Original Article
Effects of different anesthesia methods on cognitive dysfunction after hip replacement operation in elder patients

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Received November 10, 2014; Accepted January 9, 2015; Epub March 15, 2015; Published March 30, 2015

Abstract: There are many risk factors for the cause of postoperative cognitive dysfunction (POCD), however, the anesthesia selection always trigger controversy for the POCD occurrence. This study aims to explore the relationship between the anesthesia and the occurrence of POCD in elder patients, and also investigate the mechanism of the POCD. One hundred elder patients with hip replacement were included in this study, which were divided into general anesthesia (GA) and epidural analgesia (EA) group. Minimum mental state examination (MMSE) method was employed to assess the nervous and mental function (POCD) in both analgesia group patients. Aβ and tau protein levels in blood were detected by using the ELISA assay. The correlation between MMSE in POCD patients and Aβ or tau was analyzed by employing the Spearman rank correlation method. The results indicated that epidural analgesia decreases the MMSE scoring compared to general analgesia (P < 0.05). General analgesia enhanced the Aβ and tau level compared to epidural analgesia (P < 0.05). Aβ and tau level were increased in the patients with POCD. The POCD occurrence rate in GA group was significantly higher compared to EA group (P < 0.05). MMSE scores of POCD patients positively correlated with Aβ or tau level (P < 0.05). In conclusion, the epidural analgesia method was better than general analgesia method for the hip replacement in elder patients. The mechanism of the POCD may be caused by the enhancement of Aβ and Tau protein.

Keywords: General anesthesia, epidural analgesia, postoperative cognitive dysfunction, minimum mental state examination, cognitive dysfunction

Introduction
Postoperative cognitive dysfunction (POCD) is a subtle disorder of thought processes following anesthesia, surgery and injury, particularly in elderly [1]. The POCD may affect the short-term memory, cognitive functions, such as visual memory, verbal memory, attention, language comprehension, visuospatial abstraction and concentration [2]. Patients who experience cognitive decline or dysfunction account for 25% to 50% of hospitalized patients [1]. The incidence of POCD depends on the definition, composition of the test battery, and time of postoperative assessment. The previous studies showed that the incidence of POCD after surgery even achieves to 40.5% a few weeks after surgery for the elder patients [3]. There are many risk factors for the cause of POCD, however, the anesthesia selection always trigger controversy for the POCD happen. Anwer et al. [4] found that general anesthesia poses a significant risk for the occurrence of POCD compared to the epidural analgesia in elder patients. However, Williams-Russo P et al. [5] indicated that the type of anesthesia, general or epidural, does not affect the magnitude or pattern of POCD in older adults.

Aβ is derived from amyloid Precursor protein (APP) by cellular processing pathways that involve the excision of the Aβ region, possibly in distinct subcellular compartments [6]. The increased Aβ generation is central to the disease process comes from studies of very rare inherited forms of Alzheimer’s disease (AD). Tau
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Figure 1. The MMSE scores in GA and EA group at different time. \( P < 0.05 \) represents the MMSE scores in GA group compared to EA group, or presents the MMSE scores in T2 day compared to T1, T2 day. GA: general anesthesia; EA: epidural analgesia; MMSE: minimum mental state examination.

The electrocardiogram, blood pressure, heart rate and blood oxygen saturation were monitored. The general anesthesia was induced with Midazolam (0.1 mg/kg), fentanyl (2-4 μg/kg), propofol (1-1.5 mg/kg), vecuronium bromide (0.1-0.15 mg/kg), by maintaining with 1% to 3% vol isoflurane. The tidal volume was 8-10 mg/kg, respiratory frequency was 10-12 time/min, and partial pressure of carbon dioxide maintaining with 30-35 mmHg. For the epidural analgesia patients, The L1-2 or L2-3 intervertebral spaces were selected for spinal puncture. The ropivacaine (0.5%) was used to anaesthetize. For all of the patients, the fentanyl (0.001%) was venoclysized with the speed of 2-2.5 ml/h within 48 hours to keep the analgesic effect.

POCD assessment

MMSE method was employed to assess the nervous and mental function (POCD) in both analgesia group patients. There are 30 items for mental state examination, including time, location, memory, contention, calculation, object naming, language repeat, reading comprehension, making sentences and graphical pinch painting. Totally, 30 scores, one score for one item, right with one score and wrong without score. The MMSE score of < 23 was considered as the POCD patients.

ELISA examination for Aβ and tau

Five milliliters fasting venous blood were drawn at 1 day pre-operation (T1), 1 day post-operation (T2) and 5 days post-operation (T3), respectively, for both group patients. The ELISA detection kit (Boshide, Wuhan, China) was used to examine the level of Aβ and tau in both group patients. The detail of the experimental pro-
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cess was performed according to the instructions of the ELISA kit.

Statistical analysis

The statistical analysis was performed using SPSS 17.0. Student’s t-test was used to find the significance of study parameters on the continuous scale within each group. Chi-square test was used to calculate the incidence of POCD. The correlation between MMSE in POCD patients and Aβ or tau was analyzed by employing the Spearman rank correlation method. Statistical significance was accepted with $P < 0.05$.

Results

General analgesia decreases the MMSE scoring

We assessed the MMSE scores at the different time of T1, T2 and T3, respectively. The MMSE scores at T2 were significantly lower compared to T1 and T3 in GA group (Figure 1, $P < 0.05$). There were no significant changes of MMSE scores in all of the time points (T1, T2 and T3) in EA group. Furthermore, the MMSE score at T2 in EA group was significantly higher compared to the GA group (Figure 1, $P < 0.05$). However, there were no significant differences at T1 and T3 in both groups.

Aβ and tau level enhanced in GA group compared to EA group

The level of Aβ and tau in GA group at T2 day was significantly higher compared to T1 or T3 day (Figure 2, $P < 0.05$). There were not significant differences among the T1, T2 and T3 day for the EA group (Figure 2, $P > 0.05$). However, At T2 day, the level of Aβ (Figure 2A) and tau (Figure 2B) in GA group was significantly increased compared to EA group ($P < 0.05$).

POCD occurrence rate in GA and EA group

The POCD occurrence rate in GA group was 36.0% (18 cases), 16.0% in EA group. The POCD occurrence rate in GA group was significantly higher compared to EA group (Table 1, $P < 0.05$). However, there were no significant differences in GA group compared to EA group at T2 and T3 day post-operation (Table 1, $P > 0.05$).

Aβ and tau level were increased in the patients with POCD

In order to investigate the relationship between the POCD occurrence and Aβ or tau level, we...
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Figure 3. Aβ and Tau protein levels in patients with POCD and without POCD at different time points. A. Aβ levels in patients with and without POCD. B. Tau levels in with and without POCD. $P < 0.05$ represents the Aβ or Tau level in with POCD compared to patients without POCD at T2 day. POCD: postoperative cognitive dysfunction.

Figure 4. Correlation between MMSE scores and Aβ or Tau protein levels. A. Correlation between MMSE scores and Aβ protein levels. B. Correlation between MMSE scores and Tau protein levels.

MMSE scores of POCD patients correlate with Aβ or tau level

To more clearly illustrate the function of Aβ or tau level in POCD, we analyzed the correlation between MMSE scores and POCD. The results showed that the MMSE scores in POCD patients were positively correlated with the Aβ level (Figure 4A, $P < 0.05$). Furthermore, the MMSE scores in POCD patients were also positively correlated with the tau levels (Figure 4B, $P < 0.05$).

Discussion

Following with the developing of the medical techniques, the ends of analgesia in clinical setting has been required to be safe, comfortable and minimal side effects, but not only is convenient for the operation. Especially, the analgesia strategy should not affect the functions of central nerve system or minimize the influence [13]. In clinical practice, the POCD is a very normally complication after the operation or surgery, however, the specific biomarker for the complication is also un-clarified [14]. The present study investigated the different analgesia method affecting the cognitive dysfunctions in patients underwent hip replacement in elderly, and discussed the different
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The previous study [18] proved that the toxicity of Aβ protein could induce the early apoptosis of the neurons. In this study, the Aβ level was increased in GA group, which illustrates that the general analgesia drug may activate the change of Aβ protein. The enhanced Aβ, therefore, mediates the neuron-toxicity of the patients. However, the epidural analgesia drug may not involve this pathway. The retrospective study [19] also indicated that the Aβ level in mild cognitive impairment patient was significantly increased compared to the normal individuals. Tau protein is kind of functional protein in brain tissues, and is a kind of highest expressed tubulin-associated protein. The expression of tau protein could induce the cellular morphology change, synapsis decreased, and causes the cell apoptosis finally. Some scientists [20] have defined the Tau protein as the biomarker of the neuron degeneration. In this study, the Aβ and Tau level in GA group was higher compared to EA group, which hints that the POCD occurrence may associate with the Aβ and Tau protein. The correlation analysis also indicated that the POCD was positively correlated with the Aβ or Tau protein expression.

In conclusion, the POCD occurrence rate in EA group was significantly lower compared to the GA group. The Aβ and Tau level in patients with POCD was higher significant compared to the patients without POCD. Therefore, the epidural analgesia was better than the general analgesia method for the hip replacement elder patients. The mechanism of the POCD may be caused by the enhancement of Aβ and Tau protein.

Disclosure of conflict of interest

None.

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