Intensive Care Med (2011) 37:686–690
DOI 10.1007/s00134-011-2140-5

PEDIATRIC ORIGINAL

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Impact of dexmedetomidine on early extubation in pediatric cardiac surgical patients

Received: 27 August 2010
Accepted: 13 January 2011
Published online: 10 February 2011

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-011-2140-5) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* To evaluate the impact of dexmedetomidine on early extubation in post-operative pediatric cardiac patients compared to patients on standard sedation regimens without dexmedetomidine. *Methods:* Retrospective study comparing dexmedetomidine infusion (DEX) to our standard sedation regimens (control). *Results:* A total of 269 patients were included (control: $n = 180$; DEX: $n = 89$). The mean duration of DEX was 34 ± 2 h. Extubation was achieved in the operating room in 42% of the control group and 42% of the DEX group. Extubation within 24 h of surgery was achieved in 75% of the control group and 76% of the DEX group. Ventilator time in the DEX group was 35 ± 29 h compared to 29 ± 35 h in the control group. The mean cardiovascular intensive care unit (CV ICU) and hospital length of stays were 3 ± 2 and 8 ± 4 days in the DEX group and 3 ± 3 and 8 ± 5 days in the control group. Reintubation rates in the CV ICU were not significantly different. DEX patients received significantly less total intraoperative fentanyl and midazolam but significantly more midazolam rescue doses than the control group in the postoperative period. Post-extubation ventilation was clinically similar in the DEX group as measured by 1 h post-extubation $PaCO_2$ levels. *Conclusions:* Dexmedetomidine did not significantly impact the postoperative course of children compared to standard practice as measured by success of early extubation, ventilator time, and length of stay.

Keywords Dexmedetomidine · Pediatric · Cardiac surgery · Sedation · Mechanical ventilation · Anesthesia

Introduction

Mechanically ventilated patients in the intensive care unit frequently require sedative and analgesic medications. Commonly used agents, such as benzodiazepines, barbiturates, and opioids, depress the respiratory system, thus presenting a challenge when early extubation is desired post-cardiac surgery. One strategy that may allow for early extubation is the use of an agent that provides adequate sedation without respiratory depression as an alternative to standard sedation regimens.

Dexmedetomidine, a selective alpha-2-adrenergic receptor agonist, possesses sedative, anxiolytic, and mild analgesic effects without significant respiratory depression [1, 2]. Dexmedetomidine has been used as an alternative sedative agent following pediatric cardiac surgery [3, 4]. The purpose of this study is to examine the suggested efficacy of dexmedetomidine infusion (DEX) prior to extubation attempts to facilitate quick weaning from mechanical ventilation and ultimately decrease ventilator time and length of stay following pediatric cardiac surgery [5, 6].

Methods

This retrospective case cohort study was approved by the Institutional Review Board of Baylor College of Medicine/Texas Children's Hospital, and waiver of consent was granted due to the retrospective nature of the study. The pharmacy and fiscal databases were queried, along with review of anesthesia and cardiovascular intensive care unit (CV ICU) records to gather pertinent data. Patients that received continuous DEX (DEX group) in the cardiovascular operating room (CV OR) or CV ICU following pediatric cardiac surgery from January 2007 to May 2008 were identified as cases. A control group was identified, consisting of patients with similar age, diagnosis, and surgical indication admitted to the CV ICU after cardiac surgery in 2006, the year prior to the addition of dexmedetomidine to the hospital formulary. Patients were excluded if they had significant co-morbidities (resulting in extended ventilation or length of stays unrelated to the perioperative management strategy) or were admitted and ventilated for more than 48 h prior to surgery.

The following data were collected: demographics (age, primary diagnosis, surgical intervention, cardiopulmonary bypass time), mechanical ventilation information [extubation in the CV OR or CV ICU, reintubation, and arterial blood gases (pH and pCO_2) 1 h after extubation], length of CV ICU and hospital stays, and sedative and analgesic regimens in the CV OR and CV ICU. The primary end points for evaluating efficacy of dexmedetomidine were incidence of early extubation [in the operating room (EOR) or the first 24 h postoperatively], and total time on the ventilator calculated from the time of CV ICU admission to extubation. Secondary end points included CV ICU and hospital length of stays, incidence of reintubation, intra- and post-operative analgesic and sedative requirements, and post-extubation pH and pCO_2 blood gas values.

Continuous infusion of dexmedetomidine at our institution is often initiated in the immediate post-operative period in the surgical suite to decrease post-operative opioid requirements in patients who are anticipated to be extubated within the first 24 h after surgery. The infusion is often discontinued within 1 h of extubation from mechanical ventilation. Dexmedetomidine use was discouraged in patients with renal or hepatic dysfunction, heart block, hypotension, or ventricular dysfunction requiring concomitant use of multiple inotropes, vasopressors, or beta-blockers. DEX was started at 0.3–0.7 μg/kg/h and supplemented with pain and sedative medications.

The overall strategy for pain and sedation at our institution consists of either continuous infusion morphine (starting dose of 0.1 mg/kg/h) or continuous infusion fentanyl (starting at 1 μg/kg/h) supplemented with midazolam or lorazepam for those patients not expected to be extubated in the immediate post-operative period. In patients that are extubated in the immediate post-operative period, bolus morphine (0.1 mg/kg/dose), bolus fentanyl (1 μg/kg/dose), and bolus midazolam or lorazepam (both 0.1 mg/kg/dose) are used for control of pain and management of sedation.

All patients were weaned off mechanical ventilation per institutional protocol based on the patient's pathophysiology and surgical intervention (Fig. 1, ESM). Patients on the protocol were assessed every 1–2 h. The decision for extubation readiness is based on several observations including hemodynamic stability, an alert and awake patient, $ETCO_2$, SpO_2, and stable ventilation and oxygenation on delta *P*: (peak inspiratory pressure − peak end-expiratory pressure) <10 cm H_2O. Patients identified for extubation typically have normal lung function and hemodynamics, and a trial of 8 mL/kg tidal volume has usually led to successful extubations. A 20% change in time on the ventilator between groups was chosen a priori as a clinically significant end point. A sample size of approximately 50 subjects in each group was calculated to detect a statistically significant difference (alpha 0.05, power 80%). Data were analyzed for statistical significance using Student's *t* test, Wilcoxon rank sum test, ANOVA, and chi-square analysis. All data analysis was performed with Stata IC v.10 (StataCorp, College Station, TX, USA).

Results

Demographics

A total of 269 patients were included in our analysis: 180 patients in the control group (control) and 89 patients in the dexmedetomidine group (DEX). Forty-nine patients (21%) from the control group and 17 patients (16%) from the DEX group were excluded due to co-morbidities or prolonged ventilation prior to surgery. There was no statistical significance in baseline demographics (median age, surgical indication, cardiopulmonary bypass time) between the two groups (Table 1). Both groups were similar in acuity as measured by cardiopulmonary bypass time (DEX: 114 min, control: 120 min; $P = 0.57$). Patients less than 1 year old comprised 46% (83/180) of patients in the control group and 48% (43/89) in the DEX group. The average duration of DEX was 34 ± 2 h. There was no difference between the control and DEX groups in total CV ICU length of stay (3 ± 3 vs. 3 ± 2 days) and hospital length of stay (8 ± 5 vs. 8 ± 4 days).

Sedation/analgesia regimen

In the operating room, all patients received a balanced anesthetic using a combination of opioids, benzodiazepines,

Table 1 Demographics

	Control ($n = 180$)	DEX ($n = 89$)	P value
Median age [months] (range)	14.7 (1–265)	13.7 (3–215)	0.62
Median CPB duration [min] (range)	120 (33–406)	114 (14–402)	0.57
Surgical indications			
Aortic stenosis repair	35 (19%)	18 (20%)	0.87
CAVC repair	31 (17%)	13 (15%)	0.72
Bidirectional Glenn	24 (13%)	14 (16%)	0.58
TOF repair with ventriculotomy	22 (12%)	7 (8%)	0.30
Rastelli/RV-PA conduit replacement	20 (11%)	5 (6%)	0.18
RVOT procedure	18 (10%)	8 (9%)	1.0
VSD repair	10 (6%)	5 (6%)	1.0
TOF repair without ventriculotomy	9 (5%)	4 (5%)	1.0
Fontan	7 (4%)	7 (8%)	0.24
ASD repair	4 (2%)	8 (9%)	0.02

ASD Atrial septal defect, *CAVC* complete atrioventricular canal, *CPB* cardiopulmonary bypass, *DEX* dexmedetomidine, *RV-PA* right ventricle to pulmonary artery, *RVOT* right ventricular outflow tract repair, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect

Table 2 Analgesic/sedative regimens and rescue agents in the CV OR

Category	Control	DEX	P value
Fentanyl bolus (μg/kg)	65 ± 75	25 ± 24	<0.01
Morphine bolus (mg/kg)	0.2 ± 0.2	0.1 ± 0.1	0.32
Midazolam bolus (mg/kg)	0.6 ± 0.5	0.2 ± 0.2	<0.01
Propofol (mg/kg)	5 ± 9	2 ± 0.5	0.48

and inhalational agents (isoflurane at 0.5–1 MAC) (Table 2). Overall, fentanyl, morphine, and midazolam were the most frequently administered bolus doses in both groups. The control group received a significantly higher total dose of fentanyl and midazolam than the DEX group intraoperatively. There was no difference in intraoperative morphine or propofol doses between the two groups (Table 2). Dexmedetomidine was rarely used as a single analgesic agent, and most patients required a morphine infusion (26.9%) and/or scheduled morphine bolus doses (52.8%) post-operatively. In addition, the DEX group required more midazolam infusions and rescue doses per CV ICU day than the control group (Table 3).

Ventilatory outcomes

Extubation in the operating room (DEX: 37/89, 42%; control: 75/180, 42%; $P = 1.0$) or in the first 24 h post-operatively (DEX: 31/52, 60%, control: 60/105, 57%; $P = 0.88$) were similar between the two groups. Patients in the control group had a similar duration of mechanical ventilation in the CV ICU as the dexmedetomidine group (35 ± 29 vs. 29 ± 35 h; $P = 0.17$). In both groups, patients older than 24 months had the shortest ventilator time followed by patients who were 12–24 months (Table 4). Upon extubation, patients in the DEX group had clinically similar but statistically higher pH (arterial: 7.38 ± 0.05 vs. 7.35 ± 0.06, $P \leq 0.05$) and lower $PaCO_2$ (43.2 ± 5.4 vs. 45.2 ± 6.9 mmHg, $P \leq 0.05$) than the control group. Reintubation was required in two patients (2.2%) in the control and two patients (1.1%) in the DEX group ($P = 0.60$).

Table 3 Analgesic/sedative regimens and rescue agents in the CV ICU

	Control ($n = 180$)	DEX ($n = 89$)	P value
Cohort (%)			
Midazolam infusion (0.1 mg/kg/h)	0.5%	9%	<0.05
Fentanyl infusion (1 μg/kg/h)	9%	8%	1.0
Morphine infusion (0.1 mg/kg/h)	3%	27%	<0.05
Scheduled morphine bolus	77%	53%	<0.05
Rescue doses per ICU day			
Fentanyl (1 μg/kg)	0.3 ± 1	0.2 ± 0.8	0.25
Morphine (0.1 mg/kg)	4 ± 3	4 ± 3	0.99
Lorazepam (0.1 mg/kg)	1 ± 2	1 ± 2	0.33
Midazolam (0.1 mg/kg)	0.5 ± 1	1 ± 1	<0.05

Table 4 Extubation rates and ventilator time

Category	Control ($n = 180$)	DEX ($n = 89$)	P value
EOR (n, %)	75 (42)	37 (42)	1.0
Extubation in first 24 h (n, %)	135 (75)	68 (76)	0.88
All patients vent time (h)	29 ± 35	35 ± 29	0.17
Vent time (h) by age			
Patients <12 months (n, %)	82 (46%)	43 (48%)	0.69
Vent time (h)	55 ± 98	53 ± 38	0.88
Patients 12–24 months (n, %)	22 (12%)	9 (10%)	0.69
Vent time (h)	24 ± 22	38 ± 29	0.24
Patients >24 months (n, %)	76 (42%)	37 (42%)	1.0
Vent time (h)	17 ± 36	10 ± 21	0.30

EOR Extubation in the operating room

Discussion

Multiple studies in pediatric patients have demonstrated the sedative effects of dexmedetomidine [3–5]. Chrysostomou et al. [3] were the first to describe the use of dexmedetomidine as a primary sedative and analgesic agent in pediatric patients following cardiac surgery. In their retrospective study, dexmedetomidine achieved adequate pain and sedation in 80–90% of patients without significant adverse cardiovascular, respiratory, or

gastrointestinal effects. While the sedative properties of dexmedetomidine have been well described, justification of the added expense for better efficacy and the benefits of dexmedetomidine on other patient outcomes have not been evaluated. In our study, there was no difference in success of early extubation in the CV OR or within the first 24 h in the CV ICU, and no differences in ventilator time or need for reintubation between the groups. Additionally, the lengths of CV ICU and hospital stays were similar for both groups.

Considerations were made to ensure comparison of equivalent groups by matching for age, cardiac indication, and disease acuity with cardiac bypass time. However, multiple reasons may account for the lack of significant outcomes in the DEX group compared to the control group. In this cohort of patients, the CV OR extubation rate was approximately 42% in both groups, in comparison to other reports, where the intraoperative extubation rate is much lower [7]. In this patient cohort and with this extubation rate, it would be difficult for dexmedetomidine (or any other agent) to further enhance extubation rates in the CV OR. The dosing used for dexmedetomidine may not be adequate to achieve sedative goals. Loading doses of dexmedetomidine were not used in our patient cohort to avoid possible hemodynamic instability associated with dexmedetomidine in our hemodynamically unstable patient population [8]. Recent studies have found that current recommended dosing range may not be effective in children, especially in those less than 1 year of age, and higher doses may be necessary to achieve the optimal effects of dexmedetomidine [3, 9]. In a study by Chrysostomou et al. [10] that specifically studied neonates and infants after cardiac surgery, a higher maximum dose of 1.25 μg/kg/h was well tolerated and provided an adequate level of sedation. Other reports have noted a trend toward increased dexmedetomidine doses in patients less than 1 year of age [11]. The patients in our cohort, particularly the youngest patients, may not have been receiving the full potential effect of dexmedetomidine. A higher starting dose may be necessary to achieve timely and effective sedation for these younger patients.

Several limitations exist in our study as a result of comparing a new agent to existing standard agents. Data from the DEX group were collected in a consecutive, rather than parallel, fashion during a time period when the medication was first added to our hospital formulary, which largely contributed to fewer subjects in the DEX group than the control group. Furthermore, the differences in sedative and analgesic dosing requirements may also reflect practice patterns acquired and caution when introducing a new medication (dexmedetomidine) into the system while attempting to achieve a continued success with early extubation. Otherwise, no other significant changes in operative, anesthetic, and post-operative management practices were noted between the study periods.

Evaluation of intraoperative analgesic and sedative requirements showed that patients in the DEX group received significantly lower doses of fentanyl and midazolam and more scheduled morphine boluses and infusions, and midazolam rescue boluses than the control group while in the CV ICU. There could be several explanations for this observation. These differences may be attributed to the lower dosing of fentanyl and midazolam for the DEX patients in the operating room and are comparable to the study done by Hosokawa et al. who reported the common use of phenobarbital, chloral hydrate, or midazolam as rescue sedatives in patients receiving DEX, to keep Ramsey scores lower than 5 [4]. Another explanation could be the drug properties of dexmedetomidine as a potent sedative but only a modest analgesic. This is a limitation of our study because the greater need for morphine infusion in the CV ICU may have also prolonged extubation time in the DEX group. Lastly, the administration of scheduled and rescue agents was based on the patient's perceived pain and sedation scores by the bed-side nurses and may reflect caution on their part when caring for a patient on a newly introduced medication. Despite the limitations presented by a retrospective study and the potential for subtle changes in sedation and extubation practices with the introduction of a new medication, our data are informative for future applications of dexmedetomidine in the post-operative pediatric cardiac surgery patient. While we were unable to evaluate hemodynamic adverse events, which have been reported in this patient subset, it is clear that hemodynamic parameters should be routinely monitored in this patient subset while receiving dexmedetomidine therapy [3]. Patient selection appears to be critical to the success of dexmedetomidine therapy in this patient subset, and particular patient subgroups may receive benefit from dexmedetomidine therapy beyond traditional post-operative analgesic and sedative regimens.

Conclusions

In a large cohort of children with congenital heart disease, dexmedetomidine did not have a significant impact on success of early extubation, time of mechanical ventilation, or length of stays following cardiac surgery, compared to a standard narcotic/benzodiazepine-based practice. The use of dexmedetomidine is equally effective, but, considering the expense and potential of the drug for hypotension and bradycardia, should be selective in this group of patients.

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