

## Original Article

# The influence of different anesthesia techniques on cognitive dysfunction in elderly patients

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**Abstract:** This study aimed to investigate the influence of different anesthesia techniques on cognitive dysfunction in elderly patients after artificial femoral head replacement. One hundred and ninety-three elderly patients with artificial femoral head replacement included in this study were randomly divided into general anesthesia (GA) and epidural anesthesia (EA) group. Minimum mental state examination (MMSE) method was used to assess the nervous and mental function in both subjects. Amyloid-beta (A $\beta$ ) protein levels in blood plasma were detected using enzyme-linked immunosorbent assay (ELISA) method. MMSE scoring and A $\beta$  protein levels test were performed at the time of 24 hours preoperatively (T1), 24 hours postoperatively (T2) and 72 hours postoperatively (T3). The results showed that Amyloid beta protein levels in blood plasma were increased at the time of T2 compared with those at the time of T1 in GA group. Furthermore, MMSE scorings were upregulated, amyloid beta protein levels in blood plasma were downregulated and POCD incidence was decreased at the time of T3 compared with those at the time of T2 in GA group (P<0.05). Compared with GA group, MMSE scorings were elevated, amyloid beta protein levels in blood plasma were reduced and POCD incidence was decreased in EA group at the time of T2 (P<0.05). In conclusion, the general anesthesia method is more likely to exert influence on cognitive dysfunction compared to epidural anesthesia method in elderly patients after artificial femoral head replacement and general anesthesia may induce cognitive impairment by upregulating amyloid beta protein expression.

**Keywords:** General anesthesia, epidural analgesia, postoperative cognitive dysfunction, minimum mental state examination, artificial femoral head replacement

## Introduction

Postoperative cognitive dysfunction (POCD) is a common complication characterized with mental derangement, anxiety and memory impairment after surgery with general anaesthesia in the elderly [1-3]. It has been reported that the incidence of POCD is about 40.5% after surgery in the elderly [4]. Considerable data indicate that POCD might be caused by anaesthesia [5, 6]. However, the exact pathogenetic mechanism of POCD remains undetermined.

It has been shown that amyloid precursor protein (APP) plays an important role during the occurrence of Alzheimer's disease (AD) [7-9]. Considerable data indicate that dysregulation of APP expression and beta-amyloid clearance are involved in the pathophysiology of AD [10-12]. Amyloid-beta (A $\beta$ ) protein is formed after

sequential cleavage of APP and serum A $\beta$  protein concentration test is used in the diagnosis and prognostic evaluation of cognitive function [13, 14].

The incidence and precise pathogenesis of POCD after artificial femoral head replacement in the elderly remains undetermined. Therefore, we aimed to study the incidence of POCD and serum A $\beta$  protein concentration after artificial femoral head replacement with general anesthesia (GA) and epidural anesthesia (EA) in the elderly.

## Materials and methods

### Subjects

A total of 193 patients suffered from femoral neck fracture or femoral intertrochanter fracture undergoing artificial femoral head replace-

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**Table 1.** Characteristics of included subjects

Items	General anesthesia	Epidural analgesia
Number of patients	98	95
ASA classification (II/III)	42/56	43/52 <sup>a</sup>
Age (years)	67±7.2	68±8.4 <sup>a</sup>
Body weight (kg)	58±5.4	59±7.2 <sup>a</sup>
Gender (male/female)	49/49	48/47 <sup>a</sup>
Years of education	16±3.8	15±4.1 <sup>a</sup>
Operation time (min)	121±23	117±21 <sup>a</sup>
Anesthesia time (min)	167±26	163±20 <sup>a</sup>
Intraoperative hemorrhage quantity (ml)	339±101	385 ±121 <sup>a</sup>
Blood transfusion amount (ml)	172±48	191±51 <sup>a</sup>
Fluid infusion volume (ml)	1567±115	1497±120 <sup>a</sup>
Urine output (ml)	301±105	324±118 <sup>a</sup>
VAS 24 hours postoperatively	2.6±0.7	2.5±0.8 <sup>a</sup>

<sup>a</sup>P>0.05 vs GA group.

**Table 2.** MMSE score, A $\beta$  and POCD incidence comparison between two groups

Items	General anesthesia	Epidural analgesia
MMSE score		
T1	26.4±1.8	26.2±1.9
T2	22.9±2.2 <sup>a</sup>	25.1±1.7 <sup>a,c</sup>
T3	25.3±2.4 <sup>b</sup>	26.2±1.9
A $\beta$ ( $\mu$ g/L)		
T1	513±152	509±148
T2	794±131 <sup>a</sup>	532±107 <sup>c</sup>
T3	537±132 <sup>a</sup>	521±161
POCD incidence (%)		
T2	75	36 <sup>c</sup>
T3	23 <sup>b</sup>	21

<sup>a</sup>P<0.05 vs T1, <sup>b</sup>P<0.05 vs T2, <sup>c</sup>P<0.05 vs GA group.

ment were recruited in the study. The ASA classification intended to describe pre-operative physical status was II or III. All the included patients have no neuropsychiatric diseases, no vision and hearing disorders, and no antidepressant and stabilizing agent used pre-operation. The subjects were randomly divided into general anesthesia (GA) and epidural anesthesia (EA) group. Minimum mental state examination (MMSE) method was used to assess the nervous and mental function in both subjects. Amyloid beta protein levels in blood plasma were detected using enzyme-linked immunosorbent assay (ELISA) method. Detailed characteristics of included subjects were summarized in **Table 1**. This study was approved by the

ethical committee of Chengde Central Hospital and every subject provided an informed consent.

### General anesthesia

After induction with Midazolam (0.1 mg/kg), fentanyl (3-5  $\mu$ g/kg), propofol (2 mg/kg), vecuronium bromide (0.1 mg/kg), endotracheal intubation and mechanical ventilation were performed for the subjects included in general anesthesia group. Then, the general anesthesia was maintained with 1% to 3% vol isoflurane and the tidal volume was 8-10 ml/kg, respiratory frequency was 10-12 time/min, and partial pressure of carbon dioxide was maintained with 30-35 mmHg.

### Epidural anesthesia

The subjects were in the prone positions. L1-2 or L2-3 intervertebral spaces were the levels of spinal puncture. Two milliliter ropivacaine (0.5%) was applied for anaesthetization. To keep the analgesic effect, fentanyl (0.001%) was injected intravenously with the speed of 2 ml/h for 48 hours.

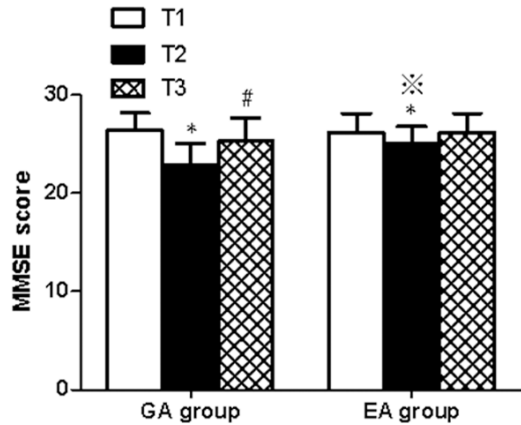
### Data collection and POCD assessment

The operation time, anesthesia time, intraoperative hemorrhage quantity, blood transfusion amount, fluid infusion volume, urine output and visual analogue scale (VAS) 24 hours postoperatively were recorded. Minimum mental state examination (MMSE) method was used to assess the nervous and mental function in both subjects at the time of 24 hours preoperatively (T1), 24 hours postoperatively (T2) and 72 hours postoperatively (T3). POCD was diagnosed when the MMSE score was less than 24 points or equal. Cognitive function was assessed by a trained and experienced professional without participating in the process of anesthesia.

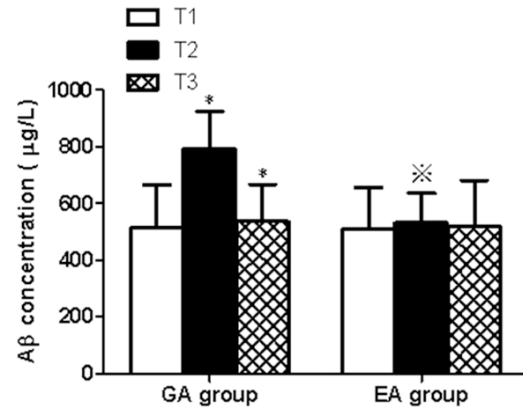
### ELISA examination for A $\beta$

A $\beta$  protein levels in blood plasma were detected using enzyme-linked immunosorbent assay (ELISA) method. Five milliliter fasting blood sample was drawn and centrifuged at 14000 rpm for 10 min. Then, the blood plasma was collected and stored at -70°C. Serum A $\beta$  level

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**Figure 1.** MMSE score comparison between GA group and EA group. \* $P < 0.05$  vs T1, # $P < 0.05$  vs T2, ※ $P < 0.05$  vs GA group.



**Figure 2.** A $\beta$  incidence comparison between GA group and EA group. \* $P < 0.05$  vs T1, ※ $P < 0.05$  vs GA group.

was assayed using specific ELISA kit (R&D systems) according to the manufacturer's instructions.

### Statistical analysis

SPSS version 16.0 software was applied to conduct the analyses and  $P$  value  $< 0.05$  was considered statistically significant. The measurement data were shown as mean  $\pm$  standard deviation. The differences of measurement data were compared with the analysis of variance test (among three groups) or  $t$  test (between two groups). Differences test about count data was employed by the  $\chi^2$  test. Correlations were assessed by Spearman's test.

## Results

### Patients characteristics

As shown in **Table 1**, there were no significant discrepancy about ASA classification, age, body weight, gender, years of education, operation time, anesthesia time, intraoperative hemorrhage quantity, blood transfusion amount, fluid infusion volume, urine output and VAS 24 hours postoperatively between GA group and EA group ( $P > 0.05$ ).

### MMSE score, A $\beta$ and POCD incidence in two groups

As shown in **Table 2; Figures 1 and 2**, there were significant downregulation of MMSE scorings at the time of T2 compared with those at

the time of T1 in GA group or EA group ( $P < 0.05$ ). Amyloid beta protein levels in blood plasma were increased at the time of T2 compared with those at the time of T1 in GA group. Furthermore, MMSE scorings were upregulated, amyloid beta protein levels in blood plasma were downregulated and POCD incidence was decreased at the time of T3 compared with those at the time of T2 in GA group ( $P < 0.05$ ). Compared with GA group, MMSE scorings were elevated, amyloid beta protein levels in blood plasma were reduced and POCD incidence was decreased in EA group at the time of T2 ( $P < 0.05$ ). Moreover, amyloid beta protein levels were negatively correlated with MMSE scorings in all patients at the time of T2 ( $r = 0.769$ ,  $P < 0.001$ ;  $n = 193$ ).

## Discussion

There is ample evidence that POCD is a subtle disorder of thought processes which may influence the short-term memory involving visual and verbal memory, attention, and visuospatial abstraction [15, 16]. Accumulating evidence has shown that POCD incidence is associated with age, trauma, anesthesia, medicine, operation type, a history of alcohol abuse, intraoperative hemorrhage quantity, intraoperative blood pressure, and concurrent brain diseases preoperatively [17-19]. In the present study, for better parallel we compared ASA classification, age, body weight, gender, years of education, operation time, anesthesia time, intraoperative hemorrhage quantity, blood transfusion amount, fluid infusion volume, urine output and VAS 24 hours postoperatively between GA group and

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EA group and found that there were no significant discrepancy about them between the two groups.

The MMSE test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment [20]. It is used to estimate the severity and progression of cognitive impairment [21]. Our results showed that there were significant downregulation of MMSE scorings at the time of T2 compared with those at the time of T1 in GA group or EA group. Compared with GA group, MMSE scorings were elevated and POCD incidence was decreased in EA group at the time of T2. These findings indicate that epidural anesthesia may be more beneficial than general anesthesia from the point of reducing POCD incidence. We speculate that the reasons resulting in such change may be as follows. First, general anesthesia could affect central nervous system and induce cognitive impairment by regulating brain cholinergic system and memory protein [22], however, the main acting site of epidural anesthesia is the spinal cord instead of central nervous system, thus central nervous system is less affected by epidural anesthesia. Second, epidural anesthesia may be more helpful than general anesthesia in reducing stress response derived from the nervous system which is a key risk factor in the prevalence of postoperative delirium [23]. Furthermore, MMSE scorings were upregulated and amyloid beta protein levels in blood plasma were downregulated at the time of T3 compared with those at the time of T2 in GA group ( $P < 0.05$ ), which indicated that anesthetic drugs were gradually metabolized, the patients gradually recovered and then their cognitive function were gradually resumed until 72 hours postoperatively.

Considerable data indicate that A $\beta$  protein is produced following sequential cleavage of the transmembrane protein APP by  $\beta$ - and  $\gamma$ -secretase and is released extracellularly in lengths ranging from approximately 37 to 43 amino acids [24-26]. Accumulating evidence has shown that intrahippocampal injection of  $\beta$ -amyloid in rats induced the impairment of learning and memory and the neuronal degeneration in or around the injection sites [27, 28].

There is ample evidence that trauma, anesthesia or surgery may induce the upregulation of IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , which are capable of

aggravating cognitive function impairment by regulating the expression of A $\beta$  protein, and inhibition of IL-1 $\beta$ , IL-6 or TNF- $\alpha$  may alleviate impairment of cognitive function [29-33]. The precise mechanisms whereby A $\beta$  protein cause neurotoxicity remain unknown. Jang et al. observed that beta-amyloid-induced apoptosis in PC12 cells is associated with COX-2 up-regulation through activation of NF- $\kappa$ B, which is mediated by upstream kinases including ERK and p38 MAPK [34].

Liu et al. investigated the role of alpha7-nAChRs in the mediation of A $\beta$ -induced neurotoxicity and found that alpha7-nAChRs are necessary for A $\beta$ -induced neurotoxicity in hippocampal neurons because chronic A $\beta$  significantly increased LDH level in hippocampal cultures, indicating a detrimental role of upregulated alpha7-nAChRs in the mediation of A $\beta$ -induced neurotoxicity [35]. Wang et al. demonstrated that acteoside increased HO-1 expression through activation of ERK and PI3K/Akt signal pathways, which may involve in the neuroprotection against A $\beta$ -induced neurotoxicity [36]. Our results showed that amyloid beta protein levels were negatively correlated with MMSE scorings in all patients at the time of T2, indicating that amyloid beta protein levels were a sensitive indicator of cognitive function. Furthermore, amyloid beta protein levels in blood plasma were increased at the time of T2 compared with those at the time of T1 in GA group. Compared with GA group, amyloid beta protein levels in blood plasma were reduced and POCD incidence was decreased in EA group at the time of T2. The results indicated that general anesthesia may induce cognitive impairment by upregulating amyloid beta protein expression.

In conclusion, the general anesthesia method is more likely to exert influence on cognitive dysfunction compared to epidural anesthesia method in elderly patients after artificial femoral head replacement and general anesthesia may induce cognitive impairment by upregulating amyloid beta protein expression.

### Disclosure of conflict of interest

None.

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