REVIEW ARTICLE

Dexmedetomidine vs midazolam as preanesthetic medication in children: a meta-analysis of randomized controlled trials

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What’s known

• Premedication reduces perioperative anxiety in children.

What this article adds

• Dexmedetomidine is more effective than midazolam in decreasing preoperative anxiety, postoperative agitation, and in providing more effective postoperative analgesia.

Implications

• Dexmedetomidine is an effective alternate sedative for premedication in children

Keywords

anesthesia-pediatric; dexmedetomidine; meta-analysis; midazolam; premedication; children

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Summary

Introduction: The preoperative period is a stressing occurrence for most people undergoing surgery, in particular children. Approximately 50–75% of children undergoing surgery develop anxiety which is associated with distress on emergence from anesthesia and with later postoperative behavioral problems. Premedication, commonly performed with benzodiazepines, reduces preoperative anxiety, facilitates separation from parents, and promotes acceptance of mask induction. Dexmedetomidine is a highly selective α₂-agonist with sedative and analgesic properties. A meta-analysis of all randomized controlled trials (RCTs) on dexmedetomidine versus midazolam was performed to evaluate its efficacy in improving perioperative sedation and analgesia, and in reducing postoperative agitation when used as a preanesthetic medication in children.

Methods: Studies were independently searched in PubMed, BioMedCentral, Embase, and the Cochrane Central Register of clinical trials and updated on August 15th, 2014. Primary outcomes were represented by improved sedation at separation from parents, at induction of anesthesia, and reduction in postoperative agitation. Secondary outcomes were reduction in rescue analgesic drugs, and duration of surgery and anesthesia. Inclusion criteria were random allocation to treatment and comparison between dexmedetomidine and midazolam. Exclusion criteria were adult studies, duplicate publications, intravenous administration, and no data on main outcomes.

Results: Data from 1033 children in 13 randomized trials were analyzed. Overall, in the dexmedetomidine group there was a higher incidence of satisfactory sedation at separation from parents (314 of 424 [74%] in the dex-
medetomidine group vs 196 of 391 [50%] in the midazolam group, RR = 1.30 [1.05–1.62], \( P = 0.02 \), a reduced incidence of postoperative agitation (14 of 140 [10%] vs 56 of 141 [40%], RR = 0.31 [0.13–0.73], \( P = 0.008 \)), and a significant reduction in the rescue doses of analgesic drugs (49 of 241 [20%] vs 95 of 243 [39%], RR = 0.52 [0.39–0.70], \( P < 0.001 \)). There was no evidence of a higher incidence of satisfactory sedation at anesthesia induction or any reduction of duration of surgery and anesthesia.

Conclusions: Dexmedetomidine is effective in decreasing anxiety upon separation from parents, decreasing postoperative agitation, and providing more effective postoperative analgesia when compared with midazolam.

Introduction

The preoperative period is a stressing occurrence for most patients undergoing surgery, especially children. It is estimated that 50–75% of children undergoing surgery will develop great anguish and anxiety throughout the whole perioperative period (1).

Premedication is commonly used to reduce preoperative anxiety, to facilitate separation from parents, and to promote acceptance of mask induction. Among the different goals that can be achieved with premedication, the primary objective in children is anxiolysis. Premedication that effectively calms the child also minimizes parental anxiety (2,3).

Benzodiazepines, and midazolam in particular, are the most frequently used premedications in pediatric patients (3–5). Efficacy of midazolam premedication in children has been widely demonstrated. However, in light of recent findings and pharmacological improvements, it should no longer be considered the drug of choice for pediatric premedication. In fact, Stewart et al. (6) showed that midazolam maintains implicit memory for potentially perioperative stressful events (e.g., mask induction) but induces scarce explicit memory for the same events. Accordingly, children premedicated with midazolam might unconsciously remember these potentially stressful events without being able to pull them consciously to mind, to elaborate, and make sense of them. Moreover midazolam, when compared to other drugs, resulted in ineffective prevention of emergence agitation and delirium in children (7).

Therefore, different drugs like the \( \alpha_2 \)-agonists have gained importance as alternatives for premedication in pediatric anesthesia.

Dexmedetomidine is a highly selective \( \alpha_2 \)-agonist with both analgesic and sedative effects. It produces a type of sedation recognized as ‘cooperative’ or ‘arousable’, which is different from the ‘clouding of consciousness’ sedation induced by drugs acting on the GABA system (8). These characteristics make it potentially useful for anesthesia premedication in children.

A meta-analysis of all RCTs on dexmedetomidine versus midazolam was performed to evaluate dexmedetomidine perioperative sedative effects as a preanesthetic medication in children.

Methods

Search strategy

Relevant studies were individually searched in PubMed, BioMedCentral, Embase, and the Cochrane Central Register of clinical trials (updated August 15th, 2014) by four expert investigators. Full PubMed search strategy aimed to include any randomized study ever performed in children with dexmedetomidine compared to midazolam in any clinical setting. Moreover, backward snowballing (scanning of references of relevant reviews and cited articles) was conducted, and international experts were contacted for additional studies. The database search was supplemented by online searching (e.g., Google), congress abstracts, and trial registers. No language restriction was imposed.

Study selection

References obtained from database and literature searches were first independently examined at a title/abstract level by four investigators, with divergences resolved by consensus, and then, if potentially pertinent, the manuscripts were retrieved. Inclusion criteria were pediatric patients and random allocation to treatment (dexmedetomidine versus midazolam with no restrictions on dose or time of administration). Exclusion criteria included intravenous administration, adult patients, and lack of data on at least one of the following endpoints: sedation at separation from parents, sedation at anesthesia induction, number of children requiring supplemental postoperative analgesia, and safety. Two investigators independently assessed compliance to selection criteria and selected studies for the final analysis, with divergences finally resolved by consensus.
Data abstraction and study

Baseline, procedural, and outcome data were independently abstracted by four trained investigators, with divergences resolved by consensus. Specifically, potential sources of significant heterogeneity, such as study design, sample size, route of administration, dose and timing, control treatment, as well as primary study endpoints, and other key outcomes were extracted. At least two separate attempts at contacting original authors were made in cases of missing data.

Co-primary endpoints of the present meta-analysis were as follows: improved sedation at separation from parents, improved sedation at induction of anesthesia, and reduction in incidence of postoperative agitation. The secondary endpoints were reduction in rescue analgesic drugs and reduction in duration of surgery and anesthesia.

Duration of surgery and anesthesia were defined as per authors’ definition.

Adverse effects (hypotension, laryngospasm, shivering, bradycardia, nausea, and vomiting) were also analyzed.

Internal validity and risk of bias assessment

The internal validity and risk of bias of included trials was appraised by two independent reviewers according to the Cochrane Collaboration methods (9), with divergences resolved by consensus. Publication bias was assessed by visually inspecting funnel plots.

Data analysis and synthesis

Computations were performed with Review Manager version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). The hypothesis of statistical heterogeneity was tested by means of Cochran $Q$ test, with statistical significance set at the two-tailed 0.10 level, whereas the extent of statistical consistency was measured with $I^2$, defined as $100\% \times \frac{(Q - df)}{Q}$, where $Q$ is Cochran’s heterogeneity statistic and df, the degrees of freedom. Binary outcomes were analyzed to compute the individual and pooled risk ratio (RR) with 95% confidence intervals (CI), by means of the same models just described. Binary outcomes from individual studies were analyzed to compute individual and pooled risk ratio (RR) with 95% CIs, by means of inverse variance method and with a fixed effect model in case of low statistical inconsistency ($I^2 < 25\%$) or with random effect model (which better accommodates clinical and statistical variations) in case of moderate or high statistical inconsistency ($I^2 > 25\%$). Mean differences (MD) and 95% CIs were computed for continuous variables using the same models as described. Sensitivity analyses were performed by sequentially removing each study and reanalysing the remaining dataset (producing a new analysis for each study removed) and by analysing only data from studies with low risk of bias. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Unadjusted $P$ values are reported throughout. This study was performed in compliance with The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (9–12).

Results

Study characteristics

Database searches, snowballing, and contacts with experts yielded a total of 890 articles. Excluding 869 nonpertinent titles or abstracts, 21 studies were retrieved in completed form and were assessed according to the selection criteria (Figure 1). Eight studies were further excluded because of our prespecified exclusion criteria: one study was excluded because it was not randomized (Supplemental Reference 1), and seven because the control group did not receive midazolam as comparator drug (Supplemental References 2–8).

The 13 included manuscripts randomized 1033 patients (531 to dexmedetomidine and 502 to midazolam) (Table 1) (13–25). Clinical heterogeneity was mostly due to type of surgery, route, dosage, and timing of drug administration (Table 1). Different routes of dexmedetomidine administration were used: intranasal in nine trials (13,14,16,17,21–25), oral in three trials (15,18,19), and sublingual in one trial (20).

![Figure 1 Flow diagram for selection of articles.](image-url)
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Type of surgery</th>
<th>Dex patients</th>
<th>Midazolam patients</th>
<th>Dex dose</th>
<th>Midazolam dose</th>
<th>Route of administration Dex</th>
<th>Route of administration midazolam</th>
<th>Timing administration Dex</th>
<th>Timing administration midazolam</th>
<th>Scale used for anxiety measurement</th>
<th>Scale used for sedation measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akin (13)</td>
<td>2012</td>
<td>Adenotonsillectomy</td>
<td>45</td>
<td>45</td>
<td>1 mcg kg⁻¹</td>
<td>0.2 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Intranasal</td>
<td>45–60 min before induction</td>
<td>45–60 min before induction</td>
<td>4–point scale</td>
<td>MOAA/S</td>
</tr>
<tr>
<td>Ghali (14)</td>
<td>2011</td>
<td>Adenotonsillectomy</td>
<td>60</td>
<td>60</td>
<td>1 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Oral</td>
<td>60 min before induction</td>
<td>60 min before induction</td>
<td>mYPAS</td>
<td>MOAA/S</td>
</tr>
<tr>
<td>Kamal (15)</td>
<td>2008</td>
<td>Strabismus surgery</td>
<td>30</td>
<td>30</td>
<td>3 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Oral</td>
<td>Oral</td>
<td>60 min before induction</td>
<td>60 min before induction</td>
<td>Modified OPS</td>
<td>Modified Vancouver sedative recovery scale</td>
</tr>
<tr>
<td>Linares Segovia (16)</td>
<td>2014</td>
<td>Elective surgery</td>
<td>52</td>
<td>56</td>
<td>1 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Oral</td>
<td>60 min before induction</td>
<td>60 min before induction</td>
<td>mYPAS</td>
<td>n.a.</td>
</tr>
<tr>
<td>Mostafa (17)</td>
<td>2014</td>
<td>Bone marrow biopsy</td>
<td>32</td>
<td>32</td>
<td>1 mcg kg⁻¹</td>
<td>0.2 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Intranasal</td>
<td>30 min before induction</td>
<td>30 min before surgery</td>
<td>4-point scale</td>
<td>4 point sedation scale</td>
</tr>
<tr>
<td>Mountain (18)</td>
<td>2011</td>
<td>Dental restoration and/or extractions.</td>
<td>22</td>
<td>19</td>
<td>4 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Oral</td>
<td>Oral</td>
<td>30 min before surgery</td>
<td>40–45 min before surgery</td>
<td>PSAS; PAEDS</td>
<td>MAS</td>
</tr>
<tr>
<td>Ozcaniz (19)</td>
<td>2011</td>
<td>Esophageal distalation</td>
<td>25</td>
<td>25</td>
<td>2.5 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Oral</td>
<td>Oral</td>
<td>40–45 min before surgery</td>
<td>20 min before surgery</td>
<td>n.a.</td>
<td>EAS</td>
</tr>
<tr>
<td>Pant (20)</td>
<td>2013</td>
<td>Inguinal hernia repair, orchidopexy or circumcision</td>
<td>50</td>
<td>50</td>
<td>1.5 mcg kg⁻¹</td>
<td>0.25 mcg kg⁻¹</td>
<td>Sublingual</td>
<td>Sublingual</td>
<td>45 min before induction</td>
<td>20 min before surgery</td>
<td>4-point scale</td>
<td>MOAA/S</td>
</tr>
<tr>
<td>Schmidt (21)</td>
<td>2007</td>
<td>Elective ambulatory surgical procedures</td>
<td>20</td>
<td>22</td>
<td>1 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Oral</td>
<td>45 min before surgery</td>
<td>30 min before surgery</td>
<td>STAIC</td>
<td>4-point scale</td>
</tr>
<tr>
<td>Sheta (22)</td>
<td>2013</td>
<td>Complete dental rehabilitation</td>
<td>36</td>
<td>36</td>
<td>1 mcg kg⁻¹</td>
<td>0.2 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Intranasal</td>
<td>45–60 min before surgery</td>
<td>45–60 min before surgery</td>
<td>4-point scale</td>
<td>4-point scale</td>
</tr>
<tr>
<td>Sundaram (23)</td>
<td>2011</td>
<td>Elective full mouth rehabilitation</td>
<td>45</td>
<td>45</td>
<td>1 mcg kg⁻¹</td>
<td>0.2 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Intranasal</td>
<td>60 min before surgery</td>
<td>60 min before surgery</td>
<td>4-point scale</td>
<td>6-point scale</td>
</tr>
<tr>
<td>Talon (24)</td>
<td>2009</td>
<td>Elective reconstructive surgery</td>
<td>50</td>
<td>50</td>
<td>2 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Oral</td>
<td>30–40 min before surgery</td>
<td>30 min before surgery</td>
<td>4-point scale</td>
<td>Ramsey–like 4-point scale</td>
</tr>
<tr>
<td>Yuen (25)</td>
<td>2008</td>
<td>Elective minor surgery</td>
<td>64</td>
<td>32</td>
<td>0.5–1 mcg kg⁻¹</td>
<td>0.5 mcg kg⁻¹</td>
<td>Intranasal</td>
<td>Oral</td>
<td>60 min before induction</td>
<td>30 min before surgery</td>
<td>4-point scale</td>
<td>MOAA/S</td>
</tr>
</tbody>
</table>

Dex: Dexmedetomidine; MOAA/S: 6-point sedation scale, modified from the observer assessment of alertness and sedation scale; mYPAS: modified Yale preoperative anxiety scale; OPS: Objective Pain Scale; n.a: not available; PSAS: Parental Separation Anxiety Scale; MAS: Mask Acceptance Scale; PAEDS: Pediatric Anesthesia Emergence Delirium Scale; EAS: emergence agitation scale; STAIC: State–Trait Anxiety Inventory for Children.
Dexmedetomidine was administered at different dosages: <2 μg·kg⁻¹ in nine trials (13,14,16,17,20–23,25), 2.5 μg·kg⁻¹ in one trial (19), 2 μg·kg⁻¹ in one trial (24), 3 μg·kg⁻¹ in one trial (15), and 4 μg·kg⁻¹ in one trial (18).

Study quality appraisal indicated that trials were of medium–high quality (Supplemental Table 1); in particular, 10 of them had a low risk of bias (13,14,16–20,22–24). Midazolam route of administration and dosages varied between comparator groups (Table 1). Timing of study drug and comparator administration is presented in Table 1.

Quantitative data synthesis

Primary outcomes

Satisfactory sedation at separation from parents was 314 of 424 [74%] in the dexmedetomidine group and 196 of 391 [50%] in the midazolam group, RR = 1.30 [1.05–1.62], P for effect = 0.02, P for heterogeneity <0.01, I² = 78% with 10 studies included, while weak evidence of a difference was noted in the incidence of satisfactory sedation at anesthesia induction (270 of 369 [73%] in the dexmedetomidine group vs 215 of 340 [63%] in the midazolam group, RR = 1.21 [0.99–1.47], P for effect = 0.06, P for heterogeneity <0.01, I² = 85% with nine studies included) (Figures 2,3).

Moreover, there was evidence of a reduced postoperative agitation in the dexmedetomidine group (14 of 140 [10%] in the dexmedetomidine group vs 56 of 141 [40%] in the midazolam group, RR = 0.31 [0.13–0.73], P for effect = 0.008, P for heterogeneity 0.08, I² = 56% with four studies included) (Figure 4).

Secondary outcomes

A significant reduction in the rescue doses of analgesic drugs was noted in the dexmedetomidine group when compared to the midazolam arm (49 of 241 [20%] vs 95 of 243 [39%], RR = 0.52 [0.39–0.70], P for effect <0.001, P for heterogeneity 0.93, I² = 0% with six studies included) (Supplemental Figure 1) together with a weak evidence of a difference in duration of surgery (MD = 2.52 [–0.14–5.17] minutes, P for effect = 0.06 with seven studies included), while there was no differ-

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ence in the duration of anesthesia (MD = −0.88 [−2.55–0.78] minutes, \( P \) for effect = 0.30, with five studies included).

No differences in the incidence of hypotension, nausea and vomiting, laryngospasm, shivering, and bradycardia were found.

Sensitivity analysis

Estimate results from both random and fixed effect models were extremely similar (Table 2). Sensitivity analyses carried out in studies with low risk of bias confirmed the superiority of dexmedetomidine in ensuring a higher incidence of satisfactory sedation at separation from parents (263 of 344 [77%] in the dexmedetomidine group vs 178 of 337 [53%] in the midazolam group, \( RR = 1.25 [1.01–1.56] \), \( P \) for effect = 0.04 \( P \) for heterogeneity <0.01, \( I^2 = 78\% \) with eight studies included), in reducing postoperative agitation (9 of 110 [8\%] in the dexmedetomidine group vs 46 of 111 [41\%] in the midazolam group, \( RR = 0.25 [0.08–0.81] \), \( P \) for effect = 0.02 \( P \) for heterogeneity 0.06, \( I^2 = 64\% \) with three studies included) and in reducing the rescue doses of postoperative analgesic drugs (32 of 191 [17\%] in the dexmedetomidine group vs 60 of 191 [31\%] in the midazolam group, \( RR = 0.53 [0.37–0.77] \), \( P \) for effect <0.001 \( P \) for heterogeneity 0.85, \( I^2 = 0\% \) with four studies included).

Visual inspection of funnel plots did not identify a skewed or asymmetrical shape (Figures 5–7; supplemental Figure 2).

Discussion

Our meta-analysis suggests that premedication with dexmedetomidine is superior to midazolam in ensuring satisfactory levels of sedation in children undergoing surgery, both at separation from parents and at emergence. Moreover, it produces a more effective postoperative analgesia with a similar side effect profile. This is the first meta-analysis of randomized clinical trials focusing on nonintravenously administered dexmedetomidine as preanesthetic medication in children.

Historically, the most commonly used drug for premedication in children is certainly midazolam. We therefore decided to choose this benzodiazepine as comparator drug in our study. A systematic review published in 2006 by Cox et al. (26) evaluated the efficacy of midazolam as a preanesthetic medication in children. It focused on behavioral outcomes and clearly showed that premedication with midazolam is effective in reducing anxiety in children, both at separation from parents and at induction of anesthesia, with little impact on recovery times.

In recent years, different drugs, like the \( \alpha_2 \)-agonists clonidine and dexmedetomidine were studied as alternatives for premedication in pediatric anesthesia (27).

Previously published meta-analyses (28,29) showed that clonidine is more effective than midazolam in enhancing postoperative analgesia and reducing the incidence of emergence agitation in children. These results strengthen our findings, suggesting the superiority of \( \alpha_2 \)-agonists in improving postoperative analgesia while ensuring comparable satisfactory levels of sedation.

However, when compared to previous meta-analyses, our study presents unique and peculiar differences: first of all, it is the first one including only children receiving nonintravenous dexmedetomidine (intranasal, sublingual, or oral) as premedication drug; moreover, our study, by adding new, recent trials in the analysis, does not confirm the superiority of dexmedetomidine in ensuring satisfactory levels of sedation at induction and in reducing postoperative agitation, in contrast with the findings of Sun et al. (29).

Dexmedetomidine is a relatively new \( \alpha_2 \)-adrenergic agonist, with increased specificity over clonidine (17). In contrast to other sedative agents, dexmedetomidine, by acting on \( \alpha_2 \) receptors in the locus caeruleus, has potential analgesic effects with minimal respiratory depression. It produces sedation acknowledged as ‘cooperative’ or ‘arousable’, which is different from the
Clouding of consciousness sedation induced by drugs acting on GABA receptors, such as midazolam or propofol (8,27). These characteristics explain why dexmedetomidine could have similar efficacy to midazolam.

Table 2 Primary and secondary outcomes and sensitivity analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of included trials</th>
<th>Dexmedetomidine patients</th>
<th>Midazolam patients</th>
<th>RR or MD</th>
<th>95% CI</th>
<th>P for effect</th>
<th>P for heterogeneity</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall trials</td>
<td>13 trials</td>
<td>531</td>
<td>502</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoints:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfactory sedation at separation from parents</td>
<td>10 (13, 14, 17, 18, 20–24)</td>
<td>314/424 (74%)</td>
<td>196/391 (50%)</td>
<td>1.30</td>
<td>1.05 to 1.62</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>78</td>
</tr>
<tr>
<td>&gt;Small study effect (fixed model)</td>
<td>8</td>
<td>263/340 (77%)</td>
<td>178/337 (53%)</td>
<td>1.25</td>
<td>1.01 to 1.56</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>78</td>
</tr>
<tr>
<td>Satisfactory sedation at anesthesia induction</td>
<td>9 (15, 16, 18, 20–25)</td>
<td>270/389 (73%)</td>
<td>215/340 (63%)</td>
<td>1.21</td>
<td>0.99 to 1.47</td>
<td>0.06</td>
<td>&lt;0.01</td>
<td>65</td>
</tr>
<tr>
<td>&gt;Small study effect (fixed model)</td>
<td>4</td>
<td>14/40 (10%)</td>
<td>56/141 (40%)</td>
<td>0.31</td>
<td>0.13 to 0.73</td>
<td>0.008</td>
<td>0.08</td>
<td>56</td>
</tr>
<tr>
<td>&gt;Small study effect (random model)</td>
<td>3</td>
<td>9/10 (9%)</td>
<td>46/111 (41%)</td>
<td>0.25</td>
<td>0.08 to 0.81</td>
<td>0.02</td>
<td>0.06</td>
<td>64</td>
</tr>
<tr>
<td>Secondary endpoints:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients requiring rescue doses of postoperative analgesics</td>
<td>6 (13–15, 21, 22, 24)</td>
<td>49/241 (20%)</td>
<td>95/243 (39%)</td>
<td>0.52</td>
<td>0.39 to 0.70</td>
<td>&lt;0.001</td>
<td>0.93</td>
<td>0</td>
</tr>
<tr>
<td>&gt;Small study effect (fixed model)</td>
<td>4</td>
<td>32/191 (17%)</td>
<td>60/191 (31%)</td>
<td>0.53</td>
<td>0.37 to 0.77</td>
<td>&lt;0.001</td>
<td>0.85</td>
<td>0</td>
</tr>
<tr>
<td>Duration of anesthesia (minutes)</td>
<td>5 (13, 17, 19, 21, 22)</td>
<td>158</td>
<td>160</td>
<td>−0.88</td>
<td>−2.55 to 0.78</td>
<td>0.30</td>
<td>0.37</td>
<td>7</td>
</tr>
<tr>
<td>Duration of surgery (minutes)</td>
<td>7 (13, 14, 17, 21–23, 25)</td>
<td>302</td>
<td>272</td>
<td>2.52</td>
<td>−0.14 to 5.17</td>
<td>0.06</td>
<td>0.10</td>
<td>44</td>
</tr>
</tbody>
</table>

RR: relative risk; MD: mean difference CI: confidence interval; P: P-value.
in achieving sedation, but it also has some advantages in providing postoperative analgesia.

On the other hand, Heard et al. (30) showed that the pharmacy acquisition cost for dexmedetomidine sedation regimen per child is significantly higher than the acquisition cost for midazolam sedation ($10.80 and $1.86, respectively). Nonetheless, healthcare costs may be potentially decreased by reducing the need of postoperative analgesia and sedation.

We acknowledge that this study has several limitations. First of all, it includes only small, monocentric clinical trials with high clinical heterogeneity (mostly due to study drugs dosages and routes of administration). In addition, there is high heterogeneity between studies in the scales and measures used for sedation and children’s anxiety assessment. The poor quality of the included RCTs adds some important limitations to our findings. One of the major biases is due to the low dose of dexmedetomidine given orally in most of the included studies.

Another limitation of our study is that it does not analyze the impact of dexmedetomidine on emergence time and/or time to discharge from postanesthesia care unit because of lack of published data.

Conclusions

Dexmedetomidine seems to be effective in providing a higher incidence of satisfactory sedation at separation from parents, in reducing the incidence of postoperative agitation, and providing more efficacious postoperative analgesia when compared to midazolam as preanaesthetic medication in children. There is still no evidence for a higher incidence of satisfactory sedation at anesthesia induction.

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Disclosure

No conflict of interests declared.

Supporting information

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

Data S1 Pubmed search strategy.

References of the excluded studies.

Table S1 Methodological quality summary: review authors’ judgments about each methodological quality item for each included study.

Figure S1 Forrest plot for rescue doses of postoperative analgesic drugs.

Figure S2 Funnel plot for rescue doses of postoperative analgesic drugs.

References


16 Linares Segovia B, Garcia Cuevas MA, Ramirez-Casillas IL et al. Pre-anesthetic medication with intranasal dexmedetomi-


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