The Effect of Intraoperative Dexmedetomidine on Postoperative Analgesia and Sedation in Pediatric Patients Undergoing Tonsillectomy and Adenoidectomy

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BACKGROUND: The immediate postoperative period after tonsillectomy and adenoidectomy, one of the most common pediatric surgical procedures, is often difficult. These children frequently have severe pain but postoperative airway edema along with increased sensitivity to the respiratory-depressant effects of opioids may result in obstructive symptoms and hypoxemia. Opioid consumption may be reduced by nonsteroidal antiinflammatory drugs, but these drugs may be associated with increased bleeding after this operation. Dexmedetomidine has mild analgesic properties, causes sedation without respiratory depression, and does not have an effect on coagulation. We designed a prospective, double-blind, randomized controlled study to determine the effects of intraoperative dexmedetomidine on postoperative recovery including pain, sedation, and hemodynamics in pediatric patients undergoing tonsillectomy and adenoidectomy.

METHODS: One hundred nine patients were randomized to receive a single intraoperative dose of dexmedetomidine 0.75 µg/kg, dexmedetomidine 1 µg/kg, morphine 50 µg/kg, or morphine 100 µg/kg over 10 minutes after endotracheal intubation.

RESULTS: There were no significant differences among the 4 groups in patient demographics, ASA physical status, postoperative opioid requirements, sedation scores, duration of oxygen supplementation in the postanesthetic care unit, and time to discharge readiness. The median time to first postoperative rescue analgesic was similar in patients receiving dexmedetomidine 1 µg/kg and morphine 100 µg/kg, but significantly longer compared with patients receiving dexmedetomidine 0.75 µg/kg or morphine 50 µg/kg (P < 0.01). In addition, the number of patients requiring >1 rescue analgesic dose was significantly higher in the dexmedetomidine 0.75 µg/kg group compared with the dexmedetomidine 1 µg/kg and morphine 100 µg/kg groups, but not the morphine 50 µg/kg group. Patients receiving dexmedetomidine had significantly slower heart rates in the first 30 minutes after surgery compared with those receiving morphine (P < 0.05). There was no significant difference in sedation scores among the groups.

CONCLUSIONS: The total postoperative rescue opioid requirements were similar in tonsillectomy patients receiving intraoperative dexmedetomidine or morphine. However, the use of dexmedetomidine 1 µg/kg and morphine 100 µg/kg had the advantages of an increased time to first analgesic and a reduced need for additional rescue analgesia doses, without increasing discharge times.

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coagulation. It has sympatholytic effects that can result in decreased arterial blood pressure and heart rate, which may be of concern in anesthetized children with a rate-dependent cardiac output.7,11 This study was designed to determine the effects of intraoperative dexmedetomidine on postoperative recovery including pain, sedation, and hemodynamics in pediatric patients undergoing tonsillectomy and adenoidectomy.

**METHODS**

This prospective, randomized, double-blind study was conducted in 109 pediatric patients undergoing tonsillectomy and adenoidectomy, after receiving approval from both the Baylor College of Medicine IRB and the Food and Drug Administration (investigational new drug, IND# 79,290). In addition, we obtained written informed consent from the legal guardian and, when appropriate, assent from the child older than 7 years. Children between the ages of 3 and 12 years with ASA classification of I or II were eligible for inclusion in the study. Exclusion criteria were a body mass index more than the 95th percentile for age, ASA classification III or more, and the presence of confirmed severe obstructive sleep apnea by a polysomnograph test. Patients with a history of snoring or sleep-disordered breathing, but without a polysomnogram test, were included.

After consent was obtained, children were randomized to 1 of 4 groups based on a computer-generated random number to receive a single IV dose of (a) dexmedetomidine 0.75 μg/kg, (b) dexmedetomidine 1 μg/kg, (c) morphine 50 μg/kg, or (d) morphine 100 μg/kg intraoperatively. Doses of dexmedetomidine were chosen to exceed those from a previous pilot study in which patients who received dexmedetomidine 0.5 μg/kg IV intraoperatively during tonsillectomy and adenoidectomy did not demonstrate a decrease in postoperative rescue analgesic requirements compared with morphine 50 μg/kg.12

After a preoperative fasting period of a minimum of 6 hours, all patients received a standardized anesthetic regimen that included premedication with oral midazolam 0.5 mg/kg (maximum of 10 mg), and induction with sevoflurane and nitrous oxide in oxygen via facemask. Endotracheal intubation was facilitated with 0.5 mg/kg atracurium. The study drug was administered over a 10-minute period immediately after endotracheal intubation. Anesthesia was maintained with sevoflurane and nitrous oxide in oxygen, adjusted to maintain heart rate and arterial blood pressure within 20% of preinduction levels. No additional opioid, acetaminophen, or propofol was used during the procedure. Intraoperative dexamethasone 0.5 mg/kg (maximum dose of 20 mg), IV antibiotics, and ondansetron 0.15 mg/kg (maximum of 4 mg) were administered per routine intraoperative management of tonsillectomy and adenoidectomy patients at our institution. All patients received a lactated Ringer solution infusion for fluid maintenance and deficit replacement. Replacement of calculated fluid deficit was commenced in the operating room and completed in the postanesthetic care unit (PACU). Neuromuscular blockade was antagonized with neostigmine 0.07 mg/kg and glycopyrrolate 0.01 mg/kg at the end of the operation and anesthetic gases were discontinued. The trachea was extubated when patients were awake as defined by eye opening, purposeful movement, or response to command. The child was then transported to the PACU with supplemental oxygen. Oxygen administration was continued after extubation until the patient was awake and could sustain room air saturations >95% for 5 minutes. Duration of oxygen requirement was recorded as the time from tracheal extubation to cessation of oxygen supplementation in the PACU.

Data for each individual patient were obtained by 1 of 2 observers who were blinded to patient assignment. Routine vital signs, Ramsay sedation score,13 and Children’s Hospital of Eastern Ontario Pain Scale14 score were measured and recorded on arrival in the PACU at 5, 10, and 15 minutes, and then every 15 minutes until the child was discharged. Patients with a Children’s Hospital of Eastern Ontario Pain Scale score >8 received morphine 25 μg/kg IV at 10-minute intervals until the score was <8. Patients in the PACU who were crying, restless, disoriented, unresponsive to the parent’s voice, with nonpurposeful thrashing movements requiring additional personnel to prevent bodily harm, and inconsolable even after parental presence, rescue analgesia and additional measures of comfort were considered to have emergence agitation.15,16 Patients were considered ready for discharge from the PACU when they attained an Aldrete score17 of 9 or more and were free from pain, nausea, and vomiting. The duration of surgery and anesthesia, time to first postoperative rescue analgesic, amount of rescue analgesic received, need for antiemetics, and total duration of PACU stay were also recorded.

**Statistical Analysis**

The primary outcome measure was the amount of postoperative rescue morphine required for analgesia during the patient’s stay in the PACU. Secondary outcome measures were the time to first analgesic rescue, the number of patients who needed more than 1 analgesic rescue dose, the degree of sedation as determined by the Ramsay sedation score, oxygen requirement, heart rate, respiratory rate, time to discharge readiness, along with the incidence of emergence agitation and postoperative nausea and vomiting.

Sample size calculation was based on the following assumptions. (1) The primary endpoint was the amount of morphine required in the PACU. (2) In a previous pilot study, there were no differences noted in postoperative rescue morphine administered to patients receiving dexmedetomidine 0.5 μg/kg or morphine 50 μg/kg.12 We therefore assumed the rescue analgesic requirements in the morphine 50 μg/kg group in the current study would be similar to those in the dexmedetomidine 0.5 μg/kg group in the pilot study (rescue analgesic requirement: 46.75 ± 25 μg/kg morphine). (3) We assumed that the rescue analgesic requirements in the group receiving dexmedetomidine 1 μg/kg would be 50% less than in the morphine 50 μg/kg group. This was based on the adult study by Arain et al.,1 which showed a 66% reduction in postoperative opioid consumption in patients who had received this dose of dexmedetomidine compared with a group receiving morphine 80 μg/kg. We thought it would be reasonable to base our power analysis on a more conservative estimate of a
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50% reduction in opioid use compared with a group receiving a smaller intraoperative dose of morphine (50 μg/kg) than in the study by Arain et al. Based on these assumptions, we calculated that a sample size of 26 would have an 80% power of detecting a difference at a 0.05 level of significance.

Data are presented as mean ± SD, numbers, and percentages. The postoperative opioid requirement, time to first analgesic rescue dose, and time to discharge readiness were compared using parametric 1-way analysis of variance (ANOVA) or the nonparametric Kruskal-Wallis test, after testing for normal distribution and equal variance. The numbers of patients who required more than 1 rescue analgesic dose in the PACU were compared by a chi² test. The Ramsay sedation scores and heart rate over time were compared among groups using the 2-way repeated-measures ANOVA. When indicated by a significant F statistic (ANOVA) or H statistic (Kruskal-Wallis) <0.05, specific significant differences were isolated using the Holm-Sidak and Dunn’s methods, respectively. P values <0.05 were considered statistically significant.

RESULTS
One hundred ninety-four patients who qualified for the study were approached and 109 consented to participate, and 85 refused. The 109 patients were randomized after obtaining consent, and all were included in the analysis. All procedures were performed by 1 of 4 otolaryngologic surgeons with an even distribution of cases among the 4. There were no differences among the groups of patients with regard to age, gender, duration of surgery and anesthesia, the time to tracheal extubation, duration of oxygen supplementation in the PACU, and time to discharge readiness (Table 1).

There were no significant differences in the mean amount of supplemental rescue opioid required among the 4 groups (Table 1). However, the median time to first postoperative rescue analgesic was significantly longer in the dexmedetomidine 1 μg/kg and morphine 100 μg/kg groups compared with the dexmedetomidine 0.75 μg/kg and morphine 50 μg/kg groups (P < 0.01) (Fig. 1). In addition, the number of patients requiring >1 rescue analgesic dose was significantly higher in the dexmedetomidine 0.75 μg/kg group compared with the dexmedetomidine 1 μg/kg (χ² = 4.293, P = 0.03) and morphine 100 μg/kg (χ² = 6.231, P = 0.013) groups, but not the morphine 50 μg/kg group (χ² = 0.885, P = 0.347).

There were no significant differences in the postoperative respiratory rate, oxygen saturation, or duration of supplemental oxygen therapy among the 4 groups. Eighty-five percent of the enrolled patients had at least 2 of 3 symptoms of obstruction: gasps while sleeping, snoring, and mouth breathing. None of these children exhibited signs of airway obstruction, prolonged oxygen requirement, or required unanticipated hospital admission after surgery.

There were no differences in the preoperative heart rate among the groups, but 2-way repeated-measures ANOVA revealed a significantly slower postoperative heart rate in patients who received dexmedetomidine compared with patients who received morphine (Fig. 2). These differences were statistically significant at 5, 10, 15, and 30 minutes after arrival in the PACU.

The Ramsay sedation score in the PACU decreased over time in all 4 groups, but there were no significant intergroup differences in sedation in the PACU over time using 2-way repeated-measures ANOVA (Fig. 3). By 60 minutes

Table 1. Demographic Data and Recovery Data in the Four Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine (0.75 μg/kg)</th>
<th>Dexmedetomidine (1 μg/kg)</th>
<th>Morphine (50 μg/kg)</th>
<th>Morphine (100 μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>26</td>
<td>27</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Age (y)</td>
<td>6.3</td>
<td>6.6</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Male/female</td>
<td>8/18</td>
<td>11/16</td>
<td>15/15</td>
<td>10/16</td>
</tr>
<tr>
<td>Duration of surgery (mean ± SD) (min)</td>
<td>22.0 ± 8.4</td>
<td>21.3 ± 9.7</td>
<td>22.8 ± 7.6</td>
<td>25.9 ± 9.5</td>
</tr>
<tr>
<td>Duration of anesthesia (mean ± SD) (min)</td>
<td>48.0 ± 19.3</td>
<td>44.7 ± 10.8</td>
<td>43.3 ± 9.7</td>
<td>49.5 ± 13.3</td>
</tr>
<tr>
<td>Rescue morphine (μg/kg) (mean ± SD)</td>
<td>45.2 ± 30.8</td>
<td>37.0 ± 25.4</td>
<td>43.3 ± 23.6</td>
<td>36.5 ± 31.0</td>
</tr>
<tr>
<td>Morphine rescue doses (n)</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>0 dose</td>
<td>2</td>
<td>14</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>&gt;1 dose</td>
<td>18</td>
<td>10*</td>
<td>16</td>
<td>8*</td>
</tr>
<tr>
<td>Mean duration of oxygen supplementation (min ± SD)</td>
<td>17 ± 11</td>
<td>19 ± 12</td>
<td>20 ± 19</td>
<td>18 ± 14</td>
</tr>
<tr>
<td>Mean time to discharge readiness (min ± SD)</td>
<td>115 ± 0.04</td>
<td>116 ± 0.03</td>
<td>117 ± 0.03</td>
<td>122 ± 0.06</td>
</tr>
<tr>
<td>Emergence agitation, n (%)</td>
<td>5 (19)</td>
<td>4 (15)</td>
<td>4 (13)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>2 (8)</td>
<td>0</td>
<td>0</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

All 4 groups were similar in patient demographics, operative timeline, and postoperative course.

* P < 0.05 versus dexmedetomidine 0.75 μg/kg.
in the PACU, patients in all 4 groups had a mean Ramsay score <4. There were also no differences among the 4 groups in the incidence of emergence agitation.

There were no unanticipated hospital admissions for analgesia, airway management, prolonged supplemental oxygen requirement, or emesis management and no patient required readmission for recurrent tonsillar bed bleeding. Of the 109 patients, 5 had nausea and 2 of these had associated emesis in the PACU, but no patient required admission for this complication.

**DISCUSSION**

This study was designed to determine the postoperative rescue opioid requirement among tonsillectomy and adenoidectomy patients receiving 2 different doses of dexmedetomidine (0.75 or 1 µg/kg) and 2 different doses of morphine (50 or 100 µg/kg). Our primary result demonstrated that there were no significant differences in postoperative morphine requirements among the 4 different treatment groups. We did demonstrate differences in 2 secondary outcomes: time to first analgesia, and number of children requiring >1 dose of morphine in the PACU. The time to first analgesia was longer and the number of children who required >1 dose of morphine in the PACU were decreased in the dexmedetomidine 1.0 µg/kg and morphine 100 µg/kg groups compared with the other groups (dexmedetomidine 0.75 µg/kg and morphine 50 µg/kg).

Dexmedetomidine is a potent α2-agonist with an affinity for α receptors that is 8 times greater than that of clonidine. The primary analgesic effect of dexmedetomidine is mediated via activation of the α2 receptors on the dorsal horn of the spinal cord and also by inhibition of substance P.18 Adult studies have shown that intraoperative use of dexmedetomidine decreases postoperative opioid consumption.1,19 However, this reduction in opioid requirement has been recently shown in only 1 pediatric study in which IV dexmedetomidine was used.20 Reduction in opioid requirement was also noted in 2 studies in which dexmedetomidine was administered in children as a caudal analgesic.21,22 The failure to show a statistically significant difference in the primary outcome in our study is related to the fact that the differences in opioid rescue requirements among the high-dose and low-dose dexmedetomidine and morphine groups was 17%, suggesting that the effect size was much lower than that assumed in the sample size calculation. Post hoc sample size calculations show that >200 patients per group would be required to
show a statistically significant difference between dexmedetomidine 1 μg/kg and morphine 50 μg/kg. The difference in effect size noted in our study may be related to differences in patient population (pediatric versus adult) and/or surgical procedure (adenotonsillectomy versus major inpatient surgery).

Based on the small differences among the postoperative rescue opioid requirements for dexmedetomidine 0.5 μg/kg used in the pilot study, and dexmedetomidine 0.75 and 1 μg/kg used in this study, there may not be a dose response for dexmedetomidine and postoperative analgesic requirements. We did not obtain time-related pain scores or data on oral opioid use after discharge. Therefore, we cannot comment on the possibility that there was a dose-related residual analgesic effect of the intraoperative study drug on the time-related area under the pain curve after discharge.

Previous studies have investigated the use of alternative non-opioid drug regimens for tonsillectomy and adenoidectomy including α-2 agonists.9 These drugs provide adequate analgesia without causing respiratory depression typically associated with opioid therapy. The perioperative use of the α-2 agonist clonidine in pediatric adenotonsillectomy has been associated with findings of increased sedation and conflicting results on its effect on postoperative opioid consumption.23,24 In our study, a single intraoperative dose of dexmedetomidine did not significantly increase sedation in the PACU, the time to tracheal extubation, discharge readiness, duration of supplemental oxygen requirement, or unanticipated hospital admission compared with the morphine groups. Our results suggest that benefits to administration of larger doses of dexmedetomidine for intraoperative analgesia in the studied patient population are limited to the secondary outcomes of a reduced frequency of additional rescue medications and the time to first rescue analgesia.

It is important, however, to note that we studied a relatively healthy patient population and excluded children with documented sleep apnea by polysomnography because we were concerned that the use of a more rigid, fixed dose of morphine or dexmedetomidine required in the study protocol may subject these children to unacceptably greater risks for postoperative respiratory complications. In our institution, the threshold for ordering a polysomnogram varies among surgeons and is usually reserved for those with severe sleep apnea or an uncertain diagnosis of sleep-disordered breathing. Our local institution criteria for considering a diagnosis of sleep-disordered breathing include, but are not limited to, a history of snoring, mouth breathing, and periods of apnea while asleep.25 and 85% of the enrolled patients had at least 2 of these symptoms. None of these children exhibited signs of airway obstruction, prolonged oxygen requirement, or required unanticipated hospital admission after surgery. A recent study suggested airway obstruction was decreased when dexmedetomidine was used for sedation for MRI scans in children with sleep apnea, compared with propofol.26 However, the patients were not randomized in this study. It is also unclear if data from children undergoing nonpainful procedures such as MRI can be applied to the tonsillectomy patient population. An appropriately powered randomized controlled trial comparing dexmedetomidine and the current standard opioid regimen needs to be performed in children with documented sleep apnea by polysomnography to determine whether the incidence of airway obstruction is reduced after tonsillectomy. In the absence of such a study, we would urge caution in the use of dexmedetomidine in children with documented sleep apnea.

Other potential side effects of concern with the use of dexmedetomidine include severe bradycardia.27–29 This was not observed in any patient in our study, although patients who received dexmedetomidine had a slower heart rate over time compared with those who received morphine. We agree that dexmedetomidine should be used cautiously in patients with a critically rate-dependent cardiac output because increased side effects may be observed.31

As reported in 1 study, the benefit of dexmedetomidine administration just before the end of adenotonsillectomy procedures was a decreased incidence of emergence agitation compared with a placebo group.30 In our study, the incidence of postoperative emergence agitation was similar after a single dose of dexmedetomidine or morphine given at induction.

In summary, this prospective, randomized, double-blind study suggests that total postoperative rescue opioid requirements were similar in tonsillectomy patients receiving intraoperative dexmedetomidine or morphine. However, the use of dexmedetomidine 1 μg/kg and morphine 100 μg/kg had the advantages of an increased time to first analgesic and a reduced need for additional rescue analgesia doses in the PACU.

**AUTHOR CONTRIBUTIONS**

OAO helped with study design, conduct of study, data analysis, and manuscript preparation; CDG, DRL, and EMF helped with conduct of study, data analysis, and manuscript preparation; JD and MFW helped with conduct of study, data analysis, and manuscript preparation.

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