SYSTEMATIC REVIEW

Outcomes of dexmedetomidine treatment in pediatric patients undergoing congenital heart disease surgery: a meta-analysis

Wanying Pan, Yueting Wang, Lin Lin, Ge Zhou, Xiaoxiao Hua & Liqiu Mo

Department of Anaesthesiology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

What is already known

• Dexmedetomidine is a safe and efficacious sedative agent, and can offer some benefit for adult patients undergoing cardiac surgery.

What this article adds

• Perioperative dexmedetomidine treatment improves the outcomes in children undergoing congenital heart disease surgery, including more stable hemodynamics, shorter ventilation duration, and lesser incidence of postoperative agitation, and rescue analgesia.

Keywords
congenital heart disease; dexmedetomidine; meta-analysis; pediatric

Correspondence
Prof. L.Q. Mo, Department of Anaesthesiology, The First Affiliated Hospital, Sun Yat-sen University, No. 58, Zhongshan 2nd Road, Guangzhou 510080, China
Email: mlqiu11220@126.com

Section Editor: Mark Thomas

Accepted 18 October 2015
doi:10.1111/pan.12820

Summary

Background: Dexmedetomidine decreases cardiac complications in adults undergoing cardiovascular surgery. This systematic review assessed whether perioperative dexmedetomidine improves congenital heart disease (CHD) surgery outcomes in children.

Methods: The PubMed, Embase, and Cochrane Library databases were searched for randomized controlled trials (RCTs) or observational studies that were published until 16 April 2015 and compared dexmedetomidine with placebo or an alternative anesthetic agent during pediatric CHD surgery. The assessed outcomes included hemodynamics, ventilation length, intensive care unit (ICU) and hospital stays, blood glucose and serum cortisol levels, postoperative analgesia requirements, and postoperative delirium.

Results: Five RCTs and nine observational studies involving 2229 patients were included. In pooled analyses, dexmedetomidine was associated with shorter length of mechanical ventilation (mean difference: −93.36, 95% CI: −137.45, −49.27), lower postoperative fentanyl (mean difference: −24.11, 95% CI: −36.98, −11.24) and morphine (mean difference: −0.07, 95% CI: −0.14, 0.00) requirements, reduced stress response (i.e., lower blood glucose and serum cortisol levels), and lower risk of delirium (OR: 0.39, 95% CI: 0.21, 0.74). The hemodynamics of dexmedetomidine-treated patients appeared more stable, but there were no significant differences in the ICU or hospital stay durations. Dexmedetomidine may increase the bradycardia and hypotension risk (OR: 3.14, 95% CI: 1.47, 6.69).

Conclusions: Current evidence indicates that dexmedetomidine improves outcomes in children undergoing CHD surgery. However, this finding largely relies on data from observational studies; high-quality RCTs are warranted because of the potential for subject selection bias.
Background

Congenital cardiovascular defects represent the most common cause of infant death due to birth defects (1). Every year, approximately 10,000 children require anesthesia for congenital heart disease (CHD) surgery during their first year of life (1,2). Surgical injury may be followed by stress-induced catabolism, which can lead to delayed convalescence and increased morbidity and mortality (3,4). Furthermore, postoperative mortality is high in patients with delirium after surgery (5), and recovery is slower than in those without delirium such that intensive care unit (ICU) stays are prolonged and hospital costs are higher (5,6).

Dexmedetomidine, a potent and highly selective α₂ adrenoreceptor agonist, is widely used in ICUs and operating rooms. In addition to analgesia, sedation, and anxiolysis, dexmedetomidine possesses numerous other desirable properties with respect to the treatment of adult patients, including reduced catecholamine release (7), a decreased incidence of postoperative delirium (8,9), and anesthetic-sparing effects (10,11). There is strong evidence that dexmedetomidine can reduce cardiac complications after cardiovascular surgery in adults (12–14). Although not currently approved by the Food and Drug Administration for use in pediatric populations, the clinical use of dexmedetomidine continues to increase in numerous pediatric contexts, including as an adjunctive anesthetic agent during CHD surgery.

However, because of their generally small sample sizes, the value of previous studies that assessed the effects of dexmedetomidine on outcomes in pediatric patients undergoing CHD surgery is limited. We aimed to provide more recent and convincing evidence of the effects and safety of dexmedetomidine in pediatric patients undergoing CHD surgery by systematically reviewing the currently available literature.

Methods

This systematic review and meta-analysis was conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (15).

Literature search and selection criteria

The PubMed, Embase, and Cochrane Library databases were searched for studies on the effects of dexmedetomidine on CHD surgery outcomes in pediatric patients. The following search keywords were used: ‘dexmedetomidine’ AND ‘cardiac surgery or heart surgery’ AND ‘children or pediatric’. No publication language restriction was imposed. The final search was run on 16 April 2015. Two investigators independently carried out the initial search, deleted duplicate records, screened titles and abstracts for relevance, and decided whether articles should be excluded or required further assessment; we then reviewed the full-text articles.

Studies that met all of the following inclusion criteria were included: (i) population: pediatric patients undergoing CHD surgery; (ii) intervention: dexmedetomidine; (iii) comparison: other anesthetics or placebo; (iv) outcome parameters: blood pressure, heart rate, duration of ventilation, ICU and hospital stays, requirement for postoperative fentanyl and morphine, perioperative blood glucose and serum cortisol levels, and incidence of postoperative delirium, bradycardia, and hypotension; and (v) study design: randomized controlled trials (RCTs) and observational studies (prospective or retrospective cohort studies).

Data abstraction and quality assessment

Data extraction was performed by Y.T.W. and confirmed independently by X.X.H. The following information was extracted from each paper and tabulated: first author, year of publication, study design, patient characteristics, number of patients enrolled, surgery time, cardiopulmonary bypass time, and dexmedetomidine and control agent doses. Information on the following outcomes was extracted if reported: blood pressure, heart rate, duration of mechanical ventilation, length of ICU and hospital stays, requirement for postoperative morphine and fentanyl, blood glucose and cortisol levels, risk of delirium, and bradycardia or hypotension requiring intervention. In instances where the same patients were included in several publications, we retained only the largest study to avoid information duplication.

The Jadad scale was used to assess the methodological quality of each RCT (16). The methodological quality of observational studies was assessed using the Newcastle–Ottawa Scale (17). Differences were resolved by discussion and consensus; if disagreement persisted, the opinions of all members of the research team were sought.

Statistical analysis

The meta-analysis was performed and forest plots were produced using the REVIEW MANAGER software package (ver. 5.2; Cochrane Collaboration, Oxford, UK). Mean differences (MD) and odds ratios (OR) were calculated to compare continuous and dichotomous variables,
respectively. All results were reported with 95% confidence intervals (CIs). For studies that presented continuous data as median and range values, standard deviations were calculated using the technique described by Hozo et al. (18). Statistical heterogeneity between studies was assessed using the chi-squared test with the significance level set at $P < 0.10$; heterogeneity was quantified using the $I^2$ statistic. The random-effects model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was used (19).

Results

Literature search and study selection

In total, 353 studies were identified during the initial database search, including 110 articles in PubMed, 207 articles in Embase, and 36 articles in the Cochrane Library. Eighty-eight records with duplicate data were excluded; a further 237 records were excluded on the basis of their titles and abstracts. Of the remaining 28 eligible studies, 14 were removed because they reported on other outcomes, they were not full-text, or two publications used the same patients. Fourteen studies were included in the final meta-analysis (20–33). The selection process is detailed in Figure 1.

Article characteristics

The main characteristics of the included studies are listed in Table 1. All of the studies were published from 2006 to 2015; the sample sizes ranged from 14 to 1088, and the total number of patients was 2229 (dexmedetomidine group, $n = 1055$; control group, $n = 1174$). Five of the included studies were RCTs (20–24), one was a post hoc analysis of RCTs (25), and the remaining eight were cohort studies (26–33): four retrospective (26,29,30,33) and four prospective (27,28,31,32).

To our best knowledge, children with cardiac disease are considered as a single diagnosis. The heterogeneity and physiologic disparity of the subgroups of children with congenital heart disease can be vast. Therefore, the anatomical defect types among the included studies are organized to take advantage of these informations (Table S1).

Quality of the included studies

The quality of the included studies was generally low. True randomization and blinding was applied in only four and three RCTs, respectively. None of the observational studies mentioned the length of follow-up, and they all provided only perioperative data (Table 1).

Effects on hemodynamics

Mean blood pressure (MBP) was investigated in five studies (356 children) (20,21,27,28,33), and systolic blood pressure (SBP) was investigated in five studies (227 children) (22–24,27,31). Heart rate data were presented in nine studies (526 children) (20–24,27,28,31,33). All of the hemodynamic values were obtained at the point of skin incision or sternotomy, when the maximal increase in heart rate and blood pressure occurred. The collective data from the RCTs and observational studies indicated that dexmedetomidine significantly reduced the heart rate ($MD_{\text{C0}} = -13.62; 95\% \text{ CI} = -20.37, -6.86; P < 0.0001$). The heart rate of the dexmedetomidine group remained $>90 \text{ b.min}^{-1}$, which is preferable for children (Figure 2). Moreover, dexmedetomidine stabilized the blood pressure at the time of surgical stimulation, such that fluctuations were smaller relative to the control group (Figure 3). In addition, the children treated with dexmedetomidine seemed to be far less vulnerable to tachycardia (OR 0.07; 95\% CI 0.02, 0.22; $P < 0.0001$) (Table 2 and Figure S1a). When the data were pooled, dexmedetomidine was found to significantly increase the risk of bradycardia and hypotension (OR 3.14; 95\% CI 1.47, 6.69; $P = 0.003$) (Table 2 and Figure S1b).

Effects on stress response

Treatment with dexmedetomidine was associated with a blunting of the sympathetic stress response, evidenced by lower blood glucose ($MD = -49.80; 95\% \text{ CI} = -66.74,$...
### Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad or NOS score</th>
<th>Year</th>
<th>Study design</th>
<th>No of patients (DEX/control)</th>
<th>Age (DEX/control)</th>
<th>Medication time</th>
<th>Comparison</th>
<th>Infusion rate</th>
<th>Surgery time (min)</th>
<th>CPB time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reput et al. (20)</td>
<td>5</td>
<td>2014</td>
<td>RCT</td>
<td>220 (110/110)</td>
<td>2.7 ± 1.57 Y/2.71 ± 1.44 Y</td>
<td>Intraoperative and postoperative</td>
<td>Saline</td>
<td>0.5 μg kg⁻¹ h⁻¹ over 10 min, then 0.5 μg kg⁻¹ h⁻¹</td>
<td>167.62 ± 35.84/167.23 ± 30.99</td>
<td>95.49 ± 26.11/96.59 ± 19.49</td>
</tr>
<tr>
<td>Nasr et al. (21)</td>
<td>5</td>
<td>2013</td>
<td>RCT</td>
<td>40 (20/20)</td>
<td>23.2 ± 10.6/265 ± 8.5 M</td>
<td>Postoperative Fentanyl</td>
<td>1 μg kg⁻¹⁻¹</td>
<td>166.5 ± 15/170.6 ± 18</td>
<td>45.2 ± 6.1/47.9 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Pasad et al. (22)</td>
<td>4</td>
<td>2012</td>
<td>RCT</td>
<td>60 (30/30)</td>
<td>6.07 ± 3.94/5.67 ± 3.34 Y</td>
<td>Intraoperative Fentanyl</td>
<td>0.5 μg kg⁻¹⁻¹</td>
<td>256 ± 16.43/242 ± 15.38</td>
<td>83.80 ± 110/76.06 ± 103</td>
<td></td>
</tr>
<tr>
<td>Klamt et al. (23)</td>
<td>3</td>
<td>2010</td>
<td>RCT</td>
<td>28 (14/14)</td>
<td>10.9 ± 21.6/244 ± 31.6 M</td>
<td>Intraoperative Midazolam</td>
<td>1 μg kg⁻¹⁻¹ for 1 h, then 0.5 μg kg⁻¹⁻¹</td>
<td>Not given</td>
<td>117.6 ± 44.2/101.9 ± 41.5</td>
<td></td>
</tr>
<tr>
<td>Muhitar et al. (24)</td>
<td>2</td>
<td>2006</td>
<td>RCT</td>
<td>30 (15/15)</td>
<td>2.3 ± 1.3/2.5 ± 1.6 Y</td>
<td>Intraoperative Saline</td>
<td>0.5 μg kg⁻¹⁻¹ over 10 min, then 0.5 μg kg⁻¹⁻¹</td>
<td>Not given</td>
<td>50 ± 4.9/49 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Observational study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naguib et al. (25)</td>
<td>6</td>
<td>2013</td>
<td>Post hoc analysis of RCT</td>
<td>31 (15/16)</td>
<td>5 (2–21)/5 (3–7) M</td>
<td>Intraoperative Saline</td>
<td>1 μg kg⁻¹⁻¹ over 10 min, then 0.5 μg kg⁻¹⁻¹</td>
<td>A similar</td>
<td>Not given</td>
<td>124 (83–173)/113(74–225)</td>
</tr>
<tr>
<td>Jiang et al. (26)</td>
<td>4</td>
<td>2015</td>
<td>Retrospective</td>
<td>174 (77/97)</td>
<td>17.7 ± 11.4/22.0 ± 11.8 M</td>
<td>Postoperative Midazolam</td>
<td>0.25–0.75 μg kg⁻¹⁻¹</td>
<td>141 ± 29/156 ± 33</td>
<td>82 ± 27/71 ± 26</td>
<td></td>
</tr>
<tr>
<td>Cheng et al. (27)</td>
<td>4</td>
<td>2014</td>
<td>Prospective</td>
<td>57 (29/28)</td>
<td>6.6 ± 2.1/6.3 ± 1.5 M</td>
<td>Intraoperative Propofol</td>
<td>0.1–0.5 μg kg⁻¹⁻¹</td>
<td>Not given</td>
<td>51 ± 6.2/52 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Chen et al. (28)</td>
<td>5</td>
<td>2014</td>
<td>Prospective</td>
<td>25 (15/10)</td>
<td>11.9 ± 3.9/11.5 ± 2.6 M</td>
<td>Intraoperative Midazolam, fentanyl</td>
<td>0.3 μg kg⁻¹⁻¹ h⁻¹</td>
<td>Not given</td>
<td>Not given</td>
<td></td>
</tr>
<tr>
<td>Moffett et al. (29)</td>
<td>5</td>
<td>2014</td>
<td>Retrospective</td>
<td>1088 (544/544)</td>
<td>0.45 (0.29–0.93)/0.48 (0.31–1.10) Y</td>
<td>Intraoperative Midazolam, fentanyl</td>
<td>0.1 mg kg⁻¹⁻¹</td>
<td>Not given</td>
<td>Not given</td>
<td></td>
</tr>
<tr>
<td>Le et al. (30)</td>
<td>6</td>
<td>2011</td>
<td>Retrospective</td>
<td>269 (89/180)</td>
<td>13.7 (13–21)/14.7 (12–28) M</td>
<td>Postoperative Midazolam, fentanyl</td>
<td>0.3–0.7 μg kg⁻¹⁻¹</td>
<td>Not given</td>
<td>120 (83–200)/114 (8–204)</td>
<td></td>
</tr>
<tr>
<td>Chrysostomou et al. (31)</td>
<td>7</td>
<td>2011</td>
<td>Prospective</td>
<td>52 (32/20)</td>
<td>4.8 (0.16–19)/2.62 (0.13–15) M</td>
<td>Intraoperative Midazolam, fentanyl</td>
<td>0.76 ± 0.04 μg kg⁻¹⁻¹</td>
<td>Not given</td>
<td>92 ± 27 ± 99</td>
<td></td>
</tr>
<tr>
<td>Hosokawa et al. (32)</td>
<td>5</td>
<td>2010</td>
<td>Prospective</td>
<td>141 (96/85)</td>
<td>1 (0.5–3)/1 (0.8–4) Y</td>
<td>Postoperative Chlorpromazine, midazolam, fentanyl</td>
<td>0.4–0.6 μg kg⁻¹⁻¹</td>
<td>233 ± 109/274 ± 124</td>
<td>118 ± 72/114 ± 86</td>
<td></td>
</tr>
<tr>
<td>Tsubakihara et al. (33)</td>
<td>5</td>
<td>2009</td>
<td>Retrospective</td>
<td>14 (9/5)</td>
<td>1.2Y (14M–11Y)/1.8Y (13M–15Y)</td>
<td>Postoperative Midazolam, propofol, buprenorphine, pentazocine</td>
<td>0.3–0.4 μg kg⁻¹⁻¹</td>
<td>Not given</td>
<td>Not given</td>
<td></td>
</tr>
</tbody>
</table>

**DEX, dexmedetomidine; Y, year; M, month; RCT, randomized controlled trial; CPB, cardiopulmonary bypass; NOS, Newcastle-Ottawa Scale.**

Values are presented as median (interquartile range) or mean ± standard deviation unless indicated otherwise.
Effects on early recovery

After pooling data from eight studies (20–22,25,26,29,30,32,33) that assessed postoperative mechanical ventilation in 2037 patients, it was found that dexmedetomidine significantly reduced the length of mechanical ventilation (MD = 93.36; 95% CI = 137.45, 49.27; *P* < 0.0001; Table 2). Our data also revealed no difference between the dexmedetomidine-treated and control patients in the length of ICU (MD = 0.18; 95% CI = −0.49, 0.13; *P* = 0.25) and hospital (MD = 0.39; 95% CI = −0.22, 1.01; *P* = 0.15) stays.

**Effects on postoperative rescue analgesia**

Four trials (526 patients) compared dexmedetomidine-treated and control patients with respect to postoperative rescue analgesia (25,26,30,31). The meta-analysis revealed that children treated with dexmedetomidine required less rescue analgesia (fentanyl [MD = −24.11; 95% CI = −36.98, −11.24] or morphine [MD = −0.07; 95% CI = −0.14, 0.00]). All the details is shown in Table 2.

**Effects on delirium**

Dexmedetomidine reduced the incidence risk of agitation or delirium following CHD surgery (OR = 0.39; 95% CI = 0.21, 0.74; *P* = 0.004) (Table 2 and Figure S1a). Meanwhile, the methods to judge whether the preverbal subjects are delirium or not in the included studies are addressed in Data S1. On visual inspection, the funnel plots did not exhibit a skewed or asymmetrical shape (Figure S2).

**Discussion**

This systematic review and meta-analysis indicates that perioperative use of dexmedetomidine is associated with better outcomes in pediatric patients undergoing CHD, including more stable intraoperative hemodynamics, shorter length of postoperative mechanical ventilation, and reduced stress responses, postoperative analgesia requirements, and postoperative delirium. Notably, the incidence of bradycardia and hypotension was higher in the dexmedetomidine-treated patients.

The hemodynamic values in this meta-analysis were obtained at the time of surgical trauma, including skin incision, sternotomy, and bypass termination. We also found that the blood pressure and heart rate of children treated with dexmedetomidine appeared to be more stable, which is consistent with a previous meta-analysis that focused on the use of dexmedetomidine as a premedication in children (34). The underlying mechanism of action of dexmedetomidine may be related to its sympatholytic effects, which attenuate the stress response to various noxious stimuli (35,36). In our analysis, dexmedetomidine use was associated with an almost three-fold increase in the risk of bradycardia or
hypotension, which is consistent with another recent meta-analysis (37) in which the incidence of bradycardia and hypotension among dexmedetomidine-treated patients was higher than that in controls (pooled ORs: 5.14 and 3.00, respectively; adult patients). Although no severe complications related to bradycardia or hypotension were reported in these studies, particular attention should be paid to patients with a transduction block and those who are in shock.

Whether dexmedetomidine reduces postoperative ventilation remains controversial. In one retrospective study with a large sample (14), perioperative dexmedetomidine did not reduce postoperative ventilation times in adults after cardiac surgery. However, a meta-analysis (8) supports the notion that dexmedetomidine can decrease postoperative mechanical ventilation times in adults. Our review offers moderate evidence that dexmedetomidine can also shorten the length of postoperative mechanical ventilation in children after CAD surgery. Consistently, we always use dexmedetomidine when we are planning an early extubation, and we rarely use it when we are not planning an early extubation. The mechanism underlying this ventilation-shortening effect may in turn relate to an anesthetic-sparing effect (10,11,36), in addition to the minimal amount of respiratory depression (36,38) produced by dexmedetomidine. Therefore, dexmedetomidine appears to facilitate decreases in the adverse effects induced by narcotics and more rapidly restores spontaneous breathing. A decreased extubation time may protect patients from ventilator-associated pneumonia and contribute to a reduction in the length of ICU stays and hospital costs.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Mean difference</th>
<th>Mean difference</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>1.2.1 RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasr 2013</td>
<td>60.4</td>
<td>6</td>
<td>20</td>
<td>71.8</td>
</tr>
<tr>
<td>Rajput 2014</td>
<td>72.69</td>
<td>12.34</td>
<td>110</td>
<td>63.01</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>130</td>
<td>130</td>
<td>42.1%</td>
<td>-0.86</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 219.84$; $\chi^2 = 94.83$, df = 1 ($p &lt; 0.00001$); $p = 99$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.98$ ($p = 0.94$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.2 Observational studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen 2014</td>
<td>78.2</td>
<td>5.3</td>
<td>15</td>
<td>78.7</td>
</tr>
<tr>
<td>Cheng 2014</td>
<td>51</td>
<td>16.3</td>
<td>29</td>
<td>57.7</td>
</tr>
<tr>
<td>Tokuhira 2009</td>
<td>63.9</td>
<td>6.5</td>
<td>9</td>
<td>75.0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>53</td>
<td>43</td>
<td>57.9%</td>
<td>-5.28</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 24.45$; $\chi^2 = 6.45$, df = 2 ($p = 0.94$); $p = 69$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.53$ ($p = 0.13$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>183</td>
<td>173</td>
<td>100.0%</td>
<td>-3.78</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 107.17$; $\chi^2 = 102.79$, df = 4 ($p &lt; 0.00001$); $p = 96$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.79$ ($p = 0.43$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: $\chi^2 = 0.16$, df = 1 ($p = 0.69$), $p = 0$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 Comparison between dexmedetomidine-treated and control patients with respect to MAP (a) and SBP (b).
Table 2  Results of the meta-analysis comparing dexmedetomidine-treated and control patients

<table>
<thead>
<tr>
<th>Outcomes of interest</th>
<th>Studies, no.</th>
<th>Dexmedetomidine patients, no.</th>
<th>Control patients, no.</th>
<th>Odds ratio or weighted mean (95% confidence interval)</th>
<th>P-value</th>
<th>P-value</th>
<th>I² test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>9</td>
<td>274</td>
<td>252</td>
<td>−13.62 (−20.37, −6.86)</td>
<td>0.0001</td>
<td>0.00001</td>
<td>95%</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>5</td>
<td>183</td>
<td>173</td>
<td>−3.78 (−13.19, 5.63)</td>
<td>0.43</td>
<td>0.00001</td>
<td>96%</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>5</td>
<td>120</td>
<td>107</td>
<td>−11.80 (−20.06, −3.53)</td>
<td>0.005</td>
<td>0.00001</td>
<td>95%</td>
</tr>
<tr>
<td>Ventilator</td>
<td>8</td>
<td>950</td>
<td>1087</td>
<td>−93.36 (−137.45, −49.27)</td>
<td>0.0001</td>
<td>0.00001</td>
<td>97%</td>
</tr>
<tr>
<td>ICU stay</td>
<td>8</td>
<td>932</td>
<td>1057</td>
<td>−0.18 (−0.49, 0.13)</td>
<td>0.25</td>
<td>0.02</td>
<td>58%</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>5</td>
<td>757</td>
<td>857</td>
<td>0.39 (−0.22, 1.01)</td>
<td>0.21</td>
<td>0.15</td>
<td>41%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>3</td>
<td>136</td>
<td>216</td>
<td>−24.11 (−36.98, −11.24)</td>
<td>0.0002</td>
<td>0.004</td>
<td>82%</td>
</tr>
<tr>
<td>Morphine</td>
<td>3</td>
<td>198</td>
<td>297</td>
<td>−0.07 (−0.14, −0.00)</td>
<td>0.07</td>
<td>0.0001</td>
<td>94%</td>
</tr>
<tr>
<td>Glucose</td>
<td>3</td>
<td>50</td>
<td>51</td>
<td>−49.80 (−66.74, −32.96)</td>
<td>0.00001</td>
<td>0.00001</td>
<td>93%</td>
</tr>
<tr>
<td>Cortisol</td>
<td>3</td>
<td>50</td>
<td>51</td>
<td>−59.17 (−111.83, −6.52)</td>
<td>0.03</td>
<td>0.00001</td>
<td>95.80%</td>
</tr>
<tr>
<td>Delirium</td>
<td>2</td>
<td>133</td>
<td>182</td>
<td>0.39 (0.21, 0.74)</td>
<td>0.004</td>
<td>0.33</td>
<td>0%</td>
</tr>
<tr>
<td>Bradycardia or hypotension</td>
<td>3</td>
<td>97</td>
<td>110</td>
<td>3.14 (1.47, 6.69)</td>
<td>0.003</td>
<td>0.43</td>
<td>0%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2</td>
<td>142</td>
<td>130</td>
<td>0.07 (0.02, 0.22)</td>
<td>0.00001</td>
<td>0.92</td>
<td>0%</td>
</tr>
</tbody>
</table>

Statistically significant results are shown in bold.

Figure 4  Comparison between dexmedetomidine-treated and control patients with respected to blood glucose (a) and serum cortisol (b).
Similar to adults, no reduction in the duration of ICU or hospital stays was observed in children (8). There are other factors, in addition to ventilation time, that influence ICU and hospital stay lengths, including medical and sociodemographic variables, self-rated health and happiness, postoperative cardiac failure, and postoperative complications (41).

Patients undergoing cardiac surgery are exposed to specific risk factors for delirium, such as cardiopulmonary bypass and circulatory arrest, and appear at high risk of delirium (42). Our results showed that dexmedetomidine reduced the risk of delirium, which is important in pediatric patients after CHD surgery to avoid poor outcomes, such as prolonged ICU and hospital stays, slower recovery from cognitive impairment, higher risk of mortality, and increased healthcare costs (43–45). Although an increasing number of studies support the notion that dexmedetomidine can effectively prevent delirium (8,46), recent (2013) American College of Critical Care medicine guidelines for the management of pain, agitation, and delirium in adult patients in ICUs suggested that there is no compelling evidence for this effect and provided no recommendations for the use of dexmedetomidine to prevent delirium (47). Therefore, more high-quality RCTs on this subject are required.

Surgical procedures and cardiopulmonary bypass during cardiac surgery produce a neuroendocrine stress response that plays an important role in the pathogenesis of perioperative cardiac complications and increases morbidity and mortality (48). Blood levels of glucose and cortisol are regarded as predictors of this stress response; as expected, our analysis convincingly demonstrates that dexmedetomidine can inhibit increased blood glucose and cortisol levels in patients undergoing cardiac surgery.

A previous meta-analysis confirmed that perioperative dexmedetomidine can decrease postoperative morphine consumption and pain intensity (49). Our analysis provides further evidence that dexmedetomidine reduces postoperative morphine and fentanyl consumption effectively in children after CHD surgery; a reduced requirement for analgesia may in turn reduce the incidence of opioid-related adverse effects, such as nausea and vomiting.

Several potential limitations should be taken into account when interpreting the results. First, among the 14 included studies, only five studies were RCTs with small sample sizes, whereas the other nine were observational studies. Inadequate blinding tended to increase the risk of bias, and observational studies were highly subject to selection bias and confounding by indication. Second, this meta-analysis was influenced by significant heterogeneity that was introduced by multiple factors that included different study design, age group, dosage, dosing regimens, and disease severity. Third, several clinical end points, such as blood glucose, serum cortisol, and adverse events, were reported in only three studies and the population was not large. Nevertheless, this meta-analysis was conducted at an appropriate time, and provided the most up-to-date information for dexmedetomidine utilization in children undergoing CHD surgery.

Conclusions

In conclusion, the present systematic review and meta-analysis offers convincing evidence that dexmedetomidine can be recommended for use in children undergoing CHD surgery. The advantages of using this agent include more stable intraoperative hemodynamics, reduced mechanical ventilation times and analgesia requirements, a lower incidence of agitation and delirium, and an attenuated stress response. However, particular attention should be paid to perioperative bradycardia and hypotension induced by dexmedetomidine.

Author contributions


Funding

This work was supported by departmental funding.

Conflicts of interest

The authors report no conflict of interest.

Supporting information

Additional Supporting Information may be found in the online version of this article:

- Figure S1 Forest plot for incidence of tachycardia (a), bradycardia (b), and postoperative delirium (c).
- Figure S2 Forrest plot for intraoperative heart rate (a) and postoperative mechanical ventilation (b).
- Table S1 The anatomical defect types among the included studies.
- Data S1 The methods to measure the children delirium or not.
References


39 Blackwood B, Murray M, Chisakuta A et al. Protocollized versus non-protocollized wean-
Dex for cardiac surgery in children

W. Pan et al.