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Effect of thyroid hormone on myocardial and cerebral ischemia reperfusion injury in valve replacement under cardiopulmonary bypass

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ABSTRACT

Objective: To study the effect of thyroid hormone (euthyrox) on myocardial and cerebral ischemia reperfusion injury in valve replacement under cardiopulmonary bypass. **Methods:** A total of 76 patients who received valve replacement under cardiopulmonary bypass in our hospital between January 2013 and December 2016 were collected and divided into control group (n=38) and observation group (n=38) according to random number table. Observation group took euthyrox orally 1 week before surgery, control group took vitamin C tablets orally at the same point in time, and both therapies lasted for 1 week. Before taking medicine and after cardiopulmonary bypass (before end of surgery), serum levels of myocardial enzyme spectrum indexes and nerve injury indexes were compared between the two groups of patients. **Results:** Before taking medicine, differences in the serum levels of myocardial enzyme spectrum indexes and nerve injury indexes were not statistically significant between the two groups of patients. After cardiopulmonary bypass, serum myocardial enzyme spectrum indexes cTnT, CK-MB, α-HBD and LDH levels in observation group were lower than those in control group; serum nerve injury indexes NSE, S100B and GFAP levels were lower than those in control group while bFGF level was higher than that in control group. **Conclusion:** Euthyrox intervention in valve replacement under cardiopulmonary bypass can effectively reduce the myocardial and cerebral ischemia reperfusion injury.

1. Introduction

Valve replacement is the surgical method that uses artificial mechanical or biological valve to replace human lesion valve, and cardiopulmonary bypass (CPB) is the necessary adjuvant means for valve replacement. CPB is a non-physiological cycle state, it affects the physiological function of various organs, and many current studies have shown that the cooling and thawing process in the process of CPB can cause the unbalanced oxygen supply to important tissue organs in the body, and lead to ischemia-reperfusion injury[1,2]. Heart and brain are the most easily involved organs in the process of CPB ischemia-reperfusion, and how to protect their function is the key of the current clinical research, and also the important basis to achieve the efficacy of valve replacement. Both domestic and foreign studies have pointed out that there is early postoperative low blood free triiodothyronine (FT3) in patients with valve replacement, and therefore, some scholars speculate that thyroid hormone is involved in the ischemia-reperfusion process during CPB[3,4]. In the study, patients who received thyroid hormone (euthyrox) and patients who received placebo (vitamin C) before valve replacement were compared, and the clinical value of thyroid hormone for reducing ischemia-reperfusion injury in the process of CPB was discussed from two aspects of myocardial injury and cerebral injury, now reported as follows:

2. Information and methods

2.1 Case information

A total of 76 patients who received valve replacement under cardiopulmonary bypass in our hospital between January 2013 and December 2016 were selected as the research subjects, patients

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were with preoperative cardiac function Ⅱ-Ⅳ grade (New York Heart Association), the research was approved by hospital ethics committee, and the family members of patients signed the informed consent. According to the random number table, the enrolled patients were divided into observation group and control group, 38 cases in each group. Observation group included 22 men and 16 women that were 42-72 years old; control group included 20 men and 18 women that were 45-69 years old. The gender and age distribution of the two groups were not statistically different (P>0.05).

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with valvular heart disease and in accordance with the operative indications; (2) without history of cardiac surgery; (3) with complete clinical data. Exclusion criteria: (1) associated with thyroid diseases such as hyperthyroidism and thyroidism; (2) with euthyrox-taking history within 6 months prior to operation; (3) with history of stroke/cerebral hemorrhage; (4) combined with Alzheimer's disease, Parkinson's and other chronic brain disorders, and associated with the history of other neurological and psychotic disorders; (5) combined with systemic infectious diseases.

2.3 Therapy

Observation group began to take euthyrox (Levothyroxine Sodium Tablets Merck KGaA, approved by H2010523) orally one week before surgery, 50 μg/d, for 1 consecutive week until the morning of the day of operation. The control group took vitamin C as a placebo, 1 tablet/d, also for 1 consecutive week until the morning of the day of operation.

2.4 Surgical method

The operation was conducted under tracheal intubation general anesthesia and medium and low temperature CPB, Terumo artificial heart-lung machine and United States Edward membrane lung were used for blood oxygenation in vitro, and the mean aortic perfusion pressure was kept at 60-80 mmHg; median sternum incision was adopted to enter into the chest, mitral valve replacement was conducted from the right atrium - the atrial septum approach, and aortic valve replacement was conducted from ascending aortic root oblique incision. 42 cases were with mitral valve replacement alone (37 cases with mechanical valve replacement, and 5 cases with biological valve replacement), 28 cases were with aortic valve replacement (26 cases with mechanical valve replacement and 2 cases with biological valve replacement), and 6 cases were with double valve replacement (mitral valve combined with aortic valve replacement) (all mechanical valve).

2.5 Observation indexes

2.5.1 Myocardial enzyme spectrum

Before taking medicine and after cardiopulmonary bypass (before end of surgery), 3.0 mL peripheral blood was extracted from two groups of patients, anti-coagulated with heparin sodium (Jiangsu Wanbang Biopharmaceuticals Co., Ltd., approved by H32020612) and centrifuged at 4 ℃ and low speed to take the upper serum, and the electrochemical luminescence instrument (Roche Diagnostics GmbH, model Elecsys 2010) was used to determine the levels of myocardial enzyme spectrum indexes, including troponin T (cTnT), creatine kinase isoenzyme (CK-MB), α-hydroxybutyrate dehydrogenase (α-HBD) and serum lactate dehydrogenase (LDH).

2.5.2 Nerve injury indexes

Before taking medicine and after cardiopulmonary bypass (before end of surgery), peripheral blood serum was obtained from two groups of patients in the same way, ELISA kit instructions were referred to determine the serum levels of nerve injury indexes, including neuron-specific enolase (NSE), S100B protein (S100B), basic fibroblast growth factor (bFGF) and glial fibrillary acidic protein (GFAP). The ELISA kit was bought from Nanjing Jin Yibai Biological Technology Co., Ltd., and the article number were KSH-091, MDH-126, DJH-187 and TAK-437 respectively.

2.6 Statistical processing

SPSS 22.0 statistical software was used for data analysis, and the statisticians had professional background and passed the exam. Myocardial enzyme spectrum indexes, nerve injury indexes belong to measurement data and were in terms of mean ± standard deviation ($\bar{x}\pm s$) and the comparison within group was by t test. Statistics $P<0.05$ indicated statistical significance in differences.

3. Results

3.1 Myocardial enzyme spectrum indexes

Comparison of serum myocardial enzyme spectrum indexes cTnT, CK-MB, α-HBD and LDH levels between two groups of patients before taking medicine and after cardiopulmonary bypass was as follows: before taking medicine, differences in serum cTnT, CK-MB, α-HBD and LDH levels were not statistically significant between the two groups of patients (P>0.05); serum cTnT, CK-MB, α-HBD and LDH levels in both groups after cardiopulmonary bypass were higher than those before taking medicine, serum cTnT, CK-MB, α-HBD and LDH levels in observation group after cardiopulmonary bypass were lower than those in control group, and differences were statistically significant (P<0.05), shown in Table 1.

3.2 Nerve injury indexes

Comparison of serum nerve injury indexes NSE (μg/L), S100B (μg/L), bFGF (pg/mL) and GFAP (ng/mL) levels between two groups of patients before taking medicine and after cardiopulmonary bypass was as follows: before taking medicine, differences in serum NSE, S100B, bFGF and GFAP levels were not statistically significant between the two groups of patients (P>0.05); serum NSE, S100B and GFAP levels in both groups after cardiopulmonary bypass were higher than those before taking medicine while bFGF levels were lower than those before taking medicine; serum NSE, S100B and

Table 1.
Comparison of serum myocardial enzyme spectrum index levels between two groups of patients before and after taking medicine (U/L).

Groups	*n*	cTnT		CK-MB		α -HBD		LDH	
		Before taking medicine	After cardiopulmonary bypass	Before taking medicine	After cardiopulmonary bypass	Before taking medicine	After cardiopulmonary bypass	Before taking medicine	After cardiopulmonary bypass
Control group	38	7.29±0.86	19.43±2.51*	4.28±0.51	13.19±1.74*	93.27±10.84	215.48±30.47*	153.28±20.19	264.91±30.65*
Observation group	38	7.25±0.84	9.06±1.74*	4.31±0.53	7.05±0.86*	92.89±10.52	121.43±15.39*	152.67±21.53	176.84±19.55*
t		0.176	15.482	0.169	13.284	0.214	19.283	0.264	23.276
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before taking medicine, *$P<0.05$.

Table 2.
Comparison of serum nerve injury index levels between two groups of patients before and after taking medicine.

Groups	*n*	NSE		S100B		bFGF		GFAP	
		Before taking medicine	After cardiopulmonary bypass	Before taking medicine	After cardiopulmonary bypass	Before taking medicine	After cardiopulmonary bypass	Before taking medicine	After cardiopulmonary bypass
Control group	38	6.52±0.78	15.91±2.05*	0.15±0.02	0.61±0.08*	3.28±0.41	1.79±0.24*	0.92±0.13	1.88±0.24*
Observation group	38	6.49±0.72	8.17±0.94*	0.16±0.03	0.24±0.04*	3.31±0.39	2.65±0.31*	0.94±0.12	1.21±0.15*
t		0.173	9.283	0.153	5.837	0.203	7.298	0.177	6.498
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before taking medicine, *$P<0.05$.

GFAP levels in observation group after cardiopulmonary bypass were lower than those in control group while bFGF level was higher than that in control group, and differences were statistically significant ($P<0.05$), shown in Table 2.

4. Discussion

During valve replacement, CPB is needed to drain venous blood to the outside of the body, artificial way was used for gas exchange to achieve the better vision in the process of valve replacement, and reduce the interference of blood that flows back[5,6], and CPB has become the essential means of open heart surgery. There are significant cardiac and brain dysfunction in some patients early after CPB, which is speculated to be directly correlated with ischemic reperfusion injury[7,8]. The CPB needs to reduce the body's circulating basic temperature, the blood flow of each tissue organ reduces accordingly, and they are in relative hypoxic state; during rewarming, the blood in the CPB pipe flows back to the body, the hypoxia-oxygen enrichment change in a short time can lead to oxidative stress in various tissues and organs, a large number of oxygen free radicals are generated and damage the viscera function, and the phenomenon is especially significant in viscera with rich blood flow[9]. Studies have shown that thyroid hormone can protect heart, liver, kidney and other important organs, some patients with valve replacement under CPB had shown low FT3 state[3,4], and therefore, many scholars think that adding exogenous thyroid hormone can optimize the curative effect of patients with valvular replacement.

There is not much research at present about the clinical application value of thyroid hormone for patients with valve replacement under CPB, the observation group who accepted euthyrox intervention and the control group who accepted vitamin C as placebo were selected as the research subjects of this study, and the perioperative myocardial injury and cerebral injury were compared between the two groups in order to clarify the protective effect of thyroid hormone on ischemia reperfusion injury in patients with cardiac surgery. Myocardial enzyme spectrum is the sensitive indicator to reflect the severity of myocardial injury, many patients with heart valve diseases are without significant cardiac dysfunction, and therefore, myocardial enzyme index levels were kept within the normal range[10,12]. In the study, serum myocardial enzyme spectrum index levels were compared between the two groups of patients before taking medicine and after CPB (before the end of surgery), and it was found that compared with those before taking medicine, serum levels of typical myocardial enzyme spectrum indexes such as cTnT, CK-MB, α -HBD and LDH levels increased in both groups of patients after CPB, showing that both groups of patients have the ischemia-reperfusion injury of myocardial cells; further compared with the control group, the observation group were with lower serum levels of cTnT, CK-MB, α -HBD and LDH after CPB, indicating that the euthyrox intervention can effectively exert myocardial protective effect. The effective component of euthyrox is levothyroxine sodium, which can reduce the roles of inflammatory factors and oxygen free radicals, reduce and even avoid the damage to myocardial cells[13].

Neurologic injury after CPB is common in clinical practice, and the specific mechanisms are that the virulence factors produced during ischemia-reperfusion injury activate the endogenous, exogenous and endoplasmic reticulum pathway so as to prompt brain edema formation, blood-brain barrier damage and neuron apoptosis, and thus lead to brain damage[13,14]. Both NSE and S100B are the neural function-related factors specifically existing in neurons and glial cells, the above factors are difficult to enter the blood circulation when blood brain barrier is complete, and therefore, their contents in serum are little[15]. As nerve cell damage occurs, NSE and

S100B are released from inside to the outside of cells, further cross through the damaged blood-brain barrier and enter in peripheral blood, so the high serum NSE and S100B expression are the direct signs of nerve injury, and joint detection of S100B and NSE is by far the most reliable biochemical indicator for brain injury[14]. bFGF is a neurotrophic factor that can induce axon growth repair, bFGF expression decreases when the nerve injury occurs, and its content is positively correlated with nerve function[16,17]. GFAP specifically exists in a variety of nervous system cells, it has been found that GFAP is highly expressed in brain tissue of rats with cerebral ischemia reperfusion injury, and it is considered as one of the essential factors involved in brain injury[18]. In the study, serum levels of these nerve injury-related indexes were compared between two groups of patients, and it was found that compared with those before taking medicine, serum NSE, S100B and GFAP contents in both groups were higher while bFGF contents were lower after CPB, indicating that ischemia-reperfusion injury after CPB can directly damage the nervous function; further compared with control group, the observation group of patients were with lower serum NSE, S100B and GFAP contents, and higher bFGF content after CPB, showing that euthyrox intervention can reduce the neurological damage caused by ischemia-reperfusion injury. Thyroid hormone can promote nerve cells to absorb glutamic acid, maintain the activity of cell membrane ion channels, maintain normal function of cells and reduce the neuronal sensitivity to virulence factors, which is one of the root causes of the above results after euthyrox intervention[19].

Above all, euthyrox therapy for patients with valve replacement under CPB can effectively reduce the myocardial and nervous system ischemia-reperfusion injury in the process of CPB, is helpful to the operation result realization and postoperative rehabilitation, is a feasible therapy and is worthy of popularization and application in clinical practice in the future. Due to the complex mechanism of heart and brain injury during CPB, the long-term effects need to be confirmed by a large number of clinical studies and more evaluation indexes.

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