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Protective effect of dexmedetomidine combined with ulinastatin on cardiopulmonary function injury caused by cardiopulmonary bypass surgery

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ABSTRACT

Objective: To analyze the protective effect of dexmedetomidine combined with ulinastatin on cardiopulmonary function impairment caused by cardiopulmonary bypass surgery. **Methods:** A total of 78 patients who received valve replacement under cardiopulmonary bypass were divided into observation group and control group (n=39) according to random number table. Control group received intraoperative ulinastatin intervention and observation group received intraoperative dexmedetomidine combined with ulinastatin intervention. Differences in the levels of cardiac function indexes, myocardial injury markers, pulmonary function parameters, inflammatory indexes and so on were compared between two groups of patients 24 hours after operation. **Results:** Cardiac function parameters LSV, RSV and RVEF values of observation group 24 hours after operation were higher than those of control group while PAP value was lower than that of control group; serum myocardial injury markers H-FABP, cTn-T, CK-MB, cTn Ⅰ and NT-proBNP levels were lower than those of control group; lung function parameters Cs and Cd values were higher than those of control group while RI, R5-R20, X5 and Fres values were lower than those of control group; serum pro-inflammatory factors IL-6 and TNF- α levels were lower than those of control group while anti-inflammatory factors sTNF-RI, IL-4 and IL-10 levels were higher than those of control group. **Conclusions:** Dexmedetomidine combined with ulinastatin can protect the cardiopulmonary function in patients with cardiopulmonary bypass, and help to reduce the occurrence of postoperative cardiopulmonary dysfunction and other severe complications.

1. Introduction

Cardiopulmonary function injury after cardiopulmonary bypass (CPB) is clinically common and directly related to the massively produced intraoperative inflammatory factor and oxidative product damage to cell function as well as ischemia/reperfusion injury. Severe cardiopulmonary function damage can lead to multiple organ dysfunction after CPB, and even death in patients[1,2]. CPB intraoperative intervention is the best way to protect patients' cardiopulmonary function, ulinastatin is the currently recognized broad-spectrum protease inhibitor that can reduce the degree of inflammation during CPB, and its mechanism of action in reducing lung injury after CPB has been studied in depth. Dexmedetomidine is a highly selective receptor agonist that is favored by many clinical scholars for its special effect of stabilizing hemodynamics and reducing myocardial oxygen consumption[3]. Dexmedetomidine is generally used as auxiliary anesthetic drug, and recently some scholars have proposed that it can be used as a specific cardiopulmonary protective drug and continuously injected through pump during CPB, which protects cardiopulmonary function from anti-oxidative stress resistance and anti-ischemia-reperfusion injury[4]. In the study, dexmedetomidine combined with ulinastatin was used in patients with CPB surgery in our hospital, and the role of dexmedetomidine combined with ulinastatin in optimizing the patients′ postoperative cardiopulmonary function was mainly elaborated.

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2. Materials and methods

2.1. General information

A total of 78 patients undergoing valve replacement under cardiopulmonary bypass in our hospital between February 2012 and February 2016 were included, and the inclusion criteria were: (1) diagnosed with valvular disease by echocardiography; (2) with ASA Ⅱ-Ⅲ grade; (3) with left ventricular ejection fraction 35%; (4) in accordance with operation indications; (5) receiving surgical treatment for the first time, (6) the patients and families signed informed consent. Exclusion criteria were: (1) with basic severe pulmonary hypertension, pulmonary stenosis and other lung diseases; (2) with severe cardiac dysfunction; (3) with long-term use of immunosuppressive agents or nonsteroidal anti-inflammatory drugs; (4) with history of dexmedetomidine or ulinastatin allergy; (5) with incomplete clinical data. 78 patients were included in the study and divided into observation group and control group (n=39) according to random number table. Control group included 21 male cases and 18 female cases, they were 45-70 years old and (58.29±7.12) years old in average, the body weight was 50-81kg and (69.38±7.13) kg in average, and the left ventricular ejection fraction (EF) was 53%-68% and (62.17±4.09)% in average; observation group included 22 male cases and 17 female cases, they were 43-72 years old and (59.76±7.53) years old in average, the body weight was 50-83kg and (69.52±7.88) kg in average, and the left ventricular ejection fraction (EF) was 52%-69% and (62.53±4.41)% in average. The two groups of patients showed no statistically significant difference in the distribution of gender, age, body weight and cardiac function (P>0.05) and they were comparable.

2.2. Intraoperative intervention

Control group received intraoperative ulinastatin intervention, specifically as follows: intravenous drip of ulinastatin 10 000 u/kg after anesthesia induction and continuous hypothermic pulmonary artery perfusion of the mixture of 20 000 u/kg and oxygenated machine blood during CPB. Observation group received intraoperative dexmedetomidine combined with ulinastatin intervention, specifically as follows: dexmedetomidine injection with pump at 1 μg/(kg•h) 15 min before anesthesia induction, injection with pump at constant 0.5 μg/(kg•h) after 15 min until the end of surgery. The usage and dosage of ulinastatin were the same as those of control group.

2.3. Observation indexes

2.3.1. Cardiac function indexes

24 hours after operation, transthoracic echocardiography was used to determine the left ventricular stroke volume (LSV), right ventricular stroke volume (RSV), right ventricular ejection fraction (RVEF) and pulmonary artery pressure (PAP) of both groups.

2.3.2. Serum indexes

24 hours after operation, 3ml of fasting peripheral venous blood was collected from two groups of patients and centrifuged to get serum, and the following indexes were determined: 1) myocardial injury markers: ELISA method was used to determine the levels of myocardial injury markers, including the heart type fatty acid binding protein (H-FABP), troponin T (cTn), creatine kinase isoenzyme (CK-MB), troponin Ⅰ (cTn Ⅰ) and N-terminal pro-brain natriuretic peptide (NT-proBNP). 2) Inflammatory indexes: ELISA method was used to determine the serum levels of pro-inflammatory factors interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) as well as anti-inflammatory factors soluble tumor necrosis factor receptor I (sTNF - RI), interleukin-4 (IL-4) and interleukin-10 (IL-10).

2.3.3. Lung function parameters

24 hours after operation, 1ml of radial artery blood was collected from two groups of patients to calculate the pulmonary static compliance (Cs), the pulmonary dynamic compliance (Cd) and respiratory index (RI). Mastscreen IOS apparatus was used to detect peripheral airway resistance (R5-R20), elastic resistance (X5) and resonance frequency (Fres).

2.4. Statistical methods

Data obtained in the study was analyzed by SPSS23.0 software, measurement data was in terms of mean±sd, comparison between two groups was performed by t test and P<0.05 was set as the standard of statistical significant differences.

3. Results

3.1. Cardiac function indexes

LSV, RSV and RVEF of observation group were significantly higher than those of control group while PAP value was significantly lower than that of control group (P<0.05), shown in Table 1.

3.2. Myocardial injury markers

Serum H-FABP, cTn-T, CK-MB, cTn Ⅰ and NT-proBNP levels of observation group were significantly lower than those of control group (P<0.05), shown in Table 2.

3.4. Lung function parameters

Cs and Cd of observation group were significantly higher than those of control group while RI, R5-R20, X5 and Fres were significantly

Table 1
Comparison of cardiac function index values 24 hours after operation.

Groups	Case No.	LSV (mL)	RSV (mL)	RVEF (%)	PAP (mmHg)
Observation group	39	49.37±5.12	45.83±5.11	58.23±6.18	30.12±4.28
Control group	39	37.18±4.28	40.74±4.68	51.45±5.89	41.43±5.32
t		9.274	6.172	7.293	8.934
P		<0.05	<0.05	<0.05	<0.05

lower than those of control group (P<0.05), shown in Table 3.

3.4. Inflammatory indexes

Serum pro-inflammatory factors IL-6 and TNF- α levels of observation group were significantly lower than those of control group while anti-inflammatory factors sTNF-RI, IL-4 and IL-10 levels were significantly higher than those of control group (P<0.05), shown in Table 4.

4. Discussion

CPB is the necessary means for safe open-heart surgery, and statistics of postoperative complications in many patients with cardiopulmonary bypass surgery show that cardiopulmonary dysfunction is the main and the most severe complication after CPB, and about 1% of the patients can die from heart failure or lung failure[5]. There have been many studies about the mechanism of CPB to cause cardiopulmonary function injury, and it generally believed to be related to systemic inflammatory response caused by blood exposure to artificial material surface as well as low cardiopulmonary perfusion-induced ischemia and the following reperfusion injury during CPB[6]. It is an urgent clinical problem how to avoid cardiopulmonary dysfunction after CPB surgery and safeguard the therapeutic safety of patients with CPB surgery.

Ulinastatin belongs to broad-spectrum protease inhibitor and is with recognized effect on anti-pancreatitis, anti-shock and other aspects. At the same time, many studies have found that ulinastatin plays a unique role in alleviating lung injury from cardiopulmonary bypass, and it is found in rabbit models with heart perfusion *in vitro* that ulinastatin can alleviate ischemia-reperfusion injury[7,8]. Ulinastatin has been a popular effective means for cardiopulmonary protection in CPB surgery, and relevant statistical data has also confirmed that it reduces the incidence of postoperative respiratory dysfunction in patients with CPB. But the latest study has shown that the probability of postoperative cardiac insufficiency is still high in CPB surgery patients with ulinastatin intervention, and some scholars blame it for the limited anti-inflammatory and anti-oxidative stress effect of ulinastatin, and propose to add new drug dexmedetomidine in the treatment[9]. Dexmedetomidine has high 2 receptor selectivity and is a common clinical auxiliary anesthetic, and it has been found in recent years that the drug can relieve the body′s ischemia-reperfusion injury and has receive clinical attention again[10]. In order to define the cardiopulmonary protective effect of dexmedetomidine for patients with CPB, dexmedetomidine was used in the intraoperative intervention of patients with CPB surgery in our hospital in the study, and the significance of dexmedetomidine in optimizing patients′ early postoperative cardiopulmonary function was mainly elaborated.

Related studies show that the inflammation and oxidative stress produced in CPB surgery reach the peaks around 24 hours after operation, and therefore, 24 hours after operation was selected as the point in time to detect the indexes. Cardiac dysfunction after CPB is mostly characterized by the decrease of stroke volume and ejection fraction, the LSV, RSV and RVEF levels of observation group 24 hours after operation were higher while PAP level was lower. PAP levels are negatively correlated with left ventricular function, and the above results indicate that after intraoperative dexmedetomidine combined with ulinastatin intervention, the patients' cardiac function parameter values are better and the CPB effect is smaller on patients' early postoperative cardiac function, speculated to be because that dexmedetomidine inhibits central sympathetic activity, prolongs the coronary perfusion time in ventricular diastole, reduces myocardial oxygen consumption and so on[11]. In addition to the echocardiography, serum markers of myocardial injury are also the reliable indicators for early detection of patients with cardiac dysfunction, and it was found in the study

Table 2
Serum myocardial injury marker levels 24 hours after operation.

Groups	Case No.	H-FABP (ng/mL)	cTn-T (ng/mL)	CK-MB (μ/mL)	CTnI (ng/mL)	NT-proBNP (pmol/mL)
Observation group	39	7.95±0.82	2.14±0.29	21.36±2.78	1.02±0.13	97.34±10.16
Control group	39	18.12±2.15	3.52±0.41	28.73±3.14	1.47±0.18	162.59±19.77
t		8.293	5.384	7.192	5.483	8.293
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 3
Comparison of lung function parameter values 24 hours after operation.

Groups	Case No.	Cs (mL/cmH_2O)	Cd (mL/cmH_2O)	X5 [kPa/(L•s)]	Fres (Hz)	RI	R5-R20
Observation group	39	89.37±9.12	50.36±5.73	-0.28±0.03	16.23±1.83	0.92±0.09	80.27±9.13
Control group	39	67.34±7.43	42.74±5.19	-0.41±0.05	22.17±2.62	1.32±0.17	124.69±15.58
t		8.394	7.124	5.283	7.192	6.384	8.293
P		<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Table 4
Comparison of inflammatory index levels 24 h after operation.

Groups	Case No.	Pro-inflammatory factors (ng/mL)		Anti-inflammatory factors (pg/Ml)		
		IL-6	TNF- α	Stnf-RI	IL-4	IL-10
Observation group	39	73.28±8.12	81.45±9.36	0.41±0.05	1.95±0.23	3.19±0.42
Control group	39	92.17±9.55	107.83±12.64	0.27±0.03	1.08±0.17	1.78±0.21
t		9.374	8.283	5.281	6.093	6.731
P		<0.05	<0.05	<0.05	<0.05	<0.05

that serum H-FABP, cTn, CK-MB, cTn Ⅰ and NT-proBNP levels of observation group 24 hours after operation were lower than those of control group. H-FABP has a high sensitivity, CK-MB, cTn Ⅰ and cTn-T are the myocardial injury markers with high clinical utility ratio, their sensitivity is not high but their joint detection is with extremely high specificity for reflecting myocardial injury[12]. NT-proBNP is produced by myocardium after certain stimulation, it has long half life and high stability, and its level is directly correlated with the degree of myocardial injury[13]. The above results indicate that after dexmedetomidine combined with ulinastatin intervention, the myocardial cell damage is less, and in combination with related literature, it is speculated to be related to the effect of dexmedetomidine pretreatment on ischemia-reperfusion-related signaling pathways.

Many studies have found that patients′ pulmonary function parameters after CPB surgery are worse than those before operation, it has to do with the pulmonary no blood flow or low blood perfusion during intraoperative cardiac arrest, large amount of blood enters into the lungs after the heart beats again and causes reperfusion injury, a large number of inflammatory factors in the blood will also directly cause cell damage, and a variety of factors result in postoperative pulmonary dysfunction together[14]. In the study, postoperative lung function parameters of two groups of patients were tested, and it was found that pulmonary Cs and pulmonary Cd values of observation group were while RI, R5-R20, X5 and Fres values were lower. Pulmonary compliance is affected by alveolar surface tension and elasticity resistance, and it can sensitively reflect the pathological changes of pulmonary parenchyma. RI is affected by ventilation flow ratio, pulmonary diffusion function, ventilation conditions and other factors, and its value can directly reflect the patients′ pulmonary function state. R5-R20 represents small airway resistance, X5 represents the elastic resistance of surrounding lung tissue, Fres is the pulse frequency when the elastic resistance and inertial resistance offset each other, and they are the sensitive indexes to reflect the viscous resistance of lung tissue[15]. The above results show that adding dexmedetomidine on the basis of ulinastatin intervention can further optimize patients′ postoperative lung function status, which is directly related to the anti-inflammatory and anti-oxidative stress effect of dexmedetomidine. The main mechanisms of pulmonary function injury after CPB are systemic inflammatory response and ischemia-reperfusion injury, and pro-inflammatory/anti-inflammatory system imbalance plays an important role in these two mechanisms. When ischemia-reperfusion injury occurs, oxygen molecules can produce a large number of oxygen free radicals under the action of reduced coenzyme of neutrophils, cause cell membrane damage and intracellular calcium overload, and further lead to mitochondrial dysfunction and lung injury[16]. It was found in the study that serum pro-inflammatory factors IL-6 and TNF- α levels of observation group 24 hours after operation were lower while anti-inflammatory factors sTNF-RI, IL-4 and IL-10 levels were higher, indicating that dexmedetomidine combined with ulinastatin has effectively inhibited inflammation and oxidative stress cascade process and avoided the lung function damage caused by the accumulation of massive inflammatory factors in the lungs.

In conclusion, adding dexmedetomidine on the basis of ulinastatin intervention can protect the postoperative cardiopulmonary function in patients with CPB, and it has positive clinical significance.

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