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ORIGINAL ARTICLE

Hemodynamic Effects of Dexmedetomidine in Critically Ill Neonates and Infants With Heart Disease

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Abstract The primary objective of this study was to evaluate the hemodynamic effects of dexmedetomidine (DEX) infusion on critically ill neonates and infants with congenital heart disease (CHD). The secondary objective of the study was to evaluate the safety and efficacy profile of the drug in this patient population. A retrospective observational study was conducted in the cardiovascular intensive care unit (CVICU) of a single tertiary care university children's hospital. The charts of all neonates and infants who received DEX in the authors' pediatric CVICU between August 2009 and June 2010 were retrospectively reviewed. The demographic data collected included age, weight, sex, diagnosis, and Risk Adjustment in Congenital Heart Surgery (RACHS-1) score. To evaluate the hemodynamic effects of DEX, physiologic data were collected including heart rate, mean arterial pressure (MAP), inotrope score, near-infrared spectroscopy, and central venous pressure (CVP). To assess the efficacy of DEX, the amount and duration of concomitant sedation and analgesic infusions over a period of 24 h were examined together with the number of rescue boluses. The potential side effects evaluated in this study included nausea, vomiting, abdominal distension, dysrhythmias, neurologic abnormalities, seizures, and signs and symptoms of withdrawal. During the study period, 50 neonates and infants received DEX for a median period of 78 h (range, 40–290 h). These patients had an average age of 3.53 ± 2.64 months and a weight of 4.85 ± 1.67 kg. Whereas 34 patients (68%) received DEX after surgery for CHD, 15 patients (30%) received DEX after heart transplantation. Of these 50 infants, 10 (20%) had a single-ventricle anatomy, whereas 13 (26%) had a risk adjustment score (RACHS-1) in the category of 4–6. The median CVICU stay was 29 days (range, 8–69 days). Despite a significant decrease in heart rate, MAP, inotrope score, and CVP, all the patients remained hemodynamically stable during DEX infusion. There was no substantial difference in major hemodynamic variables between neonates and infants, single- and two-ventricle repair, RACHS 4–6 and RACHS 1–3 categories for patients undergoing surgery, or patients undergoing heart transplantation and patients undergoing other surgical procedures. Dexmedetomidine infusion for neonates and infants with heart disease is safe from a hemodynamic standpoint and can reduce the concomitant dosing of opioid and benzodiazepine agents. Furthermore, DEX infusion may be useful for reducing vasopressor agent dosing in children with catecholamine-refractory cardiogenic shock.

Keywords Dexmedetomidine · Infants · Congenital heart disease · RACHS-1 · Heart transplantation · Hemodynamic effect

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Providing adequate sedation for critically ill infants with heart disease is a challenging clinical problem. These patients often have labile cardiovascular function and may require several days to weeks of sedation as a component of their intensive care unit management. The challenge remains to find an ideal pharmacologic agent that is not only effective but also safe, without alteration of a patient's hemodynamic status.

Although it is proposed by some that dexmedetomidine (DEX) is a useful addition to the sedation armamentarium of pediatric cardiac intensive care physicians, the effect of this agent on the hemodynamics of infants is unknown. As an α_2-adrenergic agonist of the imidazole subclass, DEX (Precedex, Hospira Worldwide Inc, Lake Forest, IL, USA) is similar in structure to clonidine but with an α_2:α_1 specificity of nearly 1,600 to 1 [21]. It acts as a sedative, anxiolytic, and analgesic agent through α_2-adrenergic agonism in the locus coeruleus [21]. The shorter half-life of DEX (2–3 vs 12–24 h for clonidine) and its availability for administration as an intravenous (IV) agent allows titration by continuous infusion [22].

Because DEX has limited effects on respiratory function, interference with weaning from mechanical ventilation is less likely. In fact, it has been used both as a bridge to tracheal extubation and as sedation for nonintubated patients [7, 8].

Enthusiasm for this newer agent stems from several factors including the lack of an ideal agent for sedation during mechanical ventilation, adverse effects associated with existing agents, and recognition over the past 10 years of the potential deleterious physiologic effects of untreated pain in the acute care setting [1, 20].

Initially, DEX received approval from the Food and Drug Administration (FDA) for the provision of sedation up to 24 h in adults during mechanical ventilation. However, the safety and hemodynamic profile of this drug for neonates and infants with critically ill heart disease still is poorly understood, particularly for infants with a single-ventricle anatomy, those undergoing complex cardiac surgeries, and those receiving an orthotopic heart transplant. In this study, we aimed to address some of these limitations by focusing on the course and hemodynamics of critically ill infants with heart disease who received infusions of DEX during their intensive care course.

Patients and Methods

We retrospectively reviewed the charts of all neonates and infants who received DEX in our pediatric cardiovascular intensive care unit (CVICU) between August 2009 and June 2010. The study population included all critically ill neonates and infants (age, $\leq$12 months) with congenital or acquired heart disease. Using the records from our pharmacy, we identified all the infants who received DEX during their CVICU stay.

The study excluded those who received any part of their DEX infusion outside the CVICU setting (i.e., operating room, floor, or radiologic suite), those with incomplete or missing medical records, those who did not have an arterial catheter for invasive blood pressure monitoring, those who received DEX infusion for less than 24 h, those who received extracorporeal membrane oxygenation (ECMO) partly or completely during DEX infusion, and those with "do not resuscitate" orders. The Institutional Review Board at Arkansas Children's Hospital approved the study protocol, and the need for informed consent or assent was waived.

According to routine clinical practice in our CVICU, DEX was initiated as a second or third continuous-infusion sedative after the perceived failure of conventional sedation agents. The decision to initiate a DEX infusion was at the discretion of the medical team caring for the patient. The most common conventional agents used in our CVICU include midazolam infusion, morphine infusion, or both. We initiated DEX as continuous infusion at a dose of 0.1–1.5 mcg/kg/h without a bolus dose.

The daily dose of DEX was determined by averaging the amount of drug each patient received over 24 h and was expressed as mcg/kg/day. Midazolam and morphine doses were determined by averaging the amount of each drug each patient received over 24 h and were expressed as mg/kg/day. The data for patients receiving more than one course of DEX per hospital admission were evaluated as separate events, provided the time between each infusion period was more than 12 h.

We collected demographic data including age, weight, sex, diagnosis, and Risk Adjustment in Congenital Heart Surgery (RACHS-1) score [15]. We also collected detailed information on the dosages of DEX, midazolam, and morphine administered by infusion in the first 24 h, in 24–48 h, and during the last 24 h before discontinuation of the therapy, together with the total duration of infusion for each drug. Given the lack of an established comfort or pain score in our unit, the infusions were adjusted according to the clinical assessment of the physician caring for the patient.

We also collected physiologic data including heart rate, mean arterial pressure (MAP), respiratory rate, systemic oxygen saturation by pulse oximetry, inotrope score [16], near-infrared spectroscopy (NIRS), and central venous pressure (CVP). It is a common practice in our unit to titrate inotropes according to signs and symptoms of cardiac output (e.g., capillary refill, urine output, mixed venous oxygen saturation, serum lactate, and/or arterial blood pH) and not solely on the basis of blood pressures. The baseline data for

these variables were collected for 6 h before initiation of DEX (expressed as the mean value over 1 h), for the first hour after initiation of DEX, for 2–6 h after initiation of DEX (expressed as the mean value over 1 h), for 7–24 h after initiation of DEX (expressed as the mean value over 1 h), for the last 6 h before termination of DEX (expressed as the mean value over 1 h), for the first hour after termination of DEX, for the sixth hour after termination of DEX, and for the 24 h after termination of DEX.

The potential side effects evaluated in our study were nausea, vomiting, abdominal distension, dysrhythmias, neurologic abnormalities, seizures, and signs and symptoms of withdrawal. Additional variables evaluated to assess the safety of DEX were blood pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and serum bicarbonate before initiation of DEX infusion, during the infusion, and after the termination of the infusion.

To assess the efficacy of DEX for sedative and analgesic requirements, we also examined the number of rescue boluses for each category before initiation of the DEX infusion, during the DEX infusion, and after termination of the DEX infusion. Given the lack of an established protocol for sedation management in our unit, the rescue agents were multiple and included midazolam, lorazepam, ketamine, chloralhydrate, and diphenhydramine for sedation and fentanyl and morphine for analgesia. For some patients, narcotics were used for both analgesia (primary effect) and sedation (sedation effect). Rescue agents were labeled as either a "sedation bolus" or an "analgesic bolus" depending on their primary effect.

Statistical Analysis

Continuous variables are presented as medians (Q1, Q3), where Q1 is the 25th percentile, and Q3 is the 75th percentile and/or means ± standard deviations, whereas categorical variables are presented as numbers and percentages. Calculation of p values was performed using the chi-square test or Fisher's exact test of independence for categorical variables and the Wilcoxon rank-sum test for continuous variables. Quantitative continuous variables were compared between groups using the Mann–Whitney nonparametric test if the variable had a non-normal distribution or using the unpaired Student's t test if the variable had a normal distribution.

Serial measurements including heart rate, MAP, inotrope score, CVP, NIRS, and respiratory rate were analyzed using random-effects mixed-linear models to account for repeated measures. Separate linear mixed models were suitable for comparing the outcomes over time between neonates and infants, between one- and two-ventricle anatomies, and between heart transplantation and no heart transplantation. Repeated measures of analyses were performed using the MIXED procedure in SAS. A compound symmetry covariance structure was used to account for correlations of measurements of the same subject. A p value of 0.05 was considered significant for study purposes. However, given that there were eight group comparisons (one per period), a Bonferroni corrected alpha level of 0.00625 (0.05/8) was used to control for multiple testing within each model. The p values were not adjusted for multiple testing. Analyses were performed using STATA/MP, version 12 (Stata Corp LP, College Station, TX, USA) or SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, 50 neonates and infants received DEX. Of these 50 patients, 27 were males (54%) and 13 were neonates (26%). The patients had an average age of 3.53 ± 2.64 months and a weight of 4.85 ± 1.67 kg. Whereas 43 patients (86%) received DEX while intubated on a mechanical ventilator, 1 patient received DEX while undergoing noninvasive ventilation. Administration of DEX was after surgery for congenital heart disease (CHD) for 34 patients (68%) and after heart transplantation for 15 patients (30%). Of these 50 infants, 10 (20%) had a single-ventricle anatomy, whereas 13 (26%) had risk adjustment scores (RACHS-1) in the categories of 4 to 6.

Administration of DEX was as a continuous infusion for a median period of 78 h (range, 40–290 h). The patients received an average dose of 9.1 ± 2.8 mcg/kg/day during the first 24 h, 8.7 ± 4.8 mcg/kg/day during the subsequent 24 h, and 7.2 ± 4.8 mcg/kg/day during the last 24 h before termination of DEX usage. The median CVICU stay was 29 days (range, 8–69 days).

Hemodynamic Effects

All the patients remained hemodynamically stable during the DEX infusion. Hemodynamic stability was defined as no need for escalation of inotropic support or IV fluid boluses and no need for holding or decreasing the DEX dose during the infusion. There was a significant decrease in heart rate, MAP, inotrope score, and CVP throughout the DEX infusion.

Heart Rate

The average heart rate increased from a baseline value of 143 to a value of 145 in the first hour after initiation of DEX ($p = 0.60$), followed by a decrease to 139 in 2–6 h ($p = 0.16$), to 131 in 7–24 h ($p < 0.001$), and to 124 in last 6 h ($p < 0.001$) of DEX infusion. The heart rate started to

increase toward baseline values after termination of DEX infusion, although the values still remained significantly lower than the baseline values, with an average heart rate of 134 in 24 h after termination of DEX ($p = 0.008$) (Fig. 1).

Comparison of the neonates and infants showed no significant difference in heart rate until last 6 h of DEX infusion, when the infants had a significantly lower heart rate ($p = 0.001$), which continued until 6 h after termination of DEX infusion ($p = 0.002$) (Table 1). There was no substantial difference in heart rate at any time point between patients with one- and two-ventricle anatomies (Table 1). The patients receiving a heart transplant had a lower heart rate before and during DEX infusion (Table 1). There was no significant difference in heart rate at any time point between patients undergoing complex surgery in RACHS categories 4 to 6 and those undergoing surgery in RACHS categories 1 to 3.

MAP and Inotrope Score

The average MAP increased from a baseline value of 69 to a value of 70 in the first hour after initiation of DEX ($p = 0.34$), followed by a decrease to 64 in 2–6 h ($p = 0.02$) to 61 in 7–24 h ($p = 0.0001$), and to 60 in last 6 h ($p < 0.001$) of DEX infusion. After termination of the DEX infusion, MAP started to increase toward baseline values, with the values reaching a baseline MAP of 66 in 24 h ($p = 0.12$) (Fig. 2).

Comparison of the neonates and infants showed that the neonates had a lower MAP at baseline ($p = 0.01$), which continued to be lower throughout the DEX infusion (Table 1). There was no substantial difference in MAP for patients with a one- versus a two-ventricle anatomy or for those undergoing surgery in the RACHS 4–6 category versus the RACHS 1–3 category (Table 1). The patients receiving a heart transplant had a higher MAP at baseline ($p < 0.001$), which continued to be higher throughout the DEX infusion (Table 1).

The inotrope score also followed the same trends as MAP, with the baseline value of 8.2 decreasing to 7.6 in first hour after initiation of DEX ($p = 0.32$), followed by a decrease to 7.4 in 2–6 h ($p = 0.14$), to 7.3 in 7–24 h ($p = 0.10$), and to 6.5 in the last 6 h ($p = 0.002$) of DEX infusion. The inotrope score started increasing toward baseline values after termination of the DEX infusion, with the values reaching the baseline value of 7.7 in 24 h after the termination of DEX ($p = 0.36$) (Fig. 3). The inotrope scores did not differ substantially between the patients in the different subgroups (Table 1).

CVP

The CVP decreased from the baseline value of 11 to the value of 9 in 2–6 h after initiation of DEX ($p < 0.001$), to 8 in 7–24 h ($p < 0.001$), and to 9 in last 6 h ($p < 0.001$) of DEX infusion. After termination of DEX infusion, CVP started increasing toward baseline values, reaching these values in 24 h after termination of DEX ($p = 0.15$) (Fig. 4). Comparison of CVP in the different subgroups did not show any substantial differences (Table 1).

NIRS

Overall, NIRS did not differ substantially after initiation of the DEX infusion. Subgroup analysis showed no difference in NIRS for neonates versus infants, for patients undergoing surgery in the RACHS 4–6 category versus the RACHS 1–3 category, and for patients undergoing heart transplantation versus no heart transplantation. However, as expected, the patients with a single-ventricle anatomy had a lower baseline NIRS ($p = 0.006$), which continued to be lower in this subgroup throughout the DEX infusion.

Effect on Sedation and Analgesia

The majority of the patients received continuous IV benzodiazepine and/or opioid infusions before and during their DEX infusion, with 42 patients receiving morphine infusion at an average dose of 2.8 ± 2.6 mg/kg/day before initiation of DEX. After initiation of DEX infusion, 39 patients continued to receive morphine infusion during the 24- to 48-h interval (at an average dose of 2.9 ± 2.8 mg/kg/day), and 34 patients continued to receive morphine infusion in the last 24 h of DEX (at an average dose of 2.4 ± 2.6 mg/kg/day).

Before initiation of DEX, 36 patients received midazolam infusion at an average dose of 3.5 ± 2.4 mg/kg/day. After initiation of DEX infusion, 32 patients continued to receive midazolam infusion in the 24- to 48-h interval

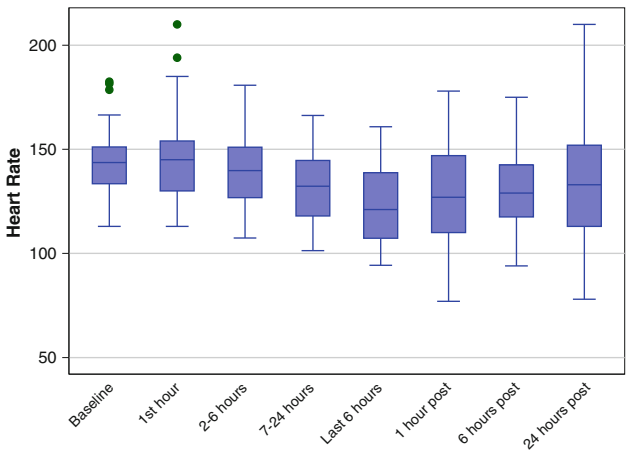

Fig. 1 Effects of dexmedetomidine (DEX) infusion on the heart rate of critically ill neonates and infants with heart disease

Table 1 Comparisons of hemodynamic variables in three subpopulations among critically ill infants with cardiac disease

	Neonates versus infants			One- versus two-ventricle anatomy			Heart transplant versus no heart transplant		
	($n = 13$) versus ($n = 37$)			($n = 10$) versus ($n = 40$)			($n = 15$) versus ($n = 35$)		
	Mean (SE)	Mean (SE)	p value	Mean (SE)	Mean (SE)	p value	Mean (SE)	Mean (SE)	p value
Heart rate									
Baseline	148.69 (5.26)	141.79 (3.21)	0.2631	143.37 (6.47)	143.63 (3.17)	0.97	136.84 (5.01)	146.42 (3.27)	0.111
1st hour	150.31 (5.26)	143.35 (3.11)	0.2557	140.60 (6.23)	146.30 (3.12)	0.414	136.07 (4.89)	149.06 (3.20)	0.027
2–6 h	141.88 (5.26)	138.28 (3.11)	0.5566	136.14 (6.23)	139.99 (3.12)	0.582	132.19 (4.89)	142.23 (3.20)	0.087
7–24 h	133.19 (5.26)	130.28 (3.11)	0.6347	130.53 (6.23)	131.17 (3.12)	0.928	123.18 (4.89)	134.41 (3.20)	0.056
Last 6 h	140.01 (5.59)	118.60 (3.25)	0.001	124.57 (6.47)	123.92 (3.27)	0.928	114.01 (5.16)	128.29 (3.35)	0.021
1 h after	145.55 (6.04)	126.15 (3.21)	0.0049	125.40 (6.23)	132.08 (3.34)	0.345	124.47 (4.89)	133.15 (3.49)	0.149
6 h after	148.10 (5.80)	127.88 (3.21)	0.0025	125.60 (6.23)	134.73 (3.30)	0.197	121.87 (4.89)	137.74 (3.44)	0.008
24 h after	143.90 (5.80)	131.75 (3.33)	0.0703	126.98 (6.74)	136.72 (3.34)	0.197	123.72 (5.16)	139.72 (3.49)	0.011
Mean arterial pressure									
Baseline	61.32 (3.44)	71.64 (2.08)	0.0107	70.20 (4.22)	68.56 (2.06)	0.728	78.47 (3.22)	64.70 (2.14)	0
1st hour	61.92 (3.44)	73.81 (2.04)	0.0032	75.90 (4.09)	69.43 (2.05)	0.158	78.80 (3.22)	67.26 (2.10)	0.003
2–6 h	58.68 (3.44)	66.94 (2.04)	0.0397	72.94 (4.09)	62.75 (2.05)	0.027	74.06 (3.22)	60.82 (2.10)	0.001
7–24 h	57.15 (3.44)	63.20 (2.04)	0.1316	67.94 (4.09)	60.04 (2.05)	0.085	68.86 (3.22)	58.52 (2.10)	0.007
Last 6 h	49.96 (3.53)	64.26 (2.12)	0.0006	66.92 (4.09)	58.82 (2.13)	0.08	64.12 (3.36)	58.91 (2.16)	0.192
1 h after	54.55 (3.90)	65.22 (2.10)	0.0166	67.70 (4.09)	61.20 (2.17)	0.162	64.57 (3.22)	62.08 (2.26)	0.527
6 h after	54.17 (3.76)	62.47 (2.14)	0.0563	63.63 (4.22)	59.50 (2.17)	0.385	59.92 (3.28)	60.96 (2.26)	0.794
24 h after	57.57 (3.76)	68.74 (2.19)	0.0108	69.22 (4.58)	64.98 (2.17)	0.403	66.66 (3.36)	65.85 (2.28)	0.841
Inotrope score[a]									
Baseline	9.65 (1.59)	7.74 (0.95)	0.3018	9.25 (1.84)	7.96 (0.92)	0.531	8.00 (1.50)	8.34 (0.97)	0.848
1st hour	8.69 (1.59)	7.34 (0.94)	0.467	9.25 (1.84)	7.31 (0.92)	0.345	7.40 (1.48)	7.82 (0.97)	0.812
2–6 h	8.28 (1.59)	7.15 (0.94)	0.542	8.82 (1.84)	7.10 (0.92)	0.402	7.11 (1.48)	7.58 (0.97)	0.791
7–24 h	8.52 (1.59)	6.92 (0.94)	0.389	8.00 (1.84)	7.17 (0.92)	0.688	6.87 (1.48)	7.54 (0.97)	0.705
Last 6 h	8.13 (1.65)	5.93 (0.95)	0.248	5.71 (1.86)	6.69 (0.93)	0.641	4.21 (1.50)	7.49 (0.98)	0.067
1 h after	7.93 (1.65)	5.09 (0.95)	0.136	4.85 (1.84)	6.06 (0.93)	0.558	3.92 (1.48)	6.64 (0.99)	0.127
6 h after	10.66 (1.63)	5.75 (0.95)	0.009	5.85 (1.84)	7.25 (0.93)	0.498	4.42 (1.48)	8.09 (0.98)	0.04
24 h after	10.32 (1.63)	6.88 (0.95)	0.068	6.87 (1.86)	7.95 (0.93)	0.603	6.05 (1.50)	8.48 (0.98)	0.175
Central venous pressure (CVP)									
Baseline	11.33 (0.88)	11.69 (0.52)	0.7313	10.70 (0.96)	11.84 (0.50)	0.296	11.92 (0.84)	11.47 (0.52)	0.647
1st hour	10.58 (0.88)	10.89 (0.52)	0.7682	10.50 (0.96)	10.89 (0.50)	0.719	10.23 (0.84)	11.03 (0.52)	0.42
2–6 h	9.25 (0.88)	9.69 (0.52)	0.6711	8.60 (0.96)	9.84 (0.50)	0.256	9.62 (0.84)	9.56 (0.52)	0.954
7–24 h	9.25 (0.88)	8.46 (0.52)	0.4399	8.40 (0.96)	8.73 (0.50)	0.762	8.69 (0.84)	8.65 (0.52)	0.964
Last 6 h	9.17 (0.88)	9.03 (0.52)	0.8929	7.80 (0.96)	9.41 (0.50)	0.141	9.08 (0.84)	9.06 (0.52)	0.985
1 h after	10.25 (0.88)	9.97 (0.52)	0.786	10.00 (0.96)	10.05 (0.50)	0.96	8.62 (0.84)	10.59 (0.52)	0.047
6 h after	9.92 (0.88)	10.14 (0.52)	0.8255	10.10 (0.96)	10.08 (0.50)	0.986	9.08 (0.84)	10.47 (0.52)	0.159
24 h after	11.17 (0.88)	10.91 (0.52)	0.8057	10.80 (0.96)	11.03 (0.50)	0.835	9.85 (0.84)	11.41 (0.52)	0.114
Near infrared spectroscopy (NIRS)									
Baseline	66.95 (3.53)	59.50 (2.22)	0.0753	51.54 (4.06)	64.21 (2.07)	0.006	63.07 (3.79)	61.07 (2.24)	0.65
1st hour	65.54 (3.53)	58.26 (2.15)	0.079	51.90 (3.93)	62.42 (2.02)	0.018	59.77 (3.61)	60.40 (2.20)	0.882
2–6 h	66.33 (3.53)	57.90 (2.15)	0.0421	53.10 (3.93)	62.05 (2.02)	0.044	60.71 (3.61)	59.99 (2.20)	0.865
7–24 h	67.73 (3.53)	58.63 (2.17)	0.0288	53.46 (3.93)	63.14 (2.03)	0.03	61.00 (3.61)	61.18 (2.22)	0.967
Last 6 h	62.03 (3.70)	59.52 (2.27)	0.5634	53.20 (3.93)	62.06 (2.17)	0.049	62.53 (3.79)	59.32 (2.32)	0.47
1 h after	62.01 (3.94)	61.05 (2.25)	0.832	54.50 (3.93)	63.36 (2.20)	0.05	62.46 (3.61)	61.10 (2.40)	0.754
6 h after	65.14 (3.82)	61.92 (2.32)	0.4717	56.38 (4.06)	64.50 (2.22)	0.081	63.05 (3.90)	62.74 (2.38)	0.946
24 h after	66.64 (3.82)	64.19 (2.32)	0.5834	58.72 (4.21)	66.51 (2.20)	0.102	66.51 (3.90)	64.28 (2.38)	0.625

Table 1 continued

	Neonates versus infants			One- versus two-ventricle anatomy			Heart transplant versus no heart transplant		
	($n = 13$) versus ($n = 37$)			($n = 10$) versus ($n = 40$)			($n = 15$) versus ($n = 35$)		
	Mean (SE)	Mean (SE)	p value	Mean (SE)	Mean (SE)	p value	Mean (SE)	Mean (SE)	p value
Respiratory rate									
Baseline	31.76 (3.25)	29.05 (1.99)	0.4773	28.43 (3.75)	30.07 (1.85)	0.695	32.86 (3.04)	28.37 (2.06)	0.222
1st hour	29.62 (3.25)	28.78 (1.95)	0.8251	28.80 (3.61)	29.05 (1.83)	0.951	31.33 (3.04)	27.97 (2.02)	0.357
2–6 h	29.24 (3.25)	27.91 (1.95)	0.7251	27.35 (3.61)	28.49 (1.83)	0.778	28.89 (3.04)	27.98 (2.02)	0.802
7–24 h	30.17 (3.25)	27.41 (1.95)	0.4667	30.55 (3.61)	27.52 (1.83)	0.456	28.99 (3.04)	27.76 (2.02)	0.736
Last 6 h	33.30 (3.35)	30.48 (2.04)	0.4728	29.58 (3.61)	31.80 (1.92)	0.588	31.69 (3.21)	31.04 (2.09)	0.865
1 h after	34.98 (3.76)	31.96 (2.02)	0.4798	34.10 (3.61)	32.27 (1.97)	0.657	35.07 (3.04)	31.46 (2.21)	0.337
6 h after	35.10 (3.60)	33.54 (1.99)	0.7045	32.10 (3.61)	34.52 (1.93)	0.555	34.60 (3.04)	33.70 (2.15)	0.808
24 h after	32.80 (3.60)	39.52 (2.07)	0.1065	55.19 (3.92)	33.76 (1.95)	<0.001	36.90 (3.21)	38.40 (2.18)	0.697

[a] Inotrope score[8]: dosages of dopamine + dobutamine (μg/kg/min) + (dosages of epinephrine + norepinephrine + isoproterenol (μg/kg/min]) × 100 + dosages of milrinone (μg/kg/min) × 15

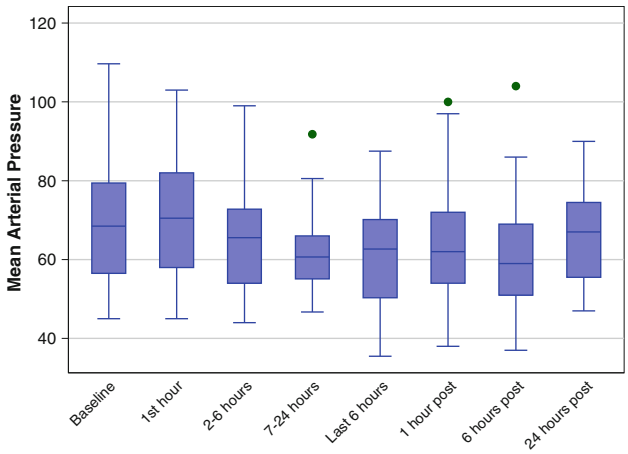

Fig. 2 Effects of dexmedetomidine (DEX) infusion on the mean arterial pressure of critically ill neonates and infants with heart disease

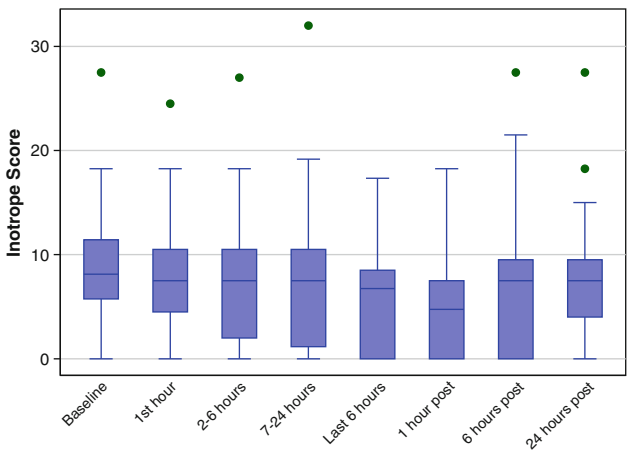

Fig. 3 Effects of dexmedetomidine (DEX) infusion on the inotrope score of critically ill neonates and infants with heart disease

(at an average dose of 4.1 ± 2.4 mg/kg/day), and 30 patients continued to receive morphine infusion in the last 24 h of DEX (at an average dose of 3.2 ± 3.0 mg/kg/day). Additional rescue boluses of sedation and analgesia were recorded during the DEX infusion, and then again after termination of the DEX therapy.

Before initiation of DEX, 45 patients received sedation rescue boluses at a median rate of 2 boluses (range, 0–3 boluses). After initiation of DEX, 43 patients needed sedation rescue boluses at a median rate of 1 bolus (range, 0–5 boluses) in the 24- to 48-h interval, and 39 patients received sedation rescue boluses at a median rate of 1 bolus (range, 0–3 boluses) in the last 24 h.

Before the initiation of DEX, 47 patients received analgesic rescue boluses at a median rate of 2 boluses (range, 1–3 boluses). After the initiation of DEX, 43 patients needed analgesic rescue boluses at a median rate of 2 boluses (range, 1–6 boluses) in the 24- to 48-h interval, and 38 patients received analgesic rescue boluses at a median rate of 1 bolus (range, 0–3 boluses) in the last 24 h.

Other Outcomes

No adverse respiratory effects were associated with DEX infusion. The respiratory rates during and after the termination of DEX infusion did not differ in our cohort. Of 43 intubated patients at the time DEX infusion was initiated, 22 were weaned off mechanical ventilation and extubated while receiving DEX infusion. The only patient receiving noninvasive ventilation also was transitioned to high-flow nasal cannula while receiving DEX infusion. No documented episodes of apnea occurred among the patients not intubated at the time DEX infusion was initiated or among the extubated patients receiving DEX infusion.

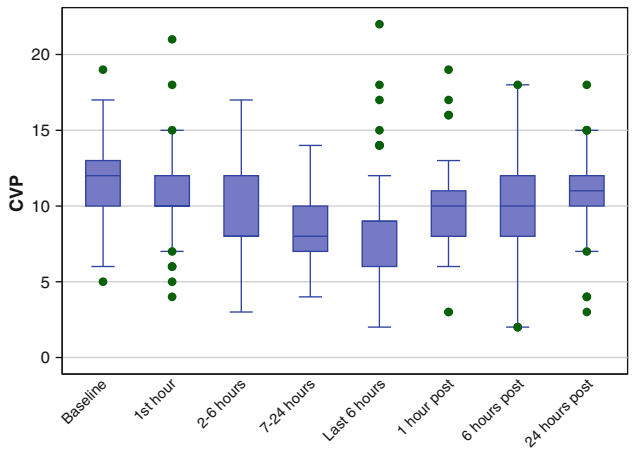

Fig. 4 Effects of dexmedetomidine (DEX) infusion on the central venous pressure of critically ill neonates and infants with heart disease

There was no difference in oxygen saturation, blood pH, PaO_2, $PaCO_2$, or serum bicarbonate values before and during DEX infusion. None of the patients had any rhythm abnormalities associated with DEX infusion. No significant abdominal signs or symptoms were noted. None of the patients had increased vomiting or a distended abdomen. No withdrawal symptoms associated with the termination of DEX were reported in the medical records. However, 37 patients (74%) in our cohort received a clonidine patch. No neurologic abnormalities were noted during or after the termination of DEX infusion.

Discussion

The use of DEX in CVICUs has been increasing across the country [2, 8, 9, 18]. We report the safe use of DEX infusion for critically ill neonates and infants with heart disease, including those with a single-ventricle anatomy, those undergoing complex surgeries, and those receiving an orthotopic heart transplant at doses of 0.1–1.5 mcg/kg/h for a median period of 78 h (range, 40–290 h). The major findings of this study were (1) a significant decrease in heart rate, MAP, inotrope score, and CVP among neonates and infants receiving DEX infusion; (2) a decrease in MAP associated with decrease in inotrope score during DEX infusion, suggesting an improved response to existing inotropes and improvement in vascular reactivity; and (3) a lack of substantial difference in major hemodynamic variables between neonates and infants, between single- and two-ventricle repair, between RACHS 4–6 and RACHS 1–3 categories for patients undergoing surgery, and between patients receiving a heart transplant and those receiving no heart transplant.

Chrysostomou et al. [8] were the first to describe the use of DEX as a sedative agent after cardiac surgery for children without significant adverse cardiovascular, respiratory, or gastrointestinal effects. The same group later demonstrated the use of this drug for infants after cardiac surgery [9].

The most frequently reported adverse effects associated with DEX infusion for children include dose-related hypotension and bradycardia [5, 12, 16, 23]. In the current study, DEX infusion was associated with similar findings of hypotension and bradycardia. Because the timing of DEX initiation was not uniform among all patients after surgery, it was difficult to differentiate whether the hemodynamic changes were caused by the potential presence of low cardiac output syndrome or by DEX.

In the current study, a decrease in MAP was not associated with escalation of inotropic support or the need for fluid boluses. In fact, it was associated with a decrease in inotropic support. It has been proposed that α_2 agonists such as DEX aid in restoring vascular reactivity to exogenously administered catecholamines for patients with catecholamine-refractory shock [19]. Sympathetic inhibitors such as α_2 agonists lower intrasynaptic catecholamine concentrations, leading to reduction in α_1 desensitization. This eventually leads to gradual re-sensitization of α_1 receptors and a better response to exogenously administered catecholamines [11, 19]. Moreover, this sympatholysis may decrease the myocardial oxygen requirement and myocardial oxygen consumption. These results should be interpreted with caution and investigated in future studies because our findings appear to be counterintuitive regarding sympatho-inhibition in the setting of catecholamine-refractory shock.

We did not observe any bradyarrythmias, clinical respiratory depressions, or significant changes in arterial blood gases or oxygen saturation. These results are consistent with the results seen with clonidine [13] and, in other studies, with DEX [4, 8, 17, 25]. Other investigators have demonstrated that DEX causes mild decreases in PaO_2 levels, oxygen saturation, and mild hypercapnia. These changes, however, are often clinically insignificant [4, 9]. We found that DEX administration significantly reduced the concomitant daily dosing of opiates and benzodiazepines via infusion, which is consistent with other pediatric studies performed in CVICU settings [3, 6, 14].

In our study, 74% of the neonates and infants received clonidine after discontinuation of DEX infusion. It is possible that they were manifesting a withdrawal phenomenon with removal of DEX. The withdrawal phenomenon after sedation with DEX is an increasing concern in the literature, with some authors reporting symptoms such as increasing agitation, hypertension, tachycardia, emesis, dilated pupils, diarrhea, increased muscle tone, sneezing,

and even seizures with abrupt discontinuation of prolonged DEX infusion (≥96 h) [10, 22, 24].

This study had several limitations. It was a single-center study, so the results may not be generalizable to all centers. The retrospective design of the study rendered it susceptible to design flaws and bias. We also lacked objective data regarding ventricular function and cardiac output during DEX infusion. The calculation for the inotrope score in our study included inodilators such as milrinone that may have falsely affected the score either during or after termination of DEX. Given the limited data, withdrawal symptoms or adverse side effects may have been missed. The decision to initiate DEX and the decision to wean opioid and benzodiazepine infusions after initiation of DEX were done at clinical assessment in the absence of any objective pain or comfort scores, which may have created a selection bias in our study.

Despite these limitations, our study provides a foundation for future prospective trials of DEX in multiple CVICUs. An additional study would be useful for a conclusion that the decrease in conventional sedation is significant. A prospective, observational study with a control group of patients receiving conventional sedation versus an experimental group receiving DEX and conventional sedation, using a comfort score, would provide an interesting opportunity to determine whether the decrease in conventional sedation has an additional value regarding the number of ventilation days and the ICU length of stay after cardiac surgery.

Conclusion

This is one of the largest studies on the use of DEX infusion in infants and children with critical heart disease. Based on our experience, we conclude that DEX infusion in neonates and infants with heart disease is safe from a hemodynamic standpoint and can reduce the concomitant dosing of opioid and benzodiazepine agents. Furthermore, DEX infusion may be useful in reducing vasopressor agent dosing for children with catecholamine-refractory cardiogenic shock. An additional study with a well-defined control group would be useful for concluding that the decrease in inotrope score and conventional sedation is significant.

References

1. Anand KJ, Hickey PR (1992) Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 326:1–9
2. Barton KP, Munoz R, Morell VO, Chrysostomou C (2008) Dexmedetomidine as the primary sedative during invasive procedures in infants and toddlers with congenital heart disease. Pediatr Crit Care Med 9:612–615
3. Bejian S, Valasek C, Nigro JJ, Cleveland DC, Willis BC (2009) Prolonged use of dexmedetomidine in the paediatric cardiothoracic intensive care unit. Cardiol Young 19:98–104
4. Belleville JP, Ward DS, Bloor BC et al (1992) Effects of intravenous dexmedetomidine in humans: Part I. Sedation, ventilation, and metabolic rate. Anesthesiology 77:1125–1133
5. Bloor BC, Ward DS, Belleville JP et al (1992) Effects of intravenous dexmedetomidine in humans: II Hemodynamic changes. Anesthesiology 77:1134–1142
6. Buck ML, Willson DF (2008) Use of dexmedetomidine in the pediatric intensive care unit. Pharmacotherapy 28:1–57
7. Chrysostomou C, Zeballos T (2005) Use of dexmedetomidine in a pediatric heart transplant patient. Pediatr Cardiol 26:651–654
8. Chrysostomou C, Di Filippo S, Manrique AM et al (2006) Use of dexmedetomidine in children after cardiac and thoracic surgery. Pediatr Crit Care Med 7:126–131
9. Chrysostomou C, Sanchez De Toledo J, Avolio T, Motoa MV, Berry D, Morell VO, Orr R, Munoz R (2009) Dexmedetomidine use in a pediatric cardiac intensive care unit: can we use it in infants after cardiac surgery? Pediatr Crit Care Med 10:654–660
10. Darnell C, Steiner J, Szmuk P et al (2010) Withdrawal from multiple sedative agent therapy in an infant: is dexmedetomidine the cause or the cure? Paediatr Crit Care Med 11:e1–e3
11. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R et al (2008) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. Int Care Med 34:17–60
12. Ebert TJ, Hall JE, Barney JA et al (2000) The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 93:382–394
13. Eisenach JC (1994) Alpha2-agonists and analgesia. Expert Opin Invest Drugs 3:1005–1010
14. Hosokawa K, Shime N, Kato Y et al (2010) Dexmedetomidine sedation in children after cardiac surgery. Pediatr Crit Care Med 11:39–43
15. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI (2002) Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 123:110–118
16. Ko WJ, Lin CY, Chen RJ, Wang SS, Lin FY, Chen YS (2002) Extracorporeal membrane oxygenation support for adult postcardiotomy cardiogenic shock. Ann Thorac Surg 73:538–545
17. Koroglu A, Demirbilek S, Teksan H et al (2005) Sedative, haemodynamic, and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results. Br J Anaesth 94:821–824
18. Le KN, Moffett BS, Ocampo EC, Zaki J, Mossad EB (2011) Impact of dexmedetomidine on early extubation in pediatric cardiac surgical patients. Intensive Care Med 37:686–690
19. Pichot C, Géloën A, Ghignone M, Quintin L (2010) Alpha-2 agonists to reduce vasopressor requirements in septic shock? Med Hypotheses 75:652–656
20. Tobias JD (2000) Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care units. Crit Care Med 28:2122–2132
21. Tobias JD (2007) Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 8:115–131
22. Tobias JD (2010) Dexmedetomidine: are there going to be issues with prolonged administration? J Pediatr Pharmacol Ther 15:4–9
23. Venn RM, Grounds RM (2001) Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth 87:684–690

24. Weber MD, Thammasitboon S, Rosen DA (2008) Acute discontinuation syndrome from dexmedetomidine after protracted use in a pediatric patient. Paediatr Anaesth 18:87–88

25. Zornow MH (1991) Ventilatory, hemodynamic, and sedative effects of the alpha2-adrenergic agonist, dexmedetomidine. Neuropharmacology 30(10):1065–1071