Dexmedetomidine as a Rapid Bolus for Treatment and Prophylactic Prevention of Emergence Agitation in Anesthetized Children

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BACKGROUND: Administration of dexmedetomidine (DEX) in the pediatric population for its sedative, analgesic, and anxiolytic properties has been widely reported, despite there being no label indication approved by the U.S. Food and Drug Administration for pediatric patients. Infusions of DEX, rather than bolus administration, are recommended to attenuate the hemodynamic response caused by the α₂-adrenoreceptor agonist. In this prospective, double-blind, randomized study, we examined the effect of rapid IV bolus injection of DEX on emergence agitation and the hemodynamic response in a large sample of children undergoing tonsillectomy with or without adenoidectomy, with or without myringotomy, and/or tympanostomy tube insertion.

METHODS: Four hundred patients, aged 4 to 10 years, undergoing tonsillectomy with or without adenoidectomy, with or without myringotomy, and/or tympanostomy tube insertion, were randomized at a 1:1 ratio into 1 of the 2 treatment groups in a double-blinded fashion. After a standardized anesthetic regimen and approximately 5 minutes before the end of surgery, patients in group DEX were administered a rapid IV bolus of 4 μg·mL⁻¹ DEX at a dose of 0.5 μg·kg⁻¹, whereas patients in group saline received a rapid IV bolus of equivalent volume saline. Baseline measurements of heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, and blood oxygen saturation were collected immediately before study drug administration and every minute thereafter for 5 minutes. In the postanesthesia care unit, vital signs were measured, emergence agitation (EA) was assessed using the Pediatric Anesthesia Emergence Delirium scale, and postoperative opioid use and complications were recorded.

RESULTS: The incidence of EA in group DEX was significantly lower than that in group saline, regardless of whether EA was defined as a Pediatric Anesthesia Emergence Delirium score >10 (36% vs 75%, respectively; P < 0.0001; relative risk [95% confidence interval] = 0.527 [0.421–0.660]; number needed to treat = 3.33) or >12 (30% vs 61%, respectively; P < 0.0001; relative risk [95% confidence interval] = 0.560 [0.458–0.684]; number needed to treat = 3.23). Both groups exhibited similar baseline vital signs before study drug injection (all P ≥ 0.602). After injection, group DEX experienced a significant decrease in heart rate for all time points in comparison with group saline (all P < 0.0001). A significant, biphasic blood pressure response was observed in group DEX, specifically, a transient increase in systolic blood pressure at 1 minute after injection (P < 0.0001) and a subsequent decrease below baseline for 3, 4, and 5 minutes (all P < 0.0001). No patients required treatment for bradycardia, hypertension, or hypotension. A significantly smaller percentage of patients in group DEX received postoperative, supplemental opioid medication compared with group saline (48% vs 73%, respectively; P < 0.0001). Group DEX appeared to experience fewer adverse events than group saline as well (9% vs 17%, respectively; P = 0.025).

CONCLUSIONS: Rapid IV bolus administration of DEX in children improved their recovery profile by reducing the incidence of EA. A statistically significant change in hemodynamics was observed, but no patients required any intervention for hemodynamic changes. Furthermore, DEX reduced the incidence of postoperative opioid administration, and a trend of fewer adverse events was observed in group DEX. (Anesth Analg 2015;121:1308–15)
dose-dependent, biphasic, hemodynamic response caused by peripheral α2-adrenoreceptor stimulation and subsequent central α2-adrenoreceptor-mediated sympatholysis. Although 2-, 5-, or 10-minute DEX infusions reduce the incidence of EA in children, a rapid bolus injection, if proven to be hemodynamically acceptable, would allow a more timely and optimum administration of the drug to both treat and prevent EA.

The present study is a follow-up to our previous observations of rapid bolus injections of DEX reported by Jooste et al. in 12 pediatric heart transplant patients undergoing cardiac catheterization. Despite limited literature on the topic, our institutional collective clinical experience has made a rapid bolus administration of DEX for the treatment and prophylactic prevention of EA as a part of our standard practice. The aims of this prospective, double-blind, randomized study were to profile the hemodynamic consequences of DEX after a rapid bolus injection and evaluate its effectiveness on reducing EA in a large sample of healthy children undergoing tonsillectomy with or without adenoidectomy, with or without myringotomy, and/or tympanostomy tube insertion.

METHODS

Patients and Procedures

An investigator-initiated U.S. FDA Investigational New Drug application (no. 113263) was approved before initiating the study. Serving as a Principal Investigator, Peter Davis, MD, registered the study with ClinicalTrials.gov (registration no. NCT01528891) on February 6, 2012, before patient enrollment. After approval from the University of Pittsburgh IRB and parental written informed consent and child assent (where applicable) were obtained, 418 ASA physical status class I, II, or III patients aged 4 to 10 years were enrolled in this prospective, randomized, double-blind study. Of the 418 patients enrolled, 400 were randomized and 18 failed screening (the Appendix lists screen failures). Inclusion criteria required patients to be free of any bleeding disorder, dysrhythmia, developmental delay, or communication disorder. Any patients scheduled for postoperative admission to the intensive care unit were not eligible for the study because of the high likelihood for needing postoperative ventilation. All patients were scheduled to undergo tonsillectomy with or without adenoidectomy, with or without myringotomy, and/or tympanostomy tube insertion. All procedures were performed at either the Children’s Hospital of Pittsburgh of University of Pittsburgh Medical Center main campus or the Children’s Hospital of Pittsburgh of University of Pittsburgh Medical Center surgery center. Surgical and anesthesia faculty and staff are the same for both sites. We used a computer-generated randomization code. The patients were allocated into 1 of the 2 groups at a 1:1 ratio, and group allocation was concealed from the patients.

No patients received preoperative anxiolytic medication. A standardized anesthetic regimen and monitors were used, beginning with an inhaled induction with a mixture of nitrous oxide, sevoflurane, and oxygen. Anesthesia was maintained with a mixture of sevoflurane, oxygen, and air (FIO2 < 0.30). Volatile anesthetic flow rates varied at the discretion of the attending anesthesiologist. Endotracheal intubation was facilitated with IV propofol (2 mg·kg⁻¹·

Dexamethasone and morphine were also administered IV before the start of surgery at dosages of 0.5 and 0.1 mg·kg⁻¹, respectively. Near the end of surgery, IV ondansetron was administered at a dose of 0.1 mg·kg⁻¹ with a maximum total dose of 4 mg. Intraoperative increases in heart rate (HR) and/or arterial blood pressure were treated with increases in the inspired inhaled anesthetic agent. Patients were kept spontaneously breathing after intubation. Approximately 5 minutes before the completion of surgery, group DEX received a rapid bolus injection of 4 μg·mL⁻¹ DEX at a dose of 0.5 μg·kg⁻¹ over 2 to 3 seconds in a free-flowing IV, whereas patients in group saline received saline in an equal volume over 2 to 3 seconds. Both DEX and saline solutions were prepared by the hospital pharmacists, and all caretakers were blinded to the study drug.

At the surgeon’s discretion, either coblation or electrocautery was used for either the tonsil or the adenoid portion of the procedure. HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), and blood oxygen saturation (Sao2) were recorded immediately before the study drug injection (baseline) and every minute for 5 minutes thereafter. After the oral pharynx and stomach were suctioned and with the patient breathing spontaneously, patients were extubated tracheally in a deep plane of anesthesia and transported to the postanesthesia care unit (PACU). Vitals were recorded again upon arrival in the PACU. The threshold values for the lower limits of HR and arterial blood pressure for age were taken from the article by Kraemer et al.

EA was assessed by the study staff upon arrival in the PACU using the Pediatric Anesthesia Emergence Delirium (PAED) scale (0–20 scale). PAED assessments were recorded every 5 minutes for 30 minutes. Because of differences in the literature, 2 different cut points were used in our current study. Patients with maximum PAED scores of >10 or >12 were thought to have been diagnosed as having EA. Patients who were considered to be in pain or agitated by either the PACU nurse or the anesthesia attending were treated with a 0.5 μg·kg⁻¹ fentanyl dose. If the patient continued to show signs of pain or agitation after 3 fentanyl doses, further treatment, including an open-label dose of DEX, could be administered at the discretion of the attending anesthesiologist. The total amount of fentanyl administered, number of fentanyl doses, and number of patients dosed with open-label DEX were recorded. Time in the phase 1 unit of the PACU was recorded from the time of entry until patients met PACU phase 1 discharge criteria (stable vital signs, pain well-controlled, patient awake or easily aroused, and an Aldrete score of 8 or 9).

Statistical Analysis

Sample size was determined using a reported incidence of EA of 40% in the placebo group and 20% in the DEX group. The 40% incidence stems from our clinical observations and is within reported ranges; a target reduction of 50% informs the 20% incidence given for the DEX group. Given an α of 0.05, a sample of 92 patients per group would yield a study power of 0.8. Sample size was increased to 400 total patients...
to better assess the hemodynamic changes after rapid bolus injection of DEX.

Statistical analysis was performed using IBM® SPSS® Statistics 21.0 (IBM Corporation, Armonk, NY). Hemodynamic changes were analyzed between groups using the t test and over time using a 2-way analysis of variance of repeated measures. Parametric data were analyzed using the t test, and nonparametric data were analyzed using the Mann–Whitney U test. The Fisher exact test was used to analyze proportions. A P value <0.01 was considered statistically significant. Relative risk and the number needed to treat were calculated with regard to the incidence of EA, as were 95% confidence intervals using the Clopper–Pearson method.

RESULTS

Of the 400 children randomized, 7 were excluded from analysis. Preoperative midazolam was administered to 5 of these 7; 1 patient did not receive any propofol for intubation at the discretion of the attending anesthesiologist; and 1 patient was administered glycopyrrolate before study drug injection. Of the remaining 393 patients, 195 and 198 were placed in groups DEX and saline, respectively. As shown in Table 1, age, weight, sex, and hospital location (main hospital or surgery center) did not significantly differ between the groups (all P ≥ 0.04). All 393 patients were included in the hemodynamic data analysis. Of the 393 patients, 11 were excluded from analysis of postoperative outcomes (PAED scores, PACU length of stay, and opioid administration). Nine of the 11 patients received additional propofol (>3.5 mg·kg⁻¹) to manage adverse events after the study drug was injected. Of the remaining 382 patients, 192 received the study drug. The incidence of EA was significantly lower in group DEX, compared with group saline (0.5%; P = 0.005 and 0.602). Open-label DEX was administered to 7 patients in the PACU for prolonged pain/ agitation. Of these 7 patients, 2 were in group DEX and 5 were in group saline. Because of extreme agitation and at the discretion of the attending anesthesiologist, 2 of these patients were administered open-label DEX after only 2 doses of fentanyl in the PACU.

Emergence Agitation

The incidence of EA was significantly lower in group DEX, regardless of whether the >10 or >12 threshold was used for the maximum PAED score (Table 2). Using a threshold of >10, the incidences of EA in groups DEX and saline were 36% and 66%, respectively (P < 0.0001; relative risk [95% confidence interval] = 0.527 [0.421–0.660]; number needed to treat = 3.33). Using a threshold of >12, the incidences of EA in groups DEX and saline were 30% and 61%, respectively (P < 0.0001; relative risk [95% confidence interval] = 0.560 [0.458–0.684]; number needed to treat = 3.23). Open-label DEX was administered to 7 patients in the PACU for prolonged pain/agitation. Of these 7 patients, 2 were in group DEX and 5 were in group saline. Because of extreme agitation and at the discretion of the attending anesthesiologist, 2 of these patients were administered open-label DEX after only 2 doses of fentanyl in the PACU.

Hemodynamics

The hemodynamic data are presented in Table 3. At baseline before study drug administration, both groups displayed similar values in HR, SBP, DBP, RR, and Sao2 (all P ≥ 0.602). After study drug injection, group DEX experienced a significant (all P < 0.0001) decrease in HR for all time points compared with group saline. Nine of the patients in group DEX (4.6%) had at least 1 HR measurement below the age-specific threshold for bradycardia compared with 1 patient in group saline (0.5%; P = 0.0103). None of the patients required treatment for bradycardia.

One minute after injection of the study drug, group DEX had significantly elevated SBP and DBP compared with group saline (P = 0.005 and P < 0.0001, respectively). Two minutes after injection, neither SBP nor DBP differed between groups DEX and saline (P = 0.819 and P = 0.312, respectively). Three minutes after injection, SBP and DBP did not statistically differ between groups (P = 0.041 and P = 0.187, respectively), but SBP and DBP in the DEX group were significantly lower than baseline values (P < 0.0001 and P = 0.0017, respectively). For all remaining time points, SBP was significantly lower in group DEX (all P ≤ 0.0035), but DBP was significantly lower only for the PACU vitals measurement (P < 0.0001). After injection of study drug, group DEX had 11 patients (5.8%) and group saline had 7 patients (3.6%; P = 0.344) with at least one SBP measurement below the age-specific threshold for hypotension, none of which required treatment. Four patients in group DEX and 3 patients in group saline had baseline SBP measurements that were below the age-specific threshold for hypotension. In these 4 patients in group DEX, SBP measurements after study drug injection did not decrease further from the baseline value, and all 4 patients had a normal SBP in the PACU (Table 4).

One patient in group DEX had sustained bradycardia from minutes 1 through 5 (range, 58–64 bpm). The patient had 100% Sao2 and a good pulse by palpation, but no arterial blood pressure recordings were obtained for the first 5 minutes after injection because of a mechanical problem with the blood pressure cuff. Upon arrival in the PACU, this patient had a normal blood pressure of 114/71 mm Hg and an HR of 64. For all time points, RR did not significantly differ between the 2 groups (all P ≥ 0.257) nor did Sao2 (all P ≥ 0.048).

Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Group DEX (n = 195)</th>
<th>Group saline (n = 198)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>6.1 ± 1.6</td>
<td>5.8 ± 1.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.9 ± 7.4</td>
<td>23.9 ± 7.5</td>
<td>0.097</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>99:96</td>
<td>101:97</td>
<td>1.00</td>
</tr>
<tr>
<td>Hospital main campus (n)</td>
<td>115</td>
<td>116</td>
<td>1.00</td>
</tr>
<tr>
<td>Outpatient surgery center (n)</td>
<td>80</td>
<td>82</td>
<td></td>
</tr>
</tbody>
</table>

Data represented as a mean ± SD. Statistical significance defined as P < 0.01.

DEX = dexmedetomidine; M = male; F = female.

Table 2. Incidence of Emergence Agitation

<table>
<thead>
<tr>
<th></th>
<th>Group DEX (n = 193)</th>
<th>Group saline (n = 189)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAED &gt;10</td>
<td>n = 69</td>
<td>Incidence (%) 36</td>
<td></td>
</tr>
<tr>
<td>PAED &gt;12</td>
<td>n = 58</td>
<td>Incidence (%) 30</td>
<td></td>
</tr>
<tr>
<td>PAED &gt;12</td>
<td>125</td>
<td>66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PAED &gt;12</td>
<td>115</td>
<td>61</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PAED = Pediatric Anesthesia Emergence Delirium score; DEX = dexmedetomidine.
For patients studied at the main hospital, length of stay in PACU phase 1 did not significantly differ between the 2 groups ($P = 0.861$). For patients studied at the surgical satellite facility, patients in group DEX had a significantly longer length of stay in PACU phase 1 (39.0 ± 13.3 vs 29.8 ± 15.0 minutes in group saline; $P < 0.0001$; Table 5). A significantly larger proportion of patients in group saline (73% vs 48% in group DEX; $P < 0.0001$; Table 5) received supplemental opioid medication.

### Adverse Events

A trend was observed in group DEX patients, wherein they seemed to experience fewer adverse events than patients in group saline (9% vs 17%, respectively; $P = 0.025$). All adverse events occurred after the study drug injection and are listed in Table 6. One patient in group DEX experienced a serious adverse event (desaturation and atelectasis associated with a prolonged hospital stay), which the investigators felt was unrelated to the study drug.

### DISCUSSION

In this prospective, double-blind, randomized study of children undergoing elective tonsillectomy with or without adenoidectomy, with or without myringotomy, and/or tube insertion, we noted that a rapid (2- to 3-second) bolus injection of DEX administered 5 minutes before the end of surgery significantly reduced the incidence of EA without causing hemodynamic instability or delaying PACU phase 1 length of stay at the main hospital. In addition, patients receiving DEX received less postoperative, supplemental opioids, and they appeared to have fewer postoperative adverse events.

### Table 3. Hemodynamic Changes

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>Baseline</th>
<th>1 min</th>
<th>2 min</th>
<th>3 min</th>
<th>4 min</th>
<th>5 min</th>
<th>PACU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group DEX ($n = 195$)</td>
<td>120 ± 16</td>
<td>107 ± 18</td>
<td>104 ± 16</td>
<td>105 ± 14</td>
<td>105 ± 15</td>
<td>105 ± 15</td>
<td>94 ± 13</td>
</tr>
<tr>
<td>Significance</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
</tr>
<tr>
<td>Group saline ($n = 198$)</td>
<td>121 ± 16</td>
<td>121 ± 16</td>
<td>120 ± 15</td>
<td>119 ± 15</td>
<td>118 ± 15</td>
<td>117 ± 15</td>
<td>108 ± 16</td>
</tr>
<tr>
<td>Significance</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>Group DEX ($n = 194$)</td>
<td>99 ± 16</td>
<td>104 ± 16</td>
<td>99 ± 14</td>
<td>95 ± 13</td>
<td>93 ± 13</td>
<td>92 ± 13</td>
</tr>
<tr>
<td>Significance</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
</tr>
<tr>
<td>Group saline ($n = 197$)</td>
<td>99 ± 16</td>
<td>100 ± 15</td>
<td>99 ± 14</td>
<td>98 ± 14</td>
<td>97 ± 15</td>
<td>96 ± 15</td>
<td>105 ± 17</td>
</tr>
<tr>
<td>Significance</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
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<td>*†</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>Group DEX ($n = 194$)</td>
<td>47 ± 9</td>
<td>52 ± 10</td>
<td>48 ± 9</td>
<td>45 ± 8</td>
<td>44 ± 8</td>
<td>43 ± 8</td>
</tr>
<tr>
<td>Significance</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
</tr>
<tr>
<td>Group saline ($n = 196$)</td>
<td>47 ± 9</td>
<td>47 ± 9</td>
<td>47 ± 8</td>
<td>46 ± 8</td>
<td>45 ± 9</td>
<td>45 ± 8</td>
<td>55 ± 11</td>
</tr>
<tr>
<td>Significance</td>
<td>*†</td>
<td>*†</td>
<td>*†</td>
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<td>*†</td>
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</tr>
</tbody>
</table>

Data are represented as a mean ± SD. HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; PACU = postanesthesia care unit; DF ($F$-)statistic; DEX = dexmedetomidine.

* Epsilon is estimated to be <0.75 so degrees of freedom are corrected according to the Greenhouse–Geisser method with $P < 0.0001$.

b Three subjects with missing data points for SBP and/or DBP are necessarily eliminated from repeated measures analysis.

* Statistically significant difference between groups; $P < 0.01$.

† Statistically significant difference from baseline; $P < 0.01$.

### Table 4. Systolic Blood Pressure Data for 7 Patients with Measurements Below the Age-Related Threshold for Hypotension at Baseline

<table>
<thead>
<tr>
<th>Time point</th>
<th>Baseline</th>
<th>1 min</th>
<th>2 min</th>
<th>3 min</th>
<th>4 min</th>
<th>5 min</th>
<th>PACU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group DEX ($n = 195$)</td>
<td>61*</td>
<td>76</td>
<td>106</td>
<td>95</td>
<td>83</td>
<td>80</td>
<td>97</td>
</tr>
<tr>
<td>Group saline ($n = 198$)</td>
<td>63*</td>
<td>68</td>
<td>74</td>
<td>75</td>
<td>79</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>Group DEX ($n = 194$)</td>
<td>62*</td>
<td>73</td>
<td>93</td>
<td>92</td>
<td>87</td>
<td>72*</td>
<td>87</td>
</tr>
<tr>
<td>Group saline ($n = 197$)</td>
<td>49*</td>
<td>48</td>
<td>54*</td>
<td>59*</td>
<td>61*</td>
<td>68*</td>
<td>87</td>
</tr>
</tbody>
</table>

PACU = postanesthesia care unit; DEX = dexmedetomidine.

* Measurement is below the age-related threshold for hypotension.

### Table 5. Postoperative Outcomes

<table>
<thead>
<tr>
<th>Postoperative Outcomes</th>
<th>Group DEX ($n = 193$)</th>
<th>Group saline ($n = 189$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU length of stay at main hospital (min)</td>
<td>75.8 ± 31.1</td>
<td>73.4 ± 24.9</td>
<td>0.861</td>
</tr>
<tr>
<td>PACU length of stay at surgery center (min)</td>
<td>39.0 ± 13.3</td>
<td>29.8 ± 15.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients receiving postoperative fentanyl (%)</td>
<td>48</td>
<td>73</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data represented as a mean ± SD. PACU = postanesthesia care unit; DEX = dexmedetomidine.

## Postoperative

For patients studied at the main hospital, length of stay in PACU phase 1 did not significantly differ between the 2 groups ($P = 0.861$). For patients studied at the surgical satellite facility, patients in group DEX had a significantly longer length of stay in PACU phase 1 (39.0 ± 13.3 vs 29.8 ± 15.0 minutes in group saline; $P < 0.0001$; Table 5). A significantly larger proportion of patients in group saline (73% vs 48% in group DEX; $P < 0.0001$; Table 5) received supplemental opioid medication.
DEX is a highly selective \( \alpha_2 \)-adrenoreceptor agonist FDA-approved for surgical or medical procedures in adults. DEX is not FDA-approved for use in children; however, off-label use of DEX in children is common, as is the off-label use of a large number of other drugs used in pediatric anesthesia.\(^{2,4,21}\) In pediatrics, off-label use of DEX has been administered in settings to provide procedural sedation and pediatric intensive care unit sedation, as well as to treat pediatric cardiac patients with junctional ectopic tachycardia, to decrease intraoperative anesthetic requirements of opioids and inhaled agents, and to attenuate the incidence of postoperative EA.\(^{3,4}\)

The hemodynamics of DEX have been well characterized in both adults and children after bolus doses infused over 10 minutes or with continuous infusions of DEX.\(^{12-15}\) The hemodynamic effects of DEX are related to the rate of infusion and dose. Petroz et al.\(^{11}\) reported that SBP decreases approximately 25% from baseline and HR decreases approximately 15% from baseline at doses of 0.66 and 1 \( \mu \text{g} \cdot \text{kg}^{-1} \) infused over a period of 10 minutes. In patients administered 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \) of DEX who were anesthetized with 1 minimum alveolar concentration of sevoflurane, SBP decreased by 10%.\(^{14}\) Larger doses of DEX are associated with a greater degree of hypotension, as well as with transient increases in blood pressure.\(^{11,14}\)

Because of concerns of bradycardia and transient hypertension followed by hypotension, the package insert recommends that a bolus dose be administered over 10 minutes.\(^{5}\)

At present, little information is available regarding the hemodynamic profile in children after a rapid bolus injection of DEX.\(^{21,26}\) In the present study, a rapid bolus of 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \) of DEX decreased HR by 22% compared with 10% in the control group. These hemodynamic changes seem similar to the 15% decrease in HR reported by Petroz et al.\(^{11}\) Mason et al.\(^{27}\) reported that the bradycardia associated with a DEX infusion seems to be inversely related to dose. Coadministration of ketamine with DEX seems to prevent the decrease in HR, whereas treatment of bradycardia with IV glycopyrrolate has resulted in an exaggerated hypertensive response.\(^{24,25}\) In dogs, administration of intraocular atropine with intramuscular DEX reversed HR changes and hypotension, but arrhythmias (atrioventricular block, premature ventricular contractions, and bigeminy) were observed.\(^{28}\) Nine patients in group DEX and 1 patient in group saline had HR measurements below the lower limit of age for all. None of the patients with bradycardia had associated hypotension or hemodynamic instability.

As reported previously, bolus DEX infusions result in a biphasic arterial blood pressure response (transient initial increase followed by a decrease).\(^{21}\) SBP initially increased in the first minute and then decreased by 8% in group DEX compared with 4% in group saline. Arterial blood pressure decreased below the lower limit for age in 11 patients in group DEX compared with 7 patients in group saline. Six patients in group DEX and 2 patients in group saline experienced either an HR or a SBP decrease >10% below the lower limit for age (range, 11-27%)

Over the past 8 years, our institutional practice has evolved into administering DEX as a rapid IV bolus for both the treatment and the prophylaxis of EA. Our initial studies investigated a rapid IV bolus of DEX in children undergoing routine surveillance cardiac catheterization with endomyocardial biopsies after heart transplantation. In this study, of the 6 patients who received 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \) of a rapid bolus injection of DEX, Jooste et al.\(^{21}\) noted that within 1 minute after injection, SBP, DBP, systolic pulmonary artery pressure, diastolic pulmonary artery pressure, pulmonary artery wedge pressure, and systemic vascular resistance had all increased but returned to baseline by 5 minutes after injection. Only HR decreased after injection and remained below the baseline measurement after 5 minutes (the last recorded time point of the study). Cardiac output, central venous pressure, and pulmonary vascular resistance did not change significantly. The noninvasive hemodynamic data of the healthy children in the present study were similar to that of the denervated cardiac transplant patients reported by Jooste et al.\(^{21}\)

We recognize that the cost of DEX may be a concern. Consequently, because of its frequent use in our operating rooms, we have collaborated with our operating room pharmacy to reduce the cost of DEX per patient. Currently, the operating room pharmacy sterilely prepares 10-mL syringes of DEX in 4 \( \mu \text{g} \cdot \text{mL}^{-1} \) solutions. This has significantly reduced the cost and waste of DEX.

EA is common following inhaled anesthesia in children. Although EA is generally self-limited, it can nonetheless result in patient and/or provider injury, increase hospital length of stay, and increase utilization of PACU.
resources. The incidence of EA in patients anesthetized with sevoflurane ranges from 10% to 80%. Patient temperament, postoperative pain, anesthetic agents, and the use of different EA scoring systems can account for the large variability in the reported incidence of EA. A number of anesthetic adjuncts (opioids, midazolam, propofol, and clonidine) have been used to successfully attenuate the incidence. The sedative properties of DEX coupled with its anesthetic-sparing and analgesic effects make it a logical agent for prophylaxis and treatment of EA. Both randomized control studies and meta-analyses support the use of DEX as an effective agent for EA. Dose–response studies suggest an effective dose range between 0.3 and 1.0 μg·kg⁻¹. However, infusing the drug over 10 minutes makes DEX impractical for treating children with EA.

One of the major issues regarding EA is the definition of what constitutes EA and how to quantitate it. Having an objective and validated scoring system to quantitate EA is critical. A number of scales have been used to assess EA, but only the 20-point PAED scale by Sikich and Lerman has been validated. Although there is no consensus as to what score constitutes EA on this 20-point scale, studies have cited scores of 10 and 12. Sikich and Lerman showed a sensitivity of 0.64 and a specificity of 0.86 with a high (0.84) interobserver reliability using a threshold of 10, whereas Bajwa et al. stated that a PAED threshold of 12 provides a sensitivity of 100% and a specificity of 94.5%, using the evaluation of an expert anesthesiologist as the gold standard. Regardless of a threshold EA score of 10 or 12, our results agree with those of other published studies on the effectiveness of DEX in reducing EA.

Prophylactic prevention of EA and less frequent opioid administration can reduce strain on PACU resources. This benefit may be blunted, if, in doing so, a rapid bolus injection of DEX delays discharge from PACU phase 1. Although the results of this study show no significant difference between the 2 groups for PACU length of stay at the main hospital, DEX does seem to prolong the length of stay for patients at the surgical satellite. A number of factors may account for this discrepancy, including different patient populations, variable PACU resources, and different patient dispositions after phase 1 discharge between the 2 groups. The results warrant further investigation.

The fact that DEX (0.5 μg·kg⁻¹) can be administered as a rapid bolus to children, coupled with it being hemodynamically well-tolerated and allowing a decrease in postoperative opioid administration, offers possible advantages in both the prophylaxis and the treatment of EA in children. Of particular interest is the trend of patients treated with DEX having fewer postoperative adverse events than patients in the saline group. Postoperative/emergence complications are not uncommon for children undergoing tonsillectomy. These children frequently have obstructed airways and underlying obstructive sleep apnea. Thus, the administration of DEX, in conjunction with less opioid medication, to a group of patients susceptible to airway complications may have other beneficial effects on recovery and quality of care. In summary, this prospective, double-blind, randomized study of 400 children demonstrated the utility and efficacy of a rapid bolus (0.5 μg·kg⁻¹) administration of DEX on reducing EA without causing hemodynamic instability. Its possible beneficial role in reducing adverse outcomes will need further investigation.

**APPENDIX**

Of the 418 patients enrolled, 400 were randomized and 18 failed screening. After obtaining consent, various scenarios necessitated subject withdrawal from the study:

- 4 subjects: After further review by the attending anesthesiologist responsible for the patient’s care, they were uncomfortable with the subject participating in the study because they felt the dose of morphine was high in view of the patient’s history of obstructive sleep apnea.
- 3 subjects: It became evident that the subject required preoperative anxiolytic midazolam.
- 1 subject: The subject’s parents changed their mind and withdrew consent.
- 1 subject: New information came to light, which met exclusion criteria.
- 8 subjects: Intraoperative complications before study drug administration for which the investigator decided not to proceed with the study (laryngospasms, bleeding, and heart arrhythmias).
- 1 subject: Surgery was cancelled for a nil per os violation.

**DISCLOSURES**

**Name:** John A. Hauber, BS.

**Contribution:** This author helped conduct the study, collect the data, analyze the data, and prepare the manuscript.

**Attestation:** John A. Hauber approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.

**Conflicts of Interest:** None.

**Name:** Peter J. Davis, MD.

**Contribution:** This author helped design the study, conduct the study, collect the data, analyze the data, and prepare the manuscript.

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**Contribution:** This author helped conduct the study.

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