

Original Article

The effects of dexmedetomidine on activin A and neuron specific enolase in the serum of patients undergoing cardiac surgery with cardiopulmonary bypass

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Received August 24, 2019; Accepted October 10, 2019; Epub December 15, 2019; Published December 30, 2019

Abstract: Objective: This paper aimed to investigate the effects of dexmedetomidine on activin A (ActA) and neuron specific enolase (NSE) in the serum of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Methods: Altogether 56 patients undergoing cardiac surgery with CPB were enrolled and evenly included into a control group and a study group. The patients in the study group were administrated dexmedetomidine, while those in the control group were administrated the same volume of normal saline. The Mini-Mental State Examination (MMSE) was used to assess the patients' cognitive function before each operation (Ta), and at 10 days (Tb), 20 days (Tc), and 30 days after each operation (Td). The incidence of postoperative cognitive dysfunction (POCD) in the patients was measured at 3, 7, 21, and 30 days after each operation. An enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of serum ActA and NSE in the patients before each operation (T1), and at 6 h (T2), 12 h (T3), and 24 h after each operation (T4). The Pearson method was used to analyze the correlations between the ActA and NSE levels and the MMSE scores, as well as between the serum ActA levels and the NSE levels. Results: At T2, T3, and T4, the MMSE scores in the study group were significantly higher than they were in the control group ($P < 0.05$). At 3, 7, and 21 days after each operation, the incidence of POCD in the study group was significantly lower than it was in the control group ($P < 0.05$). At T2, T3, and T4, the ActA and NSE levels in the study group were significantly lower than they were in the control group ($P < 0.05$). The serum ActA and NSE levels were significantly negatively correlated with the MMSE scores ($r = -0.572$, $P < 0.05$, $r = -0.549$, $P < 0.05$); the serum ActA levels were significantly positively correlated with the NSE levels ($r = 0.552$, $P < 0.05$). Conclusion: Dexmedetomidine can reduce the incidence of POCD in patients undergoing cardiac surgery with CPB, which may be related to the reduction of the serum ActA and NSE levels.

Keywords: Dexmedetomidine, CPB, ActA, NSE, cognitive function

Introduction

Cardiopulmonary bypass (CPB), an important technique for cardiovascular-related surgery, increases the success rate of the surgery [1]. However, it also causes ischemic and anoxic changes in the local brain tissue, postoperative cognitive dysfunction (POCD), and other symptoms of brain injury [2]. A study has shown that 53% of patients who receive CPB develop POCD at the time of discharge, and 36% of the patients develop it at 6 weeks after the operation [3]. POCD affects patients' recovery from diseases, prolongs their hospitalization time, and increases the incidence of complications.

Severe POCD lowers their postoperative quality of life and even increases the postoperative mortality. Therefore, it is essential to find a therapeutic method that can reduce POCD caused by CPB.

As a highly selective α_2 adrenergic receptor agonist with anti-sympathetic, anti-anxiolytic and sedative effects, dexmedetomidine is a widely used anesthetic assistant in the clinic [4]. According to one study, it reduces the symptoms of local myocardial ischemia and the incidence of nerve injury caused by transient cerebral ischemia in rats [5]. Another study has shown that it maintains hemodynamic stability

and the balance of cerebral oxygen metabolism in surgical patients, thus protecting the brain [6].

At present, neurological dysfunction is diagnosed by electroneurophysiological examination, computed tomography, and magnetic resonance imaging. However, these methods are not suitable for patients with unstable vital signs and hemodynamic disorders, and those who are not easy to move, who are not awake after surgery, or who use breathing machines. Therefore, finding a biomarker for detecting brain injury is of great significance. Neuron specific enolase (NSE), which is one of the key enzymes during glycolysis [7], has been considered a biomarker for various diseases of neuronal functional impairment, such as traumatic brain injury, stroke, ischemia-reperfusion injury, neuroblastoma, and Alzheimer's disease [8]. Activin A (ActA) is a cytokine belonging to the transforming growth factor- β (TGF- β) superfamily and a β A subunit with the same two dimers. It is expressed in many tissues and cells and is involved in regulating a variety of biological processes, which include cell proliferation, differentiation and death [9]. ActA plays a neuroprotective role in various nervous system diseases [10]. According to studies, the expression of ActA increases after nerve cells are subjected to acute injury [11]. The expression also increases in the early stage of acute ischemic brain injury. Additionally, ActA exerts its neuroprotective effect by decreasing the nitric oxide level and increasing superoxide dismutase activity and neuronal tolerance to ischemic injury [12].

At present, there are few studies on changes in ActA and NSE during CPB, as well as the effects of dexmedetomidine on ActA and NSE levels and the postoperative cognitive function of patients undergoing cardiac surgery. Therefore, in this study, dexmedetomidine was used before CPB; the levels of serum ActA and NSE at different time points were measured; the postoperative cognitive function of the patients was assessed, so as to find biomarkers for detecting brain injury and methods for reducing the incidence of POCD caused by CPB.

Materials and methods

General information

A total of 56 patients who underwent cardiac surgery with CPB in our hospital from January

2015 to September 2018 were enrolled and divided into the control and study groups. The control group consisted of 18 males and 10 females, with an average age of 45.89 ± 12.11 years. There were 22 patients undergoing coronary artery bypass grafting and 6 undergoing cardiac valve surgery in this group. The study group consisted of 21 males and 7 females, with an average age of 47.34 ± 11.23 years. There were 25 patients undergoing coronary artery bypass grafting and 3 undergoing cardiac valve surgery in this group.

Inclusion and exclusion criteria

The inclusion criteria were as follows: patients without a contraindication to surgery; patients who underwent cardiac surgery with CPB; patients aged ≥ 20 years and ≤ 65 years old; patients with an educational level above primary school; patients with complete clinical data. The exclusion criteria were as follows: those with a previous history of psychiatric and neurological symptoms; those with a language communication barrier; those with cardiac, hepatic, and renal insufficiency; those with a Mini-Mental State Examination (MMSE) [13] score ≤ 27 points. In this study, the patients and their families signed an informed consent form. This study was approved by the Medical Ethics Committee of our hospital.

Methods of anesthesia and CPB

The patients in the two groups fasted for 12 hours before their operations, and they were intramuscularly injected with morphine (10 mg) at 30 min before anesthesia. Their vital signs were monitored by a multifunctional vital signs monitor. The peripheral intravenous access was opened, and the left radial artery puncture and catheterization was performed to monitor their invasive blood pressure. The patients in the study group were administered dexmedetomidine ($0.5 \mu\text{g}/\text{kg}$) before the anesthesia induction and then continuously infused with the drug at $0.5 \mu\text{g}/(\text{kg}/\text{h})$ until the end of the operation, while those in the control group were administered with the same volume of normal saline in the same way. The patients were intravenously injected with midazolam ($0.05 \text{ mg}/\text{kg}$), sufentanil ($1 \mu\text{g}/\text{kg}$), etomidate ($0.3 \text{ mg}/\text{kg}$), and rocuronium ($0.6 \text{ mg}/\text{kg}$) in sequence. Mechanical ventilation was performed after the tracheal intubation, and an anesthesia appara-

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tus was connected. After they were continuously and intravenously pumped with propofol at 1-2 mg/(kg·h), the patients inhaled 1%~2% isoflurane, and then they were intermittently and intravenously injected with sufentanil at 2-4 µg/(kg·h), and atracurium and vecuronium bromide at 0.05-0.10 mg/(kg·h), to maintain anesthesia. The mean arterial pressure was maintained at 50-80 mmHg, and the heart rate was maintained at 60-100 beats/min.

The CPB methods were as follows: non-pulsatile perfusion was administered to patients in the two groups using a membrane oxygenator, with a perfusion flow of 2.2-2.4 L/(m²·min⁻¹) and a shallow low temperature maintained at 28-30°C. Oxygenated cold blood-potassium cardioplegia at 4°C was intermittently perfused, to keep the heart at rest during aortic occlusion. When the intracardiac operation was nearly completed, the nasopharynx temperature was raised to 35-36°C. The mean arterial pressure was maintained at 50-80 mmHg, and CPB was stopped after the circulation stabilized.

Cognitive function assessment

MMSE was used to assess the cognitive functions (memory, attention, phonological competence, etc.) of the patients in the two groups before each operation (Ta), and at 10 days (Tb), 20 days (Tc), and 30 days after each operation (Td). The total score was 30 points, and <24 points was considered POCD. The lower the score was, the more serious the POCD was. The incidence of POCD was recorded at 3, 7, 21, and 30 days after each operation.

Collection of serum samples

The patients' venous blood (3 mL) was extracted before each operation (T1), and at 6 h (T2), 12 h (T3), and 24 h after each operation (T4), respectively. The blood was sent to the laboratory for centrifugation, and the supernatant was obtained and stored in a refrigerator at -20°C for testing.

Measurement of serum ActA and NSE

The serum was taken out from the freezer, placed in a refrigerator at 4°C for dissolution, and then placed at room temperature for com-

plete dissolution. An enzyme-linked immunosorbent assay (ELISA) was used to quantify the concentrations of ActA and NSE in the serum of patients in the two groups, with steps carried out in strict accordance with the instructions of human ActA ELISA (purchased from Hengdu Biological, China, HD39920) and human NSE ELISA (purchased from CUSABIO, China, CSB-E07961h-1) kits. Blank wells, standard wells, and sample wells to be tested were set up. 50 µL of standard substances with different concentrations was added to the standard wells, but 10 µL of samples to be tested and 40 µL of diluent were added to the sample wells. 100 µL of horseradish peroxidase (HRP)-labeled detection antibodies was added to the standard and sample wells to be tested. The ELISA plate was sealed with microplate sealers and incubated in an incubator at 37°C for 1 hour. After that, the liquid in each well was discarded, and the plate was washed with washing liquid for 1 min and then dried with absorbent papers. This step was repeated 5 times. 50 µL of chromogenic agents A and B was added to each well, and then the plate was developed at 37°C for 10-15 min in the dark. 50 µL of stop solution to cease the reaction was then added to each well. A multifunctional microplate reader (purchased from BioTek, USA, model: DLK0001622) was used to determine the OD values of each well at 450 nm, so as to calculate the concentrations of ActA and NSE.

Statistical methods

SPSS 18.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis. The count data were expressed as the number of cases/percentage [n (%)], and a chi-squared test was used for the comparisons between groups. The measurement data were expressed as the mean ± standard deviation ($\bar{x} \pm s$), and an independent samples *t* test was used for the comparisons between the groups, a paired *t* test for comparisons within the groups before and after treatment. The Pearson method was used for the correlation analysis. When $P < 0.05$, the difference was statistically significant.

Results

Comparison of baseline data

There were no significant differences between the study and control groups in terms of gen-

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Table 1. Comparison of general information ([n (%)], $x \pm sd$)

Groups	Control group (n=28)	Study group (n=28)	χ^2/F	P
Gender			0.760	0.383
Male	18 (64.29)	21 (75.00)		
Female	10 (35.71)	7 (25.00)		
Age (Years)	45.89 \pm 12.11	47.34 \pm 11.23	0.465	0.644
Body weight (KG)	58.89 \pm 8.23	61.23 \pm 9.78	0.969	0.337
CPB time (min)	110.42 \pm 22.42	113.40 \pm 19.37	0.532	0.597
Hospitalization time (d)	27.78 \pm 13.26	29.23 \pm 12.26	0.425	0.673
Aortic occlusion time (min)	57.67 \pm 11.45	61.23 \pm 13.22	1.077	0.286
Operative time (min)	156.27 \pm 21.45	160.23 \pm 23.22	0.663	0.510
Operative type			1.192	0.275
Coronary artery bypass grafting	22 (78.57)	25 (89.29)		
Cardiac valve surgery	6 (21.43)	3 (10.71)		
Educational level			0.299	0.584
< Senior high school	12 (42.86)	10 (35.71)		
\geq Senior high school	16 (57.14)	18 (64.29)		
Food preference			1.310	0.252
Bland	21 (75.00)	17 (60.71)		
Spicy	7 (25.00)	11 (39.29)		
Place of residence			2.947	0.086
City	16 (57.14)	22 (78.57)		
Countryside	12 (42.86)	6 (21.43)		

Table 2. Comparison of MMSE score before and after operation (score, $\bar{x} \pm sd$)

Groups	Ta	Tb	Tc	Td
Control group (n=28)	28.71 \pm 1.78	21.92 \pm 2.91 ^a	22.61 \pm 2.62 ^a	25.61 \pm 2.23 ^{a,b,c}
Study group (n=28)	28.87 \pm 1.45	25.61 \pm 2.45 ^a	26.11 \pm 2.34 ^a	28.23 \pm 1.89 ^{b,c}
t	0.207	5.133	5.272	4.743
P	0.837	<0.001	<0.001	<0.001

Note: ^aIndicates P<0.05 compared with Ta within groups. ^bIndicates P<0.05 compared with Tb within groups. ^cIndicates P<0.05 compared with Tc within groups.

study group were significantly higher than they were in the control group (P<0.05) (**Table 2**).

The study group showed a lower incidence of POCD than the control group

der, age, body weight, CPB time, hospitalization time, aortic occlusion time, operative time, operative type, educational level, food preference, or place of residence (P>0.05) (**Table 1**).

The study group showed higher MMSE scores than the control group

At T1, there was no significant difference between the study and control groups in terms of MMSE scores (P>0.05), but at T2, T3, and T4, the scores in the control group significantly decreased (P<0.05). At T2 and T3, the scores in the study group significantly decreased (P<0.05), but at T4, the scores in the two groups significantly increased compared with T2 and T3 (P<0.05). At T2, T3, and T4, the scores in the

At 3, 7, 21, and 30 days after each operation, the incidence of POCD was 64.29% (18/28), 57.14% (16/28), 42.86% (12/28), and 21.43% (6/28) in the control group, respectively. The incidence was 35.71% (10/28), 25.00% (7/28), 17.86% (5/28), and 7.14% (2/28) in the study group, respectively. At 3, 7, and 21 days after each operation, the incidence of POCD in the study group was significantly lower than it was in the control group (P<0.05) (**Table 3**).

The study group showed lower serum ActA levels than the control group

At T1, there was no significant difference between the study and control groups in serum ActA levels (P>0.05), but at T2, T3, and T4, the

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Table 3. Comparison of the incidence of POCD [n (%)]

Groups	3 d	7 d	21 d	30 d
Control group (n=28)	18 (64.29)	16 (57.14)	12 (42.86)	6 (21.43)
Study group (n=28)	10 (35.71)	7 (25.00)	5 (17.86)	2 (7.14)
χ^2	4.571	5.976	4.139	2.333
P	0.033	0.015	0.042	0.127

Table 4. Changes in the serum ActA levels (ug/L, $\bar{x} \pm sd$)

Groups	T1	T2	T3	T4
Control group (n=28)	2.24 \pm 0.25	5.51 \pm 0.46 ^a	6.24 \pm 0.67 ^{a,b}	4.31 \pm 0.53 ^{a,b,c}
Study group (n=28)	2.34 \pm 0.34	3.41 \pm 0.62 ^a	4.11 \pm 0.51 ^{a,b}	2.87 \pm 0.54 ^{a,b,c}
t	1.254	14.394	13.386	10.072
P	0.215	<0.001	<0.001	<0.001

Note: ^aIndicates P<0.05 compared with T₁ within groups. ^bIndicates P<0.05 compared with T₂ within groups. ^cIndicates P<0.05 compared with T₃ within groups.

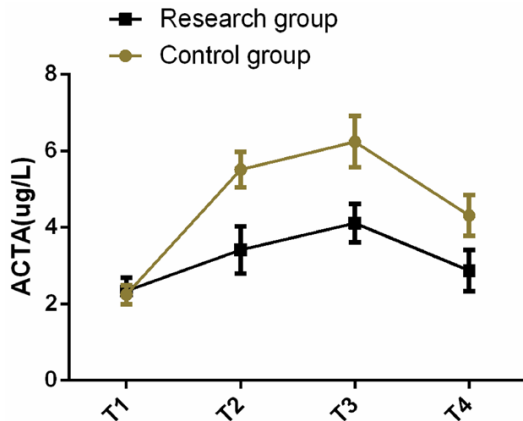


Figure 1. Changes in the serum ActA levels at each time point.

levels in the two groups significantly increased (P<0.05). At T4, the levels in the two groups significantly decreased compared with T2 and T3 (P<0.05). At T2, T3, and T4, the levels in the study group were significantly lower than they were in the control group (P<0.05) (Table 4 and Figure 1).

The study group showed lower serum NSE levels than the control group

At T1, there was no significant difference between the study and control groups in the serum NSE levels (P>0.05), but at T2, T3, and T4, the levels in the two groups significantly increased (P<0.05). At T4, the levels in the two groups significantly decreased compared with T2 and T3 (P<0.05). At T2, T3, and T4, the levels

in the study group were significantly lower than they were in the control group (P<0.05) (Table 5 and Figure 2).

Correlation analysis among the ActA, NSE, and MMSE scores

According to the Pearson method analysis, the serum ActA level was significantly negatively correlated with the MMSE score (r=-0.572, P<0.05). The serum NSE level was significantly negatively correlated with the MMSE score (r=-0.549, P<0.05) (Figure 3).

related with the MMSE score (r=-0.549, P<0.05) (Figure 3).

Correlation analysis between ActA and NSE

According to the Pearson method analysis, the serum ActA level was significantly positively correlated with the NSE level (r=0.552, P<0.05) (Figure 4).

Discussion

There are more than 2 million cardiac surgeries worldwide every year [14]. POCD is one of the most common complications after the surgery [15], but its pathogenesis and causes remain unclear currently [16]. Postoperative cognitive changes have always been the focus of patients undergoing the surgery, especially for patients receiving CPB [17]. Therefore, reducing the incidence of POCD after CPB is significant for patients undergoing cardiac surgery.

Dexmedetomidine is an α_2 adrenergic receptor agonist, which not only reduces postoperative pain and related complications, but also maintains hemodynamic stability and reduces heart and renal injuries caused by cardiac surgery [18, 19]. Commonly used to assess cognitive function, MMSE is characterized by high efficiency, reliability, ease of use and suitability for bedside use [20]. A meta-analysis has shown that dexmedetomidine reduces the incidence of POCD and improves MMSE scores in elderly patients after general anesthesia [21]. In another study, patients with ischemic cerebrovascular disease have damaged cognitive and

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Table 5. Changes in the serum NSE levels ($\mu\text{g/L}$, $\bar{x} \pm \text{sd}$)

Groups	T1	T2	T3	T4
Control group (n=28)	7.68 \pm 2.56	23.23 \pm 5.46 ^a	20.04 \pm 6.54 ^a	15.31 \pm 5.12 ^{a,b,c}
Study group (n=28)	6.98 \pm 2.18	16.65 \pm 4.24 ^a	13.65 \pm 5.67 ^a	9.31 \pm 4.43 ^{a,b,c}
t	1.102	5.037	3.906	4.689
P	0.276	<0.001	<0.001	<0.001

Note: ^aIndicates $P < 0.05$ compared with T₁ within groups. ^bIndicates $P < 0.05$ compared with T₂ within groups. ^cIndicates $P < 0.05$ compared with T₃ within groups.

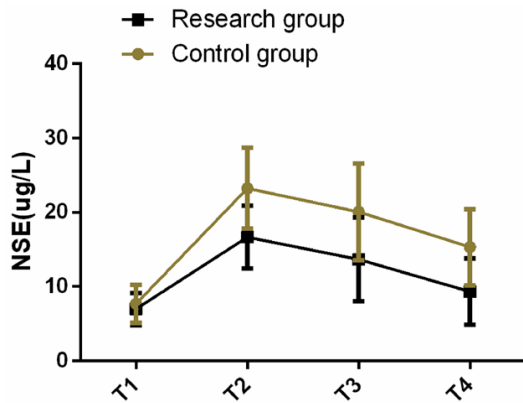


Figure 2. Changes in the serum NSE levels at each time point.

attention network functions, but the preoperative administration of dexmedetomidine improves their POCD and attention network function [22]. In a study by Chen et al., 148 elderly surgical patients were treated with dexmedetomidine (the Dex group) or normal saline (the control group) after general anesthesia. The results showed that after the operations, the MMSE scores in the two groups significantly decreased; compared with those in the Dex group, the patients in the control group had significantly lower MMSE scores but a significantly higher incidence of POCD [23]. The results of this study showed that at T₂, T₃, and T₄, MMSE scores in the study group were significantly higher than they were in the control group; at 3, 7, and 21 days after the operations, the incidence of POCD in the study group was significantly lower than it was in the control group. These findings are similar to the above research results, further indicating that dexmedetomidine can reduce the incidence of POCD after cardiac surgery with CPB.

ActA is the richest and the most characteristic member of the activin family. Its receptors and binding proteins are widely distributed throughout the brain and play a major role in activin

signal transduction in the central nervous system. ActA regulates the immune and inflammatory responses of the body and is involved in the regulation of cell death and the repair of brain injuries [24-26]. Recent studies have shown that the expression of ActA significantly changes in brain injury models, and ActA has a significant protective effect on damaged neurons in vivo and vitro. For example, according to studies, ActA is highly expressed in full-term neonates with hypoxic-ischemic encephalopathy [27] and in the serum of patients with severe traumatic brain injury [28]. He and others explored the neuroprotective mechanism of ActA in hypoxic-ischemic encephalopathy models. The results showed that ActA improves the survival rate of the PC12 nerve cell line, reduces oxygen-glucose deprivation (OGD) injury, and induces the neuroprotective effect through the ActA/Smad signal pathway [29]. The results of this study showed that at T₂, T₃, and T₄, the serum ActA levels in the two groups significantly increased, and the level in the study group was significantly lower than it was in the control group; the serum ActA level was significantly negatively correlated with the MMSE score. These findings indicate that dexmedetomidine can reduce the incidence of POCD by reducing the serum ActA levels of patients undergoing cardiac surgery with CPB.

NSE, which is a glycolytic enzyme in dimer cells and the only biomarker for brain injury, consists of two subunits - $\gamma\gamma$ and $\alpha\gamma$ - and is widely presented in neuron cells and neuroectodermal cells [30]. A study has shown that the continuously high level of NSE may be a useful biomarker for identifying patients with cognitive impairment [31]. Another study has shown that dexmedetomidine reduces NSE and IL-6 levels in children undergoing general anesthesia, and that the incidence of POCD is related to the levels [32]. According to Wang et al., compared with remifentanyl, anesthesia with dexmedetomidine for patients undergoing cardiac valve

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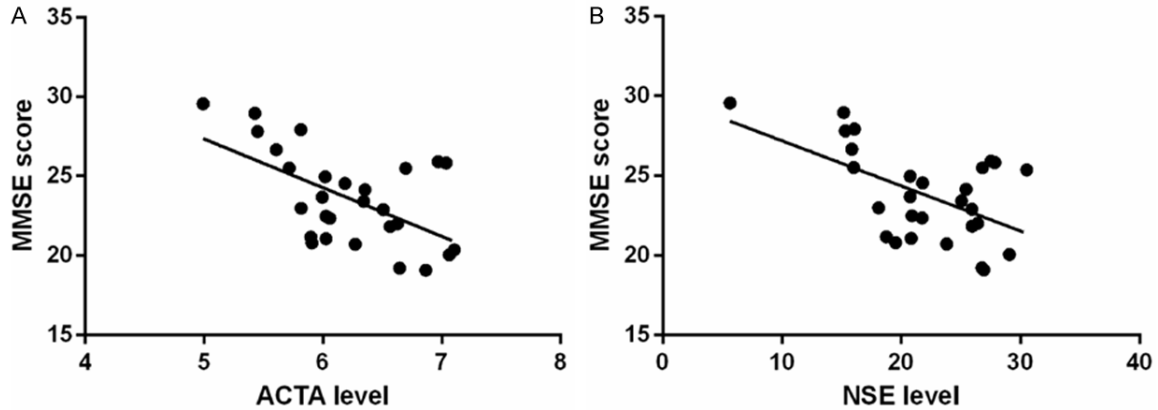


Figure 3. Correlation analysis between the ActA, NSE, and MMSE scores. A. The correlation analysis between the ActA and MMSE scores. B. The correlation analysis between the NSE and MMSE scores.

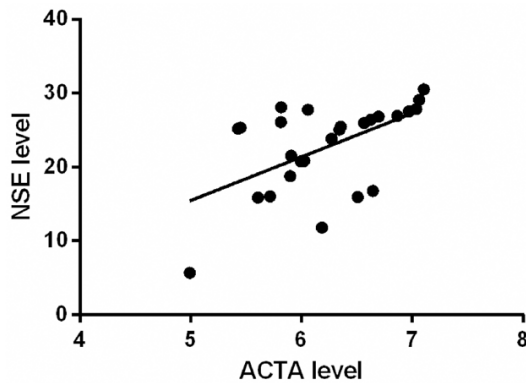


Figure 4. Correlation analysis between ActA and NSE.

replacement more effectively reduces the NSE level. Dexmedetomidine also reduces myocardial injury and cognitive dysfunction, maintains hemodynamic stability, and improves patients' prognoses [33]. The results of this study showed that at T2, T3, and T4, the serum NSE levels in the two groups significantly increased, and the level in the study group was significantly lower than it was in the control group, which was similar to the above results. The serum NSE level was significantly negatively correlated with the MMSE score, indicating that dexmedetomidine can reduce the incidence of POCD by reducing serum NSE levels in patients undergoing cardiac surgery with CPB.

Finally, the Pearson method analysis showed that the serum ActA level was significantly positively correlated with the NSE level; the levels of serum ActA and NSE were significantly negatively correlated with the MMSE score; i.e. the higher the levels were, the lower the MMSE score was. These findings suggest that there

may be a close relationship between ActA and NSE, and that the severity of brain injury may be determined by measuring the changes in the serum ActA and NSE levels combined with the clinical examinations. However, in this clinical experiment, the specific relationship between ActA and NSE was not fully explored. Therefore, we hope to further explore the relationship in later basic experiments.

In summary, dexmedetomidine can reduce the incidence of POCD in patients undergoing cardiac surgery with CPB, which may be related to the reduction of serum ActA and NSE levels.

Disclosure of conflict of interest

None.

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