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Impact of anesthesia depth on serum adiponectin, matrix metalloprotein 9 (MMP-9), and postoperative cognitive impairment in elderly patients with general anesthesia.

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Abstract

The aims of this study were to evaluate the impact of anesthesia depth on postoperative serum Adiponectin (ADP), MMP-9, S-100β protein concentration, and Postoperative Cognitive Dysfunction (POCD) in elderly patients with general anesthesia. A total of 120 elderly patients undergoing elective gastrointestinal surgery under general anesthesia were divided into 2 groups: Group A (n=60) was applied Closed Loop Target Controlled Infusion (CLTCI) to maintain the Bispectral Index (BIS) value of Electroencephalograph (EEG) as 45, and Group B (n=60) maintain the BIS value of EEG as 55. The MoCA scores in the two groups were decreased by different degrees after surgery. The MoCA scores in Group B on d's 1 and 3 after surgery were higher than Group A (P<0.05). The serum concentrations of MMP-9 and S-100β in the two groups were significantly higher at T1, T2, and T3 (P<0.05), but the serum ADP concentrations were decreased. The serum concentrations of MMP-9 and S-100β in group B were lower than group A (P<0.05), while the serum ADP level was higher than group A (P<0.05). The anesthesia depth with the BIS value as 55 has less impairment toward the early postoperative cognitive function in elderly patients than that with BIS as 45, which may be related to the increased serum ADP and decreased serum MMP-9 levels.

Keywords: Anesthesia depth, Postoperative cognitive dysfunction, Adiponectin, Matrix metalloproteinase-9, Elderly.

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Introduction

Postoperative Cognitive Dysfunction (POCD) is a common postoperative central nervous system complication in elderly patients, which can delay patients' rehabilitation and prolong their hospitalization. The occurrence of POCD may be related to such risk factors as anesthesia, surgery, or perioperative status, and its mechanism is still not fully understood yet. Adiponectin (ADP) is one adipocyte-derived hormone protein secreted by the adipose tissue, has many activities such anti-inflammation, antioxidation, and decreasing blood glucose, etc., thus exhibiting protective effects on cells, tissues, or organs [1-4]. Our previous studies have found that the postoperative serum ADP level in elderly patients with general anesthesia is negatively correlated with POCD [5]. Matrix Metalloprotein 9 (MMP-9) is a group of Zn^{2+}-dependent proteolytic enzymes, the main function of which is to degrade and remodel extracellular matrix, thus playing major roles in the degradation of brain basement membrane. It's currently considered that abnormal expression of MMP-9 is directly related to the destruction of the blood-brain barrier, and is the key factor leading to vasogenic brain edema and secondary brain injury [6]. Studies have found that MMP-9 is closely related to the occurrence of POCD in elderly patients [7]. Anesthesia depth management can improve patients' prognosis through affecting surgery-caused stress responses [8,9]. So, how to control the appropriate anesthesia depth and reduce the adverse effects caused by perioperative stress responses have been hot research items by anesthesiologists. This study explored the impact of different anesthesia depths on the serum ADP and MMP-9 levels and POCD in elderly patients with general anesthesia, hoping to provide reference for clinical anesthesia management.

Materials and Methods

General information

This study was approved by the Medical Ethics Committee of the hospital, and the patients' and their families had signed the informed consent. A total of 120 patients undergoing elective gastrointestinal surgery were selected, being classified into grade II or III (ASA), aging 65-86 y, including 66 males and 54 females. Exclusion criteria: 1. With the MoCA Score<26 points 3 d before surgery; 2. Can recognize the text in the MoCA tables; 3. With significant respiratory or circulatory system diseases, hepatonephric dysfunction, or mental and neurological diseases before surgery; 4. With preoperative diabetes; 5. Didn't take antipsychotics, sedatives, or narcotic analgesic within 2 y; 6. With a history of alcoholism or drug dependence; 7. With severe visual or hearing disorders or can't communicate with the interviewers for other reasons; 8. Can't achieve ideal surgical results and thus performed immediate second surgery; 9. Operation time>3 h; 10. Intraoperative blood loss>800 ml. The patients were divided into 2 groups (60 patients in each group) using the random number table method. Groups A and B were maintained the Bispectral Index (BIS) value as 45 and 55, respectively using Closed Loop Target Controlled Infusion (CLTCI).

Anesthesia methods

The patients were fasted before surgery. After pushed into the surgery room, Electrocardiogram (ECG), Non-Invasive Blood Pressure (NBP), SpO_2, Respiratory Rate (RR), and $PET\text{-}CO_2$ of each patient were routinely monitored, and the BIS value was monitored by one Aspect-X P-type BIS monitor (Aspect, USA). The signal input of the BIS monitor was connected with the patient by electrodes, and the signal output was connected to the Target Control Infusion pump (TCI). The TCI pump was connected to the venous access of the patient, namely the CLTCI technology. The BIS value was preset in the TCI pump, which was connected to the muscle relaxation CLTCI device simultaneously (Model of the muscle relaxation monitor: CLMRIS-I, Guangxi Weili Fangzhou Co.). Anesthesia was induced in turn through intravenously infusing midazolam 0.05~0.1 mg/kg, etomidate 0.3 mg/kg, fentanyl 5~8 μg/kg, and cisatracurium 0.2 mg/kg. The plasma target concentration of propofol by the CLTCI pump was 3 mg/L, which was followed by CLTCI-pumped cisatracurium 0.15 mg/kg when the patient fell asleep. When the muscle relation monitor showed the myoseism T1<10%, the patient can be performed endotracheal intubation, followed by mechanical ventilation with the tidal volume as 8-10 m/kg, respiratory rate as 12 breaths/min, inspiration/expiration ratio as 1:2, and PCO2 as 35-45 mmHg. Anesthesia maintenance: the CLTCI pump was used to inject propofol together with intravenous injection of remifentanil 0.15 $g•kg^{-1}•min^{-1}$ and CLTCI-pump injection of cisatracurium 0.5 $g•kg^{-1}•min^{-1}$; group A was set the upper and lower BIS values of the TCI pump as 45, and group B was set to 55. When T1 was restored to 10%, the dose of the muscle relaxant can be increased with the increasing rate as 3 $μg•kg^{-1}•min^{-1}$. Intraoperative body temperature should be monitored so as to ensure the body temperature maintained at 36°C~37°C. Intraoperative urine output, blood loss, and transfusion amount were also recorded so as to maintain the hemodynamic stability. Anesthesia recovery: The anesthesia recovery time (from the end of skin suture to the time when the patient can answer doctor's calling) and extubation time (from the end of skin suture to the extubation) were recorded. All the patients were performed postoperative PCIA (analgesic preparation: 10 μg/kg fentanyl+200 mg of flurbiprofen axetil+8 mg of tropisetron, diluted to 200 ml with saline; background infusion rate 2 ml/h, 2 ml for PCA, and locking time 15 min). The Visual Analogue Scale (VAS) scoring was used to assess the postoperative pain degree, which should be maintained ≤ 3 points (0 point as painless, 10 points as severe pain).

Monitoring indexes

Cognitive function: Patients' neuropsychological function was assessed by MoCA 3 days before surgery (D0) as well as 1 (D1), 3 (D2), and 7 d (D3) after sending back to the ward. MoCA consists of 7 items: Visual space/execution, naming, attention, language, abstraction, delayed memorization, and directional ability. The total score ranges from 0 to 30 points, with ≥ 26 points defined as normal, and the testing time is 10 min.

Collection and detection of blood samples

3 ml of fasting venous blood was collected immediately before surgery (T0) as well as 2 h (T1), 24 h (T2), and 72 h (T3) after surgery for detecting the protein levels of ADP, MMP-9, and S-100β using Enzyme Linked Immunosorbent Assay (ELISA).

Statistical analysis

The statistical analysis was performed using SPSS 17.0 software. The measurement data were expressed as mean standard deviation ($\bar{x} \pm s$). The intragroup comparison used the single-factor Analysis of Variance (ANOVA) or multivariate Analysis of Variance (ANOVA), and the intergroup comparison used the pairwise t test. The measurement data were compared using the χ^2 test, with P<0.05 considered as statistical significance.

Results

There is no significant difference in the age, body mass index, anesthesia time, operation time, and intraoperative blood loss between the two groups (P>0.05, Table 1). The patients applied ephedrine or atropine in group A are significantly more than group B (P<0.05), while there is no significant difference in the infusion volume, urine volume, and red blood cell and plasma transfusion between the two groups (P>0.05, Table 2); compared with group B, the amount of propofol application in group A is larger (P<0.05, Table 3).

Table 1. *Comparison of general information between the two groups ($\bar{x} \pm s$, n=60).*

Group	Age	BMI	Anesthesia time (min)	Operation time (min)	Intraoperative blood loss (ml)
A	76.63 ± 4.60	22.71 ± 2.48	103.69 ± 16.56	83.53 ± 13.67	355.68 ± 78.82

B	75.13 ± 5.60	22.69 ± 3.18	104.23 ± 15.66	82.96 ± 14.38	354.36 ± 80.183

Table 2. *Comparison of intraoperative data between the two groups ($\bar{x}$ ± s, n=60).*

Group	Number of intraoperative ephedrine	Number of intraoperative atropine	Number of intraoperative RBC infusion (n)	Number of intraoperative plasma infusion (n)	Intraoperative infusion amount (ml)	Intraoperative urine amount (ml)
A	23	18	11	7	2050 ± 550	280 ± 130
B	9a	6a	9	6	1950 ± 650	300 ± 110
Note: Compared with group A, ^{a}P<0.05.						

Table 3. *Comparison of intraoperative propofol amount between the two groups ($\bar{x}$ ± s, n=60).*

Group	Propofol for anesthesia induction (mg/kg)	Total amount of intraoperative propofol (mg/kg•min)
A	1.13 ± 0.18	0.130 ± 0.033
B	1.08 ± 0.28	0.073 ± 0.018^a
Note: Compared with group A, ^{a}P<0.05.		

Table 4. *Comparison of MoCA between the two groups at different time points ($\bar{x}$ ± s, n=65).*

Group	D0	D1	D2	D3
A	28.38 ± 1.93	25.36 ± 1.48^{ab}	26.73 ± 1.53^{ab}	28.06 ± 1.16
B	28.16 ± 1.66	23.89 ± 1.68^a	25.16 ± 1.64^a	27.98 ± 1.37
Note: Compared with D0, ^{a}P<0.05; Compared with group A, ^{b}P<0.05.				

There is no significant difference in the cognitive function score between the two groups on D0 (P>0.05). The MoCA scores in the two groups after surgery are decreased (P<0.05), and those in group B on D1 and D2 were higher than group A (P<0.05), while there was no significant difference in the MoCA score between the two groups on D3 (P>0.05, Table 4).

The incidence rates of POCD in groups A and B were 18.3% (11 cases) and 11.7% (7 cases), and the difference was statistically significant (P<0.05).

The serum levels of ADP in the two groups at T1, T2 and T3 are decreased than T0, but those in group B at T1 and T2 are higher than group A (P<0.05); the serum levels of MMP-9 and S-100β in the two groups are increased (P<0.05), but the levels in group B at T1 and T2 are lower than group A (P<0.05), while the levels in group A and B at T3 show no significant difference (P>0.05, Table 5).

Discussion

POCD is a common postoperative complication in elderly patients, and the incidence of POCD in the elderly after non-cardiac surgery has been reported as 13% to 47% [10]. This study showed that the incidence of POCD in elderly patients was 18.3%, basically consistent with the literatures. Presently, there is no uniform standard for the diagnosis of POCD, and the diagnosis is mainly based on neuropsychological assessment, and the more commonly used tools are the mini-mental state examination (MMSE) and MoCA. However, MMSE itself has a capping effect, which is relatively insensitive to the patients with higher POCD. In addition, education has greater impact, and the patients with higher education may exhibit false negative results [11]. The MoCA scoring used in this study is more suitable for a wider age range and education level, and has higher sensitivity and specificity than MMSE. A MoCA score<26 points indicates the occurrence of POCD. Due to prevalent anxiety in patients before surgery, which is more obvious when closer to surgery, early preoperative assessment may reduce the impact of negative emotions on the assessment results. Therefore, we detected MoCA 3 d before surgery.

Different sedation and anesthesia depth in patients have important and far-reaching impact on patients' perioperative recovery and even postoperative recovery [12]. In recent years, studies have confirmed that deeper sedation and anesthesia are associated with poor prognosis, including postoperative mortality. Lindholm et al. [13] has reported that when the time of deep anesthesia with BIS<45 points accumulates to a certain extent, it will increase postoperative 1 y mortality, and every additional 1 h of deep anesthesia status will increase the fatality rate by 20%. Therefore, adjusting anesthesia depth is of great significance to improve patients' prognosis and outcomes, as well as to reduce postoperative complications and mortality.

CLTCI is the sedative anesthetic concept firstly proposed by Kenny and Mantzaridis [14] and Liu et al. [15], in which "closed loop" means to connect the BIS monitor and the TCI pump to form a relatively closed loop. Different from previous studies, we used CLTCI and accurately controlled the anesthesia depth to specific values (BIS=45 or 55); one computer was used for scanning once every 10 s so as to control a small fluctuation range of the BIS value, thus achieving more accurate investigation about the perioperative serum levels of ADP and MMP-9 as well as postoperative cognitive function in the patients with two different anesthesia depths. The appropriate depth of anesthesia is controlling the BIS value within (60~40). In view of the fact that deep venous anesthesia (BIS<45) is a risk factor for higher postoperative morbidity and mortality [16], we set BIS=45 as our limit so as to avoid potential injury to the patients; meanwhile, shallow anesthesia status was defined as BIS=55 so as to prevent intraoperative awareness.

ADP is abundant in human plasma, and its expression and secretion is regulated by some inflammatory factors, reactive oxygen species, transcription factors, or hormones; for example, Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-6 can inhibit the expression and secretion of ADP. In recent years, the ADP expression and adiponectin receptor (AdipoR) are found distributing widely in the pituitary and brain, and the existence of AdipoR1 in the hypothalamus and the basal nucleus shows that ADP may be involved in the central nervous signal pathway-controlled energy balance and higher brain functions [17], Kamogawa et al. [18] found that increased serum ADP level can exhibit protective effects against the progression of mild cognitive dysfunction in males; another study also found that ADP can improve insulin resistance, thereby improving the blood-brain barrier function and brain receptor function [19]. MMP-9 exhibits close relationship with cerebrovascular diseases in recent years' studies. MMP-9 is lowly expressed in normal brain tissue; however, due to the presence of inflammatory factors and hypoxic-ischemic factors, the neural cells, microglia, and vascular endothelial cells can synthetize MMP-9, thus degradating the extracellular matrix, aggravating inflammation, increasing the permeability of blood-brain barrier, increasing brain tissue damage, and causing neurological damage. Studies have found that the serum MMP-9 level is significantly positively correlated with the severity of cognitive dysfunction [20]. The content change of serum S-100β protein is a specific indicator reflecting brain damage and cognitive function changes [21]. This study showed that: the serum levels of MMP-9 and S-100β in the two groups at T1 and T2 were significantly increased, while those in group B were significantly lower than group A. The postoperative serum ADP levels in the two groups were significantly decreased, and that in group B was significantly higher than group A. The MoCA scores in group B on D1-D3 were significantly better than group A, and the incidence of POCD was lower than group A, indicating that the anesthesia depth with BIS as 55 has less injury toward the early postoperative cognitive function in elderly patients than BIS=45.

Possible mechanisms: 1. Through comparing the cases applied ephedrine and atropine between the two groups, it can be seen that deep anesthesia has a certain inhibitory effect toward the circulation, which may cause ischemic changes and cell dysmetabolism in local tissue, thereby changing the inflammatory response status and promoting secretion of inflammatory cytokines under deep sedation, as well as inhibiting the expression and secretion of ADP. Certain study has shown that relative overdosing of anesthetics in the group with deep sedation and anesthesia may cause tissue dysfunction and l hypoperfusion; this study also showed that the amount of propofol applied in group A was significantly higher than group B, so it can explain the above-mentioned problems more rationally. 2. Monk once pointed out that [22] the accumulative time of deep sedation (BIS<45) and intraoperative hypotension are related to the postoperative 1 y mortality in the patients with non-cardiac surgery. Perioperative inflammatory response is a complex process, which can be changed through depth anesthesia management, thus leading to the changes of inflammatory mediators. In this study, group A may trigger inflammatory responses, thereby causing the upregulation of MMP-9 and S-100β proteins. The mechanism at the molecular level still remains to be confirmed through further studies.

The shortcoming of this study is that it didn't completely exclude the impact of hemodynamics on the results, and only the numbers of the patients applied ephedrine and atropine in the two groups were recorded, while no exact amount nor application times of ephedrine and atropine were recorded, which should be improved in future experiments.

In summary, compared with the anesthesia depth with BIS equal to 45, anesthesia depth with BIS equal to 55 exhibits mild early postoperative cognitive impairment in elderly patients, which may be associated with its less inhibition toward serum ADP as well as it can reduce the serum MMP-9 concentration.

Table 5. *Comparison of serum ADP, MMP-9, and S-100β between the two groups at different time points ($\bar{x} \pm s$, n=60).*

Time point	MMP-9 (μg/l)		S-100β (ng/l)		ADP (mg/l)	
	B	A	B	A	B	A
T0	286.6 ± 47.3	290.3 ± 49.8	123.9 ± 16.9	126.3 ± 15.6	9.43 ± 1.32	9.39 ± 1.36
T1	478.6 ± 53.3^{ab}	536.6 ± 67.6^{a}	186.6 ± 17.3^{ab}	213.9 ± 15.9^{a}	5.63 ± 1.03^{ab}	3.91 ± 1.51^{a}
T2	436.6 ± 66.3^{ab}	481.2 ± 63.7^{a}	203.8 ± 13.8^{ab}	238.8 ± 18.9^{a}	5.76 ± 1.36^{ab}	4.12 ± 1.17^{a}
T3	396.9 ± 67.6^{ab}	431.9 ± 63.9^{a}	169.7 ± 17.3^{ab}	198.3 ± 16.3^{a}	6.13 ± 1.23^{ab}	4.39 ± 1.33^{a}

Note: Compared with T0, $^{a}P<0.05$; compared with group A, $^{b}P<0.01$.

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Conflicts of Interest

The authors declare no conflict of interest.

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