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Perioperative Use of Dexmedetomidine is Associated with Decreased Incidence of Ventricular and Supraventricular Tachyarrhythmias after Congenital Cardiac Surgery

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Abstract

Background—Postoperative tachyarrhythmias remain a common complication after congenital cardiac surgery. A recent case-series has shown that dexmedetomidine, an alpha-2 adrenoreceptor agonist can have a therapeutic role in supraventricular tachyarrhythmias for either cardioversion to sinus rhythm or heart rate control. The present study was performed to determine if routine perioperative use of dexmedetomidine can decrease the incidence of supraventricular and ventricular tachyarrhythmias.

Methods—Prospective cohort study of pediatric patients undergoing cardiothoracic surgery. Thirty-two patients who were initiated on dexmedetomidine infusion (DEX-group) before surgery were compared with 20 patients who did not receive dexmedetomidine (control-group).

Results—Dexmedetomidine was started after anesthesia induction and continued through surgery and postoperative period for 38±4 hours at a mean dose of 0.76 ±0.04 mcg/kg/hr. Ten patients in control-group and 2 in DEX-group (p=0.001) had a total of 16 episodes of

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tachyarrhythmias. The incidence of ventricular tachycardia was 25% vs.0% (p=0.01) and of supraventricular arrhythmias 25% vs. 6% (p=0.05) in the control and DEX-group respectively. Two patients in the control-group and 1 in the Dex-group had transient complete heart block. Control-group had a higher heart rate 141 ± 5 vs.127 ±3 bpm (p=0.03), more sinus tachycardia episodes 40% vs. 6% (p=0.008), required more antihypertensives with nitroprusside 20 ± 7 vs.4 ± 1 mcg/kg (p=0.004) and nicardipine 13 ± 5 vs.2 ± 1 mcg/kg (p=0.02) and required more fentanyl 39 ± 8 vs.19 ± 3 mcg/kg (p=0.005).

Conclusions—Perioperative use of dexmedetomidine is associated with significantly decreased incidence of ventricular and supraventricular tachyarrhythmias without significant adverse effects.

Keywords

Arrhythmias; Perioperative Care; Atrial Fibrillation/Flutter; Cardiopulmonary Bypass; CHD Norwood

Introduction

Postoperative tachyarrhythmias remain a common complication after congenital cardiac surgery with an incidence between 25 and 50% [1,2]. Factors that have been associated with an increased risk for these arrhythmias include preexisting myocardial dysfunction, complex operation associated with myocyte damage and edema, extensive suture lines, myocardial ischemia, postoperative electrolyte disturbances, and cardiopulmonary bypass (CPB)-related inflammatory response and catecholamine surge. These arrhythmias can jeopardize hemodynamic stability and urgent treatment may often be necessary to either slow the heart rate (HR) or restore normal sinus rhythm (NSR). A number of studies have examined the efficacy of prophylactic treatment for prevention of postoperative arrhythmias, particularly in the adult population [3–6]. Prophylaxis with beta blockers appears to have a benefit in a subset of supraventricular arrhythmias; however the use of these agents has been avoided after pediatric cardiac surgery largely because of the negative inotropy. Digoxin and magnesium have had equivocal results. Amiodarone, though some studies have shown it to be more effective, particularly for atrial fibrillation, others have failed to do so. Furthermore its serious adverse effect profile including bradycardia, hypotension, heart block and negative inotropy likely outweighs its potential benefit and its routine use is considered by many excessive and not warranted in the pediatric population.

Dexmedetomidine, a highly selective alpha-2 adrenoreceptor agonist, is one of the latest sedative and analgesic agents that has earned its place in the armamentarium of anesthesiologists and intensivists, partly because of its minimal effect on respiration. Beyond its well known properties, a recent study has shown that dexmedetomidine has potential antiarrhythmic properties and can be used for the acute treatment of pediatric supraventricular tachyarrhythmias including junctional ectopic, atrial ectopic and reentrant type tachycardias [7]. In addition, animal studies have demonstrated that activation of imidazoline and alpha-2 adrenoceptors in the central nervous system, prevents adrenaline-induced ventricular tachycardia and that stimulation of the vagus nerve may be critical for this antiarrhythmic effect [8–11].

With this background we hypothesized that administration of dexmedetomidine during the perioperative period of children undergoing cardiothoracic surgery would be associated with decreased incidence of supraventricular and ventricular arrhythmias.

Material and Methods

This was a prospective cohort study of pediatric patients undergoing cardiothoracic surgery with CPB. Patients were divided into two groups according to the anesthetic technique used; patients who were initiated on dexmedetomidine (Hospira, Inc. Lake Forest, IL, USA) infusion after anesthesia induction comprised the dexmedetomidine group (DEX-group) and patients who did not receive dexmedetomidine as part of their anesthetic regimen comprised the control-group. The decision whether patients would receive dexmedetomidine or not was a clinical decision and based entirely on the preference of the primary cardiac anesthesiologist. Patients were enrolled from October 15, 2009 to June 30, 2010. The primary outcome was the incidence of postoperative supraventricular and ventricular tachyarrhythmias. Supraventricular tachyarrhythmias included reentrant supraventricular tachycardia (Reentrant-SVT), atrial ectopic tachycardia (AET), atrial flutter (AF), atrial fibrillation (AFib), sustained atrial bigeminy and junctional ectopic tachycardia (JET). Ventricular tachyarrhythmias included ventricular tachycardia (VTAC), ventricular fibrillation (VFib) and sustained or prolonged ventricular ectopy. Secondary outcomes included duration of mechanical ventilation, inotropic and vasotropic support, cardiac intensive care unit (CICU) and hospital length of stay and perioperative mortality. To ensure consistency in the surgical, anesthetic and postoperative approach, during the study period the medical team remained the same including the cardiothoracic surgeons, cardiac anesthesiologists and cardiac intensivists. The study was approved by the local institutional review board and an informed consent was obtained from all patients. A designated data and safety monitoring person reviewed the results every 3 months.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Exclusion Criteria

A subject was excluded from the study if he/she met any of the following criteria obtained from review of medical records: significant baseline neurologic impairment that prohibited accurate titration of sedative and analgesic agents; weight <2 kg; permanent pacemaker; history of arrhythmias within the last 6 months; antiarrhythmic medications and beta blockers within the last 72 hours; and use of amiodarone or dexmedetomidine within the last 30 days. Additional exclusion criteria included use of dexmedetomidine for ≤ 12 hours after the end of CPB and use of dexmedetomidine for sedation in the control-group in excess of 1 mcg/kg/day, since 1 mcg/kg intravenous load is the recommended dose by the manufacturer to reach steady-state. If dexmedetomidine was used in the control-group as a rescue agent for arrhythmia and the dose exceeded 1 mcg/kg/day then all recorded data following the initiation of dexmedetomidine, were also excluded from analysis. Currently in our center use of dexmedetomidine for the treatment of supraventricular tachyarrhythmias is considered part of standards of care.

Anesthetic Technique

Intraoperative

The anesthetic management followed pre-established guidelines. Anesthesia was induced with sevoflurane or intravenous fentanyl in unstable patients. For muscle relaxation rocuronium was used. The patients were maintained on isoflurane (end-tidal 0.5–1.6 %) and sufentanyl infusion (0.2–0.3 mcg/kg/hr). Some patients received a caudal-block (1cc/kg up to 15cc of bupivacaine (0.25%) with epinephrine (1:200000) and preservative-free morphine (40mcg/kg)). In those patients who received dexmedetomidine, it was administered prior to surgical incision as a 1mcg/kg load followed by a 0.5 mcg/kg/hr infusion that was continued

through surgery and to the CICU. Intraoperative opioids were minimized in an effort to extubate potential patients prior to leaving the operating room. In extubated patients, additional dexmedetomidine, midazolam and fentanyl were titrated to patient comfort. In patients who would remain intubated, anesthesia was further supplemented with 10–30 mcg/kg of fentanyl.

Postoperative

The DEX-group patients remained on dexmedetomidine infusion as the main sedative and analgesic agent. The dose ranged between 0.1–1.5 mcg/kg/hr and adjustments in the dexmedetomidine dose and or administration of other rescue sedative and analgesic agents were made according to standard CICU sedation and analgesia scales. For breakthrough agitation and or pain dexmedetomidine infusion was increased by 0.1–0.3 mcg/kg/hr. If this was inadequate 20 minutes after the change, a rescue agent was administered and dexmedetomidine infusion was further increased to a maximum of 1.5 mcg/kg/hr. If at the maximum dexmedetomidine dose patient still required frequent rescue doses (> 1 dose/hour) then a fentanyl infusion at a range of 0.5–2 mcg/kg/hr was started. The intermittent rescue agents included intravenous fentanyl 1 mcg/kg, morphine 0.05 mg/kg, midazolam 0.1 mg/kg and lorazepam 0.1 mg/kg every hour as needed and enteral chloral hydrate 15 mg/kg every four hours as needed. Muscle relaxation was provided with cisatracurium as necessary.

Control-group patients were maintained on a fentanyl infusion 1–4 mcg/kg/hr if intubated and subsequently or if not intubated they were administered the same rescue sedatives and analgesics used for the DEX-group using the same parameters.

Cardiopulmonary Bypass Management

Anticoagulation was initiated with heparin 350–400 U/kg with the target kaolin-ACT (HEMOCHRON® Jr. Signature Microcoagulation System, International Technidyne Corporation, ITC) value ≥ 450 seconds before initiation of CPB. Nonpulsatile CPB was performed with roller pump and a microporous hollow fiber membrane oxygenator. Pump flow rates ranged from 3.0–3.2 l/min/m^2 for temperatures 37°–30°C and from 2.0–2.5 l/min/m^2 for temperatures 29.9°–18°C. Magnesium sulphate 0.4 meq/kg and methylprednisolone 30 mg/kg was added to the pump prime. A pH-stat acid-base management strategy for patients undergoing deep hypothermic circulatory arrest was used without the addition of any continuous regional low-flow perfusion. For inotropic support epinephrine 0.02–0.1 mcg/kg/min and milrinone 0.5–1.2 mcg/kg/min were routinely used to facilitate weaning from CPB. For control of hypertension sodium nitroprusside 0.5–3 mcg/kg/min was used as needed. Modified ultrafiltration was performed following termination of CPB in all patients less than 15 kg, ultrafiltrating a volume of 30–100 cc/kg up to maximum of 600 cc. Furosemide 1 mg/kg up to 20 mg maximum was administered to all patients following termination of CPB. Protamine 4 mg/kg was given for reversal of heparin following termination of CPB and the modified ultrafiltration.

Arrhythmia Diagnosis and Definition

All patients were monitored using full-disclosure telemetry (CIC Pro-v5.0.3, GE Medical Systems Information Technologies, Inc) that stores information up to 48 hours. All telemetry tracings were reviewed manually every 12–24 hours and documented arrhythmias were printed and stored. In addition a 12-lead electrocardiogram (ECG) and an atrial electrogram were obtained when possible. All arrhythmia recordings were independently reviewed by a second cardiologist blinded to the groups. Arrhythmias during CPB or during separation from CPB where not considered significant and were excluded from analysis.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia was defined as: 1) a HR >170 bpm with a QRS morphology similar to the baseline QRS, 2) AV dissociation with ventricular rate higher than or equal to the atrial rate, 3) ventriculo-atrial (VA) association with retrograde 1:1 or Wenckebach conduction, 4) a pattern of "warm-up" phenomenon at initiation, though not necessary and 5) duration of arrhythmia ≥ 5 minutes or associated hemodynamic instability. In cases of 1:1 VA conduction, short VA interval and no obvious "p" waves or where tachycardia onset was abrupt, attempts were made to exclude a re-entrant type mechanism. An arrhythmia which met the above criteria but with HR ≤170 bpm was classified as a junctional accelerated rhythm (JAR).

Atrial Ectopic Tachycardia

Atrial ectopic tachycardia was defined by different "p" wave morphology than the sinus "p" wave, HR 150–250 bpm with substantial variability, typically a "warm-up" phenomenon though not necessary and duration of arrhythmia ≥ 5 minutes or associated hemodynamic instability.

Atrial Flutter

Abrupt onset tachyarrhythmia with no distinct "p" waves but rather typical flutter waves, HR 150–350 bpm, variable AV block or 1:1 AV conduction with QRS morphology similar to baseline and duration of arrhythmia ≥ 5 minutes or associated hemodynamic instability.

Atrial Fibrillation

Abrupt onset irregular tachyarrhythmia, with irregular ventricular response without distinct "p" waves but rather a ripple of chaotic atrial depolarization, HR 150–350 bpm and duration of arrhythmia ≥ 5 minutes or associated hemodynamic instability.

Reentrant-Supraventricular Tachycardia

Abrupt onset, regular tachycardia with QRS morphology similar to baseline and HR 200–350 bpm, atrial electrogram may show retrograde "p" waves with a short VA interval, duration of arrhythmia ≥ 3 minutes or associated hemodynamic instability. In this type of arrhythmia, the 3 minute duration was chosen because of the historical propensity of the clinical team to intervene and attempt cardioversion.

Ventricular Tachycardia

Abrupt onset, regular tachycardia with wide QRS morphology different from baseline and HR 150–350 bpm, and duration ≥ 10 beats.

Ventricular Fibrillation

Abrupt onset, irregular tachycardia without discernible "p" waves or QRS complexes but rather a ripple of chaotic ventricular depolarization.

Other Arrhythmias

Sustained atrial or ventricular contractions ≥ 30 per minute for ≥ 30 minutes.

Risk stratification

To ensure similar group comparison, patients were risk-stratified based on the complexity of their surgical procedures using the basic Aristotle score [12]. The basic Aristotle score

adjusts for the complexity of the procedures and it is based on three factors: the potential for mortality, the potential for morbidity and the anticipated technical difficulty.

Postoperative monitoring

The following parameters were monitored for up to 72 hours after the end of CPB: vital signs; duration of mechanical ventilation; requirement of sedatives, analgesics, inotropic and systemic vasodilator support; and use of antiarrhythmic medications. Laboratory monitoring included immediately post CPB and then creatinine, potassium, magnesium and ionized calcium levels, and every 4 hours lactate and blood gases with electrolytes as clinically indicated. Episodes of sinus tachycardia and hypertension (defined as values ≥90% for age) and sinus bradycardia and hypotension (values ≤5% for age, or bradycardia requiring temporary atrial pacing) were recorded for analysis.

Statistics

Based on an incidence of all arrhythmias after pediatric cardiac surgery of 15–48 % and assuming an incidence of the primary end-point of 30% in the control-group and a 50% reduction in the DEX-group, we calculated that a total of 52 patients would establish a power of 95% based on a 2-tailed α error of 0.05 [1,2].

Descriptive summaries over the 72-hour period are presented as counts and proportions for categorical variables, and means ± standard error or median with range for continuous variables. For the primary end-point of post-surgical tachyarrhythmia, the difference in the proportions between the treated and control arm were tested using the X^2 test. For the comparison of demographics, operative details, postoperative medication use, and length of stay, the 2 arms of the study were compared using the X^2 test for categorical variables. The parametric independent samples t-test and nonparametric Mann-Whitney U-test were used for continuous variables that did or did not meet the assumption of normality, respectively. Repeated measures ANOVA with Fisher's LSD post-hoc analysis was used to compare the time-varying vital signs. The Pearson correlation coefficient was used to measure the correlation between incidence of tachyarrhythmias and the use of epinephrine. All statistical comparisons were performed as 2-sided tests with a significance level of 0.05 using the statistical analysis software SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

After interim analysis a significant difference was observed between the groups with statistically higher incidence of tachyarrhythmias in the control-group. In addition, given the nature of the study design (non-blinded cohort study), there was a shift in clinical practice from an approximate use of dexmedetomidine in about 60% of the patients (based on previous 2 years of hospital data) to more than 95%. This shift in practice was based on the above observation of less tachy-arrhythmias in the DEX-group and made the continuation of the study almost impossible given the lack of adequate amount of control-group patients The study was terminated after enrollment of 52 patients.

The patient baseline characteristics and intraoperative parameters are summarized in table 1. There were no differences between DEX and control-groups. Seven patients in the control (35%) and 12 in the DEX-group (37%) had the highest surgical complexity of Aristotle level of 4 or basic Aristotle score of 10–15. Table 2 shows the surgical procedures performed in both groups. A caudal block was administered in 8 patients, 2 in the control and 6 in the DEX-group (p=0.65). Two patients in the control-group received dexmedetomidine during the study period. First patient received dexmedetomidine as a rescue treatment for AET. The patient had already received amiodarone but continued having frequent episodes of EAT

with HR >200 bpm. A 1 mcg/kg loading followed by an infusion 1 mcg/kg/hr was administered with significant decrease in the AET rate to <150 bpm. This patient was excluded from all postoperative data analysis other than the arrhythmia analysis. Second patient received 1 mcg/kg bolus of dexmedetomidine on the first and second postoperative days for JET. Patient had only partial benefit from amiodarone and continued to have breakthrough episodes of JET with a rate >170 bpm. With each dose of dexmedetomidine JET rate decreased from 193 to 162 bpm and from 183 to 169 bpm respectively.

The DEX-group received dexmedetomidine infusion for 38 ± 4 hours at a mean dose of 0.76 ± 0.04 mcg/kg/hr. During the 72-hour period 16 patients (31%) had a total of 20 episodes of arrhythmias, 16 tachyarrhythmias and 4 bradyarrhythmias (Table 3). The incidence of ventricular arrhythmias was 25% vs. 0% (p=0.01) and of supraventricular arrhythmias 25% vs. 6% (p=0.05) in the control and DEX-group respectively. Ventricular tachycardia occurred in patients after aortic arch and ventricular septal defect (VSD) repair (n=2), Rastelli (n=1), VSD closure (n=1), truncus arteriosus repair (n=1) and Norwood procedure (n=1). Atrial ectopic tacycardia occurred in patients after aortic arch and VSD repair (n=1), Norwood procedure (n=1), and right ventricular outflow reconstruction (n=1). Junctional ectopic tachycardia after VSD repair (n=1) and vascular ring repair (n=1). Re-entrant SVT after Norwood (n=2) and truncus arteriosus repair (n=1). Atrial bigeminy after Norwood (n=1). Junctional accelerated rhythm after an atrial septal defect repair (n=1). For the brady-arrhythmias, complete AV block occurred after a double switch procedure for congenitally corrected transposition of the great arteries (n=1), after an intraventricular tunnel repair (n=1) and after a VSD closure (n=1). Sinoatrial node dysfunction occurred in a patient after aortic arch and VSD repair (n=1). From the total of 20 arrhythmia episodes 15 required temporary intervention, control-group 10 and DEX-group 5 (Table 4). The 3 patients with VTAC and no intervention, one had an episode of 18-beat VTAC, second had several 10–20-beat VTAC episodes within a period of 45 minutes, and last had an episode of 15-beat VTAC. The patient with atrial bigeminy had sustained bigeminy that lasted for 65 minutes. In the DEX-group, one patient after Norwood I procedure developed 2 episodes of Reentrant-SVT while on dexmedetomidine infusion at 0.75 mcg/kg/hr. For the first episode he received 1 mcg/kg of dexmedetomidine load with immediate cardioversion to NSR, while for the second episode he received adenosine with also successful cardioversion to NSR. Of note however that while no significant hemodynamic changes were observed during the dexmedetomidine load, the patient developed significant bradycardia (HR 55 bpm) and hypotension (mean BP 29 mmHg) lasting approximately one minute after the administration of adenosine. Both episodes of JET occurred in patients with Aristotle level of 2.

The HR was significantly lower in the DEX-group during postoperative day # 0 (Table 5). However, clinically significant bradycardia requiring atrial pacing was only noted in one patient from each group (p=0.69). On the contrary, significantly more episodes of sinus tachycardia were noted in the control-group (p=0.008).

In Table 6 the remaining postoperative parameters are shown. Use of inotropic support with epinephrine and milrinone was similar in both groups and use or dose of epinephrine was not associated with occurrence of tachyarrhythmias (p=0.51, and p=0.72 respectively). Patients in the DEX-group required significantly less antihypertensive doses of both sodium nitroprusside and nicardipine. The overall sedative and analgesic requirement was similar except for the DEX-group requiring significantly less fentanyl. There was one death in the DEX-group. This patient was never separated from CPB after Norwood-I procedure due to decreased ventricular function. Subsequently developed significant intracranial hemorrhage and life support was withdrawn. Laboratory results are shown in Table 7. No significant difference was observed in creatinine level, lactates, blood gases or electrolyte levels.

Comment

Despite recent advancements in pediatric cardiac critical care, ventricular and supraventricular arrhythmias can present a challenging problem when encountered in the immediate postoperative period. The combination of excessively fast HR and the loss of atrioventricular synchrony are often poorly tolerated. Current standard therapies such as electrical cardioversion, defibrillation, overdrive pacing and intravenous antiarrhythmic agents may be undesirable, unavailable on a timely manner, ineffective, or associated with significant adverse effects.

The efficacy of pharmacologic treatment for prevention of postoperative arrhythmias has been the focus of investigation in a number of studies [3–6]. Pediatric studies are scarce and as with some adult studies, have had equivocal results. In the current study our pivotal finding was that perioperative use of dexmedetomidine decreases the incidence of ventricular and supraventricular tachyarrhythmias without significant adverse effects.

Dexmedetomidine is an alpha-2 adrenergic receptor and imidazoline receptor agonist with primarily sedative and analgesic properties. Since its approval by the US Food and Drug Administration for use in intensive care unit adult patients more than 10 years ago, it has been increasingly used in many off-label indications such as procedural and pediatric sedation, anesthetic adjunct, opioid withdrawal etc [13–15]. In a recent case-series study we also demonstrated that dexmedetomidine can be used as an antiarrhythmic agent for supraventricular tachyarrhythmias [7]. In that study dexmedetomidine was used as a primary treatment in nine and as a rescue in five patients. The primary outcome with overall rhythm or HR control was achieved in 93% of the patients. All patients with JET had conversion to NSR or HR control; all patients with Reentrant-SVT had resolution of their tachyarrhythmia; one patient with AET had an initial HR control and then NSR within 85 minutes; one patient with AF failed to respond and two patients with JAR had HR control.

Further substantiation of the antiarrhythmic properties of dexmedetomidine is elucidated in a carefully designed animal study by Kamibayashi et al [16]. In this study it was suggested that the antiarrhythmic effects are mediated through enhancement of the vagal neural activity. The dorsal motor nucleus of vagus is an important region, where an efferent parasympathetic nerve originates, and the activity of this region is directly regulated by nucleus tractus solitarius where an afferent vagal sensory input terminates [17]. Both of these nuclei are rich in alpha-2 receptors and thus it seems likely that activation of these receptors by dexmedetomidine would lead to a potent enhancement of vagal activity [18]. In this study dexmedetomidine significantly increased the arrhythmogenic threshold of epinephrine-induced ventricular arrhythmia, an effect that was abolished in vagotomized animals. Though this mechanism is unlikely to explain the antiarrhythmic process for all the arrhythmias in our current study, many reports have demonstrated that enhanced vagal activity is protective against certain types of supraventricular and ventricular arrhythmias [19–21]. Similar to beta-blockade, enhanced vagal output via a mechanism that involves decreased cyclic-AMP production, prolongs the effective refractory period of myocardial cells and decreases automaticity. Another possible mechanism involves activation of imidazoline receptors. Dexmedetomidine containing an imidazole ring, has an affinity for these receptors and recent studies have shown that activation of central imidazoline type-I receptors has been implicated in the prevention of ventricular arrhythmias [9,22].

Based on our previous study results, the current findings of decreased incidence of JET, Reentrant-SVT and AET though quite significant, were not unexpected. We were surprised however to observe such a difference in the incidence of VTAC. These findings seem to

correspond with the so far aforementioned animal studies, all of which show that dexmedetomidine decreases the incidence and or increases the threshold for VTAC.

Despite dexmedetomidine's central alpha-2 adrenoreceptor mediated sympatholysis, we did not find a difference in the dose requirement of perioperative epinephrine, or in the number of hypotensive or bradycardic episodes. On the contrary we found that DEX-group required less antihypertensive agents. We speculate that dexmedetomidine attenuates the hyper-catecholaminergic state seen after CPB resulting in less inappropriate tachycardia and less hypertension.

Limitations with the current study include the inherent nature of a nonrandomized single-institution methodology that could not establish direct causal relationships with certainty. Some arrhythmias like AF and AFib were not detected during this study period and thus conclusions cannot be drawn for these arrhythmias. Our observation period was only 72 hours and thus we may have missed arrhythmias that occurred afterwards. Supplemental data like ventricular function were not available.

Our findings suggest that the use of dexmedetomidine during the perioperative period for congenital cardiac surgery, may reduce the incidence of both ventricular and supraventricular tachyarrhythmias without significant adverse effects. The current results are of paramount importance that can be used to perform larger randomized, double-blind trials, and therefore establishing potential newer therapeutic protocols.

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References

1. Pfammatter JP, Bachmann DC, Wagner BP, Pavlovic M, Berdat P, Carrel T, Pfenninger J. Early postoperative arrhythmias after open-heart procedures in children with congenital heart disease. Pediatr Crit Care Med. 2001; 2(3):217–222. [PubMed: 12793944]
2. Valsangiacomo E, Schmid ER, Schüpbach RW, Schmidlin D, Molinari L, Waldvogel K, Bauersfeld U. Early postoperative arrhythmias after cardiac operation in children. Ann Thorac Surg. 2002; 74(3):792–6. [PubMed: 12238841]
3. Cook RC, Humphries KH, Gin K, Janusz MT, Slavik RS, Bernstein V, Tholin M, Lee MK. Prophylactic intravenous magnesium sulphate in addition to oral {beta}-blockade does not prevent atrial arrhythmias after coronary artery or valvular heart surgery: a randomized, controlled trial. Circulation. 2009; 120(11 Suppl):S163–9. [PubMed: 19752363]
4. Bagshaw SM, Galbraith PD, Mitchell LB, Sauve R, Exner DV, Ghali WA. Prophylactic amiodarone for prevention of atrial fibrillation after cardiac surgery: a meta-analysis. Ann Thorac Surg. 2006; 82(5):1927–37. [PubMed: 17062287]
5. Crystal E, Garfinkle MS, Connolly SS, Ginger TT, Sleik K, Yusuf SS. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2004; 4:CD003611. [PubMed: 15495059]
6. Manrique AM, Arroyo M, Lin Y, El Khoudary SR, Colvin E, Lichtenstein S, Chrysostomou C, Orr R, Jooste E, Davis P, Wearden P, Morell V, Munoz R. Magnesium supplementation during cardiopulmonary bypass to prevent junctional ectopic tachycardia after pediatric cardiac surgery: a randomized controlled study. J Thorac Cardiovasc Surg. 2010; 139(1):162–169. [PubMed: 19819469]
7. Chrysostomou C, Beerman L, Shiderly D, Berry D, Morell VO, Munoz R. Dexmedetomidine: a novel drug for the treatment of atrial and junctional tachyarrhythmias during the perioperative period for congenital cardiac surgery: a preliminary study. Anesth Analg. 2008; 107(5):1514–22. [PubMed: 18931208]

8. Hayashi Y, Sumikawa K, Maze M, Yamatodani A, Kamibayashi T, Kuro M, Yoshiya I. Dexmedetomidine prevents epinephrine-induced arrhythmias through stimulation of central alpha-2 adrenoceptors in halothane-anesthetized dogs. Anesthesiology. 1991; 75(1):113–7. [PubMed: 1676567]
9. Kamibayashi T, Mammoto T, Hayashi Y, Yamatodani A, Takada K, Sasaki S, Yoshiya I. Further characterization of the receptor mechanism involved in the antidysrhythmic effect of dexmedetomidine on halothane/epinephrine dysrhythmias in dogs. Anesthesiology. 1995; 83(5): 1082–9. [PubMed: 7486159]
10. Kagawa K, Hayashi Y, Itoh I, Iwasaki M, Takada K, Kamibayashi T, Yamatodani A, Mashimo T. Identification of the central imidazoline receptor subtype involved in modulation of halothane-epinephrine arrhythmias in rats. Anesth Analg. 2005; 101(6):1689–94. [PubMed: 16301242]
11. Mammoto T, Kamibayashi T, Hayashi Y, Yamatodani A, Takada K, Yoshiya I. Antiarrhythmic action of rilmenidine on adrenaline-induced arrhythmia via central imidazoline receptors in halothane-anaesthetized dogs. Br J Pharmacol. 1996; 117(8):1744–8. [PubMed: 8732285]
12. Lacour-Gayet F, Clarke D, Jacobs J, Comas J, Daebritz S, Daenen W, Gaynor W, Hamilton L, Jacobs M, Maruszsewski B, Pozzi M, Spray T, Stellin G, Tchervenkov C. Mavroudis And C; Aristotle Committee. The Aristotle score: a complexity-adjusted method to evaluate surgical results. Eur J Cardiothorac Surg. 2004; 25(6):911–24. [PubMed: 15144988]
13. Berkenbosch JW, Wankum PC, Tobias JD. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. Pediatr Crit Care Med. 2005; 6(4):435–9. [PubMed: 15982430]
14. Chrysostomou C, Sanchez De Toledo J, Avolio T, Motoa MV, Berry D, Morell VO, Orr R, Munoz R. Dexmedetomidine use in a pediatric cardiac intensive care unit: can we use it in infants after cardiac surgery? Pediatr Crit Care Med. 2009; 10(6):654–60. [PubMed: 19295456]
15. Tobias JD. Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU. J Opioid Manag. 2006; 2(4):201–5. [PubMed: 17319480]
16. Kamibayashi T, Hayashi Y, Mammoto T, Yamatodani A, Sumikawa K, Yoshiya I. Role of the vagus nerve in the antidysrhythmic effect of dexmedetomidine on halothane/epinephrine dysrhythmias in dogs. Anesthesiology. 1995; 83(5):992–9. [PubMed: 7486186]
17. Ross CA, Ruggiero DA, Reis DJ. Projections from the nucleus tractus solitarii to the rostral ventrolateral medulla. J Comp Neurol. 1985; 242(4):511–34. [PubMed: 2418079]
18. Robertson HA, Leslie RA. Noradrenergic alpha 2 binding sites in vagal dorsal motor nucleus and nucleus tractus solitarius: autoradiographic localization. Can J Physiol Pharmacol. 1985; 63(9): 1190–4. [PubMed: 2996733]
19. Zuanetti G, De Ferrari GM, Priori SG, Schwartz PJ. Protective effect of vagal stimulation on reperfusion arrhythmias in cats. Circ Res. 1987; 61:429–435. [PubMed: 3621502]
20. Delacretaz E. Clinical practice. Supraventricular tachycardia. N Engl J Med. 2006; 354:1039–1051. [PubMed: 16525141]
21. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res. 1991; 68:1471–1481. [PubMed: 2019002]
22. Wikberg JES, Uhlen S, Chhajlani V. Medetomidine stereoisomers delineate two closely related subtypes of idazoxan (imidazoline) I-receptors in the guinea pig. Eur J Pharmacol. 1991; 193:335–340. [PubMed: 1675995]

Table 1

Demographic and Intraoperative Patient Characteristics

	Control (N=20)	DEX (N=32)	*P-value*
Age, m	2.6 (0.13– 158)	4.8 (0.16 – 198)	0.29
Weight, Kg	3.9 (2.6– 99)	5.3 (2.6 – 83)	0.23
Sex, F (%)	12 (60)	11 (34)	0.13
Aristotle Score	7.3 (4.0– 14.5)	8.5 (3.0–14.5)	0.24
CICU Stay, d *	4 (1–16)	4 (1–20)	0.59
Hospital Stay, d †	7 (3–19)	8 (3–45)	0.63
Intraoperative data			
CPB Time, min	79 ± 9	93 ± 7	0.12
Aortic Clamp Time, min	30 ± 6	33 ± 6	0.84
Circulatory Arrest time, min	31 ± 6	26 ± 4	0.57
Modified Ultrafiltration, ml/kg	71 ± 5	65 ± 3	0.14
Dexmedetomidine LD, mcg/kg		1 ± 0.1	
Dexmedetomidine, mcg/kg/hr		0.5	
Sufentanyl, mcg/kg/min	0.33 ± 0.06	0.28 ± 0.03	0.40
Fentanyl, mcg/kg	25 ± 7	20 ± 4	0.85
Midazolam, mg/kg	0.33 ± 0.06	0.33 ± 0.05	0.69
Caudal-block, n (%)	2 (10)	6 (19)	0.65
Epinephrine, mcg/kg/min	0.06 ± 0.01	0.07 ± 0.01	0.92
Milrinone, mcg/kg/min	0.88 ± 0.17	0.87 ± 0.17	0.85
Methylprednisolone, mg/kg	28 ± 1	29 ± 1	0.4
Magnesium Sulphate, meq/kg	0.4 ± 0.1	0.4 ± 0.1	0.4

CICU: cardiac intensive care unit; CPB: cardiopulmonary bypass; LD: loading dose

*Length of stay from surgery to CICU discharge;

†Length of stay from surgery to hospital discharge

Table 2

Cardiac Surgeries Performed Based on the Aristotle Classification

	Control (n=20)	DEX (n=32)
Anomalous Systemic Venous Connection Repair		1
Aortic Arch Repair	1	1
Aortic Arch Repair + VSD Repair	3	1
Aortic Stenosis, Subvalvar, Repair		1
ASO		1
Atrial Septal Defect Repair, Patch		2
AVSD, Complete, Repair	1	2
AVSD, Partial, Repair	1	
Cardiac Tumor Resection	1	
Coarctation Repair, End to End, Extended		1
Congenitally Corrected TGA Repair, Atrial Switch and ASO		1
Cor Triatriatum Repair	1	
Damus–Kaye–Stansel procedure		1
DORV, Intraventricular Tunnel Repair		1
Fontan, External Conduit, Fenestrated		1
Glenn Anastomosis	1	1
Norwood Procedure	2	4
Pulmonary Atresia - VSD - MAPCA (Pseudotruncus) Repair		1
Rastelli	1	1
Right Ventricular Outflow Tract Procedure	1	
TAPVC Repair	1	
TOF Repair, No Ventriculotomy		2
TOF Repair, Right Ventricle – Pulmonary Artery Conduit		1
TOF Rrepair, Ventriculotomy, Transanular Patch		2
Truncus Arteriosus Repair	1	1
Valve Replacement, Aortic or Mitral, Mechanical	1	1
Valvuloplasty, Aortic or Mitral		2
VSD Repair, Patch	4	2

ASO: arterial switch operation; AVSD: atrioventricular septal defect; DORV: double outlet ventricle; MAPCA: multiple aortopulmonary collaterals; TOF: tetralogy of Fallot; TAPVC: total anomalous pulmonary venous connection; TGA: transposition of the great arteries; VSD: ventricular septal defect

Table 3

Patients with Arrhythmias and Arrhythmia Episodes

	Control	DEX	*P-value*
Tachy-arrhythmias, n= patients (%)	10 (50)	2 (6)	***0.001***
Ventricular Tachycardia *	6		
Atrial Ectopic Tachycardia *	3		
Junctional Ectopic Tachycardia *	2		
Re-entrant SVT *	1	2	
Atrial Bigeminy *	1		
Junctional Accelerated Rhythm *		1	
Brady-arrhythmias, n= patients (%)	2 (10)	2 (6)	0.85
Complete AV Block *	1	2	
SA Node Dysfunction *	1		

* Number of arrhythmia episodes

AV: atrioventricular; SA: sinoatrial node; SVT: supraventricular tachycardia

Table 4

Arrhythmias and Interventions

	Intervention	
	Control	**DEX**
Tachy-arrhythmias		
VTAC (n=6)	3 = None	
	1 = Defibrillation, Lidocaine, Amiodarone	
	1 = Defibrillation, 1 = Amiodarone	
AET (n=3)	1 = None	
	1 = Amiodarone	
	1 = Amiodarone, DEX	
JET (n=2)	1 = Sedation, Atrial Pacing	
	1 = Amiodarone, DEX	
Re-entrant SVT (n=3)	1 = Adenosine	1 = DEX
		1 = Adenosine
Atrial Bigeminy (n=1)	1 = None	
JAR (n=1)		1 = Atrial Pacing × 2 hrs
Brady-arrhythmias		
Complete AV Block (n=3)	1 = AV pacing × 34 hrs	2 = AV Pacing < 14 hrs
SA Node Dysfunction (n=1)	1 = Atrial Pacing × 8 hrs	

AET: atrial ectopic tachycardia; AV: atrioventricular; DEX: Dexmedetomidine; JAR: junctional accelerated rhythm; JET: junctional ectopic tachycardia; SA: sinoatrial; SVT: supraventricular tachycardia; VTAC: ventricular tachycardia

Table 5

Hemodynamic Data

	Control (N=20)	DEX (N=32)	*P- Value*
HR, bpm			
POD # 0	144 ± 5	130 ± 4	***0.03***
POD # 1	144 ± 5	132 ± 5	0.07
POD # 2	136 ± 5	136 ± 4	0.89
SBP, mmHg			
POD # 0	87 ± 5	84 ± 4	0.61
POD # 1	86 ± 4	81 ± 4	0.20
POD # 2	96 ± 4	90 ± 4	0.22
Respiratory Rate, brpm			
POD # 0	49 ± 5	45 ± 3	0.16
POD # 1	38 ± 4	33 ± 3	0.20
POD # 2	43 ± 5	37 ± 4	0.17
Tachycardia, n (%) *	8 (40)	2 (6)	***0.008***
Bradycardia, n (%) *	1 (5)	1 (3)	0.69
Hypertension, n (%) *	11 (55)	13 (40)	0.46
Hypotension, n (%) *	2 (10)	9 (28)	0.22

HR: heart rate; SBP: systolic blood pressure

* Episodes throughout the study period

Table 6

Cardiorespiratory and Sedoanalgesic Requirements During the Postoperative Period

	Control (N=20)	DEX (N=32)	*P-value*
Intubated, n (%)	13 (68)	20 (62)	0.49
Duration of Intubation, d	3.5 ± 0.6	3.0 ± 0.8	0.5
Mortality, n (%)	0	1 (3)	0.8
Inotropic/Vasotropic Support			
Epinephrine, mcg/kg	0.56 ± 0.16	0.86 ± 0.25	0.38
Patients on Epinephrine, n (%)	10 (53)	14 (44)	0.63
Milrinone, mcg/kg	49 ± 5	37 ± 4	0.06
Patients on Milrinone, n (%)	20 (100)	32 (100)	NA
Nitroprusside, mcg/kg	20 ± 7	4 ± 1	***0.004***
Patients on Nitroprusside, n (%)	11 (58)	9 (28)	0.07
Nicardipine, mcg/kg	13 ± 5	2 ± 1	***0.02***
Patients on Nicardipine, n (%)	6 (32)	9 (28)	0.9
Sedatives/Analgesics			
Dexmedetomidine, mcg/kg/hr		0.76 ± 0.04	
Dexmedetomidine Duration, hr		38 ± 4	
Fentanyl, mcg/kg	39 ± 8	19 ± 3	***0.005***
Patients on Fentanyl Infusion, n (%)	16 (84)	18 (56)	0.08
Morphine, mg/kg	0.03 ± 0.01	0.02 ± 0.01	0.7
Midazolam, mg/kg	0.09 ± 0.02	0.07 ± 0.02	0.55
Lorazepam, mg/kg	0.02 ± 0.01	0.02 ± 0.01	0.7
Chloral Hydrate, mg/kg	25 ± 6	16 ± 4	0.23

Table 7

Laboratory Results During the Postoperative Period

	Control (N=20)	DEX (N=32)	*P-value*
Creatinine, mg/dl	0.41 ± 0.04	0.47 ± 0.04	0.42
Lactate, mmol/l	2.2 ± 0.2	2.6 ± 0.3	0.98
pH	7.45 ± 0.01	7.44 ± 0.01	0.66
pCO2, mmHg	43 ± 1	42 ± 1	0.41
pO2, mmHg	98 ± 11	124 ± 12	0.11
Hemoglobin, g/dl	14 ± 4	14 ± 3	0.84
Potassium, mmol/l	3.8 ± 0.5	3.9 ± 0.6	0.48
Magnesium, mg/dl	2.6 ± 0.4	2.7 ± 0.4	0.87
Ionized Calcium, mmol/l	1.4 ± 0.2	1.3 ± 0.1	0.09