Effects of Dexmedetomidine on Postoperative Recovery Profile after Sevoflurane Anesthesia in Pediatric Patients: A Meta-analysis

Chen Jin-hui, Yu Yong-qi, Chu Hui-jun, Han He, Cao Ya and Dai Ze-ping*
Department of Anesthesiology, Yijishan Hospital, Wannan Medical College, Wuhu, Anhui, China

Abstract

Objective: We aim to evaluate whether dexmedetomidine can reduce incidence caused by sevoflurane anesthesia in pediatric patients systematically.

Methods: We have searched the Cochrane Library, PubMed, EBSCO, Springer, Chinese Journal Full-text Database (CNKI), Chinese Biomedical Literature Database (CBM) and WanFang Data (all the materials selected from these databases range from the date of establishment of the databases to April 2013). Reference lists of all studies have also been checked. Two valuators performed the process of RCT, quality assessment, and data extraction with inclusion and exclusion criteria, and conduct the Meta-analysis with the software RevMan5.2.

Results: The meta-analysis which including 27 randomized trials and 1882 children showed that dexmedetomidine extended the incidence of the children’s recovery time [MD=2.39, 95% CI (1.27, 3.51)] and discharge time [MD=6.09, 95% CI (3.42, 8.77)] compared with placebo. Nevertheless, there were no obvious differences in exultation time [MD=0.75, 95% CI (0.45, 1.05)]. While reducing the incidence of early emergence agitation, dexmedetomidine showed a large advantage [RR=0.31, 95% CI (0.26, 0.38)] and could reduce agitation score [MD=0.89, 95% CI (-0.74, -0.4)]. Also could reduce pain score [MD=0.89, 95% CI (2.02, 0.52)]. What’s more, on reducing occurrence of nausea and vomiting [RR=0.59, 95% CI (0.56, 0.97)], occurrence of bucking [RR=0.39, 95% CI (0.23, 0.68)], dexmedetomidine also showed some preventive effects. There were no serious side effects on respiratory and circulatory system in all included studies.

Conclusion: Dexmedetomidine can be used safely in children and improve the awakening quality after sevoflurane anesthesia.

Keywords: Dexmedetomidine; Sevoflurane anesthesia; Child; Recovery period; Agitation; Meta-analysis

Introduction

Sevoflurane is a popular inhalational anesthetic for general anesthesia in children. It is especially characterized by a lower blood/gas partition coefficient, less irritation to the airway, less cardio depressive effect, lower hepatotoxicity and easier to obtain with children as compared with other volatile anesthetics. Anesthesiologists prefer those characteristics for pediatric use. However, concern has been raised over its propensity to cause significant emergence agitation and other adverse reactions during the immediate recovery phase of sevoflurane anesthesia [1,2]. Theoretically, Dexmedetomidine (DEX) is a new type of highly selective alpha2-adrenergic receptor agonist with sedative, analgesic, anti-sympathetic activity, and has minor respiratory inhibition, but the safety and efficacy of DEX in pediatric patients below 18 years old is still not clear in its package insert. Here in this case, whether dexmedetomidine can safely and effectively improve the children’ wake quality remains uncertain. According to the methods of the Cochrane systematic review, we reviewed the Randomized Controlled Trials (RCTs) about dexmedetomidine for prevention of emergence agitation and other side effects in pediatric patients after sevoflurane anesthesia. These data are either in English or non-English language publications, and the main purpose of this meta-analysis is to evaluate whether dexmedetomidine can reduce postoperative agitation and other adverse reactions in children, thereby improve the quality of awakening, and provide an important basis for the clinical application and further research.

Materials and Methods

Inclusion and exclusion criteria

Inclusion criteria: The type of research: clinical Randomized Controlled Trials (RCTs). Research object: the children who are below 12 years old received sevoflurane anesthesia. The children had no neurological disorders and behavioral disorders before operation. Intervention measures: experimental group, intravenous dexmedetomidine; control group only received placebo.

Exclusion criteria: Case reports with sample size of less than 10 studies. Simply medical examination rather than a surgical operation. Repeat published literature those that cannot obtain data directly or indirectly.

Systematic search and strategy

A systematic search of the relevant literature was performed without any language limitation restricted to RCTs available in English. We searched the Cochrane Library, PubMed, EBSCO, Springer, Chinese Journal Full-text Database (CNKI), Chinese Biomedical Literature Database (CBM) and WanFang Data (all the materials selected from these databases range from the date of establishment of the databases to April 2013). Reference lists of all studies have also been checked.

*Corresponding author: Dai Ze-ping, Chief physician, Department of Anesthesiology, Yijishan Hospital, Wannan Medical College, Wuhu, Anhui, China, Tel: 0553-3932598; E-mail: zpdai@wnmc.edu.cn

Received November 07, 2013; Accepted November 27, 2013; Published November 29, 2013


Copyright: © 2013 Jin-hui C, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Published articles contained key words such as “dexmedetomidine”, “α2-adrenoceptor agonist”, “sevoflurane”, “anesthesia”, “pediatric”, “children”, “postanesthesia”, “postoperative”, “PACU”, “Recovery Room”, “restlessness”, “agitation”, “delirium” in their titles or abstracts. The search strategy consisted of a combination of free text words such as “dexmedetomidine or α2-adrenoceptor agonist” and “sevoflurane” and “children or pediatric” and “Recovery or postanesthesia or restlessness or agitation or delirium”.

Data extraction and quality assessment

The two valuators independently categorized these data by reading the citations, abstracts and qualified the data left using a standardized data extraction by going through the whole article. A third reviewer resolved all the disagreements. If data needed clarification, we contacted the original authors.

The quality of each study was assessed according to the modified Jadad scale score, we assessed whether the patients were randomly assigned, whether the randomization procedures were appropriate, whether the study was double-blinded, whether the blinding was appropriate and whether the authors reported the numbers and reasons for dropouts. The study with the modified Jadad score 1 to 3 was divided into low-quality literature, and 4 to 7 was divided into high-quality literature.

Statistical analysis

The software package RevMan 5.2 provided by the Cochrane

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Patient age(years)</th>
<th>Surgery type</th>
<th>D/C (No. of patients)</th>
<th>Intervention</th>
<th>Main outcome measures</th>
<th>New Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’zcengiz [3] 2011</td>
<td>3~9</td>
<td>esophageal dilatation procedures</td>
<td>25/25</td>
<td>DEX 2.5 μg/kg, given orally</td>
<td>saline</td>
<td>6</td>
</tr>
<tr>
<td>Erdil [4] 2009</td>
<td>2~7</td>
<td>adenoidectomy</td>
<td>30/30</td>
<td>DEX 0.5 μg/kg IV after tracheal intubation</td>
<td>saline</td>
<td>6</td>
</tr>
<tr>
<td>Guler [5] 2005</td>
<td>3~7</td>
<td>adenotonsillectomy</td>
<td>30/30</td>
<td>DEX 0.5 μg/kg IV, 5 min before the end of surgery</td>
<td>placebo</td>
<td>6</td>
</tr>
<tr>
<td>Jia-Yao [6] 2013</td>
<td>2~7</td>
<td>strabismus surgery</td>
<td>27/24</td>
<td>DEX 1 μg/kg, IV</td>
<td>saline</td>
<td>7</td>
</tr>
<tr>
<td>Masami [7] 2010</td>
<td>1~9</td>
<td>same-day surgery or overnight stay surgery</td>
<td>39/42</td>
<td>DEX 0.3 μg/kg IV over 10 min after anesthetic induction</td>
<td>saline</td>
<td>6</td>
</tr>
<tr>
<td>Shukry [8] 2005</td>
<td>1~10</td>
<td>outpatient surgical procedures</td>
<td>23/23</td>
<td>A continuous perioperative infusion of 0.2 μg/kg/h DEX</td>
<td>saline</td>
<td>7</td>
</tr>
<tr>
<td>Mauricio E [9] 2004</td>
<td>1~10</td>
<td>Inguinal hernia repair and circumcision</td>
<td>60/30</td>
<td>DEX 0.15 μg/kg OR 0.3 μg/kg IV after anesthetic induction loading dose: DEX 1 μg/kg, 0.5 μg/kg/h to maintain</td>
<td>saline</td>
<td>6</td>
</tr>
<tr>
<td>Nidhi [10] 2013</td>
<td>8~12</td>
<td>spinal dysraphism</td>
<td>18/18</td>
<td>lactated Ringer’s saline</td>
<td>1, 2, 3, 6</td>
<td>1</td>
</tr>
<tr>
<td>Qing-tao [11] 2012</td>
<td>5~13</td>
<td>tonsillectomy</td>
<td>80/40</td>
<td>loading dose: DEX 0.5 μg/kg OR 1 μg/kg IV over 10 minutes</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Liu [12] 2012</td>
<td>3~11</td>
<td>not mention</td>
<td>42/21</td>
<td>DEX 0.2 μg/kg OR 0.4 μg/kg IV before the end of surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Zhang [13] 2012</td>
<td>2~8</td>
<td>Lower abdominal surgery</td>
<td>40/20</td>
<td>DEX 0.5 μg/kg IV after the start of surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Fang [14] 2010</td>
<td>3~10</td>
<td>Oral and ENT surgery</td>
<td>30/30</td>
<td>DEX 0.5 μg/kg IV before the surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Wen [15] 2012</td>
<td>3~11</td>
<td>Oral and ENT surgery</td>
<td>30/30</td>
<td>DEX 0.5 μg/kg IV before the surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Cao [16] 2012</td>
<td>3~6</td>
<td>High ligation of the hernia sac and circumcision adenoidectomy</td>
<td>40/20</td>
<td>DEX 0.5 μg/kg OR 0.7 μg/kg IV</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Zhu [17] 2011</td>
<td>3~8</td>
<td>Laryngeal papilloma resection</td>
<td>40/40</td>
<td>DEX 0.5 μg/kg IV before anesthesia induction</td>
<td>saline</td>
<td>2</td>
</tr>
<tr>
<td>Zhu [18] 2012</td>
<td>3~8</td>
<td>Inguinal hernia repair and circumcision</td>
<td>30/30</td>
<td>DEX 0.5 μg/kg IV before anesthesia induction</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Du [19] 2012</td>
<td>3~9</td>
<td>Inguinal hernia repair and circumcision</td>
<td>28/28</td>
<td>DEX 1 μg/kg IV after the start of surgery</td>
<td>saline</td>
<td>2</td>
</tr>
<tr>
<td>Gan [20] 2011</td>
<td>4~7</td>
<td>ENT surgery</td>
<td>150/150</td>
<td>DEX 0.5 μg/kg IV before anesthesia induction</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Xue [21] 2011</td>
<td>3~9</td>
<td>Oral, Ophthalmologic, abdominal surgery adenoidectomy</td>
<td>40/40</td>
<td>DEX 0.5 μg/kg IV after the start of surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Jia [22] 2012</td>
<td>2~7</td>
<td>Ophthalmologic operation</td>
<td>30/30</td>
<td>loading dose: DEX 1 μg/kg, 0.3 μg/kg/h to maintain</td>
<td>saline</td>
<td>6</td>
</tr>
<tr>
<td>Jin [23] 2011</td>
<td>3~12</td>
<td>Ophthalmologic operation</td>
<td>40/40</td>
<td>DEX 1 μg/kg IV after tracheal intubation</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Zhong [24] 2012</td>
<td>4~10</td>
<td>tonsillectomy</td>
<td>40/40</td>
<td>loading dose: DEX 0.1 μg/kg, and 0.3 μg/kg/h to maintain</td>
<td>saline</td>
<td>2</td>
</tr>
<tr>
<td>Chen [25] 2012</td>
<td>2~8</td>
<td>High ligation of the processus vaginalis</td>
<td>15/15</td>
<td>DEX 1 μg/kg IV before anesthesia induction</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Wei [26] 2012</td>
<td>3~7</td>
<td>Inguinal hernia repair</td>
<td>45/23</td>
<td>DEX 0.15 μg/kg OR 0.3 μg/kg IV before surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Huang [27] 2012</td>
<td>1~3</td>
<td>cleft lip and cleft palate repair</td>
<td>15/15</td>
<td>DEX 1 μg/kg IV, 30 min before the end of surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Huang [28] 2011</td>
<td>5~8</td>
<td>Hypospadias and ENT surgery</td>
<td>30/30</td>
<td>DEX 0.2 μg/kg IV, 30 min before the end of surgery</td>
<td>saline</td>
<td>1</td>
</tr>
<tr>
<td>Zhao [29] 2012</td>
<td>2~8</td>
<td>High ligation of the hernia sac and Orchidopexy</td>
<td>20/20</td>
<td>DEX 1 μg/kg, IV</td>
<td>saline</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: ① recovery time ② extubation time ③ discharge time ④ occurrence of bucking ⑤ emergence agitation or agitation score ⑥ other adverse events

Table 1: Characteristics of included studies and Jadad score.
showed that compared with placebo, dexmedetomidine extended the recovery time [MD=2.39, 95% CI (1.27, 3.51)], [4,5,9-11,15-19,22-28] (Figure 1).

Sensitivity analysis: exclude low-quality literature with modified Jadad score less than 3 points to redo a meta-analysis, there were no heterogeneity present among the groups, so we used a fixed-effect model for Meta-analysis, the outcome remained similar [MD=1.39, 95% CI (0.65,2.13)].

Extubation time: Sixteen RCTs (1183 children) compared both extubation time. There was no statistically significant heterogeneity present among the groups, so we used a fixed-effect model for statistical analysis, the results showed no statistically significant difference between DEX and placebo group [MD=0.75, 95% CI (0.45, 1.05)] [4,6-9,11,14,17,18,20-22,24,25,28,29] (Figure 2).

Sensitivity analysis: Exclude low-quality literature with modified Jadad score less than 3 points to redo a meta-analysis, there was still no statistically significant difference between the two groups [MD=0.95, 95% CI (0.27,1.63)].

Funnel plot analysis: no obvious asymmetric distribution, suggesting that little possibility of the publication bias (Figure 3).

Recovery room residence time (discharge time): Eight RCTs (447 children) compared both discharge time. There was significant heterogeneity among the 8 studies. Thus, a random-effects model was used for these statistical analyses. The results are shown: Compared with placebo, dexmedetomidine extended the recovery room

Collaboration was used for analysis. We computed the Relative Risk (RR) with corresponding 95% confidence intervals (95%CI) for dichotomous outcome data, and Mean Difference (MD) with 95% CI for continuous outcomes data, using a fixed-effect model, if there were no heterogeneity present. Otherwise, a random-effects model was applied. Heterogeneity was judged with the I²-test, assuming heterogeneity if an I² value of more than 25% was observed. If severe heterogeneity was presented (I² ≥ 75%) and could not be explained by differences across the trials in terms of clinical or methodological features or by subgroup analysis, we did not combine the trials in the meta-analysis, but presented the results in a forest plot. Removal the low-quality literature for sensitivity analysis. If more than 10 trials were included: a funnel plot was used to assess publication bias. A P-value<0.05 was used to determine statistical significance.

**Result**

The basic characteristics of the included studies

Using electronic databases, we initially identified 216 articles for review after reading title, abstract and full text based on the inclusion and exclusion criteria and ultimately left 27 RCTs with 9 English articles and 18 Chinese articles, a total of 1882 pediatric patients were included. The basic characteristics and quality of the selected trials were summarized in Table 1 [3-29].

**Meta-analysis results**

**Recovery time:** Sixteen RCTs (948 children) provided data on recovery time. The heterogeneity test showed a severe heterogeneity among the trials, a random-effects model was applied, the results

**Sensitivity analysis:** exclude low-quality literature with modified Jadad score less than 3 points to redo a meta-analysis, there were no heterogeneity present among the groups, so we used a fixed-effect model for Meta-analysis, the outcome remained similar [MD=1.39,95% CI (0.65,2.13)].

**Extubation time:** Sixteen RCTs (1183 children) compared both extubation time. There was no statistically significant heterogeneity present among the groups, so we used a fixed-effect model for statistical analysis, the results showed no statistically significant difference between DEX and placebo group [MD=0.75, 95% CI (0.45, 1.05)] [4-6,9-11,14,17,18,20-22,24,25,28,29] (Figure 2).

**Sensitivity analysis:** Exclude low-quality literature with modified Jadad score less than 3 points to redo a meta-analysis, there was still no statistically significant difference between the two groups [MD=0.95, 95% CI (0.27,1.63)].

**Funnel plot analysis:** no obvious asymmetric distribution, suggesting that little possibility of the publication bias (Figure 3).

**Recovery room residence time (discharge time):** Eight RCTs (447 children) compared both discharge time. There was significant heterogeneity among the 8 studies. Thus, a random-effects model was used for these statistical analyses. The results are shown: Compared with placebo, dexmedetomidine extended the recovery room

**Figure 1:** Effect of dexmedetomidine on children’s recovery time.

**Figure 2:** Effect of dexmedetomidine on extubation time.
residence time [MD=6.09, 95% CI (3.42, 8.77)], as shown in Figure 4 [6,8,9,11,17,18,23,25].

Sensitivity analysis: exclude low-quality literature and redo statistical analysis, the outcomes remained similar [MD=6.57, 95% CI (1.99, 11.15)].

Cough, nausea and vomiting

There are 4 studies and 5 studies which compared DEX with placebo about the incidence of cough or nausea and vomiting. No heterogeneity present in each group, the results showed: dexmedetomidine reduced the occurrence of cough [RR=0.39, 95% CI (0.23, 0.68)] and the occurrence of nausea and vomiting [RR=0.59, 95% CI (0.36, 0.97)] (Figure 5) [4-7,10,12,17,18].

Pain score

Four studies adopt “mean ± SD” pattern to provide data on pain score. A severe heterogeneity among studies, a random-effects model was used for meta-analysis, the results showed that DEX can reduce pain score [MD=-2.66, 95% CI (-3.81, -1.51)], [10,11,17,29] (Figure 6).

The demand of painkillers

Six studies compared DEX with placebo on children’ demand
for the painkillers, no statistically significant heterogeneity appeared among the groups, so a fixed-effect model for statistics analysis was used. Results: DEX can reduce children’ demand for the painkillers [RR=0.34, 95% CI (0.22, 0.52)] [4,7,10,11,14,22] (Figure 7).

Emergence agitation

Twenty-six studies compared DEX with placebo over the incidence of early emergence agitation in recovery room. No statistically significant heterogeneity appeared among the groups, a fixed-effects model used for statistical analysis. The results showed that dexmedetomidine can significantly reduce the incidence of emergence agitation [RR=0.31, 95% CI (0.26, 0.38)] [3-28] (Figure 8).

Sensitivity analysis: the analysis excluded low-quality literature and redo statistical analysis, the outcomes remained similar [RR=0.36, 95% CI (0.27, 0.48)].

Funnel plot analysis: there were no obvious asymmetric distributions, suggesting that little possibility of the publication bias (Figure 9).

Agitation score

Seven studies adopt "mean ± SD" pattern to provide data on agitation score, statistical analysis shows: DEX can reduce the patients’ agitation score [MD=-0.89, 95% CI (-1.04, -0.74)] (Figure 10) [3,10,11,17,18,25,29].

Reference


Figure 6: Effect of dexmedetomidine on pain score.

Figure 7: Effect of dexmedetomidine on children’s demand of painkillers.

Figure 8: Effect of dexmedetomidine on children’s early emergence agitation.
Discussion

Pediatric surgery is usually featured with small scale, short operational time and length of stay, and fewer complications, etc [30]. Therefore, recovery time and the incidence of postoperative complications are important indicators for the evaluation of pediatric anesthesia. How to improve the recovery quality of anesthesia and reduce the incidence of complications in recovery period, and shorten the residence time in the operating room or PACU, is a focus attention for anesthesiologists in recent years.

This study included 27 RCTs involving 1,882 children. These RCTs are measured by key words such as the recovery time, extubation time, discharge time, the incidence of early emergence agitation, the occurrence of cough, nausea and vomiting, pain score, agitation score and the need for painkillers respectively and then rates one by one for statistical pooled analysis one by one. The results of the meta-analysis showed that compared with placebo saline, dexmedetomidine can extend the recovery time and discharge time, while the time of extubation was no significant difference, dexmedetomidine can significantly reduce the incidence and the severity of the early postanesthetic emergence agitation, children's need for painkillers, and DEX may play a preventive role in decreasing the occurrence of nausea and vomiting, choking cough. What's more, the hemodynamic in Perextubate period was steady in the 27 trials, and without one case of respiratory and circulatory system complications.

As mentioned above, Sevoflurane is widely used in pediatric anesthesia now. However, sevoflurane may be associated with a high incidence of emergence agitation and is observed more frequently in preschool aged children. A study by Sanford et al. reported that the occurrence of emergence agitation in children after sevoflurane anesthesia may be as high as 67%. Another study reported the agitation occurrence rate range from 18% to 80%. In this article, we included 27 trials, which were divided into two groups [31]. In placebo group, 864 children, the number of patients with emergence agitation reached 348, and the incidence is as high as 40.3%. In dexmedetomidine group the incidence is only 13.0%. Though emergence agitation is mostly self-limiting, severe cases can affect surgical outcomes, and cause a great impact on children's physical and psychological health; therefore children's postoperative agitation after sevoflurane anesthesia has become a concern of clinicians focus.

Dexmedetomidine is a novel highly selective α2-adrenergic receptor agonist, the α2:α1 activity ratio of DEX is 1620:1 compared with 220:1 for clonidine, this results in a more specific and selective α2-adrenoceptor agonism. It can affects the brain and spinal cord alpha 2 adrenergic receptor, inhibition of neural discharge to produce sedative, analgesic, anxiolytic effects. The Locus Coeruleus is a verified key part of the brain responsible for the regulation of arousal and sleep. Dex affects the brainstem locus coeruleus alpha 2 adrenergic receptors, produces sedative, hypnotic, and anxiolytic. Compared with the benzodiazepine, DEX also reduces the movement of the stomach and intestines, and inhibits glandular secretion as well as reducing the incidence of postoperative nausea and vomiting. In addition, DEX can inhibit sympathetic activity, reduces plasma epinephrine and norepinephrine levels and maintain hemodynamic stability. DEX sedative effect is unique in many ways, and has a dose-dependent manner [32]. Moreover, DEX has no addiction, and has a very slight respiratory inhibition. Based on all the advantages of the dexmedetomidine and the comprehensive statistical analysis results of this study, we have reason to believe that, the combination of dexmedetomidine and sevoflurane will be more widely used for the future pediatric surgeries.
Although our study does find some significant things, our review also has some limitations. First, among the 27 RCTs, although the 9 English articles can get 6 to 7 score from the modified Jadad scale score, and belong to high-quality literature. While the 18 Chinese articles belong to low-quality literature, the main problem was that these studies have not report the concealment of the allocation scheme and the random method, may exist a selection bias; unused blinded, may result in the presence of observer bias. Second, dexmedetomidine dosage was different from 0.1 to 1 μg/kg, usage ranging from preoperative and intraoperative. Third, in some ill-defined text, each hospital or researcher may not have a same standardization for test or record such as recovery time, the different grasp of the timing of the recovery, extubation and discharge time may have contributed to the heterogeneity between each experiment. In this case, we still should carefully look at the above meta-analysis conclusion.

References


