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Original Article

Study on the cerebral protective effects of dexmedetomidine during anesthesia for surgical correction of congenital heart disease with cardiopulmonary bypass

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Abstract: Objective: To evaluate the cerebral protective effects of dexmedetomidine (DMED) during anesthesia for surgical correction of congenital heart disease (CHD) with cardiopulmonary bypass (CPB). Methods: One hundred patients who would undergo elective surgery for CHD with CPB were included in this study. According to the method of random number table, they were divided into two groups: DMED group and control group, with 50 cases in each group. In DMED group, patients received intravenous injection of 1.0 μg/kg DMED within 10 min before the routine anesthesia induction, followed by an intravenous infusion of 0.5 μg/kg/h DMED until the end of surgery; while in control group, patients were given the same volume of normal saline at the same rate. The heart rate and blood pressure were measured respectively at the beginning (T1) and end (T2) of CPB, 12 h (T3) and 24 h after CPB (T4). The value of jugular venous oxygen saturation (SjvO2), arterial venous oxygen content difference (Da-jvO2) and cerebral oxygen extraction ratio (CERO2) at these four time points were analyzed. The concentration of plasma S-100β protein, TNF-α and serum neuron-specific enolase (NSE) were also detected using ELISA across different time points. The levels of postoperative agitation and pain in patients were scored according to the Sedation-Agitation Scale (SAS) and the Visual Analogue Scale (VAS). Emergence from anesthesia was assessed for comparison between two groups. Results: There was no significant difference between two groups in terms of general information, such as age, gender, body mass index (BMI), preoperative left ventricular ejection fraction (LVEF), and time spent on CPB, aortic cross-clamping and operation (P>0.05). No intergroup difference was observed in heart rate and blood pressure at T1, T2, T3 and T4 during the perioperative period (P>0.05). Compared with T1, both groups showed an evident decrease in Da-jvO2 and CERO2, as well as increase in SjvO2 (P = 0.000). However, compared with control group at T2, the decrease in Da-jvO2 and CERO2 and increase in SjvO2 were much greater in DMED group (all P = 0.000). The values of TNF-α, S-100β protein and NSE at T2 and T3 were also higher in both groups compared to those at T1 (all P = 0.000), but the levels of these markers at T2 and T3 in DMED group were much lower than those in control group (all P = 0.000). The incidences of moderate and severe agitation, total occurrences of agitation, and VAS score were also much lower in DMED group than those in control group (P = 0.000). No significant difference was found in regard to the time for awakening and full recovery of consciousness, extubation time and length of stay in CICU between two groups (P>0.05). Conclusion: DMED has cerebral protective effect in some degree during anesthesia for the surgical correction of CHD with CPB. It could significantly improve the balance between cerebral oxygen supply and consumption, reduce the expression of markers of brain injury, as well as ameliorate the agitation and pain during the emergence after general anesthesia. Besides, it would barely affect the hemodynamics and awakening. These findings might be related to the fact that DMED could reduce the cerebral oxygen metabolism and inhibit inflammatory response.

Keywords: Congenital heart disease, intracardiac operation under direct vision, dexmedetomidine, cardiopulmonary bypass, cerebral protection

Introduction

The surgical correction of congenital heart disease (CHD) with cardiopulmonary bypass (CPB) is one of the main methods for treating CHD. In recent years, the cure rate of CHD has increased substantially, in contrast to a great reduction of the mortality rate related to CPB operation.

However, the incidence of central nervous system diseases caused by cerebral ischemia-reperfusion injury (CIRI) during CPB has not decreased significantly [1]. Some studies have reported that the occurrence of stroke in patients undergoing cardiac surgery with CPB is about 1.8-2.4% [2]. Since the cerebral perfusion during CPB is non-physiological, which could induce inflammatory mediators and embolic effects to aggravate the brain damage in patients, it would be of great importance to choose an appropriate anesthetic adjuvant with cerebral protective effect for reducing the brain injury in relation to CPB [3].

In recent years, there have been studies demonstrating that dexmedetomidine (DMED) can not only protect the myocardium, but also significantly reduce the CIRI in rats [4, 5]. As a highly selective α2-adrenergic receptor agonist, DMED is a good anesthetic adjuvant clinically, with the characteristics of fast onset of action, strong selectivity and short half-life [6, 7]. Intravenous pumping of DMED before anesthesia for coronary bypass surgery could reduce the hemodynamic fluctuations during the operation [8]. Using DMED in the surgical treatment for traumatic brain injury could also protect brain by inhibiting the inflammatory response [9]. However, there has been no clear finding by other studies on whether or not DMED has any cerebral protective effect in the surgical correction of CHD with CPB. Therefore, the aim of this study was to explore the effects of DMED in this area and to obtain some useful information for the clinical application.

Materials and methods

General information

As a prospective study, one hundred patients with CHD who were admitted to the department of cardiac surgery in our hospital from January 2015 to December 2016 were included as subjects. All of them were prepared for surgical corrections of CHD with CPB. According to the random number table, patients were divided into two groups: DMED group and control group, with 50 cases in each group. Among them, there were 43 cases of atrial septal defect and 57 cases of ventricular septal defect. The numbers of male and female patients were 55 and 45 respectively (mean age 14.6±3.6 years, mean body mass index (BMI) 23.5±3.1 kg/m^2).

Inclusion criteria: It would be patients' first time to receive the heart surgery; patients with New York Heart Association (NYHA) class I-II; patients' left ventricular ejection fraction (LVEF) >50%; patients with the American Society of Anesthesiologists (ASA) class I-II; patients had no atrioventricular block and carotid atherosclerosis; patients had no history of diabetes and hypertension; patients had no liver, kidney and lung dysfunction.

Exclusion criteria: Patients had preoperative complications of craniocerebral injury and nerve injury; patients had consciousness disorder and pulmonary arterial hypertension. The study was approved by the Ethics Committee of the hospital and informed consents had been obtained from the patients or their families.

Methods

Patients in both groups were given intramuscular injection of 0.2 mg/kg morphine 30 min prior to the operation. Upon entering the operating room, the patient received oxygen inhalation via mask and was connected to monitor for detecting indices including heart rate, blood pressure, bispectral index, and pulse blood oxygen saturation etc. The anesthesia was induced by intravenous injections of 1 μg/kg sufentanil, 0.05 mg/kg midazolam, 0.6 mg/kg rocuronium, and 0.3 mg/kg etomidate. Then the tracheal intubation was performed and the anesthesia machine was connected. The radial artery and internal jugular vein (IJV) were cannulated for monitoring blood pressure and central venous pressure (CVP) respectively. Patients in DMED group were injected with 1.0 μg/kg DMED within 10 min, followed by an intravenous pumping of 0.5 μg/kg/h until the end of surgery, while in control group, patients were given the same amount of normal saline at the same rate using same infusion and injection method.

The patient was lying in supine position, and the heart was exposed through median sternotomy. The ascending aorta and superior and inferior vena cava were cannulated following total heparinization. The surgical correction of CHD began after the activated clotting time (ACT) reached above 480 s. CPB was performed by heart-lung machine German Sorin S5. The proportion of crystal and colloidal solution in priming solution was 3:1. The non-pulsatile

Table 1. Comparison of general generation in two groups

Group	Case	Age (years old)	Male/Female (cases)	BMI (kg/m^2)	Preoperative LVEF value (%)	CPB time (min)	Aortic cross-clamping time (min)	Operation time (min)
DMED group	50	13.8±2.6	29/21	22.9±1.8	55.6±5.9	51.8±11.7	53.2±12.2	122.5±17.6
Control group	50	15.1±3.4	26/24	24.1±2.0	55.5±5.1	53.2±12.1	54.1±13.1	124.4±18.5
t/χ^2		2.532	2.049	1.943	1.044	0.956	0.572	0.735
P		0.107	0.131	0.143	0.311	0.335	0.568	0.422

Table 2. Comparison of heart rate at different time points in two groups

Group	T1	T2	T3	T4	F	P
Control group	97.4±11.8	97.5±11.4	95.6±10.5	96.3±11.6	1.863	0.608
DMED group	95.3±11.3	94.2±10.6	92.1±10.5	93.9±11.4	2.158	0.568
t	2.472	2.153	2.042	1.829		
P	0.114	0.125	0.139	0.158		

Table 3. Comparison of mean arterial pressure at different time points in two groups

Group	T1	T2	T3	T4	F	P
Control group	64.6±9.1	66.2±9.9	67.1±10.1	66.9±9.8	1.550	0.691
DMED group	72.1±9.8	74.8±10.2	76.7±9.6	75.5±9.4	2.367	0.497
t	2.505	2.345	2.147	1.967		
P	0.108	0.112	0.126	0.141		

perfusion was applied, with a flow rate of 2.0-2.5 $L/m^2/min$, and the mean arterial pressure (MAP) was controlled between 50-80 mmHg. The body temperature and red blood cell specific volume (HCT) was kept at 28°C, 25%-35% respectively. Blood gas was maintained in a steady state, with venous blood oxygen saturation at 60%-70%. The rewarming was conducted following the intracardiac operation. Dose of dopamine was increased to 1 μg/kg/min after the release of ascending aortic clamp. Circulation was maintained while the bypass system was removed gradually. Intravenous injection of 3 mg/kg protamine was done to neutralize heparin after machine off.

Outcome measures

Main outcome measures: Blood gas analysis: the blood sample was taken from the radial artery and internal jugular vein at different time points for blood gas analysis. The jugular venous oxygen saturation (SjvO2), arterial venous oxygen content difference (Da-jvO2), and cerebral oxygen extraction ratio (CERO2) were calculated according to Fick's equation (Formula: SjvO2 = SaO2 - CMRO2/CDRO2, CMRO2 stands for cerebral metabolic rate of oxygen, CDRO2 stands for cerebral delivery rate of oxygen; Da-jvO2 = CaO2-CjvO2, CaO2 = Hb * 1.39 * SaO2 + 0.003 * PaO2, CjvO2 = Hb * 1.39 * SjvO2 + 0.003 * PjvO2; CERO2 = Da-jvO2/CaO2). Biochemical markers of brain injury: the levels of plasma S-100β protein, neuron-specific enolase (NSE) and TNF-α were detected by ELISA at each time point.

Secondary outcome measures: Hemodynamic indicators: the heart rate and blood pressure were recorded at the beginning (T1) and end (T2) of CPB, 12 h (T3) and 24 h (T4) after CPB. Sedation-Agitation Scale (SAS) and Visual Analogue Scale (VAS) score: patients were assessed by the SAS 4 h after operation and VAS 6 h after extubation, and the criteria was as follows: total score in SAS were 4; breathe but not awake, drowsy, 0 score; conscious, quiet and able to cooperate, 1 score; cry, restless, but able to calm down after being soothed, 2 scores; agitated, cry and restless, unable to calm down, but not need to be immobilized, 3 scores; agitated, disoriented, and need to be immobilized, 4 scores; if the score was no less than 2, the agitation was considered positive; grading of the agitation: severe, 4 scores; moderate, 3 scores; mild, 2 scores [10, 11]. VAS was applied to assess the level of wound pain 6 h after extubation, and the score was on a scale of 0-10: a score of 0 was defined as no pain, and 10 was defined as the most severe intolerable pain. Emergence after anesthesia: the time for awakening and full recovery of consciousness, extubation time and length of stay in cardiac intensive care unit CICU were recorded in both groups.

Table 4. Comparison of SjvO2, Da-jvO2 and CERO2 values at different time points in groups

Group	SjvO2 (%)	Da-jvO2 (mmol/L)	CERO2 (%)
Control group			
T1	64.9±8.9	54.1±7.5	35.8±8.4
T2	72.3±9.2*	36.2±8.5*	27.2±7.5*
T3	66.2±9.6	55.7±8.8	42.1±7.9
T4	67.8±10.1	58.2±9.2	41.8±8.6
DMED group			
T1	64.7±8.2	52.3±8.7	36.1±8.3
T2	82.8±6.4*,#	25.1±9.4*,#	17.4±6.7*,#
T3	67.2±7.8	54.2±8.2	39.5±7.7
T4	68.9±9.2	56.5±9.7	40.2±8.1

Note: Compared with T1, *P = 0.000; compared with the control group at the same time point, #P = 0.000.

Table 5. Comparison of S-100β protein, NSE and TNF-α levels at different time points in two groups

Group	S-100β protein (μg/L)	NSE (μg/L)	TNF-α (pg/L)
Control group			
T1	0.16±0.054	6.3±1.9	0.32±0.03
T2	4.21±1.23*	22.4±4.6*	0.52±0.05*
T3	5.67±1.27*	29.2±5.7*	0.79±0.08*
T4	0.17±0.06	7.9±3.3	0.31±0.02
DMED group			
T1	0.15±0.04	6.2±1.9	0.33±0.02
T2	3.97±1.18*,#	19.4±4.2*,#	0.44±0.03*,#
T3	4.12±1.21*,#	24.2±5.1*,#	0.69±0.05*,#
T4	0.16±0.07	7.1±3.1	0.31±0.03

Note: Compared with T1, *P = 0.000; compared with control group at the same time point, #P = 0.000.

Statistical analysis

SPSS 20.0 was applied for statistical analysis in this study. The measurement data was presented as mean ± standard deviation. T test was used for comparison between two groups. Comparison across different time points within a group was conducted using one-factor analysis of variance. The count data was examined by χ^2 test. P<0.05 was considered statistically significant.

Results

General information between two groups

There was no difference in age, sex ratio, BMI, preoperative LVEF value, time spent on CPB, aortic cross-clamping and operation between two groups (P>0.05, see **Table 1**).

Heart rate and blood pressure between two groups

The heart rate and MAP at each time point of the perioperative period in both groups are displayed in **Tables 2** and **3**. Compared with the control group, patients in DMED group appeared to have lower heart rate and higher MAP across different time points, however, their differences were not statistically significant (P>0.05). Meanwhile, the heart rate and MAP at different time points within each group were not significantly different (P>0.05).

Levels of SjvO2, Da-jvO2 and CERO2 between two groups

Compared with T1, there was a significant increase in the level of SjvO2 and an evident decrease in Da-jvO2 and CERO2 in both groups at T2 (all P = 0.000). In addition, the level of SjvO2 in DMED group was much higher, while the level of Da-jvO2 and CERO2 was much lower as compared to the control group at T2 (all P = 0.000, **Table 4**).

Values of plasma TNF-α, S-100β protein and NSE between two groups

At time point T1, there was no intergroup difference in the levels of S-100β protein, NSE and TNF-α (P>0.05). The levels of TNF-α, S-100β protein and NSE at T2 and T3 in both groups all rose significantly compared to T1 (all P = 0.000). In addition, compared to control group, the levels of S-100β protein, NSE and TNF-α in DMED group were much lower at T2 and T3 (all P = 0.000, **Table 5**).

Agitation and pain scores between two groups

There was no significant difference in the incidence of mild agitation between two groups (P>0.05). Compared with control group, the incidence of moderate and severe agitation and total occurrence of agitation in DMED group were much less (all P = 0.000, **Figure 1**), and in terms of pain score, the VAS at 6 h after extubation in DMED group was significantly

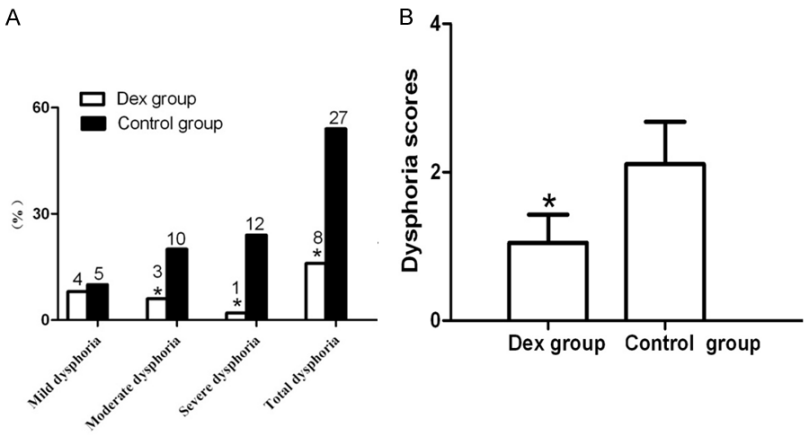

Figure 1. Comparison of agitation level and agitation score in two groups. A. Comparison of the agitation level (mild, moderate and severe) and the total occurrences of agitation between DMED group and control group, *P<0.001; B. Comparison of the agitation score between DMED group and control group, *P<0.001.

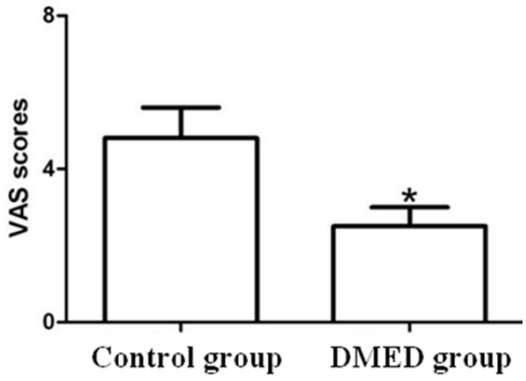

Figure 2. Comparison of VAS scores in two groups. Compared with control group, *P = 0.000.

lower (4.8±0.8 vs. 2.5±0.5, P = 0.000, **Figure 2**).

Emergence after anesthesia in two groups

Compared with control group, the time for awakening and full recovery of consciousness, and the length of stay in CICU in DMED group were longer, however, the differences were not statistically significant (P>0.05 **Table 6**).

Discussion

In recent years, it has been believed that the mechanism behind the brain injury caused by CPB might be related to the process such as cooling and rewarming, which would give rise to the inflammatory cascade and cause increased permeability of blood-brain barrier, the imbalance between cerebral oxygen supply-consumption and CIRI [12, 13]. At present, there is no safe effective anesthetic adjuvant that could prevent and cure brain damage related to CPB. Therefore, in this study, patients who were prepared for surgical correction of CHD with CPB were included as subjects to investigate the cerebral protective effects of DMED during anesthesia for the surgery.

The study found that there was no evident difference in heart rate and blood pressure between two groups at each time point, which indicated that the sedation caused by DMED had no significant impact on hemodynamic stability of patients after CPB.

In regard to the balance between cerebral oxygen supply and consumption, the results of the study showed that the level of SjvO2 in both groups at T2 was significantly higher, while Da-jvO2 and CERO2 values were much lower compared to those at T1. Furthermore, the SjvO2 level in DMED group at T2 increased much more and the levels of Da-jvO2 and CERO2 decreased much more compared to control group (P<0.05). As indicators of cerebral oxygen metabolism, SjvO2, with a normal range of 55%-75%, could reflect the balance of cerebral oxygen supply and consumption. If its level is below 55%, it could be deemed that the cerebral oxygen supply is insufficient to meet the need of brain metabolism [14, 15]. Both Da-jvO2 and CERO2 serve as indicators of cerebral oxygen consumption, and a higher value means more cerebral oxygen consumption [16]. From the results of this study, it could be seen that using DMED during surgical correction of CHD with CPB could slow down the cerebral oxygen metabolism, reduce oxygen consumption, improve cerebral oxygenation, and increase cerebral tolerance of hypoxia in patients, which constituted good cerebral protective effects. These results aligned with other former reports [17].

In terms of brain injury markers, TNF-α is an important cytokine in the inflammatory

Table 6. Comparison of revival process between the two groups

Group	Case	Awakening time (min)	Time for full recovery of consciousness (min)	Extubation time (min)	CICU length of stay (h)
Control group	50	42.8±6.7	79.2±11.4	159.2±28.5	13.2±5.3
DMED group	50	45.9±7.2	84.6±12.1	166.3±30.1	13.6±5.8
t		1.672	1.403	2.558	2.320
P		0.262	0.287	0.126	0.248

response and tissue damage during CPB, which plays a key role in the mechanism of organ injury after surgery. Normally, S-100β protein and NSE are not expressed in healthy human serum, but in the case of traumatic brain injury and CPB with a higher blood-brain barrier permeability, the release of these markers would be increased. Some studies have documented that S-100β protein and NSE could be used as important indicators to evaluate nervous system injury relating to CPB [18]. The results in this study demonstrated that the levels of S-100β protein, NSE and TNF-α in both groups at T2 and T3 were significantly higher than those at T1 ($P<0.05$), however, the S-100β protein, NSE and TNF-α levels in DMED group were significantly lower than those in control group at T2 and T3 ($P<0.05$). Therefore, it could be suggested that the use of DMED in surgical correction of CHD with CPB could reduce the brain injury, which might be related to the fact that DMED could greatly inhibit inflammatory reaction during the process.

Agitation after general anesthesia is a common complication, especially in pediatric anesthesia [19]. Some reports argued that factors including inhalation anesthesia, postoperative wound pain, urethral catheter stimulation, preoperative anxiety, surgery could all affect the emergence agitation after general anesthesia [20]. During the emergence period, the wound pain, light anesthesia and hypoxia would cause patients to experience agitation, choking, delayed recovery of consciousness and delirium. All these could cause serious damage to the patients, and need to be treated immediately. If no appropriate treatment is performed, there would be disorders of respiratory and circulatory systems such as cerebrovascular accident, and tracheospasm, which could endanger patients' life. Thus, maintaining a stable emergence after general anesthesia would be conducive to a safe perioperative period for patients. The results of this study showed that the agitation and VAS scores in DMED group were significa-ntly lower than those in control group, with statistical significance ($P = 0.000$). This suggested that as an anesthetic adjuvant in surgical correction of CHD with CPB, DMED had a quite good performance in sedation and analgesia, inhibition of the stress reaction, and reduction of the incidence of postoperative agitation. Combined with findings from other studies [21, 22], the results suggested that the cause of a less incidence of agitation in DMED group might be due to the fact that it was able to reduce the postoperative pain, increase the anxiolytic effects and the chill threshold. In addition, the awakening time, time for full recovery of consciousness, extubation time, and the length of stay in CICU in DMED group were slightly longer than those in control group, with no statistical significance, indicating that DMED, as an anesthetic adjuvant, wouldn't affect patient's postoperative emergence.

In summary, DMED, as an anesthetic adjuvant, has cerebral protective effect to some degree. It could significantly improve the balance of cerebral oxygen supply and consumption, reduce the expression of markers of brain injury, and reduce the agitation and pain during emergence after general anesthesia. Meanwhile, it doesn't affect the hemodynamics and the emergence in patients. Different from other previous studies, the effects of DMED on markers of brain injury and some brain functions were observed in this study. But there are still some limitations in this research, such as a relatively small sample size; therefore, a prospective clinical study with a big sample volume would be needed in the future to further verify the application value of DMED in surgical correction of CHD with CPB.

Disclosure of conflict of interest

None.

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