fig. 7). Subgroup analyses of timing of IV DEX did not influence the pooled results. Sensitivity analysis did not significantly alter the summarized results. No evidence of publication bias was observed on Begg's funnel plot ($P=0.75$) or Egger's test ($P=.18$).

3.7. Postoperative vomiting

Four trials including 307 patients investigated the occurrence of POV after surgery. The incidence of POV in the DEX group was 72% lower than that in the control group (95% CI: 0.13 to 0.61, $P=.001$, $I^2=0.0\%$) (Fig. 8). Subgroup analyses of timing of IV DEX did not influence the pooled results. Sensitivity analysis did not significantly alter the summarized results. Because of the small number of studies included, Begg's funnel plot or Egger's test was not performed for publication bias.

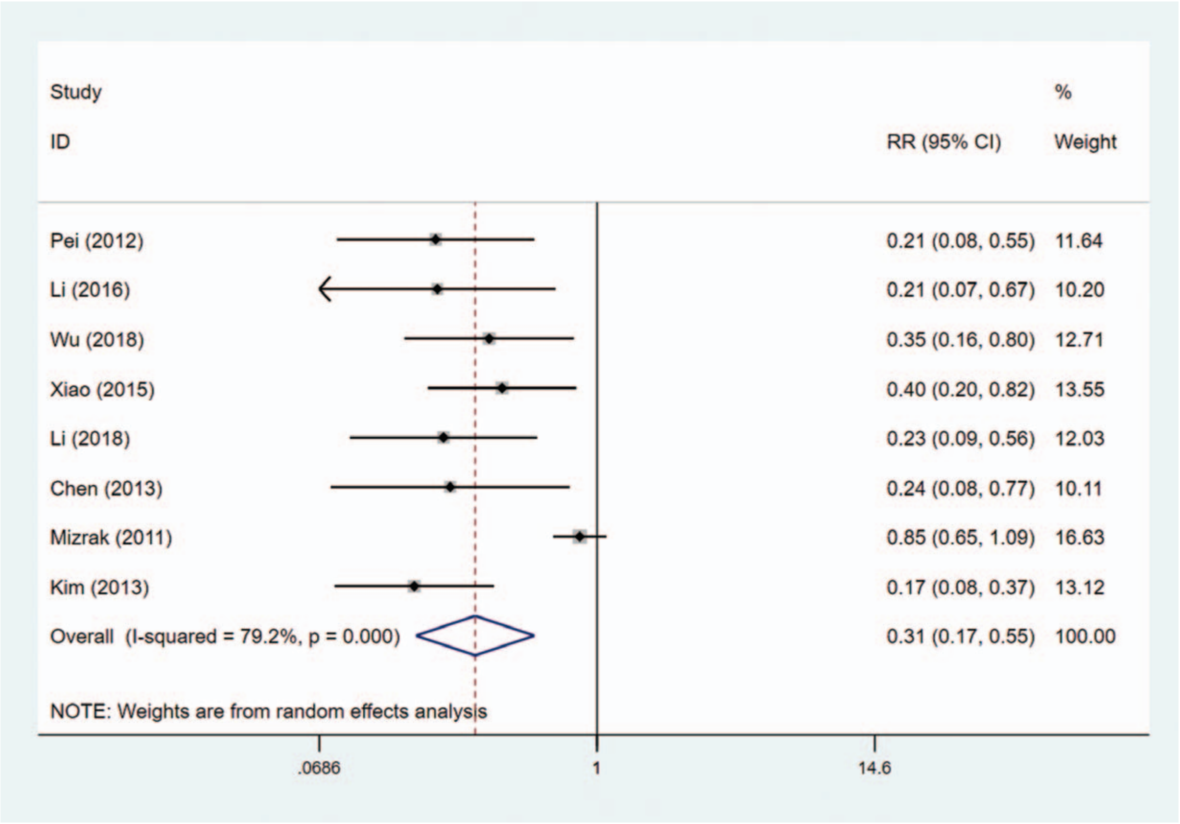

Figure 4. Forest plot depicting postoperative EA. CI = confidence interval, EA = emergence agitation, WMD = weighted mean difference.

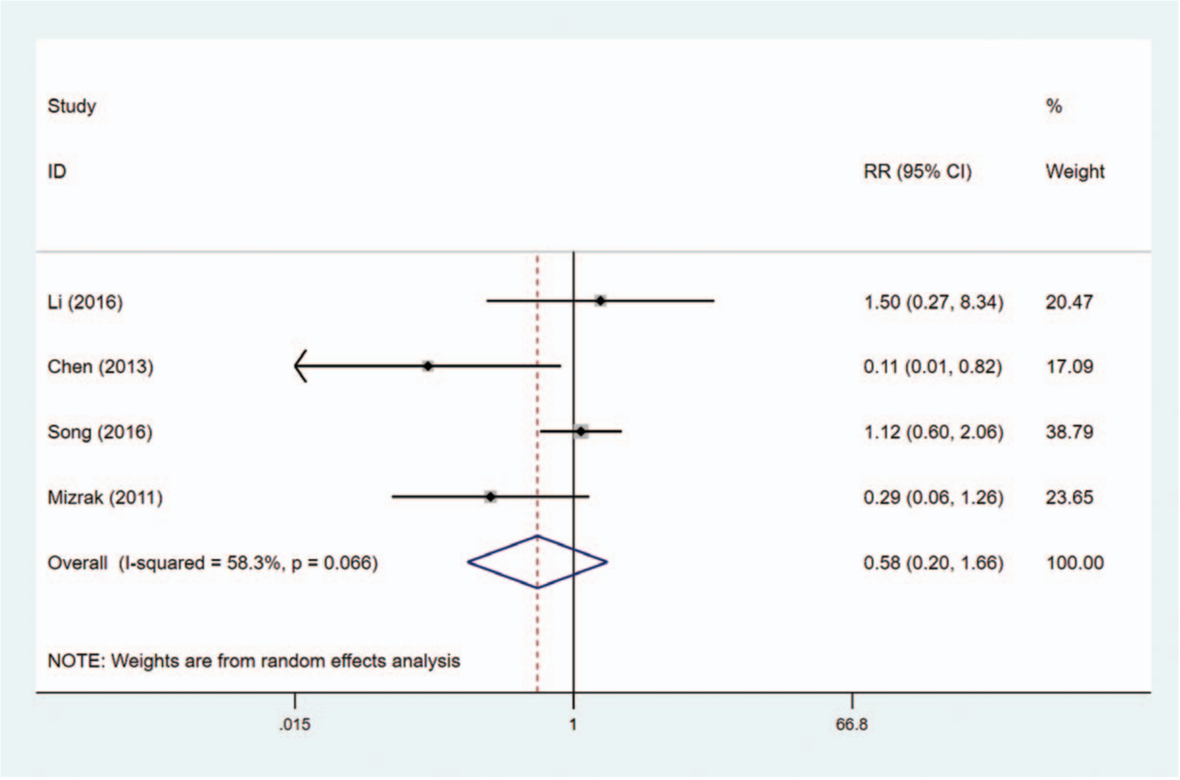

Figure 5. Forest plot depicting postoperative OCR. CI = confidence interval, OCR = oculocardiac reflex, WMD = weighted mean difference.

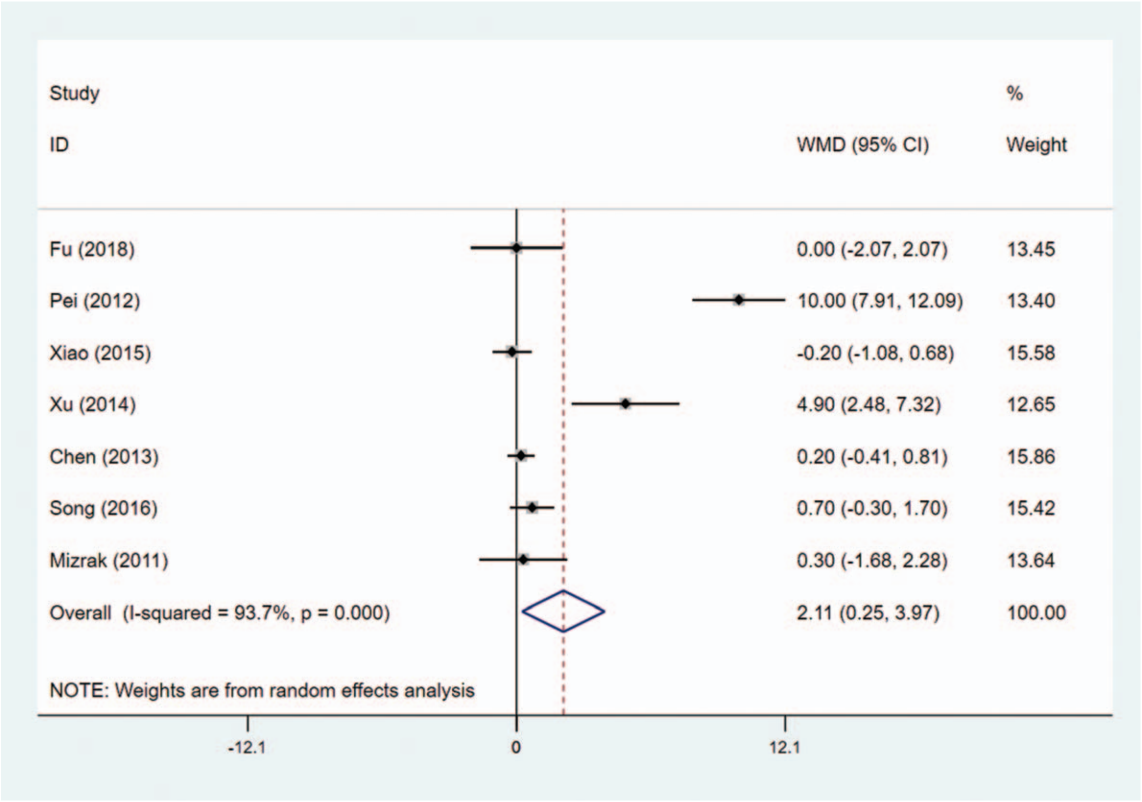

Figure 6. Forest plot depicting postoperative extubation or LMA removal time. CI = confidence interval, LMA = laryngeal mask airway, WMD = weighted mean difference.

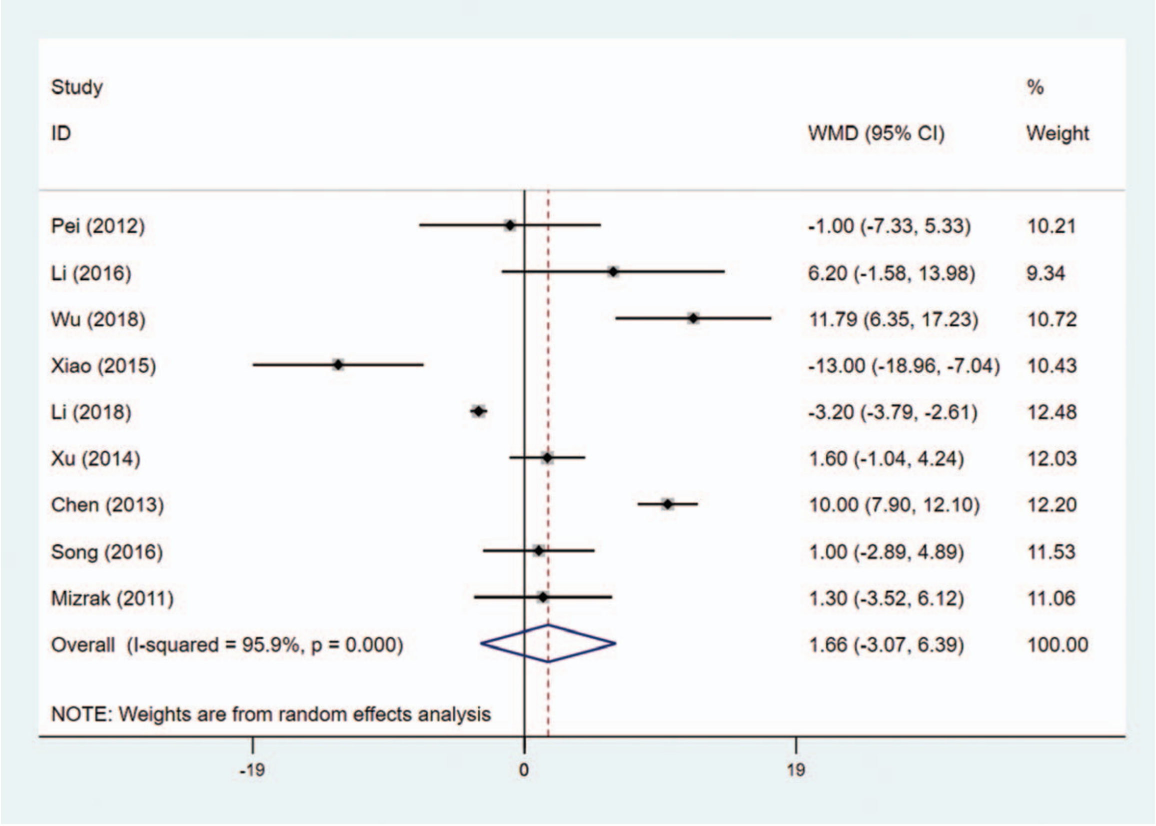

Figure 7. Forest plot depicting PACU stay time. CI = confidence interval, PACU = postanesthetic care unit, WMD = weighted mean difference.

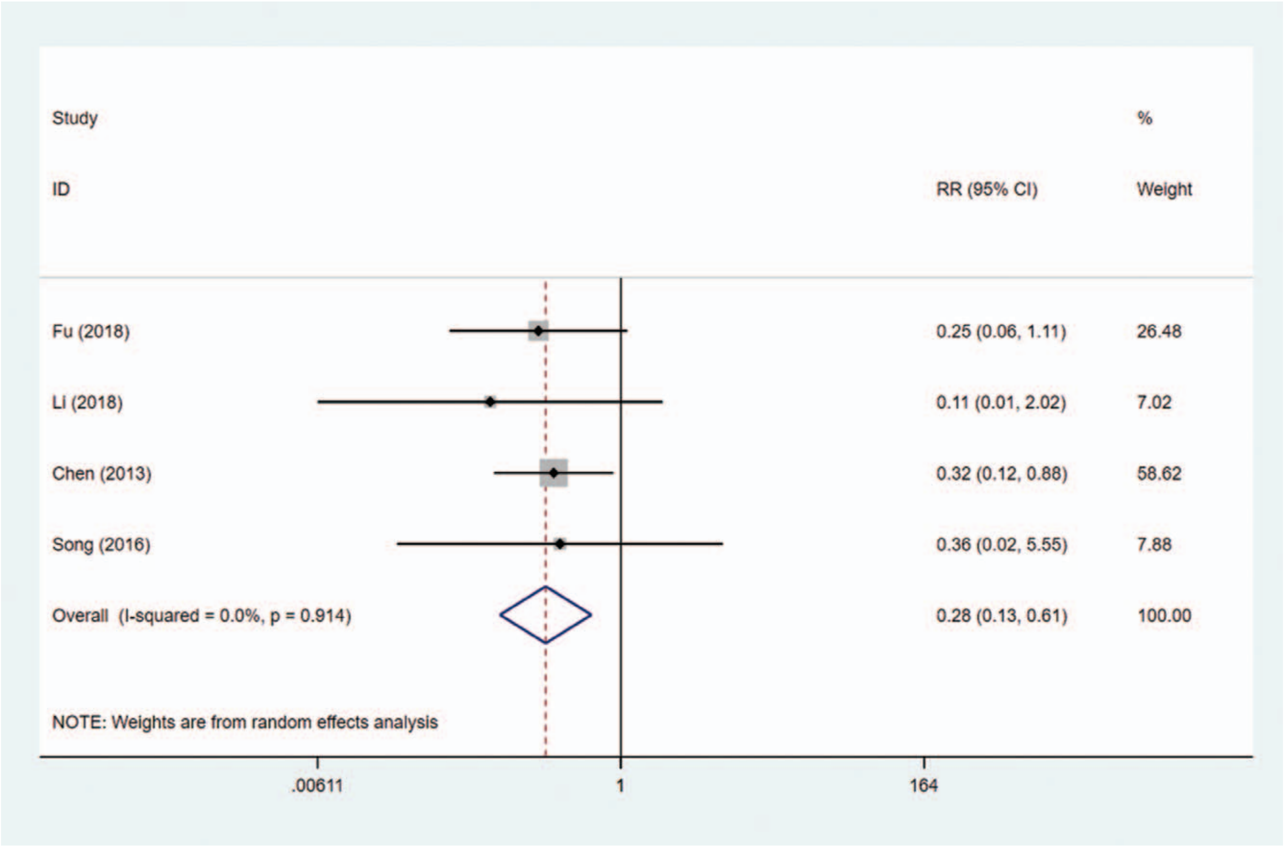

Figure 8. Forest plot depicting POV. CI = confidence interval, POV = postoperative vomiting, WMD = weighted mean difference.

4. Discussion

This meta-analysis involved 11 RCTs to assessed the effect of DEX in pediatric patients undergoing strabismus surgery. The results showed that perioperative DEX administration reduced the incidence of EA without increasing OCR. It also indicated that DEX infusion was associated with a longer extubation time, while PACU stay time didn't differ significantly between groups. Furthermore, DEX administration significantly decreased the incidence of POV in children.

Delirium is a common, serious complication following general anesthesia in children. It has been reported that the incidence of EA ranges from 10% to 80%.[30,31] Till now, the precise mechanism of EA is unknown. The risk factors associated with EA include postoperative pain, anxiety, preschool age, the type of surgery, and disorientation on rapid awakening.[30–32] In an attempt to minimize postoperative EA, various pharmacological interventions have been used. Recent meta-analysis found that propofol, ketamine, fentanyl, alpha 2-adrenoceptors and preoperative analgesia had a preventive effect on EA.[33] In this meta-analysis, DEX treatment decreased postoperative PAED score by 3.05 points. Meanwhile, DEX administration reduced the incidence of EA after strabismus surgery. Similar results already described by other meta-analysis.[34,35] Although the delirium-sparing effect has been deeply researched in recent years, the mechanism of DEX reducing EA in children remains unclear. The following aspects may contribute to this effect. First, DEX improve sleep quality after general anesthesia.[36,37] Second, DEX has proven to have opioid-sparing effects without respiratory depression.[38] Third, DEX has a strong anti-inflammatory effect.[39] Finally, DEX may reduce the deleterious effect of apoptosis.[40]

Bradycardia and hypotension have been associated with DEX administration. Therefore, there are still some concerns with respect to its safety during strabismus surgery. Arnold and colleagues reported that intravenous fast-push DEX can potentiate oculocardiac reflex.[15] Sinha and colleagues demonstrated that intravenous DEX bolus should be administered over 10 min to prevent hemodynamic changes.[41] Rapid bolus DEX administration will lead to decrease the HR without traction of muscle.[41] In this meta-analysis, DEX was infused over 10 min in most included studies. Due to their slow infusion of DEX, no significant differences in the incidence of OCR were detected between the DEX and the control groups.

In this study, the time of extubation or LMA removal were considered statistically higher in DEX group, but without clinical repercussions. Regarding the PACU stay time, this meta-analysis found no statistically significant difference between DEX and control groups. POV is a common postoperative complication in children undergoing general anesthesia. The present meta-analysis revealed that DEX infusion reduced the incidence of POV. Our results are consistent with another recent meta-analysis that showing that intravenous DEX had the advantage to prevent postoperative nausea and vomiting.[42] The addition of DEX could reduce the perioperative opioids consumption may explain the decreased incidence of POV.[42,43]

This meta-analysis has several potential limitations. First, the present meta-analysis included a relatively small size of studies, so overestimation of the treatment effect is more likely in smaller trials compared with larger trials. Second, most of the studies included in this meta-analysis were conducted in China, and our study might be influenced by publication bias (Begg's funnel plot and Egger's test). More studies conducted in different countries are still needed to confirm our findings. Third, because limited number of available studies that could be included in some meta-analytical comparisons, we were unable to examine publication bias and the resource of heterogeneity. Fourth, some of the outcomes had small sample sizes (e.g., OCR and POV), which may result in a small-study effect. Finally, the doses of DEX in the retrieved trials are varied. This demonstrated that the clinical use of DEX is not strictly regulated.

In summary, this current meta-analysis suggested that the use of DEX reduced the incidences of EA without increasing OCR in pediatric patients undergoing strabismus surgery. Meanwhile, DEX infusion decreased the incidence of POV in children. However, some results in this study might be weakened by the unavoidable heterogeneity and insufficient data. Further studies are needed to determine the optimal time and dose of DEX use.

Author contributions

Conceptualization: Qianchuang Sun, Guangyu Li.
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Writing – original draft: Qianchuang Sun, Guangyu Li.
Writing – review & editing: Qianchuang Sun, Guangyu Li.

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