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Original Article

Myocardial protection effects of dexmedetomidine priming on cardiopulmonary bypass surgery for children with congenital heart disease

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Abstract: *Background and aim:* Priming administration can reduce the inflammatory response and protect the myocardial function in cardiopulmonary bypass (CPB) surgery. However, the application of dexmedetomidine (DEX) priming to CPB surgery for children with CHD is less reported. This study aimed to investigate the myocardial protection effects of DEX priming in CPB surgery for children with CHD. *Methods:* Ninety CHD children were randomly divided into groups A, B and C, which received physiological saline priming, DEX priming and intravenous DEX infusion after anesthesia in CPB surgery, respectively. At the time point before anesthesia induction (T1), 30 min after CPB (T2), 6 h after CPB (T3), 20 h after CPB (T4) and 28 h after CPB (T5), the serum lactate dehydrogenase (LDH), creatine kinase isoenzyme MB (CK-MB), cardiac troponin I (cTnI), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels were detected. *Results:* There was no significant difference of operation time, CPB time, aortic occlusion time or heart rebound among three groups ($P > 0.05$). At T4 and T5, the serum LDH level in group B was significantly lower than that in groups A and C ($P < 0.05$). At T5, the serum CK-MB level in group B was significantly lower than that in groups A and C ($P < 0.05$). At T4, the serum cTnI level in group B was significantly lower than that in groups A and C ($P < 0.05$). At T4 and T5, the serum TNF-α and IL-6 levels in group B were significantly lower than that in groups A and C ($P < 0.05$). *Conclusion:* In CPB surgery for children with CHD, DEX priming can reduce the inflammatory response, and alleviate the myocardial injury, thus improving the cardiac function of patients.

Keywords: Dexmedetomidine, priming, congenital heart disease, cardiopulmonary bypass, myocardial injury

Introduction

At present, the infantile congenital heart disease (CHD) is very common in clinic. If not treated in time, the cardiac function of CHD patient will be significantly reduced, which seriously affects the health and growth of body [1]. The surgical treatment with cardiopulmonary bypass (CPB) is often performed in many CHD patients [2]. In the process of open-heart surgery with CPB, the cardioplegic solution and low temperature protection measures are used [3, 4]. However, as the myocardial cell metabolism is not completely stopped during the aortic occlusion peroid, the anaerobic metabolism still occurs, leading to the myocardial cell damage and necrosis. During the process of CPB, the contact of blood with artificial materials, low temperature in flow period, blood cell destruction and surgical trauma can activate neutrophils and other inflammatory cells. This causes the activation and release of inflammatory mediators including cytokines, chemokines and adhesion molecules, which results in the systemic inflammatory response syndrome, thereby increasing the occurrence of myocardial damage and postoperative complications [5]. Myocardial ischemia and reperfusion in CPB can lead to the formation of large amounts of oxygen free radicals, which causes the oxidative stress and aggravates the inflammation reaction [6]. In addition, the abnormal pulsation of blood flow under CPB may cause insufficient perfusion of surrounding organs and form an

ischemic reperfusion injury, resulting in multiple organ dysfunction and severe complications [7]. Therefore, the myocardial preservation in open-heart surgery with CPB has always been the focus of attention in cardiothoracic surgery. Dexmedetomidine (DEX) is the active dextroisomer of medetomidine, and has the sedative, hypnotic, analgesic and sympathetic blocking effect. It can cause the dose-related decrease of blood epinephrine concentration, and correspondingly decrease the heart rate and blood pressure [8]. During the coronary artery bypass surgery, the application of DEX can reduce the hemodynamic fluctuations caused by anesthesia and surgical operation [9]. In addition, DEX can accelerate the functional recovery of myocardial ischemia reperfusion injury, and inhibit the ventricular arrhythmia induced by myocardial reperfusion [10]. It is found that, priming administration can reduce the inflammatory response and protect the myocardial function in CPB surgery [11]. However, the application of DEX priming to CPB surgery for children with CHD is less reported. This study investigated the myocardial protection effects of DEX priming in CPB surgery for children with CHD. The objective was to provide a reference for further application of DEX priming to CHD surgery.

Materials and methods

Subjects

A total of 90 cases of CHD children treated in our hospital from June 2015 to March 2017 were enrolled in this study. There were 50 males and 40 females. The age of patients was 1 month-13 years, with average of 4.47±2.13 years. The body weight was 3-31 kg, with average of 14.44±3.65 kg. In CHD type, there were 55 cases of ventricular septal defect, 31 cases of atrial septal defect and 4 cases of pulmonary stenosis. All the patients were with grade II heart function. The cases with respiratory disease, abnormal liver and kidney function or abnormal coagulation function were excluded.

Anesthesia treatment

Ninety CHD children were randomly divided into physiological saline priming group (A), DEX priming group (B), and intravenous DEX infusion after anesthesia induction group (C), 30 cases in each group. All the patients received the anesthesia using sevoflurane inhalation by mask. The peripheral venous channel was opened after the eyelash reflex disappeared. After monitoring ECG and blood oxygen saturation, the intravenous induction using midazolam (0.1 mg/kg), sufentanil (1 μg/kg) and cis-atracurium (0.15 mg/kg) was performed, followed by tracheal intubation and mechanical ventilation with pressure-control mode. The intraoperative infusion of sufentanil (1.0-3.0 μg/(kg·h)) and inhalation of sevoflurane (1%-2%) were performed for the anesthesia maintenance. The cis-atracurium was intermittently added. The radial artery was punctured. The blood pressure, heart rate, arterial systolic pressure, diastolic pressure, mean arterial pressure, nasopharyngeal temperature and central venous pressure were monitored.

CPB surgery

CPB surgery of all patients was performed by the surgeons in the same department. The median sternotomy approach was selected. Heparin (400 U/kg) was intravenously injected to establish the conventional CPB. After blocking the ascending aorta, the hyperkalemic cold cardioplegic solution (potassium ion concentration, 20-22 mmol/L) was antegradely infused. During the CPB peroid, the mean arterial pressure was maintained at 30-55 mmHg, and the hematocrit was controlled at 0.25-0.30. The nasopharyngeal temperature was decreased to 31-32°C. Stockert artificial heart lung machine and Kuwait membrane oxygenator were used for CPB, and the Ringer acetate solution and plasma were used for priming. The priming drugs included heparin (5000 U), 5% sodium bicarbonate (1 ml/kg), furosemide (0.2 mg/kg), and methylprednisolone (30 mg/kg). In addition, in group B, 1 μg/kg DEX was added. In group A, normal saline with volume the same with DEX solution was added. In group C, 1 μg/kg DEX was intravenously infused immediately after anesthesia induction, and the infusion was completed within 15 min. At the end of surgery, the operation time, CPB time and aortic occlusion time were recorded, and the heart rebound was observed. The intracardiac defibrillation (10-20 J) was performed for cases with continued ventricular fibrillation but not self-recovery. The number of intracardiac defibrillation was recorded. The patients were sent to the ICU for continued treatment. After the

Table 1. Preoperative basic data of three groups

Group	A	B	C	P
n	30	30	30	
Gender (male/female, n)	17/13	14/16	17/13	> 0.05
Age (years)	4.3±1.6	3.7±1.3	5.2±3.5	> 0.05
Body weight (kg)	13.3±3.7	15.2±2.8	14.2±3.4	> 0.05
CHD type (n)				> 0.05
VSD	19	18	18	
ASD	10	10	11	
Pulmonary stenosis	1	2	1	

CHD, congenital heart disease; VSD, ventricular septal defect; ASD, atrial septal defect.

Table 2. Comparison of operation situation among three groups

Group	n	Operation time (min)	CPB time (min)	Aortic occlusion time (min)	Heart rebound (self-recovery/defibrillation, n)
A	30	100.03±27.05	55.42±11.25	31.34±8.71	26/4
B	30	96.56±19.44	51.78±12.18	29.05±7.23	27/3
C	30	105.12±22.47	53.25±12.17	30.17±8.21	26/4
P		> 0.05	> 0.05	> 0.05	> 0.05

CPB, cardiopulmonary bypass.

consciousness was awake and the respiration and circulation were stable, the patients were moved from ICU.

Observation indexes

At the time point before anesthesia induction (T1), 30 min after CPB (T2), 6 h after CPB (T3), 20 h after CPB (T4) and 28 h after CPB (T5), 5 ml of venous blood was extracted, and was added with 40 μL EDTA-Na_2, followed by mixing. After centrifugation at 256×g and 4°C for 5 min, the serum was separated and stored at -20°C. The serum lactate dehydrogenase (LDH), creatine kinase isoenzyme MB (CK-MB) and cardiac troponin I (cTnI) levels were detected using automatic biochemical analyzer. The serum tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels were detected by double antibody sandwich ELISA. Each determination was repeated for 3 times. The experimental operation was according to the instruction of kits.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). The enumeration data were presented as number, and were compared using χ^2 test. Measurement data were expressed as the mean ± SD and compared with single factor analysis of variance with SNK-q test. A *P* value of less than 0.05 was considered statistically significant.

Results

Preoperative basic data of three groups

The preoperative basic data of three groups were shown in **Table 1**. There was no significant difference of gender, age, body weight or CHD type among three groups (P > 0.05).

Comparison of operation situation among three groups

Table 2 showed that, there was no significant difference of operation time, CPB time, aortic occlusion time or heart rebound among three groups (P > 0.05).

Comparison of serum LDH level among three groups

As shown in **Table 3**, at T1, there was no significant difference of serum LDH level among three groups (P > 0.05). At T2, T3, T4 and T5, the serum LDH level in each group was significantly lower than that at T1. In addition, at T4 and T5, the serum LDH level in group B was significantly lower than that in groups A and C, respectively (P < 0.05), and that in group C was significantly higher than that in group B, respectively (P < 0.05).

Comparison of serum CK-MB level among three groups

Table 4 showed that, at T1, there was no significant difference of serum CK-MB level among three groups (P > 0.05). At T2, T3, T4 and T5, the serum CK-MB level in each group was significantly higher than that at T1. In addition, at T5, the serum CK-MB level in group B was sig-

Table 3. Comparison of serum LDH level among three groups (U/L) [4/7]

Group	n	T1	T2	T3	T4	T5
A	30	265.45±56.88	476.67±78.44*	573.28±93.10*	861.79±89.16*,#	956.93±130.89*,#
B	30	272.67±76.45	468.32±87.83*	543.94±98.05*	669.33±84.02*	723.11±113.87*
C	30	259.56±56.82	487.27±78.38*	559.32±93.72*	779.05±89.36*,#,&	847.93±130.28*,#,&

*P < 0.05 compared with T1; &P < 0.05 compared with group A; #P < 0.05 compared with group B. LDH, lactate dehydrogenase.

Table 4. Comparison of serum CK-MB level among three groups (U/L)

Group	n	T1	T2	T3	T4	T5
A	30	9.33±2.05	23.45±4.53*	29.88±6.01*	42.11±7.26*	45.05±7.88*,#
B	30	8.96±2.35	22.89±5.01*	28.06±5.87*	36.81±8.12*	37.24±8.32*
C	30	9.18±3.21	23.01±5.21*	28.45±4.89*	38.94±6.67*	40.02±8.11*,&

*P < 0.05 compared with T1; &P < 0.05 compared with group A; #P < 0.05 compared with group B. CK-MB, creatine kinase-MB.

Table 5. Comparison of serum cTnI level among three groups (μg/ml)

Group	n	T1	T2	T3	T4	T5
A	30	0.021±0.004	0.338±0.056*	0.814±0.103*	1.045±0.137*,#	0.606±0.108*
B	30	0.026±0.005	0.302±0.078*	0.646±0.101*	0.823±0.129*	0.473±0.145*
C	30	0.023±0.005	0.318±0.061*	0.705±0.128*	0.945±0.139*,&	0.512±0.101*

*P < 0.05 compared with T1; &P < 0.05 compared with group A; #P < 0.05 compared with group B. cTnI, cardiac troponin I.

Table 6. Comparison of serum TNF-α level among three groups (pg/ml)

Group	n	T1	T2	T3	T4	T5
A	30	304.56±31.41	313.89±45.92	652.35±80.21*	1156.31±123.19*	1291.38±145.05*
B	30	296.02±41.93	322.36±47.36	578.78±74.55*	831.23±99.34*,#	891.04±90.81*,#
C	30	295.44±44.35	290.88±53.78	602.81±71.01*	938.61±112.93*,#,&	1101.72±120.63*,#,&

*P < 0.05 compared with T1; #P < 0.05 compared with group A; &P < 0.05 compared with group B. TNF-α, tumor necrosis factor-α.

Table 7. Comparison of serum IL-6 level among three groups (pg/ml)

Group	n	T1	T2	T3	T4	T5
A	30	32.78±3.17	34.72±4.12	88.24±9.61*	123.45±12.21*	142.71±15.26*
B	30	33.56±4.12	36.89±4.56	74.62±7.23*	98.51±9.44*,#	102.83±13.91*,#
C	30	34.67±44.27	34.55±3.91	80.72±7.23*	109.15±11.24*,#,&	122.32±12.62*,#,&

*P < 0.05 compared with T1; #P < 0.05 compared with group A; &P < 0.05 compared with group B. IL-6, interleukelin-6.

nificantly lower than that in groups A and C, respectively (P < 0.05).

Comparison of serum cTnI level among three groups

At T1, there was no significant difference of serum cTnI level among three groups (P > 0.05). At T2, T3, T4, the serum cTnI level in each group was gradually increased, and it decreased at T5. At T4, the serum cTnI level in group B was significantly lower than that in group A and group C, respectively (P < 0.05, **Table 5**).

Comparison of serum TNF-α level among three groups

As shown in **Table 6**, at T1 and T2, there was no significant difference of serum TNF-α level among three groups, respectively (P > 0.05). At T3, T4 and T5, the serum TNF-α level in each group was significantly higher than that at T1. In

addition, at T4 and T5, the serum TNF-α level in group B was significantly lower than that in groups A and C, respectively ($P < 0.05$), and that in group C was significantly lower than that in group A, respectively ($P < 0.05$).

Comparison of serum IL-6 level among three groups

As shown in **Table 7**, there was no significant difference of serum IL-6 level among three groups at T1 and T1, respectively ($P > 0.05$). At T3, T4 and T5, the serum IL-6 level in each group was significantly higher than that at T1. In addition, at T4 and T5, the serum IL-6 level in group B was significantly lower than that in groups A and C, respectively ($P < 0.05$), and that in group C was significantly lower than that in group A, respectively ($P < 0.05$).

Discussion

DEX is a new type of highly selective α2 adrenergic receptor agonist, which has strong sedative, anti-anxiety and analgesic effect [8]. The selective agitating effect of DEX on α2 adrenergic receptor is 8 times higher than that of the similar drug clonidine [12]. It is found that, the application of DEX before and during anesthesia can significantly reduce the dosage of narcotic drugs in operation, and easily control the hemodynamics [13]. In addition, it is confirmed that, in valve replacement surgery with extracorporeal circulation, the perioperative application of DEX can reduce the myocardial damage of patients, and shorten the postoperative ventilation time [14]. The open-heart surgery under extracorporeal circulation is the main method currently used to treat the CHD. The structure and function of organs in children are different from the adults, with the reaction mechanism to injury not the same with adults. The organ protection measures effectively used in adults may not be applicable to the infants. This study had compared the physiological saline priming, DEX priming and intravenous DEX infusion after anesthesia in CPB surgery. Results found that, there was no significant difference of operation time, CPB time, aortic occlusion time or heart rebound among three groups ($P > 0.05$). This indicates that, the DEX priming can obtain the operation situation the same with saline priming and intravenous DEX infusion after anesthesia, and can be applied to the clinic.

The myocardial enzymes including LDH and CK-MB are the important markers for evaluation of myocardial injury, which have the most sensitive and specific characteristic [15, 16]. cTnI is the protein regulating the myocardial contraction and relaxation. It is the inhibitory subunit of myofibril ATP. In the intact state of cell membrane, cTnI is not expressed in the blood. When subjected to myocardial ischemia reperfusion injury, cTnI is highly expressed in the blood [17]. In clinic, cTnI is a good indicator in diagnosis of myocardial injury due to its low specificity and high sensitivity. In this study, LDH, CK-MB and cTnI were used as the indicators to evaluate the myocardial injury in CPB. Results showed that, the serum levels of LDH, CK-MB and cTnI in each group changed at different time points. In addition, In addition, at T4 and T5, the serum LDH level in group B was significantly lower than that in groups A and C, respectively ($P < 0.05$). At T5, the serum CK-MB level in group B was significantly lower than that in groups A and C, respectively ($P < 0.05$). At T4, the serum cTnI level in group B was significantly lower than that in groups A and C, respectively ($P < 0.05$). This indicates that, compared with saline priming and intravenous DEX infusion after anesthesia, the DEX priming can obviously alleviate the myocardial injury in CPB surgery.

The systemic inflammatory response syndrome due to inflammatory cell release and activation of inflammatory cytokines in CPB is an important factor leading to aggravated myocardial injury [5]. The changes of inflammatory factor level should obtain more attention in the evaluation of myocardial damage. TNF-α is one of the most important endogenous transmitters. It is the factors the earliest released after ischemia reperfusion. TNF-α can induce the vascular endothelial cells and neutrophils to produce adhesion molecules, thus aggravating the tissue damage [18]. As a proinflammatory cytokine with key initiating action, TNF-α can direct reflect the intensity of inflammatory response. IL-6 is produced by lymphocytes, endothelial cells, macrophages and other cells. The plasma level of IL-6 is a sensitive and specific indicator of inflammatory response in the body [19]. IL-6 plays an important role in the process of inflammation caused by infection and injury. It is confirmed that the occurrence and development of cardiovascular disease are closely related to

infection immunity [20]. Tanaka *et al.* [21] find that, the serum level of IL-6 in the acute phase of viral myocarditis increases, while it gradually decreases to normal levels in the recovery stage. This study selected serum TNF-α and IL-6 levels to evaluate the inflammatory response extent in CPB. Results showed that, at T3, T4 and T5, the serum TNF-α and IL-6 levels in each group were significantly higher than T1. In addition, at T4 and T5, the serum TNF-α and IL-6 levels in group B were significantly lower than that in groups A and C, respectively ($P < 0.05$). This indicates that, compared with saline priming and intravenous DEX infusion after anesthesia, the DEX priming can obviously mitigate the inflammatory response in CPB surgery, which indirectly reflects its protective effect on the myocardial injury.

In conclusion, in CPB surgery for children with CHD, the DEX priming can reduce the inflammatory response, and alleviate the myocardial injury, thus improving the cardiac function of patients. This study has provided a reference for further application of DEX priming to CHD surgery. However, this study has only observed the short-term effect of DEX priming in CPB. The short-term outcome of DEX priming and its effect on patient survival rate need to be further studied.

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Disclosure of conflict of interest

None.

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