

Evaluation of the postoperative cognitive dysfunction in elderly patients with general anesthesia

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Abstract. – OBJECTIVE: The present study is aimed to study the neuron-specific enolase (NSE) and S100 β proteins in the evaluation of postoperative cognitive dysfunction in elderly patients with general anesthesia.

PATIENTS AND METHODS: A total of 142 aged patients, who were treated with transurethral resection of the prostate (TURP) surgery under general anesthesia with propofol from June 2014 to December 2015, were randomly divided into two groups. The experiment group was given scopolamine butylbromide by intramuscular injection before the operation, while the control group had no preoperative intramuscular injection. The propofol was used for maintenance during the operation. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scales were adopted for testing the patients on preoperative day 1, postoperative day 2 and postoperative day 9. After the surgery, there were 4 cases of postoperative cognitive dysfunction (POCD) patients in experiment group, while 21 cases of POCD patients in control group. While the 142 healthy adult volunteers, who were admitted to physical examination center of our hospital in the corresponding period, were selected as healthy controls. The expression levels of S100 β and NSE of patients, as well as healthy controls, were detected by ELISA.

RESULTS: In POCD patients, serum S100 β and NSE levels were evidently higher than those of patients without POCD and healthy control group ($p < 0.05$). S100 β and NSE levels of POCD patients in experiment group were significantly lower than those of control group ($p < 0.05$). Serum S100 β and NSE levels are higher, the longer duration of POCD is, as the correlation coefficient $r_s = -0.1342, -1.6644, p < 0.05$.

CONCLUSIONS: The expression levels of S100 β protein and plasma NSE in the serum of POCD patients increased, which indicated the severity of the disease. The preoperative intramuscular injection of scopolamine butylbromide has important clinical significance for the prevention of POCD.

Key Words:

Postoperative cognitive dysfunction, NSE, S100 β protein.

Introduction

Postoperative cognitive dysfunction (POCD) after general anesthesia is now common all over the world¹. POCD refers to the patients, who have no mental disorders before anesthesia, but the persistent disorders of memory, abstract thinking, and directional force would exist after anesthesia, along with the significant decline in social activities. Especially in aged patients, the proportion of POCD after surgery is high, as high as 10-62%, which seriously affects the social life ability and quality of life of aged patients². Therefore, the study of etiology and pathogenesis of POCD after general anesthesia has important clinical significance for clinical diagnosis and prevention of the occurrence and development of POCD.

S100 β protein is a member of the nerve tissue protein family, whose expression levels in glial cells and Schwann cells are significantly prominent³. The content in serum is very low in the conditions of physiology; however, the permeability of blood brain barrier will evidently increase when the individual nerve cells damaged or in various pathological conditions, while the S100 β protein level in serum abnormally increases. The phenomenon of increased serum S100 β level can be observed in the patients with Alzheimer's disease, neuroglioma and hepatic encephalopathy⁴. But its function and clinical significance in POCD need to be further discussed.

Neuron-specific enolase (NSE): the serum NSE, which is a specific acid protease of neurons and neuroendocrine cells, is a specific sign of neuroendocrine tumor, including neuroblastoma,

medullary thyroid carcinoma and small cell lung cancer (70% increases), which could be used for differential diagnosis, condition monitoring, curative effect evaluation and recurrence. But the role of NSE in POCD is still controversial⁵⁻⁷. The present work was designed to detect the postoperative expression levels of S100 β in 142 cases of aged patients with transurethral resection of the prostate (TURP) and 142 cases of healthy control volunteers, to provide a theoretical basis for the development and research of targeted therapeutic drugs.

Patients and Methods

Selected Cases

A total of 142 aged patients, who were treated with TURP surgery under general anesthesia with propofol from June 2014 to December 2015, were selected, with the average age of (64.5 $\pm$ 8.7) years old.

Inclusion criteria: (1) The patients have prostatitis or prostatic hyperplasia that meets indication of TURP. (2) The age is more than 60 years old.

Exclusion criteria: (1) patients with application of immunosuppressive agents; (2) patients with acute or chronic bacterial and/or virus infection; (3) patients with autoimmune disease; (4) patients with connective tissue disease; (5) patients with malignant tumor; (6) patients with liver and kidney insufficiency; (7) patients with chronic muscle disease; (8) patients with peripheral vascular disease, chronic heart failure, thyroid disease, liver and renal insufficiency, tumor, major trauma in the past half year, or have history of surgery; (9) diabetes; (10) the Grade III and IV of New York heart function classification; (11) patients have history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting in past half year, adrenal cortical hormone or other immune modulator drugs in recent period, patients and their families cannot cooperate with the study, and the patients had a history of mental illness².

Diagnostic criteria⁸: the America Psychiatric Association: The awareness for environment diminished, also with transfer, and the attention of concentrating and maintaining environmental stimulation declined; At least two of the following: (1) perceptual disturbance; (2)

incoherence of speech; (3) sleep-wake rhythm disorders; (4) nerve motor activities increase or decrease. Orientation disorder and hypomnesia; Clinical manifestations last for a few hours, a few days, sometimes there are fluctuations within a day. The patients have a history of surgical anesthesia.

Research Method

Mini-Mental State Examination (MMSE)⁹:

Each correct answer is 1 point, and error or unknown is 0 point. The unsuitable one is 9 points, and refusing to answer or incomprehension is 8 points. In the total score, 8 points and 9 points are calculated by 0 points. The highest score is 30 points. The division of dementia or not is related to the degree of education. The dementia is affirmed by the patient who is illiterate and less than 17 points, the primary school is less than 20 points, and more than middle school is less than 24 points. The scores which from 27 to 30 is normal, 21 to 26 of mild, 10 to 20 of moderate, and from 0 to 9 is severe.

Montreal Cognitive Assessment (MoCA)¹⁰

The visual spatial executive ability, naming, memory, attention, language fluency, abstract thinking, delayed memory and directional force are included in the test, a total of 30 points.

The subjects whose have less than 12-year of education were added 1 point in the testing result, with correction of bias in the degree of culture. The patients whose get higher scores indicate that the cognitive function is better, 26 points as normal.

Collection of Specimens

Morning fasting elbow vein blood 3 mL was taken and injected into the ordinary plastic pipe. 1.8 mL was injected into an anticoagulation tube containing 0.2 mL 3.8% natrium citricum. Within 1 hour after the collection of specimens, we took centrifugation for 10 min at 3000 r/r min. The serum or plasma was extracted and packed into 0.5 mL EP tubes, respectively, for preservation at -30°C and detection within one month.

The serum S100 β and NSE expression levels were detected by ELISA. The expression levels of S100 β and NSE were detected by ELISA. All reagents were purchased from Wuhan Boshide Biological Engineering Co. Ltd., China, and the operation is fully carried out in accordance with the instructions.

Operation method: (1) Routine preoperative fasting was lasting for 8h. The peripheral venous access was opened after entering, and then under local anesthesia, the arterial blood pressure was monitored by radial artery puncture setting tube connected to a pressure transducer. S100 β protein was detected after extracting venous blood 4 ml. (2) The preoperative intramuscular injection of scopolamine butylbromide was used in experiment group. (3) Anesthetic induction mediations including intravenous injection of midazolam 0.05 mg/kg, etomidate 0.3 mg/kg, fentanyl 10 mg/kg, cisatracurium 0.5 mg/kg were used in experiment. Then the mechanical control ventilation was performed after tracheal intubation. (4) To keep patients in the lithotomy position, Shunkang F25.6 resectoscope was put in the bladder. The electric cutting power was set as 207w, and electric coagulation power was set as 70w. (5) The electric cutting was started from six o'clock of the middle bladder, along with bladder neck to bladder neck fibrae circulars, gradually to the deep and the sides as well as the tip. The depth was till nuclear envelope layer of the striate structure. (6) The apex of the prostate, hyperplasia prostate tissues on both sides of verumontanum and the former union of the prostate were taken an electric cutting, and the surface of the wound was repaired. (7) Hemostasis of the wound was completely performed, then washed bladder by ELLIS irrigator, and sucked the prostate tissue fragments. (8) 300 ml water was injected into the bladder, then pulled out the resectoscope sheath and pressed bladder, getting the urine flow satisfaction, without urinary incontinence. A F20 three-antrum catheter was put into the urethral canal, with 30 ml water injecting into the sac. The flushing liquid was pale red.

Statistical Analysis

All measurement data were expressed as mean $\pm$ standard deviation. SPSS17.0 software (SPSS Inc., Chicago, IL, USA) was used for the statis-

tical analysis. The variance analysis of repeated measurement data was applied for statistical treatment. The *t*-test of two independent samples was adopted for measurement data between groups. Paired *t*-test was used in comparison in each group. Chi-square test was applied for count data. $p < 0.05$ means the difference has statistical significance.

Results

Comparison of Baseline Data of Enrolled Patients

The age, weight, BMI and other baseline data of 142 patients with TURP and 142 healthy control patients were recorded for statistical analysis. The baseline data of enrolled patient had no significant difference ($p > 0.05$) (Table I).

Comparison of MMSE and MoCA Scores of the Enrolled Patients

The MMSE and MoCA scales were adopted for testing the patients on preoperative day 1, postoperative day 2 and postoperative day 9. The results showed that in experiment group, there were 4 cases of patients with POCD after surgery, 67 cases of patients without POCD. In control group, there were 21 cases of patients with POCD, 50 cases of patients without POCD. The comparison of MMSE and MoCA scores of patients in each group indicated that the MMSE and MoCA scores in POCD patients of two groups significantly decreased, and the difference was statistically significant ($p < 0.05$) (Table II, Figures 1 and 2).

The S100 β and NSE Levels in Peripheral Blood of Patients and Healthy Controls were Detected by ELISA

S100 β and NSE levels of enrolled 142 patients who were treated with TURP surgery and 142 healthy control volunteers were detect-

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

Groups	No.	Age (years old)	BMI (kg/m ²)	MAP (mmHg)
Experiment group	142	64.5 $\pm$ 12.7	20.7 $\pm$ 1.8	79.3 $\pm$ 12.4
Healthy control	142	65.6 $\pm$ 10.8	20.7 $\pm$ 1.3	78.5 $\pm$ 10.9
<i>t</i> -value		0.33	1.29	1.43
<i>p</i> -value		0.47	0.32	0.48

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

Item	Groups	No.	Preoperative day 1	Postoperative day 2	Postoperative day 9	p-value
MMSE	Experiment group POCD	4	27.3 ± 1.9	21.3 ± 1.4	24.3 ± 1.2	0.01
	Experiment group without POCD	67	28.2 ± 1.7	27.5 ± 2.8	28.4 ± 2.2	0.38
	Control group POCD	21	28.3 ± 1.1	20.3 ± 0.9	23.4 ± 2.3	0.02
	Control group without POCD	50	27.6 ± 0.8	26.9 ± 0.8	26.4 ± 1.6	0.33
	t-value	—	0.33	0.36	10.29	—
	p-value	—	0.69	0.22	0.02	—
MoCA	Experiment group POCD	4	28.6 ± 0.4	21.1 ± 1.9	25.4 ± 1.3	0.03
	Experiment group without POCD	67	28.7 ± 1.5	27.3 ± 2.4	28.3 ± 0.8	0.98
	Control group POCD	21	28.4 ± 0.3	20.5 ± 1.0	23.8 ± 2.4	0.005
	Control group without POCD	50	28.2 ± 0.6	26.1 ± 1.7	29.2 ± 0.3	0.44
	t-value	—	0.42	0.44	0.68	—
	p-value	—	0.38	0.67	0.12	—

ed, showing that serum S100 β level of POCD patients was significantly higher than that of control group and healthy control group, with statistical significance ($p < 0.05$) (Table III, Figures 3 and 4).

Correlation Analysis of S100 β and MMSE as Well as MoCA Scores

With using S100 β as an independent variable, correlation of BMI, MMSE, and MoCA scores were analyzed, showing that the ex-

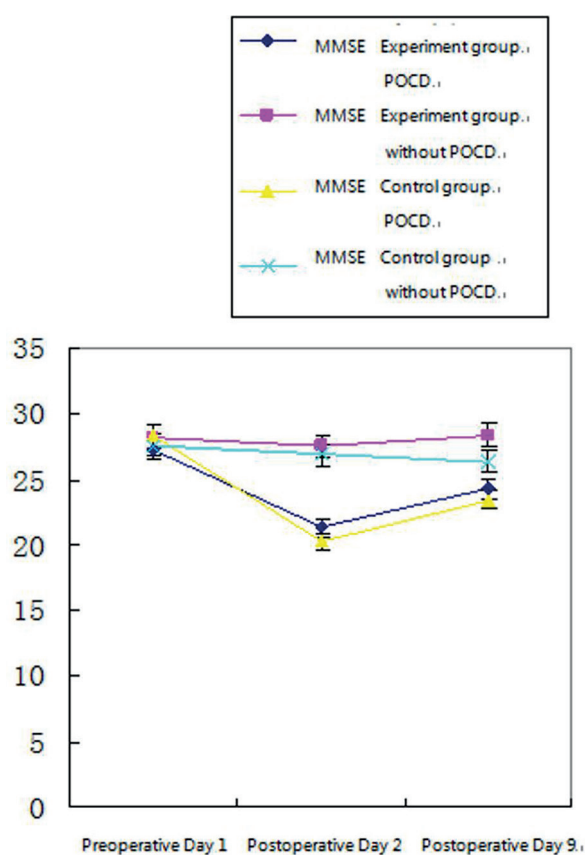


Figure 1. The MMSE scores of POCD patients in each group significantly decreased, and the difference has statistical significance ($*p < 0.05$).

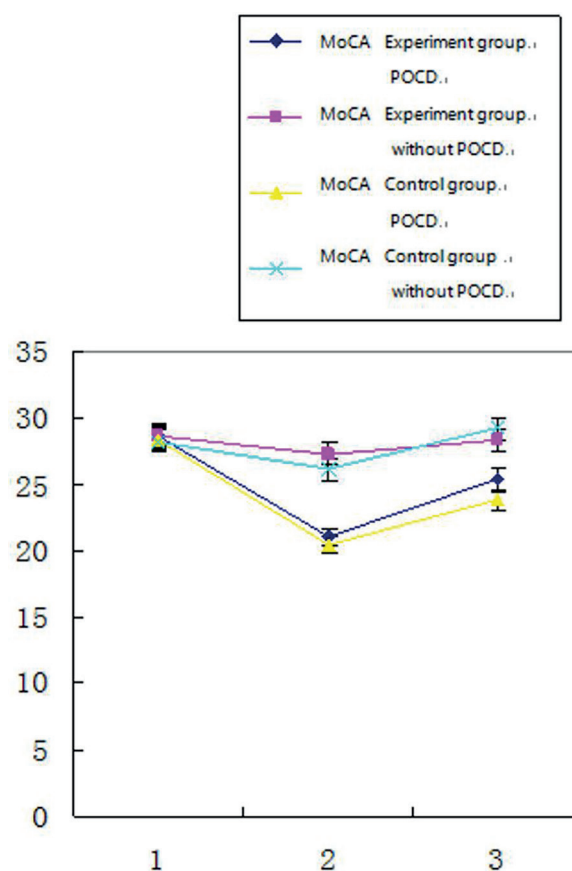


Figure 2. The MoCA scores of POCD patients in each group significantly decreased, and the difference has statistical significance ($*p < 0.05$).

Table III. MMSE and MoCA scores of patients in each group.

Item	Groups	No.	Preoperative day 1	Postoperative day 2	Postoperative day 9	p-value
S100 β (ng/ μ l)	Experiment group POCD	4	0.081 $\pm$ 0.012	1.227 $\pm$ 0.045*	1.043 $\pm$ 0.427	0.002
	Experiment group without POCD	67	0.064 $\pm$ 0.003	0.075 $\pm$ 0.031**	0.082 $\pm$ 0.021	0.231
	Control group POCD	21	0.077 $\pm$ 0.004	1.203 $\pm$ 0.041	1.004 $\pm$ 0.012	0.003
	Control group without POCD	50	0.063 $\pm$ 0.033	0.052 $\pm$ 0.025	0.073 $\pm$ 0.004	0.482
	t-value	—	0.28	18.18	21.33	—
	p-value	—	0.33	0.02	0.001	—
NSE (ng/ μ l)	Experiment group POCD	4	11.2 $\pm$ 1.65	34.2 $\pm$ 10.81	43.2 $\pm$ 1.65	0.003
	Experiment group without POCD	67	12.7 $\pm$ 1.78	18.8 $\pm$ 1.92	12.3 $\pm$ 2.15	0.252
	Control group POCD	21	13.4 $\pm$ 1.73	36.9 $\pm$ 9.43	39.7 $\pm$ 4.98	0.001
	Control group without POCD	50	10.9 $\pm$ 0.78	16.4 $\pm$ 3.33	12.8 $\pm$ 1.89	0.372
	t-value	—	0.42	10.20	21.38	—
	p-value	—	0.55	0.02	0.001	—

pression level of S100 β was negatively correlated to MMSE scores, with the correlation coefficient $r_s = -0.1342$, and the difference has statistical significance ($p < 0.05$) (Tables IV and V, Figure 5).

Correlation Analysis of NSE and MMSE as Well as MoCA Scores

With using NSE as an independent variable, correlation of BMI, MMSE, and MoCA scores were analyzed, showing that the expres-

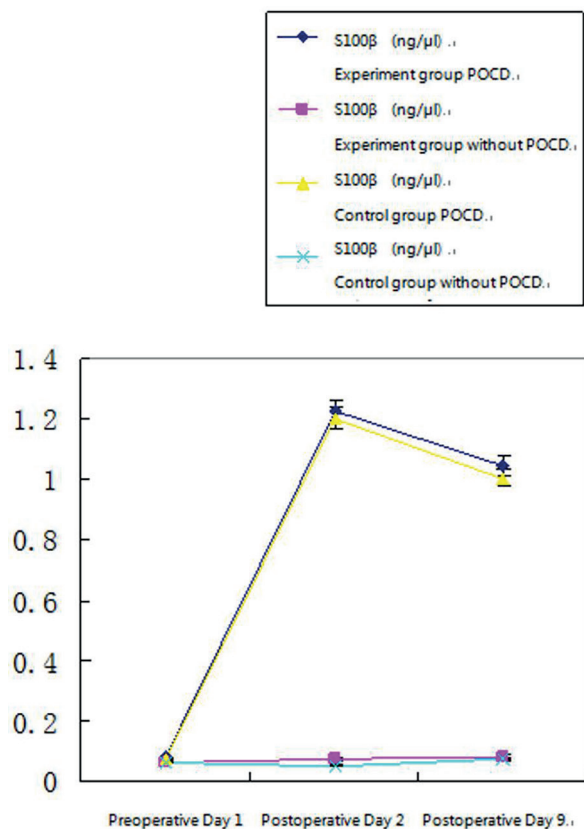


Figure 3. The S100 β levels in peripheral blood of patients and healthy controls were detected by ELISA, showing that serum S100 β level of POCD patients in each group significantly increased, but has no statistical significance between two groups ($p > 0.05$).

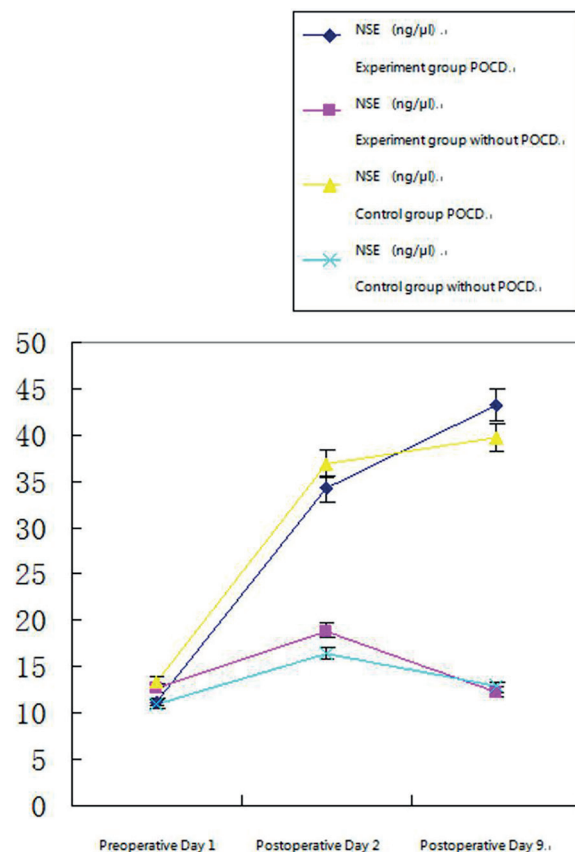


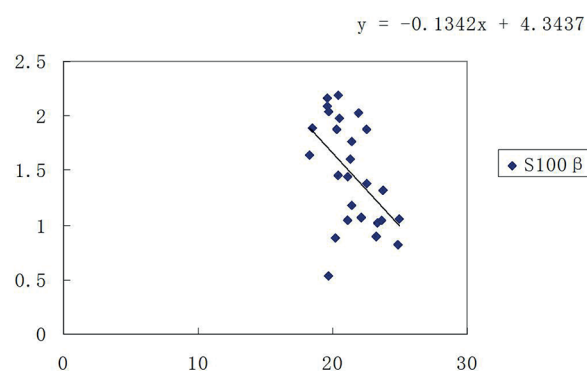
Figure 4. The NSE levels in peripheral blood of patients and healthy controls were detected by ELISA, showing that serum NSE level of POCD patients in each group significantly increased, but has no statistical significance between two groups ($p > 0.05$).

Table IV. Correlation analysis of S100 β and clinical detection index (r).

Index	Gender	Age	MMSE	MoCA	NSE
S100 β					
<i>r</i>	0.003	0.39	-0.13	-0.34	0.27
<i>p</i>	> 0.05	> 0.05	< 0.05	> 0.05	> 0.05

Table V. Multivariate linear regression analysis of influencing factors of S100 β level.

Variable	β	SE	β'	<i>t</i>	<i>p</i>	(95% CI)	
						Upper limit	Lower limit
MMSE	0.531	0.14	0.764	0.412	< 0.05	0.26	0.81

**Figure 5.** Correlation analysis of S100 β protein and MMSE $y = -0.1342x + 4.3437$.

sion level of NSE was negatively correlated to MMSE scores, with the correlation coefficient $r = -1.6644$, and the difference has statistical significance ($p < 0.05$) (Tables VI and VII, Figure 6).

The Postoperative POCD of Experiment Group and Control Group

The postoperative POCD cases of two groups were compared, showing that the number of POCD patients in experiment group was significantly less than that of the control group, with statistical difference ($p < 0.05$). The surgery and postoperative stay in hospital in two groups of POCD patients were further compared, which indicated that the postoperative stay in hospital of POCD patients in experiment group significantly shortened, with statistical difference ($p < 0.05$). The result implied that preoperative intramuscular injection of scopolamine butylbromide has a great effect on the prevention of POCD (Tables VIII and IX).

Discussion

At present, the pathogenesis of POCD is not clear and it mainly involving the central nervous system, endocrine system, and immune system⁵⁻¹¹.

Table VI. Correlation analysis of NSE and clinical detection index (r).

Index	Gender	Age	MMSE	MoCA	S100 β
NSE					
<i>r</i>	0.001	0.19	-1.66	-0.34	0.27
<i>p</i>	> 0.05	> 0.05	< 0.05	> 0.05	> 0.05

Table VII. Multivariate linear regression analysis of influencing factors of NSE level.

Variable	β	SE	β'	<i>t</i>	<i>p</i>	(95% CI)	
						Upper limit	Lower limit
MMSE	0.521	0.19	0.665	0.412	< 0.05	0.27	0.791

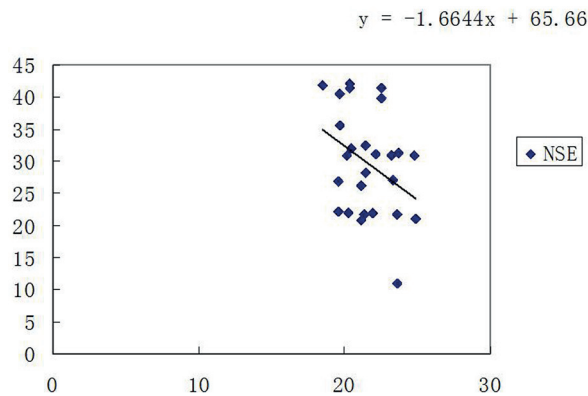


Figure 6. Correlation analysis of NSE protein and MMSE $y = -1.6644x + 65.66$.

The studies have indicated that neurotoxic effects of β -amyloid protein, a dysfunction of the central cholinergic system, a disorder of the cholesterol metabolism, various stress stimulation and inflammatory response induced by the immune system activation could lead to the occurrence of POCD after general anesthesia^{6,7}. The study has shown that the prevalence of postoperative elderly patients (aged 75 or more) with mental disorders was three-fold higher than the patients who aged from 65 to 75 years old¹². The above age relation might related to the hemodynamic regulation ability and central nervous system dysfunction of the elderly patients.

In the present study, we found that in the postoperative POCD patients, the expression levels of serum S100 β and NSE were evidently higher than those of patients without POCD and healthy controls, and the difference was statistically significant ($p < 0.05$). S100 β protein is a kind of nervous tissue protein. The contents of S100 β protein in serum is very low; however, the permeability of blood brain barrier would evidently increase when the individual nerve cells got damaged or in various pathological conditions, while the S100 β protein level in serum abnormally increases¹³. In previous studies, it was considered that S100 β is a kind of calcium binding of two polymer acid,

Table VIII. Comparison of POCD in two groups.

	No.	POCD	Without POCD
Experiment group	71	4	67
Control group	71	21	50
χ^2	—	33.27	
p -value		0.002	

which is mainly located in brain glia cells. After brain injury, serum S100 β level is usually significantly increased. Prohl et al¹⁴ indicated that serum S100 β protein level of CPB postoperative 3d was associated distinctly with a neuropsychological assessment of learning, memory and executive function in patients after six months of surgery. Based on this, we considered that it might be due to postoperative pain and stress stimulation, the serum inflammatory reaction occurs that further cause platelet aggregation and micro-thrombosis formation, causing cerebral micro artery injury, resulting in POCD. In this study, we found that POCD could evidently prolong the postoperative stay in the hospital, which was consistent with previous studies.

Carbohydrate decomposition has multiple poly isomers, which consists of three kinds of subunits, such as α , β , and γ . Enolase α subunit was found in many types of mammalian tissues, while β subunit was mainly found in the heart and muscle tissues. $\alpha\gamma$ and $\gamma\gamma$ enzyme isomers are called neuron-specific enzyme (NSE) or γ enzyme, which are high in nerve cells, neuroendocrine cells and tumor cells induced by these cells¹⁵. Rasmussen et al¹⁶ considered that the increase of serum NSE levels of postoperative 24h in patients was evidently associated with cognitive function at discharge. In the present study, we noticed that the serum levels of NSE were significantly higher in the patients with POCD. We believed that inflammatory mediators *in vivo* could be released by the co-stimulation of surgical trauma, plus a variety of factors including the contact of blood

Table IX. Comparison of surgery and postoperative stay in hospital in two groups of POCD patients.

Groups	No.	Operation time (min)	Amount of bleeding (ml)	Postoperative stay in hospital (day)
Experiment group POCD	4	87.4 $\pm$ 11.4	87.4 $\pm$ 8.7	4.4 $\pm$ 2.8
Control group POCD	21	90.3 $\pm$ 10.3	98.6 $\pm$ 8.2	7.3 $\pm$ 1.7
t -value	—	1.28	0.59	18.5
p -value	—	0.21	0.48	0.012

with non-biological products¹². In the course of occurrence and development of inflammatory reaction, peripheral cytokines could affect the function of the central nervous system by direct and indirect ways. On the one hand, it could activate the active transport through the blood-brain barrier; on the other hand, it could promote the interaction of cytokine-mediated neurons and glia cells indirectly by the stimulation of the vagus nerve¹⁷. The levels of pro-inflammatory cytokines in the brain significantly increased, and the interaction of these pro-inflammatory factors could stimulate synthesis and secretion of NSE. This in turn induces brain inflammation or directly damage neuronal cells that further lead to the autoimmune reactions in the brain, resulting in aggravating the neuronal injury¹⁸⁻²⁰. In general, NSE could be detected in the early stage, and the combination of S100 β protein has important clinical significance for hinting POCD. For the clinical manifestations, postoperative consciousness disorder could be observed in patients, along with coma, convulsions, hemiplegia, brain death and other manifestations^{21,22}. Therefore, there is an urgent need for a clinical index, which could provide an early warning for the emergence of postoperative POCD²³. In the study, we indicated that on postoperative day 2, the expression level of S100 β protein significantly increased, showing that S100 β protein has a strong sensitivity in the early stage of POCD, which could evidently enhance the level of early diagnosis of POCD²⁴.

Also, acetylcholine (ACh) is thought to have a certain relationship with the occurrence of POCD. Under physiological conditions, ACh involved in attention, memory, and sleep, is highly sensitive to the metabolic and toxic violation. The drug and pathological changes can cause the further decline of ACh level in the central nervous system. Moreover, the levels of ACh are also low in aged patients and low ventilation during general anesthesia could further exhaust ACh. Some scholars considered that the application of anti-cholinergic drugs before surgery might have a significant effect on improving ACh depletion of general anesthesia²⁵⁻²⁷. In the present study, we noticed that in experiment group, the patients with POCD significantly decreased after the application of preoperative intramuscular injection of scopolamine butylbromid.

In the meantime, there were also some defects in this study. The sample size in this study is small. Due to the small number of enrolled patients, also as a nonspecific protein, NSE can

increase the expression in POCD as well as in patients with bacterial infection or myocardial infarction, especially for patients who treated with OPCABG, the specificity of NSE was poor^{12,17-18}.

Conclusions

In this work, we found that S100 β was negatively correlated with MMSE scores, while has no evident relativity with NSE, which indicated no interaction between these two indexes. Therefore, we believed that the combined application of S100 β protein could significantly improve the diagnostic efficiency of NSE. However, this observation also needs to be further confirmed by a large sample size of the study.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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