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Original Research Article

Effect of dexmedetomidine on postoperative arrhythmias in children undergoing direct cardiac surgery with extracorporeal circulation (cardiopulmonary bypass)

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Abstract

Purpose: *To investigate the potential of dexmedetomidine in preventing or reducing postoperative arrhythmias in pediatric patients undergoing direct vision cardiac surgery with extracorporeal circulation (cardiopulmonary bypass (CPB)).*

Methods: *62 children undergoing elective CPB cardiac surgery in Northwest Women and Children's Hospital, Xian, China between May 2020 and June 2023 were randomly and equally divided into study and control groups. The study group received a loading dose of 1 μg/kg dexmedetomidine followed by continuous intravenous infusion during surgery, while control group received an equivalent volume of saline infusion during surgery. Clinical data, perioperative indices (adverse reactions and intraoperative use of vasoactive drugs), levels of lactic acid, blood urea nitrogen (BUN) glomerular filtration rate (GFR), and postoperative arrhythmias were compared between the two groups at the end of the surgery.*

Results: *The study group showed significantly lower postoperative lactate and BUN levels compared to the control group ($p < 0.05$). There was no significant difference in incidence of intraoperative hypotension, bradycardia, tachycardia, and vasoactive drug use between the two groups ($p > 0.05$). The study group showed significantly lower incidences of postoperative nausea and vomiting as well as supraventricular and ventricular arrhythmias compared to control group ($p < 0.05$). Furthermore, mean arterial pressure (MAP) at T2 and T3 was significantly lower in study group compared to control group ($p < 0.05$).*

Conclusion: *Dexmedetomidine reduces postoperative lactate, BUN levels, incidence of postoperative supraventricular and ventricular arrhythmias, maintains hemodynamic stability, attenuates stress responses, preserves renal function, and decreases postoperative nausea and vomiting in pediatric CPB cardiac surgery. Large-sample multicenter clinical trials are needed for validation in further studies.*

Keywords: *Dexmedetomidine, Extracorporeal circulation, Cardiac direct vision surgery, Arrhythmia*

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INTRODUCTION

Congenital heart disease is prevalent in children, and its incidence is closely related to factors such as genetics, drug use, and intrauterine infection [1]. With the progress of modern medical technology, the detection rate of congenital heart disease in children is increasing, with only a small proportion of children recovering naturally. For most children with

congenital heart disease, complications gradually increase with age, and the condition gradually worsens.

Currently, extracorporeal circulation (cardiopulmonary bypass (CPB)) cardiac catheterization is the main clinical treatment for children with congenital heart disease [2]. Due to the damage of cardiomyocytes and activation of the sympathetic nervous system during CPB surgery, the systemic inflammatory response is aggravated, which triggers arrhythmia [2]. Coupled with their young age, and the fact that they are light in weight with underdeveloped organs, low immunity and imperfect compensatory function, they are less tolerant to anesthesia and surgery, and the probability of arrhythmia after operation is further increased [3]. This is detrimental to postoperative recovery, and in severe cases, may even slow down the recovery process. The high probability of postoperative arrhythmia is not favorable to postoperative recovery and even affects the growth and development of children in serious cases. Therefore, it is important to achieve efficient and safe anesthetic, analgesia and sedation to reduce the incidence of postoperative arrhythmia.

Dexmedetomidine is a new highly selective alpha-2 (α_2)-adrenergic agonist with hypnotic, sedative, analgesic and anxiolytic effects, which has been widely used in adult anesthesia and sedation of patients in the intensive care unit [4,5]. Previous studies have shown that dexmedetomidine prevents postoperative arrhythmias [6], but the studies have mostly focused on adults, while fewer studies have been reported in children. This study therefore investigated the effect of dexmedetomidine on postoperative arrhythmias in children undergoing direct CPB cardiac surgery, to provide new information for reducing the incidence of postoperative arrhythmias.

METHODS

Participants

A total of 62 children who underwent elective general anesthesia CPB direct cardiac surgery in Northwest Women's and Children's Hospital between May 2020 and June 2023 were randomly and equally divided into study and control groups (n = 31 in each group). This study was approved by the Ethics Committee of Northwest Women's and Children's Hospital (approval no. 2020264). All parents or legal guardians of the children signed the informed consent for surgery, and the study was conducted in accordance with the guidelines of Declaration of Helsinki [7].

Inclusion criteria

Participants who met the diagnostic criteria for congenital heart disease or ventricular septal defect, and met the indications for CPB direct cardiac surgery, age < 14 years, meet the American Society of Anesthesiologists (ASA) classification II to III, meet the preoperative New York Heart Association (NYHA) cardiac function class I or II and voluntary consent to participate in the study.

Exclusion criteria

Upper respiratory tract infection within the last 2 weeks, allergy to dexmedetomidine components, secondary surgery, presence of severe abnormalities of hepatic and renal function, preoperative ventricular rate < 50 bpm or MAP < 60 mmHg, serious adverse effects during operation such as surgical accidents, temporary change of surgical method, intraoperative recirculation of extracorporeal circulation and uncooperative postoperative evaluation.

Anesthesia methods

Preoperative fasting was required for 2 h without drinking and 6 h without eating. General anesthesia with inhalation of a combined anesthetic was administered. Atropine 0.01 mg/kg was injected intramuscularly 30 min before operation. Peripheral venous access was established, oxygen was administered, and electrocardiogram (ECG), heart rate, MAP, blood pressure, pulse, oxygen saturation and electroencephalogram as well as bifrequency index (BIS) were monitored using a monitor connected to the room.

Induction of anesthesia

Intravenous vecuronium 0.1 mg/kg, fentanyl 3-8 μg/kg and isoproterenol 1-3 mg/kg were used to induce anesthesia. There was manually assisted expiration for 3-5 min, and a waiting period until the BIS reached 45-60, then tracheal intubation was carried out through the mouth, and the anesthesia machine was connected to the ventilator for mechanical ventilation after tracheal intubation. There was inhalation of 50 % oxygen, while respiratory parameters were set at tidal volume (6-8 mL/kg), respiratory rate (15 – 32 breaths/min), inhalation and exhalation rates (15 – 32 times/min) with an inspiratory/expiratory ratio (1:1.5), and partial pressure of end-

expiratory carbon dioxide (PETCO2) (35 - 45 mmHg).

Anesthesia maintenance

There was continuous inhalation of sevoflurane 1 %, intraoperative continuous pumping of veclobemide 80.0 μg/kg/h, fentanyl 1- 3.0 μg/kg/h, and continuous pumping of isoproterenol 2 - 10 mg/kg/h to maintain BIS at 45 – 60. The BIS was maintained (1 - 1.5 mm Hg) at 45 – 60, and the dose of isoproterenol and fentanyl was adjusted according to BIS. Study group received loading dose of dexmedetomidine (1 μg/kg) which was pumped for 10 min before anesthesia induction, followed by a maintenance dose at 0.5 μg/kg/h till the end of the. In the control group, the same volume of saline was continuously infused until the end of the procedure. If bradycardia (slowing of the heart rate by up to 20 % of basal value) occurred before the start of CPB, it was corrected with intravenous atropine 0.01 mg/kg. If hypotension (systolic blood pressure < 60 mmHg) occurred, phenylephrine 25 μg was administered intravenously, and if tachycardia (heart rate > 170 beats/min) occurred, esmolol 0.5 mg/kg was administered intravenously. Sevoflurane and vecuronium bromide were discontinued when the chest was closed and sutured subcutaneously, and propofol and dexmedetomidine were stopped at the end of the procedure. The patient was transferred to the intensive care unit (ICU) for anesthesia resuscitation after the operation.

Cardiopulmonary bypass (CPB) cardiac direct vision surgical method

Cardiopulmonary bypass (CPB) was performed with Stockert SII artificial heart-lung machine, Dideco 902 membrane oxygenator, paediatric extracorporeal circulatory tubing, were pre-filled with crystalloid, gelatin succinate, and deleterious erythrocytes by same group of surgeons. Before CPB, heparin 3.0 - 3.5 mg/kg was injected intravenously to prevent coagulation, and the aorta, vena cava, and descending vein were cannulated sequentially to establish CPB. Activated coagulation time (ACT) was maintained at > 480 s, MAP at 30-70 mmHg, central temperature was kept at 30 – 34 ^{o}C during the diversion period, the aorta was rewarmed to 33 – 34 ^{o}C before it was opened, and rewarmed again to 36 – 37 ^{o}C before shutdown, and a moderate temperature of 36 - 37 ^{o}C was maintained before shutdown. The following conditions were maintained; moderate haemodilution (36 – 37 ^{o}C), erythrocyte pressure product (0.25 - 0.35), perfusion volume in CBP (100 – 200 mL/min), MAP 50 – 70 mmHg, extracorporeal circulation machine set at an air-blood ratio of 0.5-1.0:1.0, and for ventilation, the perfusion volume ratio was about 1:2 - 3.

After the aorta was opened, dopamine 3 - 6 μg/kg/min and nitroglycerin 0.3 μg/kg/min were pumped intravenously, and the dose was adjusted according to blood pressure and central venous pressure. At the end of the extracorporeal circulation, cavitriol was slowly injected intravenously to neutralize heparin at a ratio of 1:1, and then more cavitriol was added according to ACT results.

Evaluation of parameters/indices

Baseline clinical data

Gender, age and weight of the children in the two groups were recorded and compared

Perioperative indices

Perioperative indices (intraoperative fluid replenishment, intraoperative bleeding, CPB time, operation time, postoperative extubating time and ICU stay time) of the two groups were compared.

Haematological indices

Arterial blood gas specimens of the two groups of children were collected before and 24 h after the operation, and level of blood lactic acid was evaluated in both groups and compared. Also, blood urea nitrogen (BUN), creatinine and GFR of the two groups recorded before and after surgery and compared.

Incidence of postoperative acute kidney injury (AKI)

Incidence of postoperative acute kidney injury was recorded using the KDIGO criteria for AKI [8].

Perioperative adverse effects

Perioperative adverse effects (hypotension (systolic blood pressure < 60 mmHg)), bradycardia (heart rate < 7 0 beats/min), tachycardia (heart rate > 170 beats/min), postoperative nausea and vomiting, and use of intraoperative vasoactive drugs in the two groups were compared.

Incidence of arrhythmia

The incidence of arrhythmia within 48 h after surgery was recorded and compared between

the two groups. Arrhythmias included supraventricular arrhythmias, ventricular arrhythmias and bradyarrhythmias (sinus bradycardia, second-degree and third-degree atrioventricular block), which were diagnosed by bedside 12-lead electrocardiogram.

Perioperative hemodynamics

Perioperative hemodynamics of the two groups were recorded and compared, within the first 10 min before induction of anesthesia (T0), first 10 min before start of CPB (T1), first 10 minutes after start of CPB (T2), and the last 30 min after start of CPB (T3). Also, HR (Heart Rate) and MAP levels at the end of surgery (T4) were also compared.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) 17.0 statistical software (IBM, Armonk, NY, USA). Normally distributed measurement data was expressed as mean ± standard deviation (SD), and compared using t-test. Measurement data that did not conform to normal distribution was expressed as median (interquartile spacing) (median IQR), and compared using Mann-Whitney U test. Categorical data were expressed as frequency and percentages (%), and compared using chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline clinical data and perioperative indices

There was no significant difference in baseline clinical data (gender, age, weight, intraoperative rehydration volume, intraoperative bleeding volume, CPB time and operation time) between the two groups ($p > 0.05$). Furthermore, study group showed significantly improved postoperative extubating time and ICU stay compared to control group ($p < 0.05$, Table 1).

Haematological indices

There was no significant difference in GFR, and incidence of AKI before and after surgery between the two groups ($p > 0.05$). However, study group showed significantly lower postoperative lactate and BUN levels compared to control group ($p < 0.05$) (Table 2).

Perioperative adverse reactions and intraoperative vasoactive drug use

There was no significant difference in incidence of intraoperative hypotension, bradycardia, tachycardia and the use of intraoperative vasoactive drugs between the two groups ($p > 0.05$). However, study group showed significantly lower incidence of postoperative nausea and vomiting compared to control group ($p < 0.05$, Table 3).

Table 1: Baseline clinical data and perioperative indices (N = 31, mean, IQR)

Index	Study	Control	χ^2/Z	*P*-value
Sex (m/f)	17/14	18/13	0.067	0.798
Age (Years)	0.7(0.7)	0.7(2.2)	-0.410	0.682
Weight (kg)	8.0(5.0)	7.5(5.3)	-0.077	0.938
Intraoperative fluid replacement (mL)	300(150)	220(100)	-1.431	0.152
Intraoperative haemorrhage (mL)	30(30)	30(30)	-0.044	0.965
CPB time (min)	51(44)	5 (19)	-1.014	0.311
Surgical time (min)	160(60)	18 (40)	-0.637	0.524
Postoperative extubating time (min)	12(37)*	6. (21.5)	-2.009	0.045
ICU length of stay (h)	46(98)*	21(34.25)	-3.438	0.001

*$P < 0.05$ significantly different from control group

Table 2: Haematological indices (N = 31, mean ± SD)

Indices		Study	Control	χ^2/Z/t	*P*-value
Lactic acid (mmol/L)	Pre-operative	1.2(0.5)	1.2 (0.8)	-0.031	0.975
	Post-operative	2.65±0.76	4.66±1.59	6.350	< 0.001
BUN (mmol/L)	Pre-operative	3.34±1.23	4.01±1.58	1.856	0.068
	Post-operative	5.17±1.99	7.20±2.81	3.265	0.002
Glomerular filtration rate (mL/min)	Pre-operative	68.23±24.51	67.30±32.24	-0.127	0.900
	Post-operative	70.22±38.83	63.29±38.90	-0.678	0.500
Incidence of AKI		11(34.5)	12(38.7)	0.069	0.793

Table 3: Perioperative adverse reactions and intraoperative vasoactive drug use (N = 31, N, %)

Indices		Study	Control	χ^2	*P*-value
Serious adverse effect	Hypotension	5(16.13)	4(12.90)	0.130	0.719
	Bradycardia	3(9.68)	2(6.45)	0.218	0.641
	Tachycardia	0(0)	3(9.68)	3.153	0.076
	Postoperative Nausea and vomiting	1(3.23)	9(29.03)	7.631	0.006
Vasoactive drug	Atropine	2(6.45)	3(9.68)	0.218	0.641
	Phenylephrine	1(3.23)	1(3.23)	-	1.000
	Esmolol	0(0)	1(3.23)	1.016	0.313

Table 4: Incidence of postoperative arrhythmias (N = 31, N, %)

Indices	Study	Control	χ^2	*P*-value
Supraventricular arrhythmias	1(3.23)	8(25.81)	6.369	0.012
Ventricular arrhythmias	1(3.23)	6(19.35)	4.026	0.045
Bradyarrhythmias	1(3.23)	2(6.45)	0.350	0.554

Table 5: Heart rate (N = 31, mean ± SD)

Group	T_0	T_1	T_2	T_3	T_4
Study	129.56±12.57	110.24±10.89	-	-	109.82±10.64
Control	127.88±13.89	111.57±10.65	-	-	110.05±10.97
***T*-value**	0.499	0.486	-	-	0.084
***P*-value**	0.619	0.629	-	-	0.933

Values are beats/min. T_0: 10 min before induction of anesthesia; T_1: 10 min before the start of CPB; T_2: 10 min after the start of CPB; T_3: 30 min after the start of CPB; T_4: end of surgery

Table 6: Mean arterial pressure (MAP) (N = 31, mean ± SD)

Group	T_0	T_1	T_2	T_3	T_4
Study	67.82±6.63	49.67±6.29	58.81±5.63	56.15±5.17	55.42±4.87
Control	67.19±6.82	52.23±5.36	64.15±4.28	61.66±5.29	56.82±5.07
***T*-value**	0.369	1.725	4.204	4.148	1.109
***P*-value**	0.714	0.090	<0.001	<0.001	0.272

Values are mmHg. T_0: 10 min before induction of anesthesia; T_1: 10 min before the start of CPB; T_2: 10 min after the start of CPB; T_3: 30 min after the start of CPB; T_4: end of surgery

Incidence of postoperative arrhythmias

There was no significant difference in incidence of postoperative bradyarrhythmias between the two groups ($p > 0.05$). However, study group showed significantly lower incidence of supraventricular and ventricular arrhythmias compared to control group ($p < 0.05$, Table 4).

Heart rate (HR)

There was no significant difference in perioperative heart rate between the two groups ($p > 0.05$), and there was no heart rate at T2 and T3 because the patients were in extracorporeal myocardial arrest (Table 5).

Mean arterial pressure (MAP)

There was no significant difference in MAP at T_0, T_1 and T_4 in the two groups ($p > 0.05$). However, study group showed significantly lower MAP at T_2 and T_3 compared to control group ($p < 0.05$, Table 6).

DISCUSSION

The immature development of various systems in children results in less myoplasmic fibers in immature myocardial tissues, a large proportion of non-contractile material, and a lack of oxidative phosphorylation enzymes in cardiomyocytes. Greater reliance on glycolysis for energy supply results in poorer myocardial contractility, and a higher incidence of postoperative arrhythmias after CPB cardioplegia in children compared to adult patients. Previous studies have pointed out [9] that intraoperative physical injury, aortic blockade, repeat beating and other operations during CPB cardiac surgery are very likely to cause myocardial ischemia-

reperfusion injury coupled with surgical stress. Postoperative application of various vasoactive medications significantly increases the release of catecholamines, and oxidative stress is thought to be an important pathological mechanism causing myocardial ischemia-reperfusion injury. During CPB, the body is in a non-physiological state, resulting in hypothermia, acid-base imbalance, electrolyte disorders, drastic changes in hemodynamics and perfusion all of which cause the body to initiate severe stress responses. This causes a series of changes in neuroendocrine function, linked to the excitation of the sympathetic-adrenomedullary system (which releases a large number of catecholamines into the bloodstream), and the excitation of the hypothalamus-pituitary-adrenocortex caused by the release of corticotrophin and adrenal glucagon.

Adrenocorticotropic hormone and adrenoglucocorticotropic hormone release results in significant changes in hemodynamics and neuroendocrine function in children [10], which causes significant functional damage to the heart, lungs, brain, liver, kidney and other organs, and may lead to nausea and arrhythmia after surgery. Therefore, the selection of appropriate anesthesia drugs is important in alleviating the functional stress, and reducing the incidence of postoperative cardiac arrhythmias. Dexmedetomidine is a highly selective α2-adrenoceptor agonist with good sedative, analgesic and anxiolytic effects with no obvious respiratory inhibition. The mechanism of action is mainly through the activation of presynaptic and postsynaptic α2 receptors in the centre of the locus coeruleus to exert a sedative-hypnotic effect, thus inducing a state of unconsciousness similar to natural sleep, and its uniqueness lies in the fact that the patient is easily awaken [11].

Numerous studies have shown that dexmedetomidine stabilizes hemodynamic changes, reduce dosage of opioids and sedative drugs, weak respiratory depression, reduce dosage of catecholamines, reduce incidence of postoperative delirium in patients, and at the same time have a good neuroprotective effect [12,13]. These features have led to the widespread use of dexmedetomidine in perioperative anesthesia and as an anesthetic adjuvant drug for cardiothoracic surgery. The results of an animal experiment on myocardial ischemia showed that dexmedetomidine administered before ischemia exerts a significant myocardial protective effect, which suggests that the administration of dexmedetomidine may help to reduce myocardial oxygen consumption, increase myocardial energy reserve, and reduce myocardial ischemia/reperfusion injury caused by surgery [14]. The results of this study showed that MAP levels increased significantly at T_2 and T_3 in both groups, but MAP levels in the study group were significantly lower compared to control group, suggesting that dexmedetomidine reduced the stress response produced by severe stimuli such as CPB aortic block in CPB cardiac direct surgery anesthesia. The stress response is a non-specific response produced by the interaction of the nervous, immune and endocrine systems, and changes in lactate levels during perioperative period. Results of this study revealed that lactate level was significantly lower in study group after surgery compared to control group. This suggests that dexmedetomidine reduces the body's stress response, maintains organ and tissue perfusion, balances oxygen supply to the organs and tissues, and reduces anaerobic metabolism, which would in turn reduce lactate level. Also, this study also evaluated the effect of dexmedetomidine on renal function, and the results showed that postoperative BUN levels increased in both groups, but study group significantly lower level compared to control group. This suggests that dexmedetomidine had a lower negative effect on renal function in children. Also, there was no significant difference in incidence of postoperative AKI between the two groups, suggesting that dexmedetomidine does not have any significant negative effect on renal function in children which is in agreement with Loomba *et al* [15]. Elevated catecholamine levels are predisposing factors for adverse cardiovascular effects, especially tachyarrhythmias [16].

Previous study demonstrated that the use of dexmedetomidine reduces incidence of ventricular and supraventricular tachyarrhythmias arising from the inhibition of sinoatrial node, atrioventricular node function, and reduction of sympathetic excitability [17]. Incidence of supraventricular arrhythmias and ventricular arrhythmias in study group was significantly lower compared to control group suggesting that the use of dexmedetomidine in paediatric CPB cardiac surgery may reduce the incidence of postoperative tachyarrhythmias without increasing the risk of bradyarrhythmias. The main adverse reactions of dexmedetomidine are hypotension and bradycardia. This study evaluated the occurrence of perioperative adverse reactions, and the results showed that there was no significant difference in the incidence of intraoperative hypotension, bradycardia, tachycardia and the rate of intraoperative use of vasoactive drugs in both groups. The reasons for the occurrence of hypotension and bradycardia may be related to

the dose of dexmedetomidine, the input speed, and surgical straining. Furthermore, study group showed significantly lower incidence of postoperative nausea and vomiting compared to control group. This suggests that dexmedetomidine may help to reduce the incidence of nausea and vomiting, which is similar to previous reports [18].

Limitations of the study

This study is a single-center randomized controlled trial, and may limit the generalizability of the results.

CONCLUSION

Dexmedetomidine maintains perioperative hemodynamic stability, reduces incidence of postoperative arrhythmia, reduces stress response, preserves renal function, and reduces the incidence of postoperative nausea and vomiting. Large-sample multicenter clinical trials are needed in further studies.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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