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A Dose-Response Study of Dexmedetomidine Administered as the Primary Sedative in Infants Following Open Heart Surgery

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Abstract

Objective—To evaluate the dose-response relationship of dexmedetomidine in infants with congenital heart disease post-operative from open heart surgery.

Design—Prospective open-label dose-escalation PK-PD study

Setting—Tertiary pediatric cardiac intensive care unit

Patients—36 evaluable infants, ages 1 month – 24 months, post-operative from open heart surgery requiring mechanical ventilation

Interventions—Cohorts of 12 infants were enrolled sequentially to one of three intravenous loading dose – continuous infusion dexmedetomidine regimens: 0.35–0.25, 0.7–0.5, or 1–0.75 mcg/kg – mcg/kg/hr for up to 24 hours.

Measurements and Main Results—Dexmedetomidine plasma concentrations were obtained at timed intervals during and following discontinuation of infusion. Pharmacodynamic variables evaluated included sedation scores, supplemental sedation and analgesia medication administration, time to tracheal extubation, respiratory function and hemodynamic parameters. Infants achieved a deeper sedation measured by the University of Michigan Sedation Scale score (2.6 vs. 1) despite requiring minimal supplemental sedation (0 unit doses/hour) and fewer analgesic medications (0.07 vs. 0.15 unit doses/hour) while receiving dexmedetomidine when compared to the 12-hour follow-up period. Thirty-one patients were successfully extubated while receiving the dexmedetomidine infusion with only 1 patient remaining intubated due to oversedation during the infusion. There was a decrease in heart rate while receiving dexmedetomidine compared to baseline, 132 vs. 161 beats/minute (bpm), but a higher heart rate when compared to post-infusion values, 132 vs. 128 bpm. There was no statistically or clinically significant change in mean arterial blood pressure.

Conclusions—Dexmedetomidine administration in infants following open heart surgery can provide improved sedation with reduction in supplemental medication requirements leading to successful extubation while receiving a continuous infusion. The post-operative hemodynamic changes that occur in infants post-operative from open heart surgery are multi-factorial. Although

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dexmedetomidine may play a role in decreasing heart rate immediately post-operative, the changes were not clinically significant and did not fall below post-infusion heart rates.

Keywords

dexmedetomidine; sedation; pharmacodynamics; infant; congenital heart disease

Introduction

Dexmedetomidine is a sedative-anxiolytic α_2 -agonist administered off-label to pediatric patients in intensive care units and operating rooms both as a single sedative-analgesic agent and as an adjunct to other sedative-analgesic regimens. It has gained increasing popularity for sedation in intensive care units due to its limited effects on respiratory function. In the general pediatric population, the administration of dexmedetomidine is most commonly associated with decreased heart rate and/or blood pressure during continuous infusion as well as hypertension during rapid infusion or loading dose administration. While these hemodynamic changes are commonly observed, clinically significant bradycardia and hypotension are infrequent (1–5).

Infants post-operative from open heart surgery are particularly vulnerable to adverse cardio-respiratory side effects associated with sedatives and analgesics. Retrospective studies of dexmedetomidine administered to children post-operative from cardiac surgery report bradycardia in 0–12.5% of patients and hypotension in 0–34% of patients without significant changes in respiratory function (6–8). Other pharmacodynamic (PD) studies of dexmedetomidine have evaluated its effect on electrophysiology, tachyarrhythmias and pulmonary artery pressure (9–13). Despite its current widespread off-label use in these children, the dose-exposure-effect relationship of dexmedetomidine on the quality of sedation and cardiorespiratory function has not been previously explored. We therefore conducted a dose escalation PK-PD study of dexmedetomidine administered as the primary sedative agent in infants following open-heart surgery. The primary endpoint of this study was to define the PK and safety profile of dexmedetomidine in infants following open heart surgery, and has been previously published (14). We now report the pharmacodynamic effects of dexmedetomidine in this infant population.

Materials and Methods

Clinical Trial

Between 2004–2006, an open-label dose-escalation study of dexmedetomidine was conducted under an investigational new drug application (IND 69,758) with the FDA. Written informed parental consent was obtained for all patients for this IRB-approved protocol. Infants, 1 – 24 months, with congenital heart disease undergoing open heart surgery with anticipated tracheal extubation within 24 hours of completion of surgery were deemed eligible for this study. Patients with significant hepatic or renal insufficiency, heart block, sustained hypotension or bradycardia defined by age upon arrival in the cardiac intensive care unit (CICU) were excluded. Patients received standardized intra-operative anesthetic induction of fentanyl 20 mcg/kg, additional intra-operative fentanyl immediately following initiation of bypass as needed and isoflurane, titrated to effect for the remainder of the surgical case. Immediately upon arrival in the CICU, patients received an intravenous loading dose of dexmedetomidine over 10 minutes followed by a continuous infusion of dexmedetomidine for no longer than 24 hours in three cohorts:

	<u>Loading Dose</u>	<u>Infusion Rate</u>
	(mcg/kg)	(mcg/kg/hr)
Low dose cohort	0.35	0.25
Intermediate dose cohort	0.7	0.5
High dose cohort	1	0.75

Dexmedetomidine doses were selected to cover the range of doses included in the drug monograph. A total of 36 evaluable patients were enrolled with twelve patients enrolled in each dosing cohort. The sample size was selected to meet the primary PK endpoint. Dose escalation to the next higher dose cohort was separated by several months following interim PK analysis and safety review by the FDA and the Data and Safety Monitoring Board.

Patients were extubated while receiving dexmedetomidine if possible. The dexmedetomidine infusion was discontinued at the discretion of the clinical team following extubation as deemed appropriate, but no longer than 24 hours. If sedation was required beyond 24 hours, an alternative sedation regimen was initiated. Dose titration within a cohort was not permitted. Supplemental analgesic and sedative medications were administered as standard of care at the discretion of the clinical care providers. If a patient was deemed oversedated, the dexmedetomidine infusion was discontinued and not restarted.

Pharmacokinetics

Multiple pharmacokinetic (PK) samples were drawn at predetermined timepoints during and after the discontinuation of the dexmedetomidine infusion (14), and selected to meet the primary PK endpoint. Dexmedetomidine plasma concentrations were determined using a validated high-performance liquid chromatography-tandem mass spectrometry assay (15).

Pharmacodynamics

Pharmacodynamic assessments occurred during 3 time periods: 1) at baseline immediately prior to initiation of dexmedetomidine, 2) during the dexmedetomidine infusion and 3) during the 12 hours following discontinuation of infusion. Respiratory rate (RR), heart rate (HR), mean arterial blood pressure (MAP), University of Michigan Sedation Scale (UMSS) scores and administration of continuous vasoactive medications were recorded hourly.

Dexmedetomidine concentrations obtained within ten minutes of hourly UMSS scores and vital sign recordings were used for correlation with sedation depth, respiratory function and hemodynamic measures. However, dexmedetomidine concentrations measured within one hour following the administration of supplemental sedation or opioid medications were excluded for correlation with sedation depth since the additional sedative could bias the sedation scale.

Sedation and Analgesia—Supplemental sedation and analgesia were administered as standard of care based on routine clinical assessment. For data analysis, supplemental sedation and analgesia were standardized into weight-based unit doses. One unit dose was defined based on the hospital's drug monograph initial dosing recommendations as: midazolam 0.1 mg/kg, fentanyl 1 mcg/kg, morphine 0.1 mg/kg, or acetaminophen 15 mg/kg. Supplemental sedation and analgesia were analyzed for each patient as the total number of unit doses administered per hour. Analysis of supplemental analgesia requirements was performed including and excluding acetaminophen administration.

Quality of sedation was measured using the University of Michigan Sedation Scale (UMSS) for research purposes only (16):

UMSS Score	Description
0	Awake and alert
1	Minimally sedated <ol style="list-style-type: none"> Tired appearing, drowsy Responds appropriately to verbal conversation
2	Moderately sedated <ol style="list-style-type: none"> Somnolent, sleeping Easily aroused with light tactile stimulation Responds to simple verbal command
3	Deeply sedated <ol style="list-style-type: none"> Deep sleep Arousable only with significant physical stimulation
4	Unarousable

Scores were assessed by the bedside nurse until two consecutive scores of zero were obtained following the discontinuation of the dexmedetomidine infusion. The average UMSS score was calculated in each patient while receiving dexmedetomidine and following the discontinuation of infusion for up to 12 hours.

Respiratory Function and Hemodynamic Measurements—Extubation readiness evaluation occurred as standard of care. Planned tracheal extubation was to occur while the patient was receiving dexmedetomidine if deemed appropriate by the clinical care team. For each patient who was tracheally extubated while receiving dexmedetomidine, the RR following tracheal extubation while still receiving dexmedetomidine was used for data analysis. Arterial pCO₂ immediately following extubation was also recorded for each patient. Vasoactive inotropic score, VIS = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 10*milrinone dose (mcg/kg/min) + 100*epinephrine dose (mcg/kg/min) + 100*norepinephrine dose (mcg/kg/min) + 10,000*vasopressin dose (units/kg/min) (17), was calculated for each patient.

Statistical analysis

Non-parametric analytical methods were utilized due to small sample sizes that were not uniformly normally distributed. Results are expressed as median (range). A *p*-value<0.05 was considered statistically significant.

Comparisons within each patient—Comparisons between pharmacodynamic measures 1) while receiving dexmedetomidine and 2) following the discontinuation of the dexmedetomidine infusion were made using each patient as his/her own control. These comparisons were analyzed with the entire study population collectively and then stratified by individual dosing cohorts. The following pharmacodynamic measures were evaluated: supplemental sedation requirement, supplement analgesic requirement, UMSS score, RR following extubation, HR, MAP and VIS. Additionally, each patient's HR, MAP and VIS during the dexmedetomidine infusion was compared to his/her baseline prior to the initiation

of dexmedetomidine. A Wilcoxon signed-rank test was used for comparison of continuous variables at baseline, during the dexmedetomidine infusion and following the discontinuation of the infusion.

Comparisons between dosing cohorts—The following pharmacodynamic measures were compared between dosing cohorts during the dexmedetomidine infusion: supplemental sedation medications, supplemental analgesic medications, UMSS score, RR following extubation, HR, MAP and VIS. Additionally, the magnitude of change in the following pharmacodynamic parameters while receiving the infusion vs. post-infusion was compared between dosing cohorts: UMSS score, RR following extubation, HR and MAP. The chi-squared test was used to compare categorical variables between cohorts and Kruskal-Wallis test for comparison of continuous variables between cohorts.

Correlation with plasma concentration—The following variables were assessed for correlation with plasma concentration: UMSS score, RR following extubation, arterial pCO₂ immediately following extubation, HR and MAP. Non-parametric Spearman rank correlation (r_s) was used to evaluate the correlation of variables to plasma concentrations. A correlation was considered strong if $|r_s| \geq 0.7$ and moderate if $0.5 < |r_s| < 0.7$ with a p -value < 0.05 considered statistically significant. A weak or no correlation was found if $|r_s| < 0.5$.

Safety Monitoring

Safety and adverse event monitoring included continuous heart rate and blood pressure measurements to evaluate for bradycardia or hypotension as defined by age, serial electrocardiogram evaluation for cardiac ischemia, serial plasma alanine aminotransferase measurements to evaluate for hepatotoxicity, clinical monitoring for adrenal suppression and ocular dryness, clinical assessment of oversedation or any serious adverse event possibly, probably or definitely related to dexmedetomidine administration.

Results

Study Conduct

Thirty-eight patients were enrolled to achieve a total of 36 evaluable patients, with twelve in each dosing cohort. Of the two inevaluable patients, one was withdrawn due to peripheral intravenous catheter malfunction during dexmedetomidine administration and the other due to ongoing post-operative hemorrhage with resultant hypotension and blood replacement. All patients received standardized intra-operative anesthetic and dexmedetomidine as the primary sedation and analgesic medication immediately on arrival in the CICU. Two patients from the intermediate dose cohort and one patient from the high dose cohort were removed from the final data analysis due to administration of neuromuscular blockade during the study period. Demographics and baseline characteristics of the 33 remaining patients are listed in Table 1. The median age and weight of the patients were 7.7 months and 7.2 kg, respectively. Median duration of dexmedetomidine infusion was 7.5 (3.2–24) hours. There was no statistical difference between cohorts in terms of demographic characteristics, duration of dexmedetomidine infusion, cardiac physiology, cardiopulmonary bypass duration, baseline and post-infusion hemodynamic parameters and sedation scores.

Quality of Sedation and Analgesia

Of the thirty-three patients who received dexmedetomidine, none required continuous infusions of supplemental sedation or analgesic medications. The most commonly administered intermittent supplemental medications for sedation was midazolam (93%) and for analgesia included morphine (63%), acetaminophen (26%) and fentanyl (10%).

Comparisons within each patient—Supplemental sedation and analgesia requirements and comparisons of the sedation scores while receiving dexmedetomidine to the 12-hour time period following the discontinuation of infusion are detailed in Table 2. Overall for the entire study cohort, supplemental sedation medication requirements were minimal with a median requirement of 0 units/hour both while receiving dexmedetomidine and during the post-infusion period. Supplemental analgesia medication requirements were 0.07 units/hour while receiving dexmedetomidine versus 0.15 units/hr during the post-infusion period ($p=0.0046$). Inclusion of acetaminophen from analysis yielded similar results with supplemental analgesia medication requirements of 0.16 units/hour while receiving dexmedetomidine versus 0.22 units/hr during the post-infusion period ($p=0.0061$). Evaluation of individual dosing cohorts also showed statistically significant differences between infusion and post-infusion values with the exception of the intermediate dose cohort.

The overall median patient UMSS score while receiving dexmedetomidine was 2.6 compared to 1 during the 12-hour post-infusion period ($p<0.0001$). This finding was consistent in all individual dose cohorts ($p<0.05$).

Comparisons between dosing cohorts—Comparisons between dosing cohorts while receiving the dexmedetomidine infusion did not show a statistically significant difference in supplemental medication requirements or UMSS scores despite dose escalation.

Respiratory Function

Thirty-one patients were extubated while receiving the dexmedetomidine infusion (12/12, 9/10 & 10/11 patients in low, intermediate and high dose cohorts, respectively). Median time to extubation while receiving dexmedetomidine was 312 (84–1397), 251 (98–335) and 196 (4–1103) minutes in the low, intermediate and high dose cohorts respectively ($p=0.0558$). Only two extubated patients had unplanned re-intubations. Both were deemed unrelated to dexmedetomidine and occurred greater than 15 hours following discontinuation of the dexmedetomidine infusion and initial extubation. One patient was re-intubated during resuscitation for hemorrhage following cardiac pacing wire removal and the second patient developed cardiogenic pulmonary edema due to coronary artery occlusion and subsequent heart failure. Among the two patients who were not extubated on infusion, one patient in the intermediate dose cohort was not eligible for extubation due to concern of a mediastinal clot requiring surgical intervention. One patient in the high dose cohort was not eligible for extubation due to oversedation. This patient was successfully extubated 45 minutes after termination of the dexmedetomidine infusion.

Comparisons within each patient—The overall median respiratory rate following extubation while still receiving dexmedetomidine was 26 breaths/minute compared to 30 breaths/minutes during the 12-hour period following the discontinuation of the infusion ($p=0.0532$) (Table 3).

Comparisons between dosing cohorts—Comparing across dosing cohorts, the change in respiratory rate during infusion versus post-infusion is greater at the intermediate and high dose cohorts, possibly secondary to a relatively lower RR occurring while receiving dexmedetomidine (Table 3). However, the difference in the absolute RR between dosing cohorts while receiving dexmedetomidine was not found to be statistically significant.

Hemodynamic Effects

There was no difference in VIS scores within patients in each dose cohort and in all patients combined while receiving dexmedetomidine 8 (0–13), compared to baseline 5 (0–13), $p=0.9922$, and post-infusion values 8.8 (0–13), $p=0.4686$. There was also no difference in median VIS scores at baseline, during dexmedetomidine administration or during the 12-hour post-infusion period between dosing cohorts.

Comparisons within each patient—Patients experienced a statistically significant decrease in heart rate while receiving dexmedetomidine compared to baseline values obtained immediately prior to dexmedetomidine administration (Figure 1). The overall median heart rate while receiving dexmedetomidine was 132 beats/minute (bpm) compared to 161 bpm at baseline ($p<0.0001$). This decrease in heart rate was also statistically significant within each individual dosing cohort ($p<0.01$). For all patients, heart rate during the dexmedetomidine infusion was higher than post-infusion, 132 versus 128 bpm, respectively ($p=0.0081$). The magnitude of heart rate reduction was not statistically different across the age range studied ($p=0.8926$). There was no statistically significant change in mean arterial pressure when comparing values while receiving dexmedetomidine to either baseline or post-infusion values within any individual cohort or all cohorts combined ($p=0.6258$).

Comparisons between dosing cohorts—The patients in the high dose cohort had the greatest decrease in heart rate (40 bpm), followed by the intermediate dose cohort (24 bpm) and the low dose cohort (15 bpm) when compared to baseline values ($p=0.0298$). Figure 1 illustrates the change in heart rate in each cohort between baseline, during dexmedetomidine administration and the 12-hour post-infusion period. There was no statistically significant change in mean arterial pressure while receiving dexmedetomidine across the dosing cohorts ($p=0.6272$).

Correlation with Plasma Concentration

Measured dexmedetomidine plasma concentrations ranged from 5 – 1340 pg/mL. The maximum concentration measured at the discontinuation of the dexmedetomidine infusion for the low, intermediate and high dose groups was 206 pg/mL, 375 pg/mL and 659 pg/mL, respectively. When compared to dexmedetomidine plasma concentrations, University of Michigan Sedation Scale scores revealed a moderate positive correlation (Table 4) with the high dose cohort exhibiting the strongest correlation, Spearman's $r_s=0.6081$, $p<0.0001$ (Figure 2). Median plasma concentration associated with a UMSS score of 1 (minimally sedated), 2 (moderately sedated) and 3 (deeply sedated), were 123 pg/mL, 367 pg/mL and 430 pg/mL, respectively, ($p=0.0001$). Respiratory rate and arterial pCO_2 following extubation, heart rate and mean arterial blood pressure did not show any correlation with dexmedetomidine plasma concentration.

Safety Evaluation

The safety evaluation during this study was reported in our previous publication (14). In summary, no clinically significant hypotension, hypertension, cardiac ischemia, hepatotoxicity, adrenal insufficiency or ocular dryness occurred in any of the 36 evaluable patients. One patient in the intermediate dose cohort developed intermittent complete heart block following a bidirectional Glenn and atrial septectomy resulting in bradycardia. The heart block occurred five hours following initiation of dexmedetomidine infusion and did not recur following the discontinuation of dexmedetomidine and was classified as a dose-limiting toxicity. In the high dose cohort, one patient experienced oversedation resulting in responsiveness only to deep stimulation while receiving dexmedetomidine as the sole post-

operative sedative and analgesic medication for four hours. The patient had an intrinsic respiratory rate of 30 breaths/min, fever at 38.6°C and arterial pH 7.35 and pCO₂ of 56mmHg resulting in increased ventilator support. The plasma concentration at the time of event was 680 pg/mL. The infusion was discontinued with endotracheal extubation successfully occurring 45 minutes later. The maximum tolerated dose was not exceeded nor determined.

Discussion

Dexmedetomidine is a relatively common medication administered in pediatric intensive care units to provide sedation and analgesia. Despite its off-label use in pediatrics, no prospective studies of dexmedetomidine administered as a continuous infusion have been performed to explore the PK-PD effects of dexmedetomidine. To our knowledge, this is the only prospective cohort of children with congenital heart disease evaluating the PK-PD relationships of dexmedetomidine administered as the first-line sedative-analgesic agent to children immediately post-operative from open heart surgery. The reduction in supplemental sedation and analgesic medication requirements, allowing successful removal from mechanical ventilatory support while receiving a sedative infusion, offers a distinct advantage in this post-operative cardiac population where fast-track recovery is desired to minimize risks associated with prolonged intubation, indwelling central catheters and difficulty with advancing enteral feeds (18).

The reduction in supplemental analgesia medication in this study population is similar to published literature describing general pediatric ICU populations. In a retrospective study of all patients admitted to a pediatric intensive care unit who received dexmedetomidine while initially intubated, Czaja found a 36–42% reduction in opiate and benzodiazepine administration while receiving dexmedetomidine when compared to the preceding 24 hours using each patient as their own control (19). The finding of a similar 53% reduction in analgesia medication and minimal administration of sedation medications in our study is of particular significance because our study patients were post-operative from open heart surgery and therefore expected to experience significant pain and anxiety following surgery.

Prior retrospective studies have reported tracheal extubation success of 50–75% in critically ill pediatric patients while receiving dexmedetomidine (6, 7). Neither study reported the dexmedetomidine dose at the time of extubation. In our study, we found a 94% overall extubation success rate within 24 hours post-operative while receiving continuous dexmedetomidine infusion in the dose range 0.25–0.75 mcg/kg/hr. Of the remaining 2 patients, one was ineligible for a trial of extubation within 24 hours post-operative due to ongoing surgical issues and one patient, receiving 0.75 mcg/kg/hr of dexmedetomidine, was considered oversedated by the clinical care team and extubated shortly after discontinuation of the dexmedetomidine. With higher dexmedetomidine infusion doses, there is a trend towards decreased time to extubation from ICU admission. We hypothesize that this finding is a result of two key factors: 1) improved sedation and/or analgesia with larger doses of dexmedetomidine requiring fewer supplemental medications that are associated with respiratory depression, and 2) increased clinician comfort with extubation while receiving mild to moderate sedation with dexmedetomidine as this study was performed prior to the availability of dexmedetomidine for general use in our CICU. The high successful extubation rate in our post-operative cardiac patient population supports the concept of fast-track post-operative care. With careful selection of patients, many infants post-operative from cardiac surgery can be rapidly weaned and removed from mechanical ventilatory support while receiving dexmedetomidine in the immediate post-operative period.

The influence of dexmedetomidine on heart rate specific to patients with congenital heart disease has been previously reported with variable findings. In a study of 80 children post-operative from cardiac surgery who received dexmedetomidine, 0.1–1.5 mcg/kg/hr, Chrysostomou found a 13% decrease in the lowest measured heart rate while receiving dexmedetomidine when compared to the baseline measurement taken prior to initiation of dexmedetomidine (129 bpm vs. 149 bpm) (6). Bradycardia occurred in 12.5% of their study patients. In contrast, a study of 54 children administered dexmedetomidine, 0.2–2 mcg/kg/hr, in a cardiac intensive care unit, Bejian reports no clinically significant change in heart rate while receiving dexmedetomidine when compared to the heart rate recorded at 2 hours post-infusion (7). In fact, the heart rate measured during infusion was statistically higher than the post-infusion heart rate (133 bpm vs. 124 bpm). The results of our study offer insight regarding the discrepant findings from these two published reports (Figure 1). Intrinsic heart rate is affected by multiple factors in patients post-operative from congenital heart disease. Immediately post-operative, these patients appear to demonstrate a relative tachycardia that may be a result of hypovolemia, decreased cardiac function, chronotropic medication administration, pain and awakening post-anesthesia resulting in a relative hypercatecholaminergic state that resolves during the ICU recovery phase. In relation to these factors, we found that dexmedetomidine administered in the immediate post-operative period elicits a dose-dependent decrease in heart rate: 10%, 15% and 24% reduction in heart rate with 0.25, 0.5, and 0.75 mcg/kg/hr infusions, respectively. This is consistent with Chrysostomou's study findings of decreased heart rate and bradycardia defined as a 30% decrease from baseline when comparing the lowest heart rate during dexmedetomidine infusion to the baseline heart rate. As patients recover in the CICU following open heart surgery, their initial tachycardia resolves over time. Although we found a dose-dependent reduction in heart while receiving dexmedetomidine compared to baseline, all of the dosing cohorts had higher heart rates during infusion when compared to heart rates during their respective 12-hour post-infusion period. Dexmedetomidine administration did not result in bradycardia when compared to post-infusion values. This finding is consistent with those of Bejian who utilized post-infusion heart rates for their comparison group.

This dose escalation PK-PD study was designed to meet a primary safety and PK endpoint. As such, there are limitations in describing the pharmacodynamics without the comparison to a control group due to the influence of multiple confounders in this historically difficult to study patient population. This study was not powered to detect minor dose escalation relationships particularly with multiple confounders related to critically ill infants with congenital heart disease. Despite the inability to compare to a control group, this dose escalation study does allow for comparison between dosing groups and observations of any clinically significant alterations due to dose escalation. Additionally, PR intervals while receiving dexmedetomidine were not evaluated limiting the ability to characterize the relationship between dexmedetomidine and the development of heart block.

Conclusions

Dexmedetomidine, administered post-operative to infants with congenital heart disease is relatively safe without clinically significant hemodynamic or respiratory alterations in the dose range 0.25–0.75 mcg/kg/hr. It provides adequate sedation as a single first-line agent while reducing supplemental analgesic requirements when compared to post-infusion measurements. With careful selection of patients, tracheal extubation can occur successfully while receiving dexmedetomidine at doses up to 0.75 mcg/kg/hr. The post-operative hemodynamic changes that occur in infants post-operative from open heart surgery are multi-factorial. Administration of dexmedetomidine in patients immediately post-operative from open heart surgery results in a dose-dependent decrease in heart rate. This reduction in

heart rate was not found to be clinically significant in the dose range studied and did not fall below post-infusion heart rates.

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Figure 1.
Change in Heart Rate

Figure 2.
UMSS Correlation to Dexmedetomidine Concentration

Table 1

Demographics and Baseline Characteristics^a

	Low Dose	Intermediate Dose	High Dose	Overall	p-value
Age (months)	9.3 (3.3–20.4)	7.8 (4.0–18.5)	6.9 (2.6–19.6)	7.7	0.7276
Weight (kg)	7.5 (5.3–11.9)	7.8 (5.4–10.2)	6.8 (5.1–11.2)	7.2	0.9345
Gender (%)					
Female	5 (42)	5 (50)	4 (36)	14 (42)	0.817
Male	7 (58)	5 (50)	7 (64)	19 (58)	
Surgical procedure					
Two-ventricle physiology (%)	7 (58)	4 (40)	4 (36)	15 (45)	
Atrial septal defect repair			1		
Common atrioventricular canal repair		1			
Right ventricle – pulmonary artery conduit revision	1				
Subaortic membrane resection		1			
Partial anomalous pulmonary venous return repair	1				
Rastelli		1			
Ross-Konno		1			0.525
Tetralogy of Fallot repair	3		2		
Ventricular septal defect repair	2		1		
Single-ventricle physiology (%)	5 (42)	6 (60)	7 (64)	18 (55)	
Bidirectional Glenn	5	4	3		
Bidirectional Glenn & Damus-Kaye-Stansel		1			
Bidirectional Glenn & TAPVR ^b repair			1		
Kawashima			1		
Hemi-Fontan		1	2		
Cardiopulmonary bypass (minutes)	53 (16–70)	57 (24–76)	57 (28–75)	56	0.4973
Baseline characteristics					
Respiratory rate	20 (16–20)	20 (18–32)	19 (10–20)	20	0.0695

	Low Dose	Intermediate Dose	High Dose	Overall	p-value
Heart rate	156 (112–184)	156 (142–201)	165 (117–205)	160	0.7324
Mean arterial pressure	71 (62–97)	68 (41–80)	69 (61–96)	71	0.4026
University of Michigan Sedation Scale score	4 (1–4)	4 (4)	4 (3–4)	4	0.6385
Average value during 12 hr post-infusion per patient					
Respiratory rate	29 (18–47)	33 (17–39)	29 (21–51)	31	0.9629
Heart rate	126 (99–153)	127 (97–151)	122 (99–144)	126	0.987
Mean arterial pressure	72 (64–84)	68 (55–85)	66 (60–95)	69	0.4406
University of Michigan Sedation Scale (UMSS) score	1.5 (0.4–2.3)	1 (0.1–2.2)	0.8 (0–2.1)	1	0.2093
Dexmedetomidine duration per patient (hours)	6.9 (4.4–24)	7.9 (3.2–10.4)	8.5 (4.4–22.3)	7.5	0.6259

^aValues expressed as median (range) except for gender and surgical procedure (%)

^bTAPVR - Total anomalous pulmonary venous return

Table 2Supplemental Sedation & Analgesia Requirements and UMSS Scores During and After Infusion^a

	Dexmedetomidine Infusion	0–12 Hours Post-infusion	Difference (<i>p</i> -value)
Sedation units (per hour)			
All cohorts	0 (0–0.11)	0 (0–0.09)	0 (<i>p</i> =0.0818)
Low dose	0 (0)	0 (0–0.09)	0
Intermediate dose	0 (0)	0 (0–0.08)	0
High dose	0 (0–0.11)	0 (0–0.06)	0
Analgesic units (per hour) ^b			
All cohorts	0.07 (0–1.33)	0.15 (0–0.6)	–0.08 (<i>p</i> =0.0046)
Including acetaminophen	0.16 (0–1.33)	0.22 (0.05–0.67)	–0.06 (<i>p</i> =0.0061)
Low dose	0.07 (0–0.39)	0.13 (0–0.32)	–0.06 (<i>p</i> < 0.02)
Intermediate dose	0.19 (0–1.33)	0.22 (0–0.6)	–0.03 (<i>p</i> >0.05)
High dose	0.05 (0–0.3)	0.15 (0.04–0.47)	–0.1 (<i>p</i> <0.05)
UMSS score			
All cohorts	2.6 (1.2–4)	1 (0–2.3)	1.6 (<i>p</i> =0.0000)
Low dose	2.4 (1.3–3.3)	1.5 (0.4–2.3)	0.9 (<i>p</i> < 0.05)
Intermediate dose	2.7 (1.2–4)	1 (0.1–2.2)	1.7 (<i>p</i> < 0.05)
High dose	2.3 (1.6–4)	0.8 (0–2.1)	1.5 (<i>p</i> < 0.05)

^aValues expressed as median (range)^bExcluding acetaminophen except where noted

Table 3Respiratory Function During Dexmedetomidine Infusion Compared to Post-Infusion^a

	Dexmedetomidine Infusion	0–12 Hours Post-infusion	Difference (<i>p</i> -value)
Respiratory rate following extubation			
All cohorts (<i>n</i> =31)	26 (16–46)	30 (17–51)	–4 (<i>p</i> =0.0532)
Low dose (<i>n</i> =12)	33 (19–46) ^b	29 (18–47)	4 (<i>p</i> >0.1)
Intermediate dose (<i>n</i> =9)	26 (21–37) ^b	32 (17–39)	–6 (<i>p</i> =0.05)
High dose (<i>n</i> =10)	23 (16–42) ^b	29 (21–51)	–6 (<i>p</i> <0.05)

^aValues expressed as median (range)^bComparison between dosing cohorts while receiving dexmedetomidine, *p*=0.1060

Table 4

UMSS Correlation with Plasma Concentration

	r_s	p -value
All cohorts	0.5485	<0.0001
Low dose	0.4921	0.038
Intermediate dose	0.4016	0.018
High dose	0.6081	<0.0001