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The significance of S100β protein on postoperative cognitive dysfunction in patients who underwent single valve replacement surgery under general anesthesia

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Abstract. – OBJECTIVE: To analyze the effect of S100β protein on postoperative cognitive dysfunction (POCD) in patients who underwent single valve replacement surgery.

PATIENTS AND METHODS: Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were applied to evaluate 178 patients who underwent single valve replacement surgery under general anesthesia from June 2014 to December 2015. Patients were assessed 1 day before surgery and on postoperative days 2 and 9. Thirty-two patients were identified as having postoperative cognitive dysfunction (the POCD group), while 146 cases did not experience POCD (the control group). A total of 155 healthy adult volunteers from the Medical Center were simultaneously chosen (healthy comparison group). Serum S100β levels from the three groups of patients were measured by ELISA.

RESULTS: In the POCD group, serum S100β levels were significantly higher than those of the control group and healthy comparison group ($p < 0.05$). The postoperative length of stay in the hospital for patients in the POCD group was significantly increased ($p < 0.05$).

CONCLUSIONS: The expression of serum S100β in patients with POCD was significantly increased. S100β may represent a potential target for the diagnosis and treatment of cognitive dysfunction after cardiac surgery under general anesthesia.

Key Words:
Postoperative cognitive dysfunction, Single valve replacement surgery, S100β protein.

Introduction

Postoperative cognitive dysfunction (POCD) is a condition where patients experience ongoing dysfunction of memory, abstract thoughts, and disorders of orientation after surgery under anesthesia. It is accompanied by a decline in social abilities, i.e. changes in personality, sociability, and cognitive competence[1,2]. It severely affects the social abilities and survival quality of patients who undergo valve replacement surgery[3-5].

S100 is a protein expressed by nerve tissue. It is expressed at high levels in neurogliocytes and Schwann cells[6-8]. Under physiological conditions, the serum levels of S100 protein are extremely low[9]. They increase abnormally when blood-brain barrier permeability increases significantly and when individual nerve cells are damaged or affected under various pathological conditions. It was shown that S100 levels increase in patients with Alzheimer's disease[4,10]. However, S100 expression and its clinical significance in cognitive dysfunction after cardiac surgery are not clear.

In the present study, we measured the postoperative S100 levels in 178 patients who underwent single valve replacement and in 155 healthy volunteers (healthy comparison group), to determine the clinical significance of S100 in patients with POCD. The results of this study may serve as a basis for the development of targeted therapies.

Patients and Methods

Patients

A total of 178 patients who underwent single valve replacement surgery under general anesthesia from June 2014 to December 2015 were selected. The average age of patients was 54.5 ± 12.7 years old. Also, 155 healthy participants (average age: 55.6 ± 10.8 years old) were enrolled as controls. The investigation has been approved from the Ethical Committee of our Hospital.

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Inclusion Criteria

1. Patients who required valve replacement surgery because of rheumatic valvular heart disease or other causes; 2. Patients who required single valve replacement.

Exclusion Criteria

1. Patients taking immunosuppressive agents; 2. Patients with acute or chronic bacterial and/or viral infections; 3. Patients with autoimmune diseases; 4. Patients with connective tissue diseases; 5. Patients with malignant tumors; 6. Patients with liver or kidney dysfunction; 7. Patients with chronic myopathies; 8. Patients with peripheral vascular diseases, chronic cardiac failure, thyroid disease, major trauma that occurred within 6 months before the study, or history of surgery; 9. Patients with diabetes mellitus; 10. Patients with New York Heart Association (NYHA) class III and IV heart failure; 11. Patients who experienced myocardial infarction, those who underwent percutaneous transluminal coronary angioplasty, those who underwent coronary artery bypass grafting within 6 months before the study, patients who were recently administered adrenocortical hormones or other immunomodulatory drugs, patients and relatives who failed to comply with treatment, or patients with a history of psychiatric disease[2].

Mini Mental State Examination (MMSE)

A score of 1 was assigned for one correct answer, and a score of 0 was assigned for wrong or unknown answers. The highest possible score was 30. Dementia was associated with educational level. Dementia was evaluated as follows: if an older person was illiterate and had a score of less than 17; if the patient had primary school education level and had a score of less than 20; or if the patients had middle school education or above and had a score of less than 24. Scores from 27-30 were considered normal; scores from 21-26 were considered mild cognitive impairment; scores from 10-20 were considered moderate cognitive impairment; and scores from 0-9 were considered severe cognitive impairment.

Montreal Cognitive Assessment (MoCA)

The test included orientation, denomination, memory, attention, language, abstract thoughts, delayed memory, and directive force, with a total score of 30. One point was added to the test results of subjects with less than 12 years of education to correct bias for an educational degree. Higher scores implied better cognitive function. A score of 26 was considered normal.

Sample Collection

A total of 3 ml of fasting venous blood from the elbow was drawn in the morning. Blood was transferred to common plastics tubes. Next, 1.8 ml of blood was transferred to anticoagulation tubes containing 0.2 ml of 3.8% sodium citrate. Samples were then centrifuged at 2,500 × g for 10 min. Serum or plasma was extracted and transferred to 0.5 ml EP tubes and stored at -30°C until testing within 1 month.

Measurement of Serum Levels of S100β by ELISA

ELISA was used to measure the serum levels of S100 . All reagents in this study were from Wuhan Boster Biological Engineering (Co., Ltd, Wuhan, Hubei, China) and used according to the manufacturer's instructions.

Surgical Methods

Patients fasted for 8 h before surgery, the peripheral venous pathway was established after entering the operating room, and a radial artery puncture cannula was connected to a pressure sensor to monitor pulse pressure under local anesthesia. 2. For induction of anesthesia, 0.05 mg/kg midazolam, 0.3 mg/kg etomidate, 10 g/kg fentanyl, and 0.5 mg/kg cisatracurium were injected. Mechanical controlled ventilation was used after insertion of the tracheal cannula, and double cavity central venous catheters were inserted in the right subclavian vein to monitor Central Venous Pressure (CVP) and the use of vasoactive agents. 3. Intubation was retrograded for the right internal jugular vein, and the jugular bulb was extracted to measure S100 protein levels. 4. The chest was opened, cardiopulmonary bypass (CPB) was established in the ascending aorta, intubation of the superior and inferior vena cava was performed, and cold blood cardioplegia was perfused in the aortic root. Flake ice was used to cool the pericardial cavity, a mechanical valve was placed by interrupted suture, and gas in the cardiac chambers was fully exhausted before reopening the ascending aorta. CPB was stopped after establishing satisfactory hemodynamics. Next, hemostasis was thoroughly performed, and the chest was closed layer-by-layer.

Table I. Comparison of baseline parameters of enrolled patients ($x \pm s$).

Group	Cases	Age (years)	BMI (kg/m^2)	MAP (mmHg)
Patient group	178	54.5 ± 12.7	21.7 ± 1.2	78.3 ± 12.4
Healthy comparison	155	55.6 ± 10.8	20.7 ± 1.3	76.5 ± 10.9
t-value	–	0.33	1.49	1.33
p-value	–	0.47	0.12	0.28

Statistical Analysis

SPSS17.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Numerical data are presented as a mean ± standard deviation. Repeated measures ANOVA were used for statistical analyses. A *t*-test was used for comparisons of numerical data between groups, paired *t*-test was adopted for intra-group comparisons, and a ^{2}-test was adopted for categorical data. $p < 0.05$ was considered statistically significant.

Results

Comparison of Baseline Parameters of Enrolled Patients

We recorded and statistically analyzed baseline parameters such as age, weight, and body mass index (BMI) of the 178 patients who underwent single valve replacement and the 155 subjects in the healthy comparison group. There were no significant differences in baseline parameters ($p > 0.05$) (Table I).

MMSE and MoCA Scores of Patients in the Two Groups

We performed MMSE and MoCA assessment for patients 1 day before surgery and on postoperative days 2 and 9. There were 32 cases with postoperative cognitive dysfunction (the POCD group), and 146 cases without POCD (the control group). MMSE and MoCA scores of patients in the POCD group were significantly lower compared with the control group ($p < 0.05$) (Table II).

S100β Levels in Peripheral Blood

We measured the levels of S100 in the 178 patients who underwent single valve replacement and in the 155 subjects of the healthy comparison group. Serum levels of S100 in patients with POCD were significantly higher than those in the control group and healthy comparison group ($p < 0.05$) (Table III and Figure 1).

Correlation Analysis between S100β, and MMSE and MoCA Scores

We set S100 as the independent variable and conducted correlation analyses of mean arterial pressure, BMI, MMSE, and MoCA scores. S100 expression level was negatively correlated with the MMSE score, and the difference was statistically significant ($p < 0.05$) (Table IV and Figure 2).

Comparison of Surgical Conditions and Postoperative Length of Stay in Hospital Between the POCD Group and Control Group

Surgical conditions and postoperative length of hospital stay were compared between patients with POCD and those in the control

Table II. MMSE and MoCA scores for patients in each group.

Items	Group	Cases	1 day before surgery	2 days after surgery	9 days after surgery	*p*-value
MMSE	POCD group	32	28.3 ± 1.6	24.3 ± 1.4	21.3 ± 3.2	0.01
	Control group	146	29.2 ± 1.7	27.5 ± 2.8	28.4 ± 2.2	0.38
	t-value	–	0.33	0.36	0.29	–
	p-value	–	0.69	0.22	0.77	–
MoCA	POCD group	32	29.6 ± 0.4	22.1 ± 1.8	21.4 ± 1.3	0.03
	Control group	146	28.7 ± 1.5	27.3 ± 2.6	28.3 ± 0.8	0.98
	t-value	–	0.42	0.44	0.78	–
	p-value	–	0.38	0.67	0.22	–

Table III. 100β levels in peripheral blood (ng/μl).

	Cases	1 day before surgery	2 days after surgery	9 days after surgery	*p*-value
POCD group	32	0.081 ± 0.012	1.027 ± 0.045*	1.243 ± 0.427#	0.002
Control group	146	0.064 ± 0.003	0.075 ± 0.031**	0.082 ± 0.021##	0.231
Healthy comparison group	155	0.055 ± 0.001	0.067 ± 0.025	0.052 ± 0.008	0.819

*$p < 0.05$ compared with control group; **The comparison with the healthy comparison group showed no statistical significance ($p > 0.05$); #$p < 0.05$ compared with control group; ##The comparison with the healthy comparison group showed no statistical significance ($p > 0.05$).

group. There were no significant differences ($p > 0.05$) in operative time, surgical bleeding volume, or CPB time. In contrast, postoperative length of hospital stay was significantly increased in the POCD group ($p < 0.05$) (Table VI and Figures 3, 4, and 5).

Discussion

The pathogenesis of POCD remains unclear. It may involve the central nervous system, the endocrine system, and the immune system. The possible causes of POCD include[11] -neurotoxicity from amyloid proteins, excessive phosphorylation of Tau proteins in neuronal microtubules, central cholinergic system dysfunction, changes in hormone levels, disorders of cholesterol metabolism, neurotoxicity from nitric oxide, and inflammatory responses caused by various stimuli[12-14].

In the present work, we found that the serum levels of S100 in patients with POCD were significantly increased compared with patients

Table IV. Correlation analysis between S100β and indexes of clinical detection.

Index	Gender	Age	MMSE	MoCA
S100β				
r	0.02	0.35	-0.14	-0.28
p	> 0.05	> 0.05	< 0.05	> 0.05

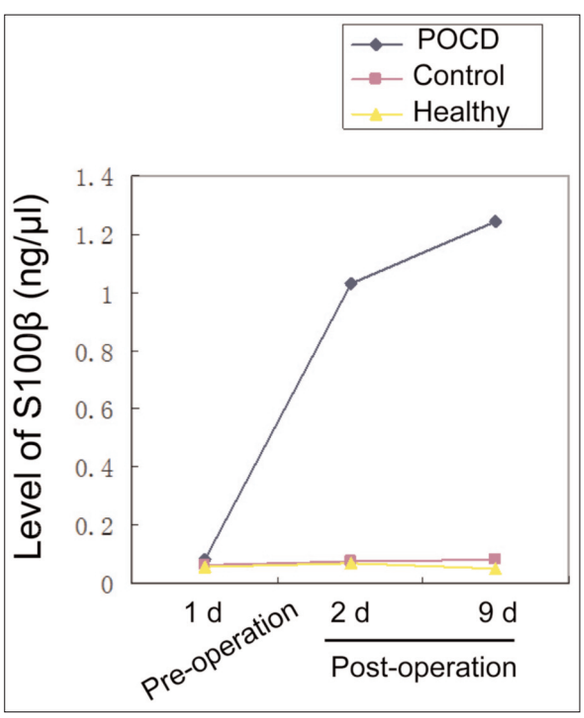

Figure 1. Line graph of the comparison of S100β levels in peripheral blood as determined by ELISA. On postoperative day 9, serum S100β levels in the POCD group increased significantly ($p < 0.05$) compared with the other two groups.

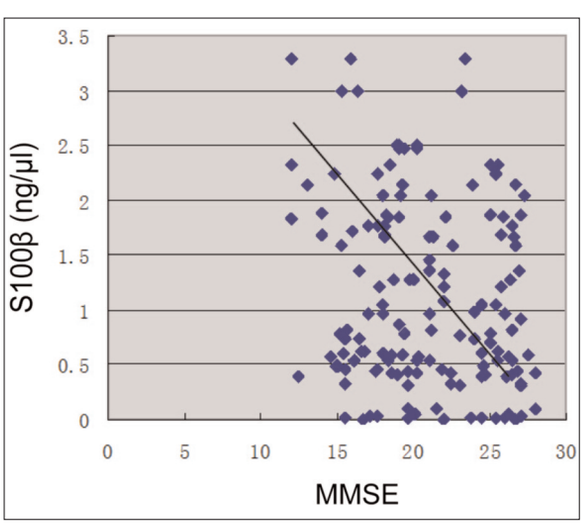

Figure 2. Correlation analysis between S100β protein and MMSE; y = -0.14 × + 38.261.

Table V. Multiple linear regression analysis of S100β level influencing factors.

Variable	β	SE	β′	*t*	*p*	(95% CI)	
						Upper limit	Lower limit
MMSE	0.531	0.14	0.764	0.412	< 0.05	0.26	0.81

Table VI. Surgical conditions and postoperative length of stay in hospital between the POCD group and control group.

Group	Cases	Operative time (min)	Bleeding volume (ml)	Postoperative length of stay in hospital (day)
POCD group	32	187.4 ± 21.4	287.4 ± 68.7	22.4 ± 2.8
Control group	146	190.3 ± 25.3	298.6 ± 48.2	14.3 ± 1.7
t-value	–	1.28	0.59	18.5
p-value	–	0.21	0.48	0.012

in the control group and those in the healthy comparison group ($p<0.05$). S100 is a nerve tissue protein, and it is expressed at high levels in neurogliocytes and Schwann cells. Under physiological conditions, S100 protein is expressed at extremely low levels in serum. It increases abnormally when blood-brain barrier permeability is increased significantly. Furthermore, the levels increase under various pathological conditions and when individual nerve cells are damaged[15]. We suggested that extracorporeal circulation (CPB) contributed to the increase of S100 . It is known that CPB results in systemic or local inflammation, neuronal damage caused by the formation of cerebral microemboli, and changes in cerebral perfusion

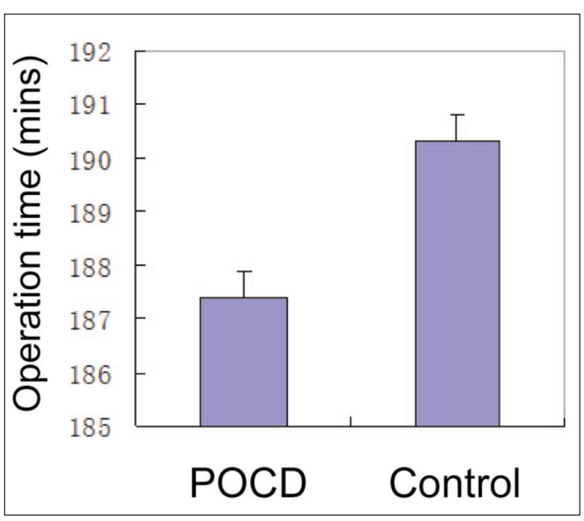

Figure 3. Comparison of operative time between both groups. The difference was not statistically significant ($p > 0.05$).

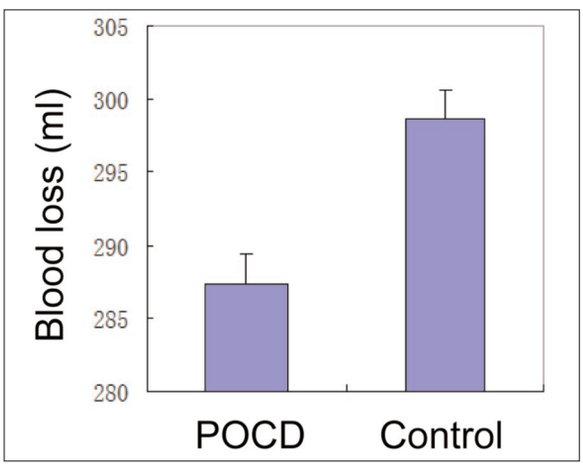

Figure 4. Comparison of bleeding volume between both groups. The difference was not statistically significant ($p > 0.05$).

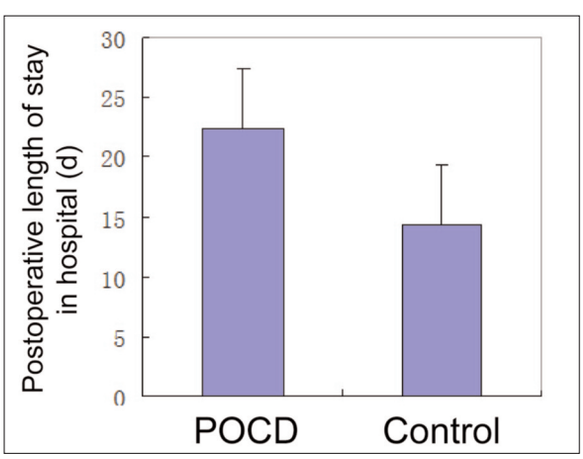

Figure 5. Comparison of postoperative length of stay in hospital between both groups. The difference was statistically significant ($p < 0.05$).

volume, which cause further release of S100 protein. Also, to reduce surgical bleeding and brain tissue damage, hypotension was controlled during surgery. In this study, we found that the postoperative length of hospital stay was significantly increased in patients with POCD. This observation was consistent with previous studies. Ramlaw et al[10] showed that the plasma levels of inflammatory cytokines in patients with cognitive decline after CPB increased significantly at an early stage compared with patients without cognitive decline, which directly affected the postoperative length of hospital stay. Given this observation, anesthetists should ensure cerebral protection in patients undergoing single valve replacement surgery by CPB, particularly in older patients with hypertension and hyperlipidemia, or with any other basic conditions. Increased attention should be paid to tissue injury caused by cerebral ischemia when patients receive anticoagulant or thrombolytic drugs.

Under CPB, large amounts of inflammatory mediators are released as a consequence of surgical trauma and ischemia-reperfusion injury. When large amounts of inflammatory mediators are released, systemic inflammatory response syndrome occurs[11,16]. During the process of inflammation, peripheral cytokines are directly transported through the blood-brain barrier or are indirectly stimulated by the vagus nerve, thus triggering the interaction of nerve cells and neuroglial cells, which affects the central nervous system[17-19]. Increases of pro-inflammatory factors such as IL-6, IL-1, and TNF- in the brain can induce cerebral inflammation, directly damage nerve cells, and generate complement, resulting in autoimmune responses and further increasing neuronal damage[14,20]. Clinical manifestations were shown to include postoperative disturbances of consciousness, severe coma, convulsions, hemiplegia, and brain death, which severely affected the postoperative recovery of patients[12-14]. Therefore, it is mandatory to identify markers of early onset of POCD[14,15]. We observed that S100 protein expression was increased significantly when patients appeared with mild disturbance of consciousness on the second postoperative day, indicating that S100 protein is a sensitive marker of early POCD. Measurement of S100 can significantly improve the rate of early diagnosis of POCD, and allow for the implementation of measures to prevent disease progression[20].

Conclusions

S100 has important application value for the early detection of POCD. It should be considered as a target for the diagnosis and treatment of cognitive dysfunction after cardiac surgery under general anesthesia.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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