Prophylactic application of dexmedetomidine reduces the incidence of Emergence delirium in children A systematic review and meta-analysis

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Research Article

Keywords:

Posted Date: April 4th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2678444/v1

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Abstract

**Background** Emergence delirium (ED) is a postoperative cognitive dysfunction that not only causes distress to patients and their families in the early post-anesthesia period, but also has long-term adverse effects in children. There are assumptions that non-delirium sedatives reduce adverse outcomes in children admitted to PACU (Post anesthesia care unit) ।.

**Main purpose** to verify whether dexmedetomidine can reduce the occurrence of PACU ED in children. To compare the effects of different administration methods of dexmedetomidine on reducing ED. And exploring whether giving dexmedetomidine at different times during the perioperative period affects the incidence of ED.

**Research type** A systematic review and meta-analysis of randomized controlled trials.

**Data acquisition** We searched WOS, WHO Trials, Cochrane Library, Clinical Trials.gov and PubMed for all published studies from the establishment of the library up to 23 Oct.2022.

**Eligibility criteria** If the subjects were actively given dexmedetomidine before entering the PACU, and the occurrence of ED was used as the outcome measure, and the sample mean / median age was no more than 18 years old, they were included in the study. Studies examining the use of dexmedetomidine after surgery were excluded.

**Results** A data analysis from seven studies involving 512 patients showed that prophylactic use of dexmedetomidine reduced the incidence of ED in children (risk ratio [RR] 0.40; 95% confidence interval [CI] 0.30–0.55; \( P < 0.00001 \)). Compared with intravenous infusion of dexmedetomidine (n = 350, [RR] 0.48, 95% [CI] 0.31–0.76, \( P = 0.002 \)), intranasal injection of dexmedetomidine (n = 162, [RR] 0.29, 95% [CI] 0.16–0.52, \( P < 0.0001 \)) has a lower risk ratio and may better reduce the incidence of ED, although no difference in incidence was observed in subgroup analysis. Compared with dexmedetomidine given at the end of surgery (n = 213, [RR] 0.41, 95% [CI] 0.17–0.98, \( P = 0.05 \)), dexmedetomidine given before and during surgery (n = 162, [RR] 0.29, 95% [CI] 0.16–0.52, \( P < 0.0001 \). / n = 137, [RR] 0.56, 95% [CI] 0.35–0.90, \( P = 0.02 \)) has a better effect on reducing the incidence of ED. In addition, prophylactic application of dexmedetomidine can reduce the occurrence of PONV (postoperative nausea and vomiting): 7 studies: n = 512 patients; [RR] 0.24; 95% [CI] 0.12–0.49; \( P = 0.0001 \). The occurrence of bradycardia was not statistically significant (2 studies: n = 157; [RR] 3.24; 95% [CI] 0.52–20.40; \( P = 0.21 \)). Otherwise, because there was only one case of hypotension, we did not perform a meta-analysis. Prophylactic application of dexmedetomidine reduced PACU stay time after extubation (n = 446; mean difference [MD] -1.57; 95% [CI] -3.07 to -0.07, \( P = 0.04 \)). However, sensitivity analysis of PACU stay time after extubation was not statistically significant and stable (n = 296; [MD] -0.55; 95% [CI] -1.30-0.19, \( P = 0.15 \)).

**Conclusion** Prophylactic use of dexmedetomidine can reduce the occurrence of ED in children and the adverse events no significant increase. In pediatric surgery, the anesthesiologist should consider the use
of dexmedetomidine. In the future, we hope to confirm our findings through multi-center trials and clarify and explain the mechanism behind the reduction of ED with dexmedetomidine.

TRIAL REGISTRATION

PROSPERO: CRD42022371840.

**Key Points**

1. This article is only for children.

2. The occurrence of delirium in pediatric patients as the Main Measure.

3. This article summarizes the effects of dexmedetomidine on delirium in children.

**Introduction**

Emergence delirium (ED), a behavioral disorder in pediatric, typically presents with crying, mental confusion, restlessness, and disorientation after anesthesia. The prevalence of ED in pediatric under sevoflurane anesthesia has been reported as high as 80%. In addition, the development of ED increases the risk of self-harm and surgical wound dehiscence, catheter accidental removal, postoperative bad behavior, and ultimately pose a threat to patients, parents and primary caregivers.

More and more evidences show that dexmedetomidine is effective in the prevention of ED. Dexmedetomidine is a highly selective α2 adrenergic receptor agonist. It has been considered as a possible therapeutic measure to prevent anesthesia-related ED. Dexmedetomidine can exert sedative and anxiolytic effects by acting on receptors in the nucleus ceruleus of the pons. It can also bind to α2 receptors in the spinal dorsal horn and supraspinal region to exert a dose-dependent analgesic effect.

Some clinical studies have shown effectiveness the effective of intravenous administration of 1.0 and 1.43 ug/kg dexmedetomidine after induction of anaesthesia in the prevention of ED in children with sevoflurane anesthesia. Prophylactic use of dexmedetomidine may reduce the occurrence of ED. However, there are no literature comparing the efficacy of dexmedetomidine in reducing ED by different modes of administration, nor to explore whether dexmedetomidine given at different times during perioperative period affects the occurrence of ED. In this study, we carefully assessed the included trials, compared the effects of different administration methods of dexmedetomidine on reducing ED, and explored whether the administration of dexmedetomidine at different times during the perioperative period affected the incidence of ED. We assessed the efficacy of dexmedetomidine for prophylactic use in children with ED. Also, we compared their effect on PACU recovery time after extubation (defined as the interval from extubation to PACU discharge), PONV, Hypotension (defined as lower than the same age normal systolic blood pressure 20 mmHg. Normal systolic blood pressure: systolic blood pressure 70-80mmHg at 1 years old, systolic blood pressure after two years old = age*2 + 80mmHg), and bradycardia
(defined as 1–6 years old: heart rate less than 80 times per minute, over 6 years old: heart rate less than 60 times per minute).

**Methods**

**Protocol registration**

Articles are based on priority reporting items in the guidelines for systematic reviews and meta-analysis claims and registered in PROSPERO (CRD: 42022371840).

**Literature search**

A researcher conducted a comprehensive search of MEDLINE, Web of Science, Cochrane Library, ClinicalTrials.gov, and WHO Trials from inception to Oct.23, 2022. The search strategy consisted of subject words and free words, including dexmedetomidine, delirium and children. There is no language restriction, but animal studies are excluded. Figure 8 describes the strategy. In addition, additional literature search strategy was manually retrieved by a researcher to obtain relevant literature titles and use Google Scholar for forward reference search. All references are uploaded to the Endnote (v.X20, Corevion, Philadelphia, Pennsylvania, USA) and the researchers removed duplicates.

**Eligibility criteria**

1. The age was 1-18 years old.

2. Study site was set in PACU.

3. The incidence of ED was the main measurement index.

We excluded meetings, abstracts and lecture papers. Diagnostic data were incomplete or incorrect and postoperative use of dexmedetomidine was excluded.

**Study screening**

Two researchers (SH and YX) screened retrieved articles separately. Literature screening begins with initial screening: reading titles and abstracts, followed by rescreening: reading the full text. Both initial and rescreening are tested for consistency (Kappa statistics) to ensure the accuracy of the screening results. All screening was carried out by two investigators based on a list of inclusion and exclusion criteria. Any differences between evaluators are resolved through consensus and discussion. The reviewers screened the articles using EndNote.

**Risk of bias in individual studies**

The investigators assessed risk of bias using the Cochrane Risk of bias assessment tool. The assessment includes the following aspects:
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

If one aspect was assessed as “high risk”, this bias in the study was present and may have affected the findings. However, if assessed as “low” or “unclear risk”, the bias was absent or uncertain whether it affected the findings. Risk of bias assessment was performed separately by two review groups, and inconsistencies in results were resolved by discussion with a third review group.

**Data extraction**

First, a screener performs data pre-extraction to build a comprehensive extract template. The template content should preferably include the following aspects: literature title, first author, Country, Year of study, subjects, Methods, Sample Size, Patient Characteristics, Outcome Indicators, Time given to interventions, PACU stay after extubation, Incidence of adverse events and methods to reduce the risk of population bias. Second, two screeners performed the data extraction separately. Inconsistencies in the data extraction results are resolved through consultation with a third screener. Finally, the data that were missing but critical to our study were obtained by a fourth screener contacting the authors.

**Statistical analysis**

The endpoint metrics was the occurrence of ED during PACU, and the secondary outcome measures were length of stay after extubation, incidence of PONV, hypotension, and bradycardia. For indicators reported as incidence such as ED, hypotension, bradycardia, PONV, we extract the number of events. For continuous data, we extract the mean and standard deviation. In addition, we convert the data reported as median and quartile into mean and standard deviation by the method of wan et al\(^8\).

We used Review Manager 5.4 software for meta-analysis\(^9\), reporting dichotomous data as a 95% confidence interval risk ratio, reporting continuous data as a 95% confidence interval weight mean difference. \(P\)-value \(\geq 0.05\) was not considered statistically significant. We used the I\(_2\) statistic (heterogeneity of included studies/total variation) to assess the heterogeneity of included studies. If \(I_2 > 50\%\), it shows that the heterogeneity of the study is relatively high, and the random effect model is suitable. If \(I_2 < 50\%\), it shows that the heterogeneity of the study is small, and the fixed effect model is suitable\(^10\). The publication bias of included studies was assessed by funnel plot. However, due to the small sample size we obtained, the type 2 error risk for detecting symmetry is high. We can only evaluate publication bias by visual inspection of funnel plot (the closer the point in the funnel plot is to the line in
the middle, the lower the risk of bias of the study represented by this point.), not symmetry test. Finally, we perform a sensitivity analysis to explore the stability of the results.

**Results**

**Identification of studies**

A total of 510 articles were retrieved. However, only 7 randomized controlled trials were included in our study\(^1,^{11-16}\). Among the excluded literature, 486 studies were excluded after reading the title and abstract (Kappa statistic k: 0.9), 10 articles were excluded because they did not meet the inclusion criteria (Kappa statistic k: 0.9), and seven articles were excluded after reading the full text according to the reasons stated in Table 1.

**Description of included studies**

Table 1 describes the basic characteristics of the studies included in this meta-analysis. We analyzed 512 patients from seven included studies. The study included 230 pediatric patients who underwent strabismus surgery (three studies)\(^{13,15,16}\). There were 80 pediatric patients undergoing cataract surgery (one study)\(^14\), 156 pediatric patients undergoing tonsillectomy (two studies)\(^1,^{11}\), and 47 pediatric patients undergoing high ligation of hernia sac\(^12\). Among the seven studies, four studies assessed the incidence of ED using the PAED (Peadiatric Assessment of Emergence Delirium) scale, one study assessed the incidence of ED using the five-point scale, one study assessed the incidence of ED using the PAED scale and the Watcha scale, and one study assessed the incidence of ED using the PAED scale and the four-point scale.

**Risk of bias appraisal**

Figure 9 describes the risk of bias results. Overall, the difference in risk bias between studies was small, and all randomized studies were well assigned to a random sequence. Subjects, researchers and outcome evaluators all performed blinding and allocation concealment. However, some research data are incomplete, and some factors such as selective bias are difficult to evaluate. In addition, due to our small sample size, there may be differences in response and participation rates. We judged six of the seven studies to be at low risk of bias and of good overall quality.

**Outcomes of pooled studies**

**Occurrence of ED**

7 studies reported the occurrence of ED in dexmedetomidine and control groups. Dexmedetomidine group 45/257 cases (17.51%) and control group 110/255 cases (43.14%). After meta-analysis, compared with control group, Dexmedetomidine reduced the risk of ED: 512 patients; [RR] 0.40; 95% confidence interval [CI] 0.30–0.55; \(P<0.00001\). Heterogeneity between studies was not statistically significant (\(I^2 = 34\%\), \(P=\))
0.17) (Fig. 1a). Sensitivity analysis including RCTs showed that our effect estimates were still statistically significant (n = 373 patients, [RR] 0.44, 95% [CI] 0.32–0.61, P < 0.00001). This indicated the stability of the results of the study (Fig. 6). We also performed subgroup analysis of different administration methods of dexmedetomidine and administration of dexmedetomidine at different time periods during the perioperative period. Subgroup differences were statistically significant. And the results showed that intranasal injection of dexmedetomidine (n = 162, [RR] 0.29, 95% [CI] 0.16–0.52, P = 0.0001) may better than intravenous infusion of dexmedetomidine (n = 350 patients, [RR] 0.48, 95% [CI] 0.31–0.76, P = 0.002) in reducing the risk of ED (Fig. 2a), but there was no obvious difference in the effect of reducing ED during hospitalization with PACU. Dexmedetomidine given before and during surgery (n = 162, [RR] 0.29, 95% [CI] 0.16–0.52, P < 0.0001/n = 137, [RR] 0.56, 95% [CI] 0.35–0.90, P = 0.02) was better correlated with reducing the risk of ED than dexmedetomidine given at the end of surgery (n = 213 patients, [RR] 0.41, 95% [CI] 0.17–0.98, P = 0.05). (Fig. 1a)

Table 1: the basic characteristics of the studies included in this meta-analysis

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<th>Country</th>
<th>The first author</th>
<th>Year of study</th>
<th>Incidence of PONV</th>
<th>Incidence of ED</th>
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**Incidence of PONV**

5 studies reported the occurrence of PONV in dexmedetomidine and control groups1,11,13–15. Dexmedetomidine group 8/205 cases (3.90%) and control group 34/201 cases (16.92%). After meta-analysis, compared with placebo, The application of dexmedetomidine was significantly related to a reduction in the risk of PONV: n = 406 patients; [RR] 0.24; 95% confidence interval [CI] 0.12–0.49; P = 0.0001(Fig. 3a). There was no significant heterogeneity between studies (I² = 0%, P = 0.78). Sensitivity analysis including RCTs showed that our effect estimates were still statistically significant (n = 316; [RR] 0.20; 95% confidence interval [CI] 0.09–0.45; P = 0.0001), reflecting the stability of our results. (Fig. 3b).

**Occurrence of hypotension**
One study reported the occurrence of hypotension\textsuperscript{14}. Data analysis of 80 children revealed no statistically obvious difference in the occurrence of hypotension between dexmedetomidine and placebo. Meta analysis, heterogeneity test and sensitivity analysis could not be performed due to only one study.

**Occurrence of bradycardia**

Two studies monitored the incidence of bradycardia and a meta-analysis of 157 children found no statistically prominent difference in the occurrence of bradycardia between dexmedetomidine and placebo\textsuperscript{1,15}; n = 157, [RR] 3.24; 95% [CI] 0.52–20.40; \textit{P} = 0.21(Fig. 5). Heterogeneity between the studies was no statistically significant (\textit{I}^2 = 0%; \textit{P} = 0.52). Because there were only two studies, no sensitivity analysis was performed.

**PACU stay time after extubation**

Seven studies(n = 512) reported PACU stay time after extubation, although one study was excluded due to lack of data. We used wan et al. to convert the median and quartile reported in the three studies into mean and standard deviation\textsuperscript{1,11,13}. This meta-analysis, which combined data from six studies, showed a statistically significant difference in PACU stay time after extubation between dexmedetomidine and control groups: n = 446; MD -1.57; 95%[CI] -3.07 to -0.07, \textit{P} = 0.04 (Fig. 4a). Heterogeneity across studies was significant (\textit{I}^2 = 90%; \textit{P} < 0.00001). Sensitivity analysis of RCTs showed that our effect estimates were not statistically significant and stability (n = 296 patients; MD -0.55; 95% [CI] -1.30-0.19, \textit{P} = 0.15) (Fig. 4b)

Figure 2a: Forest plot of delirium incidence in different administration methods

**Publication bias**

Our observations of the funnel plot revealed a possible risk of bias for delirium incidence results (Fig. 1b / 2b). And, judging by the study 's estimated distribution of inequality, published data are relatively scarce and the results are negative. However, given the sample size is not large of studies in the funnel chart, its statistical significance cannot be tested by the Egger ‘s method. By observing the funnel chart, we can get limited results.

**Discussion**

This review shows that compared with placebo, Prophylactic administration of dexmedetomidine has a good effect in reducing the occurrence of ED, reducing the occurrence of PONV, and reducing the PACU stay time after extubation. The risk of hypotension and bradycardia did not increase significantly. Moreover, Subgroup analysis of delirium incidence indicated that intranasal dexmedetomidine better reduced the risk of ED compared with intravenous dexmedetomidine infusion. Compared with dexmedetomidine given at the end of surgery, dexmedetomidine given before and during surgery show a significant effect on reducing ED. This is different from other similar meta-analysis. In addition, our meta-analysis has novel points different from other similar meta-analysis: 1, Our outcome measures included
the incidence of hypotension and bradycardia in the subjects to evaluate the safety of dexmedetomidine; 2, the heterogeneity of the main outcome (ED) was low.

In this review, under sevoflurane-related anesthesia, the occurrence of ED during awakening accounted for 30.3% of the total number of people, it will cause potential harm to children, such as unplanned extubation, risk of falling out of bed, prolonged hospital stays, etc. And these will increase patient suffering, use of analgesics, hospital costs and family burden. However, there are currently no drugs approved for the treatment and prevention of ED in children. Some of the current recommended methods include preoperative medication of propofol, fentanyl, clonidine, dexmedetomidine, midazolam, ketamine and magnesium sulfate\textsuperscript{17,18}. But no studies have shown that these drugs have a good effect on reducing ED in children at recovery stage at large sample size. Moreover, for pediatric patients, preoperative coordination is low, and sometimes it is difficult to establish a venous access, so these preventive drugs cannot be administered intravenously. At present, nasal administration is a good alternative, which is convenient and rapid. Therefore, this article reviews the related studies on dexmedetomidine reducing ED, and integrates these studies that meet the inclusion criteria and exclusion criteria for analysis. This study aimed to investigate the effect of dexmedetomidine on ED in large sample sizes, and to compare the effects of dexmedetomidine administration on the incidence of ED convalescent in different modes of administration and perioperative periods.

In these seven studies, among the 257 patients, 45 patients developed delirium using dexmedetomidine before or during surgery, and of the 255 patients, 110 developed deliriums with placebo or drugs. The meta-analysis indicated that compared with the control group, dexmedetomidine in reducing the risk of ED under sevoflurane anesthesia was statistically significant. We analyzed seven included studies and obtained the results of this meta-analysis. And these results indicated that dexmedetomidine may reduce the occurrence of ED. However, in order to get accurate results, we should explore the mechanism of dexmedetomidine in reducing sevoflurane anesthesia-related ED from the molecular, biochemical and pathophysiological levels. At present, there may be related mechanisms: Sun et al. showed that dexmedetomidine and clonidine can inhibit sevoflurane-induced tau phosphorylation and cognitive dysfunction by activating α-2 adrenergic receptors, thus reducing the occurrence of ED\textsuperscript{19}; Preoperative use of dexmedetomidine has anti-anxiety, sedative, and analgesic effects, reducing stress during intubation and extubation\textsuperscript{20}; inhibition of spontaneous activity of the central monoaminergic system is essential for sleep and wakefulness, and therefore has a natural sleep sedative effect; l-aminobutyric acid (GABA) is a receptor-preserving property with better pain management due to its analgesic effect\textsuperscript{21}. Or dexmedetomidine may reduce delirium in children by avoiding medications that may increase ED. For example, γ receptor agonists, benzodiazepines, opioids, etc.

Data from the study suggested that there were no obvious differences in the occurrence of hypotension and bradycardia in children. But accuracy may not be high. The main reason for the inaccurate results may be the small sample size. Future research needs to increase sample size and improve the accuracy of analysis results. In addition, PONV can lead to water electrolyte disturbance, aspiration pneumonia, prolonged discharge time, increased hospital costs. In this review, dexmedetomidine can lower the
morbidity of PONV. The occurrence of PONV was only 3.9% (8/205 cases) in the dexmedetomidine group. According to relevant studies, the mechanism of dexmedetomidine reducing postoperative nausea and vomiting is as follows. 1. Dexmedetomidine directly inhibits postoperative nausea and vomiting: biomolecules such as catecholamines, opioids, substance P, acetylcholine, histamine, 5-HT₃, and neuropeptides have been implicated in the control of vomiting. Dexmedetomidine can reduce the occurrence of PONV by inhibiting the release of norepinephrine in the locus coeruleus, reducing the release of 5-HT, reducing the extracellular dopamine level in the nucleus accumbens in a dose-dependent manner, and inhibiting the expression of histamine-induced proinflammatory cytokine interleukin-6. 2. Dexmedetomidine reduces PONV through synergistic analgesia: pain is an independent risk factor for PONV, and Dexmedetomidine reduces PONV through synergistic analgesia. In the brain, dexmedetomidine binds to the α₂-adrenoceptor in the locus coeruleus of the brainstem, preventing the pain signaling. Activation of α2-adrenergic receptors in the presynaptic membrane of posterior horn neurons and in the postsynaptic membrane of interneurons in the spinal cord opens up potassium channels, leading to hyperpolarization of cell membranes that ultimately inhibit the signal transmission of pain to the brain. Peripherally, Dexmedetomidine inhibits pain neurons by stimulating Aδ and c-type nerve fibers. 3. Dexmedetomidine reduces PONV by reducing opioid dosage: previous studies have shown that dexmedetomidine exerts a synergistic analgesic effect in addition to its procedural sedative effect during surgery. Postoperative severe pain, commonly used strong opioids for postoperative analgesia. Tian C et al. found that dexmedetomidine significantly reduced postoperative analgesia 24 compared to the control group. 28 Future studies hope to reveal the biochemical and pathophysiological mechanisms by which dexmedetomidine prevents postoperative nausea and vomiting.

Our meta-analysis included seven RCTs. No obvious heterogeneity was found in the occurrence of ED, PONV, ED before and after anesthesia induction and ED in different administration methods of dexmedetomidine. The nature of dexmedetomidine is more likely to influence these results. Our results indicated that the ES (effect size) is congruous and steady. However, there was notable heterogeneity in the PACU stay time after extubation (I² = 90%; P < 0.00001) and the incidence of ED given dexmedetomidine before the end of surgery (I² = 62%; P = 0.05). The reason for this heterogeneity may be the diversity of patients. The duration of anesthesia, the duration of surgery, the dosage and usage of anesthetics are different, which may all affect the PACU stay after extubation and the incidence of ED before the end of surgery. This heterogeneity was partially explained by sensitivity analysis. Hypotension and bradycardia reported in these seven studies were not statistically significant. The possible reason is insufficient sample size (only 1 or 2 studies were included).

Our research has some limitations. Differences in the use and dosage of anesthetics, differences in the dosage of analgesics, underlying diseases, type of surgery, duration of surgery, and preoperative anxiety all may affect the results of the study. Two of the studies used propofol and thiopental sodium anesthesia induction, unlike the other five studies using sevoflurane anesthesia induction. This may lead to overall heterogeneity. However, the sensitivity analysis of ED incidence induced by different anesthetics showed that our effect estimates were still statistically significant (n = 399 patients, [RR] 0.35, 95%[CI]
0.25 to 0.50, \( P < 0.00001 \).) (Fig. 7). In addition, postoperative pain scores were not collected in this study. Postoperative pain may affect the incidence of ED\(^{29}\). Possible explanations were: postoperative pain behavior and ED were difficult to distinguish; the tools used to assess delirium (PAED, etc.) included descriptions of pain behaviors. Thus, postoperative pain may affect the overall heterogeneity. This study also did not report the duration of ED. In this study, bradycardia and hypotension occurred in fewer patients, so we should expound these results with caution. Second, similar to other meta-analyses, we found type I or type II errors. However, we did not conduct trial sequential analyses to reduce type I or type II errors. Our study is consistent with the common statement of the Cochrane scientific committee\(^{30}\), and this sequential approach is not recommended here. We aim for maximum inclusion by implementing extensive and comprehensive search strategies, including high-quality RCTs, and by expanding the search coverage for children.

**Conclusion/summary**

The use of dexmedetomidine should be considered for prophylactic use in pediatric surgery to reduce the incidence of ED and postoperative nausea and vomiting. Further research is needed in the future to explore the mechanisms behind ED and dexmedetomidine in reducing ED.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication:**

Not applicable

**Availability of data and materials:**

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

**Funding:**

This study was funded by grants 82271209 and 81901110 from the National Natural Science Foundation of China.

**Conflicts related to interests:**

All authors have no conflict of interest

**Authors’ contributions:**
1. Sai-hao Fu, Jing Bian and Yun-xiang Fu screened literature and collected data.

2. Sai-hao Fu is responsible for analyzing data and drawing charts.

3. Sai-hao Fu, Meng-rong Miao and Lu-yao Zhang are responsible for the accuracy of data.

4. Sai-hao Fu, Ming-yang Sun and Jia-qiang Zhang are responsible for contribution and magazine editor exchange and feedback.

All authors reviewed the manuscript.

**Acknowledgements:**

I would like to thank Professor Ming-yang Sun for her expert advice and encouragement. She helped me to complete a lot of difficult work.

**References**


**Figures**
Figure 1

a: Forest plot of perioperative delirium incidence at different time periods

b: Funnel plot of perioperative delirium incidence at different time periods
### Figure 2

**a:** Forest plot of delirium incidence in different administration methods

**b:** Funnel plot delirium incidence in different administration methods
Figure 3

a: Forest plot of PONV incidence

b: Sensitivity analysis of PONV incidence
**Figure 4**

a: Forest plot of PACU residence time after extubation  

b: Sensitivity analysis of PACU stay time after extubation

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**Figure 5**

Forest plot of bradycardia incidence
Figure 6

Sensitivity analysis of delirium incidence excluding medium-high risk studies

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<td>19</td>
<td>33</td>
<td>22.5%</td>
<td>0.31 [0.14, 0.67]</td>
</tr>
<tr>
<td>Yingying Sun 2014</td>
<td>3</td>
<td>23</td>
<td>7</td>
<td>24</td>
<td>8.0%</td>
<td>0.45 [0.13, 1.52]</td>
</tr>
<tr>
<td>Yusheng Yao 2014</td>
<td>5</td>
<td>29</td>
<td>14</td>
<td>30</td>
<td>0.0%</td>
<td>0.37 [0.15, 0.89]</td>
</tr>
<tr>
<td>Yusheng Yao 2020</td>
<td>6</td>
<td>52</td>
<td>25</td>
<td>51</td>
<td>25.5%</td>
<td>0.24 [0.11, 0.53]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>38</td>
<td>188</td>
<td>185</td>
<td>100.0%</td>
<td>6.44</td>
<td>[0.32, 0.61]</td>
</tr>
</tbody>
</table>

Total events 38 185
Heterogeneity: Chi² = 7.17, df = 4 (P = 0.13); I² = 44%
Test for overall effect: Z = 4.97 (P < 0.00001)

Figure 7

Sensitivity analysis of delirium incidence induced by different anesthetics

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DEX Events</th>
<th>DEX Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eun-Ah Cho 2019</td>
<td>9</td>
<td>34</td>
<td>10</td>
<td>32</td>
<td>0.0%</td>
<td>0.85 [0.40, 1.81]</td>
</tr>
<tr>
<td>Ghada F. Amer 2022</td>
<td>2</td>
<td>40</td>
<td>11</td>
<td>40</td>
<td>11.8%</td>
<td>0.18 [0.04, 0.77]</td>
</tr>
<tr>
<td>Mengzhu Shi 2018</td>
<td>14</td>
<td>45</td>
<td>24</td>
<td>45</td>
<td>25.7%</td>
<td>0.58 [0.35, 0.97]</td>
</tr>
<tr>
<td>Mona Raafat Elghamry 2021</td>
<td>6</td>
<td>34</td>
<td>19</td>
<td>33</td>
<td>20.7%</td>
<td>0.31 [0.14, 0.67]</td>
</tr>
<tr>
<td>Yingying Sun 2014</td>
<td>3</td>
<td>23</td>
<td>7</td>
<td>24</td>
<td>0.0%</td>
<td>0.45 [0.13, 1.52]</td>
</tr>
<tr>
<td>Yusheng Yao 2014</td>
<td>5</td>
<td>29</td>
<td>14</td>
<td>30</td>
<td>14.8%</td>
<td>0.37 [0.15, 0.89]</td>
</tr>
<tr>
<td>Yusheng Yao 2020</td>
<td>6</td>
<td>52</td>
<td>25</td>
<td>51</td>
<td>27.1%</td>
<td>0.24 [0.11, 0.53]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>200</td>
<td>199</td>
<td>100.0%</td>
<td></td>
<td>0.35</td>
<td>[0.25, 0.50]</td>
</tr>
</tbody>
</table>

Total events 33 93
Heterogeneity: Chi² = 5.60, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 6.00 (P < 0.00001)
Figure 8
flow chart

The flow chart outlines the screening steps for this Meta-analysis, the source of the literature, the number of articles retrieved, the reasons for excluding the literature, and the number of studies that were eventually included.
### Figure 9

**Risk of bias assessment form**

The figure includes seven bias risk assessments included in the study: green represents low risk; yellow represents unknown risk; red represents high risk.

### Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx