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## Postoperative Delirium in Elderly Patients May be Associated with Perioperative Blood Pressure Fluctuations

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ABSTRACT

Postoperative delirium (PD) is a common complication of surgery in elderly patients, but its pathophysiological mechanism remains unclear. In order to clarify the role of intraoperative hypotension and fluctuation of blood pressure in the development of PD, we conducted a follow-up study in elderly patients with intraoperative hypotension and fluctuation of blood pressure. A total of 237 patients underwent hip surgery between July 2018 and September 2019, and 158 patients who were eligible for inclusion were enrolled in the study. One day before the operation, the mentality of patients was evaluated by Mini-mental State Examination (MMSE), and the sex, age, height, and weight of the patients were recorded. Radial artery puncture was performed in all patients before anesthesia, intraoperative SBP, MAP and DBP were recorded, and the surgical events of the patients was recorded. The markers associated with PD (TNF- $\alpha$ , IL-6 and S-100 $\beta$ ) were determined before and after surgery. Perioperative delirium (PD) was assessed by the prevailing standard of assessment, Confusion of Consciousness Assessment (CAM). Cognitive assessment was evaluated using the Mini-mental State Examination (MMSE). In addition, the timing and type of delirium were recorded. There were 158 patients which were accorded with the inclusion criteria came into the study. The results of our data showed that delirium occurred in 41 patients (25.9%) during the first week after surgery. In the comparison between the PD group and the non-PD group, it was found that the patients with postoperative delirium were older, lower body mass index and higher MMSE score before operation. Intraoperative blood pressure is low, usually more than 30% lower than preoperative blood pressure. The levels of TNF- $\alpha$ , IL-6 and Smur100  $\beta$  were higher after operation. The increased incidence of postoperative delirium may be related to intraoperative hypotension and intraoperative blood pressure fluctuation. The pathophysiological mechanism may be that hypotension causes low cerebral perfusion, which in turn causes local inflammation in the brain. In addition, postoperative delirium is also more likely to occur in older patients with lower body mass index.

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## 1. Introduction

Elderly patients who receive surgical treatment are usually characterized by weakness, more underlying diseases, high surgical risk, and significantly increased risk of death. A variety of adverse consequences can occur after operation, including postoperative delirium, pulmonary infection, myocardial infarction, and cerebrovascular accident<sup>[1]</sup>.

Delirium is a common neurological syndrome. Delirium is defined as an attention, consciousness, and cognitive disorder in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). The onset of the disease is usually urgent, and the condition fluctuates obviously. The syndrome is common in elderly patients. The cognitive function of the patients decreased, the degree of awakening changed, the perception was abnormal, and the night and day were reversed<sup>[2]</sup>. Among the elderly patients who received surgical treatment, the incidence of postoperative delirium (PD) was very high, and some studies showed that it was 8-73%<sup>[3]</sup>. Postoperative delirium, a clinical syndrome that can lead to serious complications, has a high incidence, and is associated with prolonged hospitalization, a gradual decline in cognitive ability and learning, a decline in postoperative self-care ability, and an increase in mortality<sup>[4]</sup>. The causes of delirium are considered to be multiple factors, and there is a correlation between preoperative health and predisposing factors<sup>[5]</sup>. At present, many studies have confirmed that the causes of postoperative delirium may be related to age, basic basis, type of operation, intraoperative hypotension, intraoperative blood transfusion, prolonged operation time, use of anesthetics and other risk factors, but the pathophysiology of its occurrence is still little known<sup>[6]</sup>. Some scholars have proposed that insufficient cerebral perfusion caused by intraoperative hypotension is one of the mechanisms of postoperative delirium. A large observational study shows that the risk of hypotension in the elderly during surgery is very high, and 66-85% of patients with hip fractures develop hypotension during surgery<sup>[7]</sup>. A recent clinical trial suggests that in order to reduce the incidence of postoperative delirium, avoiding intraoperative hypotension should be part of the intervention strategy<sup>[8]</sup>. However, when looking at other literatures, it is found that some research results are contradictory to those on this subject: some studies have suggested that intraoperative hypotension does not play a role in the development of postoperative insanity<sup>[8]</sup>. In addition, other studies have shown that intraoperative hypertension and vasopressor use can also lead to postoperative delirium. Therefore, the relationship between intraoperative blood pressure and postoperative

delirium is controversial<sup>[9]</sup>. Whether intraoperative blood pressure management should be performed to avoid postoperative delirium is still controversial. In order to prove the role of blood pressure in the occurrence of delirium during operation, the blood pressure of elderly patients who needed surgical treatment was selected for an observational study.

## 2. Methods

### 2.1 Patient Recruitment

The study was approved by the Medical Research Ethics Committee, Affiliated Hospital of North China University of Science and Technology. Written informed consent was obtained preoperatively from each study patient. Inclusion criteria: Age $\geq$ 65, ASA 2~3, Non-cardiac surgery, Operation time was less than three hours, All patients had no preoperative mental illness, normal cognitive ability, no long-term use of neuropsychiatric drugs or alcohol abuse, no serious illness (such as sepsis, renal or liver failure, severe respiratory failure), and no history of brain injury or stroke<sup>[10]</sup>. Exclusion criteria: Patients refused the study, unable to communicate verbally, had severe cognitive impairment preoperatively, and had advanced malignant tumors, patients with COPD, patients received intraoperative blood transfusion treatment. A total of 237 patients underwent hip surgery between July 2018 and September 2019, and 158 patients who were eligible for inclusion were enrolled in the study (M: 56, F: 102, mean age: 72 years, range: 65-98 years, mean body weight 60.9 kg, mean Body Mass Index (BMI) 23.1).

### 2.2 Preoperative Assessment

The mini-mental state examination scale (MMSE) can comprehensively, accurately, and quickly reflect the participants' mental state and the degree of cognitive impairment<sup>[11]</sup>. The scale includes the following seven aspects: time orientation, place orientation, immediate memory, attention and calculation, delayed memory, language, visual space. A total of 30 questions, the correct answer to each score of 1, wrong answer or do not know the score of 0, the total score of the scale ranges from 0 to 30. The score was 27-30: normal score < 27: cognitive impairment 21-26, mild 10-20, moderate 0-9, severe. Delirium was assessed by confusion assessment method (CAM), to screen participants for delirium before operation and 7 days after operation. Delirium has four characteristics: 1) rapid occurrence of disturbance of consciousness after operation, which changes greatly day and night, 2) lack of attention, 3) disturbance of perception, and 4) decline of cognitive ability. Typical patients with delirium may have characteristics (1) and (2) or (3) or (4),

which can be defined as delirium when the criteria are met. According to the situation when delirium occurs, there are motor manifestations of hyperactivity or inactivity, and the type of delirium can be judged. Patients with low activity delirium may have decreased movement, confusion, lethargy, or coma, while patients with hyperactive delirium show restlessness, sleep disorders, irritability, and irritability. Data about the basic characteristics of the patient (such as age, sex, basal blood pressure, body mass index [BMI], underlying disease and type of operation) were obtained from the patient's medical records before operation. The preoperative physical condition was evaluated using the classification system of the American Association of Anesthesiologists (ASA). Blood samples were taken before operation, on the first day (24 h) and the third day (72 h) after operation, and the concentrations of serum tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6) and protein S-100  $\beta$  (S-100  $\beta$ ) were measured.

### 2.3 Surgical and Anesthetic Techniques

The selected patients were all patients undergoing hip surgery. ASA physical status class was 2~3. The choice of type of anesthesia is spinal anesthesia or general anesthesia, depending on the general condition of the patient, the type of surgery and the need for the depth of anesthesia. During general anesthesia, tracheal intubation was performed with etomidate (0.15~0.3 mg/kg), fentanyl (2~5  $\mu$ g/kg) and cisatracurium besylate (0.1~0.2 mg/kg). Sevoflurane or combined propofol was used to maintain anesthesia during operation. Intermittent injection of fentanyl and cisatracurium besylate were used to maintain analgesia and muscle relaxation. Combined spinal-epidural anesthesia (CSEA) was used in regional anesthesia, and 0.5% ropivacaine was used in spinal anesthesia for 12~18 mg.

### 2.4 Measurement of Intraoperative Blood Pressure

During the operation, each patient received standard monitoring of blood pressure, electrocardiogram, blood oxygen saturation, pulse, end-respiratory carbon dioxide and body temperature. The heart rate and blood pressure of each patient were measured before operation in order to compare with intraoperative blood pressure. The preoperative basal blood pressure of each patient was calculated as a 3-day average. Before the beginning of anesthesia, the blood pressure of patients with continuous monitoring of invasive artery was established by means of local anesthesia. Items that need to be closely monitored include systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). The highest

MAP(Max) and the lowest MAP (Min), were measured during the operation, and the difference between them was defined as blood pressure fluctuation ( $\Delta$ MAP). The definition of intraoperative hypotension: (1) intraoperative relative hypotension, defined as SBP or MAP 30% or more than 30% lower than the patient's baseline, and (2) blood pressure below MAP 50 mmHg.

### 2.5 Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 statistical software with intention to treat, measurement data was presented by mean  $\pm$  standard deviation ( $\bar{x}\pm S$ ), comparison in the group used analysis of variance of repeated measurement, comparison between groups used *t*-test, count data were compared using the  $\chi^2$  test. A *p*-value < 0.05 was considered statistically significant.

## 3. Results

### 3.1 Incidence of Delirium

On postoperative delirium was present in 41/158 patients (25.9%). The results showed that the onset of delirium was related to age, body mass index, and MMSE score. (Table 1)

**Table 1.** Baseline characteristics

| Characteristics            | NO<br>n=117        | Delirium | Yes<br>n=41      | <i>p</i> |
|----------------------------|--------------------|----------|------------------|----------|
| Age, $\bar{x}\pm sd$       | 73.67 $\pm$ 7.81   |          | 81.95 $\pm$ 9.12 | 0.001    |
| BMI, n(%)                  |                    |          |                  | 0.001    |
| <20                        | 3(2.5)             |          | 6(14.9)          |          |
| 20-25                      | 71(60.5)           |          | 23(56.1)         |          |
| 26-30                      | 35(30.2)           |          | 10(24.3)         |          |
| >30                        | 8(6.8)             |          | 2(4.7)           |          |
| MMSE, $\bar{x}\pm sd$      | 28.53 $\pm$ 0.64   |          | 18.86 $\pm$ 0.98 | 0.001    |
| Type of Anesthesia, n(%)   |                    |          |                  |          |
| General anaesthesia        | 46(39.5)           |          | 19(47.3)         | 0.194    |
| Regional (CSEA)            | 71(60.5)           |          | 22(52.7)         |          |
| <b>Anaesthetic Drugs</b>   |                    |          |                  |          |
| Etomidate(mg)              | 12.6 $\pm$ 2.01    |          | 13.2 $\pm$ 1.22  | 0.43     |
| Fentanyl(mg)               | 0.65 $\pm$ 0.11    |          | 0.67 $\pm$ 0.12  | 0.79     |
| Cisatracurium besylate(mg) | 13.5 $\pm$ 2.41    |          | 13.9 $\pm$ 2.09  | 0.69     |
| Sevoflurane(min)           | 82.77 $\pm$ 10.62  |          | 80.55 $\pm$ 8.23 | 0.62     |
| Propofol(mg)               | 390.88 $\pm$ 22.27 |          | 383 $\pm$ 29.66  | 0.53     |
| Ropivacaine(mg)            | 13.23 $\pm$ 1.16   |          | 13.92 $\pm$ 1.84 | 0.26     |
| Coronary disease           |                    |          |                  |          |
| Hypertension, n (%)        | 26(22.2)           |          | 18(43.9)         | 0.16     |
| Diabetes, n (%)            | 5(4.2)             |          | 3(7.5)           | 0.45     |
| Atrial fibrillation n (%)  | 12(10.2)           |          | 6(14.6)          | 0.33     |
| Duration of hypotension    | 9.78 $\pm$ 12.2    |          | 8.98 $\pm$ 9.5   | 0.84     |

### 3.2 Intraoperative Hemodynamic

The statistical results of intraoperative blood pressure of patients showed that postoperative delirium was easy to occur when intraoperative hypotension and blood pressure fluctuation occurred. (Table 2)

**Table 2.** Intraoperative blood pressure in patients with and without delirium

| Characteristics     | NO<br>n=117        | Delirium | Yes<br>n=41         | p      |
|---------------------|--------------------|----------|---------------------|--------|
| SBP max             | 151.54±18.65       |          | 152.01±16.25        | 0.4980 |
| DBP max             | 91.43±12.16        |          | 89±8.74             | 0.821  |
| SBP min             | 129.22±14.24       |          | 104.66±13.84        | 0.001  |
| DBP min             | 75.65±7.86         |          | 55.46±6.76          | 0.001  |
| MAP max             | 109.18±16.40       |          | 108.38±7.89         | 0.712  |
| MAP min             | 95.35±7.41         |          | 81.68±9.76          | 0.001  |
| ΔMAP, med (min-max) | 12.9 (-5.87-96.87) |          | 17.23 (-2.58-55.46) | 0.006  |

### 3.3 The TNF-α, IL-6 and S-100β Levels of Patients with PD

Patients with delirium had higher levels of TNF-α, IL-6 and S-100β than those without delirium. (Table 3, 4, 5)

**Table 3.** The levels of TNF-α in patients with and without delirium

| Characteristics | NO<br>n=117 | Delirium | Yes<br>n=41 | p     |
|-----------------|-------------|----------|-------------|-------|
| TNF-α           |             |          |             |       |
| preoperative    | 63.95±7.21  |          | 62.84±10.98 | 0.863 |
| Day1            | 69.73±9.92  |          | 81.68±12.35 | 0.001 |
| Day2            | 75.17±16.79 |          | 92.13±10.30 | 0.001 |
| Day3            | 68.26±6.55  |          | 95.17±11.18 | 0.001 |

**Table 4.** The levels of IL-6 in patients with and without delirium

| Characteristics | NO<br>n=117  | Delirium | Yes<br>n=41  | p     |
|-----------------|--------------|----------|--------------|-------|
| IL-6            |              |          |              |       |
| preoperative    | 335.95±11.18 |          | 333.21±34.69 | 0.695 |
| Day1            | 337.49±18.74 |          | 377.79±28.37 | 0.001 |
| Day2            | 341.95±15.23 |          | 384.95±22.34 | 0.001 |
| Day3            | 338.95±13.45 |          | 379.65±16.46 | 0.001 |

**Table 5.** The levels of S-100β in patients with and without delirium

| Characteristics | NO<br>n=117 | Delirium | Yes<br>n=41 | p     |
|-----------------|-------------|----------|-------------|-------|
| S-100β          |             |          |             |       |
| preoperative    | 0.18±0.03   |          | 0.22±0.05   | 0.512 |
| Day1            | 0.30±0.02   |          | 0.51±0.05   | 0.001 |
| Day2            | 0.27±0.04   |          | 0.49±0.03   | 0.001 |
| Day3            | 0.23±0.08   |          | 0.38±0.05   | 0.001 |

### 3.4 Multivariate Analysis of Postoperative Delirium

In the multivariate analysis, postoperative delirium was taken as the dependent variable (0 = no, 1 = yes), and the significant variable in the univariate analysis (Age, BMI, MMSE, SBP, DBP, MAP, postoperative TNF-α, IL-6 and S-100β) was used as the independent variable for logistic regression analysis. The results showed that ΔMAP, TNF-α, IL-6, Age, BMI was a high-risk factor for postoperative delirium. (Table 6)

**Table 6.** Multivariate logistic regression analysis

|         | β     | p     | OR     | 95%CI        |
|---------|-------|-------|--------|--------------|
| Age     | 2.365 | 0.010 | 7.963  | 4.148~10.652 |
| BMI     | 3.764 | 0.007 | 8.749  | 6.473~10.886 |
| MMSE    | 1.496 | 0.021 | 4.252  | 2.019~6.748  |
| SBP min | 1.435 | 0.024 | 4.085  | 2.352~6.649  |
| DBP min | 2.063 | 0.012 | 5.123  | 3.748~7.191  |
| MAP min | 2.718 | 0.011 | 5.492  | 3.965~7.024  |
| ΔMAP    | 4.742 | 0.000 | 16.452 | 10.81~22.248 |
| TNF-α   | 4.012 | 0.001 | 13.742 | 7.285~20.360 |
| IL-6    | 3.891 | 0.005 | 10.257 | 8.876~12.541 |
| S-100β  | 2.573 | 0.010 | 6.652  | 3.358~8.872  |

### 4. Discussion

There were 158 patients which were accorded with the inclusion criteria came into the study. And our results showed that delirium occurred in 41 patients (25.9%) after surgery. The high intraoperative ΔMAP, elevated postoperative inflammatory factors (TNF-α, IL-6, S-100β), advanced age and low body mass index (BMI) were the main risk factors of postoperative delirium. Low systolic blood pressure, diastolic blood pressure and low MAP are also associated with postoperative delirium (PD). Other

factors such as anesthetic methods, anesthetic drugs, and mild underlying diseases did not cause postoperative delirium. In addition, we also found that the preoperative and postoperative MAP values were also very significant between the non-delusional group and the delusional group. During surgery, even transient episodes of hypotension can lead to early or late postoperative delirium. Therefore, the occurrence of perioperative PD is related to blood pressure fluctuation, which can be used as a danger signal.

With the improvement of social economy and medical level, the global elderly population is increasing year by year. The increase of the elderly population leads to the problem of aging population. Among the patients receiving surgical treatment, the proportion of the elderly population is getting higher and higher. According to statistical analysis, a considerable proportion of elderly patients have temporary postoperative delusions of (PD), after surgery. Some patients have left behind long-term postoperative cognitive dysfunction (POCD) [12]. This phenomenon has aroused widespread concern among surgeons and anesthesiologists. At present, the pathophysiological mechanism of postoperative delirium is not completely clear. Several studies have shown that intraoperative hypotension and blood pressure fluctuations play a role in the development of delirium. But at the same time, studies have shown that the occurrence of delirium is not related to intraoperative hypotension and blood pressure fluctuations. Therefore, we established this study to verify the relationship between intraoperative hypotension and delirium by studying intraoperative hypotension and blood pressure fluctuations.

The results of this study showed that by comparing the PD group and the non-PD group, the larger the range of intraoperative blood pressure fluctuation, the higher the  $\Delta$ MAP value, the higher the probability of postoperative PD. When there is a drop in blood pressure, we usually give corrective treatment, so that low blood pressure will not exist for a long time. Even though our anesthesiologist dealt with hypotension in time, delirium was inevitable after surgery. This suggests that even a short-term drop in blood pressure may lead to postoperative delirium. From this, we can conclude that maintaining the stability of blood pressure is good for elderly surgical patients. In the analysis of the risk factors of delirium, we found that the older the age, the lower the body mass index, the higher the risk of delirium. This may be related to the brain dysfunction caused by cerebrovascular self-regulation and insufficient glycogen supply in elderly patients. High preoperative MMSE scores suggest that patients may

have cognitive impairment, and these patients also have a higher risk of postoperative delirium.

Another hypothesis of the pathophysiological mechanism of postoperative delirium is that insufficient cerebral perfusion during hypotension leads to local ischemia, which leads to brain dysfunction. Low cerebral perfusion can cause an increase in the production of reactive oxygen species. Increased production of reactive oxygen species in the brain can lead to increased excitatory transmitters, apoptosis, and local inflammation [13]. In this study, it was found that the serum levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6) and S-100  $\beta$  in patients with postoperative delirium were significantly higher than those without postoperative delirium. It is estimated that intraoperative hypotension and blood pressure fluctuations lead to insufficient cerebral perfusion and local inflammation caused by cerebral ischemia. The invasion of inflammatory factors into the hippocampus may be the cause of postoperative insanity.

## 5. Conclusions

To sum up, we concluded that perioperative blood pressure decrease and blood pressure fluctuation are associated with postoperative delirium. Cerebral ischemia and local inflammation caused by intracranial hypoperfusion may be the pathological mechanism of delirium. The best treatment for postoperative delirium is prevention. Early identification and treatment of potential perioperative risk factors can prevent the occurrence of postoperative delirium.

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