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CLINICAL RESEAPCH

Effects of Sedation Depth on POCD Incidence and Inflammatory Factors in Elderly Patients with Mild Cognitive Impairment

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Keywords

Mild cognitive impairment; Sedation depth; POCD; Inflammatory factor

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Abstract

Objective The study investigated the effects of sedation depth on POCD incidence and inflammatory factors in elderly patients with mild cognitive impairment. **Method** A total of 80 elder people with mild cognitive impairment who underwent general anesthesia in the hospital from Nov. 2018 to Mar. 2020 were selected and classified using random number table method as the A group (bispectral index（BIS）between 40~50, n=40) and B group (BIS between 50~60, n=40). Intraoperative clinical indicators, cognitive scores, and tumor necrosis factor (TNF-α), interleukin-10 (IL-10), and soluble protein-100β (S-100β) levels were compared between the two groups. **Results** There were no significant differences in intraoperative clinical indicators (anesthesia time, operation time, intraoperative blood loss and intraoperative urine volume) between two groups by comparison. Compared to one day before operation, the MMSE and MoCA scores of two groups were significantly decreased in seven days after operation; the MMSE and MoCA scores of B group in seven days after operation were significantly lower than those of A group, and the incidence of POCD in B group was significantly higher than that in A group. The TNF-α level of both groups in seven days after operation was significantly increased in contrast with one day before operation, whilst IL-10 level was significantly decreased. Seven days after operation, the TNF-α level of B group was elevated significantly while IL-10 level dropped when compared to A group. S-100β level was significantly increased in both groups after operation. Moreover, S-100β level one day after operation was significantly lower than that immediately after operation; the S100-β level in B group immediately after operation and one day after operation was significantly lower than that in A group . **Conclusion** During operation in elderly patients with MCI under general anesthesia, the mild sedation depth could effectively reduce the POCD

incidence of MCI patients and mitigate systemic inflammatory response of patients.

Introduction

Mild cognitive impairment (MCI) among the elder refers to the state of cognitive function between normal and aging dementia during aging process of the human body [1]. With increasing aging population, the morbidity of MCI gradually rises. Current research shows that MCI patients receiving deep sedation in operative treatment possess a higher incidence of POCD which is characterized by decreases of memory, abstract thinking and cognitive ability, leading to a series of cognitive dysfunction [2]. It has been reported that POCD of elder patients could be ameliorated by regulating the depth of sedation [3]. Therefore, the present study aimed to explore the effect of sedation depth on POCD of elder patients and relevant inflammatory factors, trying to provide further evidence of anesthesia choices in clinical operation for patients with MCI.

Materials and methods

Clinical data

Research object

A total of 80 elder people with MCI who underwent operation under general anesthesia in our hospital from Nov. 2018 to Mar. 2020 were selected as the research objects and classified using random number table method into the A group (n=40) which BIS (bispectral index) was between 40~50 and B group (n=40, BIS between 50~60). The clinicopathological variables of each case including gender, age and Body Mass Inde (BMI) were collected from patient records. A group: gender, 18 males and 22 females; average age, 69.54±7.62 years; BMI, 23.14±2.57 kg/m^2. B group: gender, 16 males and 24 females; average age, 70.32±7.47 years; BMI, 22.89±2.46 kg/m^2. There was no significant difference of sex, age and BMI between the two groups (P>0.05). The work was approved by the Ethics Committee of , Zhejiang , Zhoushan Putuo People's Hospital and the informed consent was obtained from all patients.

Inclusion and exclusion criteria

Inclusion criteria were: 1. 60 years old ≤ age ≤ 80 years old; 2. 15 < Montreal Cognitive Assessment (MoCA) score < 24; 3. 21 < mini-mental state examination (MMSE) < 27. Exclusion criteria were: 1. diseases related to nervous system; 2. long-term alcohol abuse; 3. sedatives or antidepressants used within 30 days; 4. anesthesia or surgery received within 3 years.

Method

experimental design

Patients of both groups were regularly fasted over 8 h. After patients went into operating room, Sodium Lactate Ringer's Injection was infused into the vein of upper limb to construct the peripheral venous access. Routine clinical indicators such as electrocardiogram, heart rate, blood pressure, arterial oxygen saturation and partial pressure of end-tidal carbon dioxide were continuously monitored during the operation and BIS Monitor was employed to monitor anesthesia depth of patients.

Establishment of anesthesia induction: intravenous injection of 0.05 mg/kg midazolam (YICHANG HUMANWELL PHARMACEUTICAL CO., LTD., Hubei, China, http://www.ycrenfu.com.cn/index.php), 0.3 μg/kg sufentanil (YICHANG HUMANWELL PHARMACEUTICAL CO., LTD., China), 0.25 mg/kg etomidate (Jiangsu Hengrui Medicine Co.,Ltd., Jiangsu, China, http://www.hrs.com.cn/index.html) and 0.2 mg/kg cisatracurium (Jiangsu Dongying Pharmaceuticals Co., Ltd., Jiangsu, China) was given successively to patients of the two groups. Respiratory parameters: Tidal volume (TV) = 8-10 mg/kg; inspiration expiration ratio (I:E) = 1:2; respiratory rate (RR) = 8-12 times/min; arterial oxygen saturation = 0.98; partial pressure of end-tidal carbon dioxide = 30-40 mmHg (1mmHg=0.133 kPa). Propofol was infused through a BCP-100 close-loop target-controlled infusion management system of propofol (Beijing Slgo Medical Technology Co., Ltd., Beijing, China, http://www.silugao.cn/index.jsp) with an initial plasma target concentration set at 3 μg/mL.

Anesthesia maintenance: both groups were treated with total intravenous anesthesia via close-loop

target-controlled infusion of propofol (170852, Sichuan Guorui Pharmaceutical Co., Ltd., Sichuan, China) and plasma target concentration of remifentanil was set at 2.0-6.0 ng/kg. The BIS of A group was maintained at 40-50 while that of B group was at 50-60, as the intermittent intravenous infusion of cisatracurium 8 μg/(kg·h) was adopted for maintenance of muscle relaxation during the operation. Propofol infusion was stopped when the insufflator closed and remifentanil infusion was stopped at the end of the operation. Patients were subjected to tracheal extubation after wakefulness.

Specimen collection

Peripheral venous blood (3 mL) was taken at several time points (one day before operation, before anesthesia, immediately after operation, one day after operation and seven days after operation), followed by 2-hour standing time at room temperature. Then the blood was centrifuged at 3000 rpm/min for 15 min and the supernatant was harvested and stored at -20℃.

Outcome measures

Clinical indicators

The intraoperative clinical indicators consisting of anesthesia time, operation time, intraoperative blood loss and intraoperative urine volume were recorded.

MMSE and MoCA scores & POCD determination

The cognitive function was evaluated through MMSE and MoCA scores one day before the operation and seven days after operation. The determination of POCD: the Z value or composite Z value of MMSE and MoCA scores > 1.96 was considered as the occurrence of POCD.

Inflammatory factors

The serum soluble protein-100β (S-100β) level was measured before anaesthesia, immediately after operation and one day after operation whereas the levels of serum tumor necrosis factor (TNF-α) and interleukin-10 (IL-10) in plasma was measured one day before operation and seven days after operation, as the enzyme linked immunosorbent assay (ELISA) kit (Genzyme Corporation, Cambridge, MA, USA) was used for measurement.

Statistical analysis

Statistical analysis was made through SPSS 19.0 (IBM, Armonk, NY, USA). The enumeration data were compared by the χ^2 test and the measurement data were presented as the means ± standard deviation with Student's *t* test utilized for contrast. A statistically significant difference was accepted when $P < 0.05$.

Results

Clinical indicators

As shown Table 1, the anesthesia time, operation time, intraoperative blood loss and intraoperative urine volume did not differ obviously between the two groups ($P>0.05$).

Table 1 Clinical indicators between two groups

Group	Case	Anesthesia time（min）	Operation time(min）	Intraoperative blood loss（mL）	Intraoperative urine volume（mL）
A	40	79.12±18.65	64.24±11.96	78.62±16.33	174.34±38.65
B	40	77.31±19.38	63.87±11.45	74.57±17.23	169.54±41.37
t		0.426	0.141	1.079	0.536
P		0.672	0.888	0.284	0.593

Cognitive score

No marked difference of MMSE and MoCA scores between the two groups was viewed one day before operation (Table 2, $P>0.05$). In comparison with one day before treatment, both groups notably decreased MMSE and MoCA scores seven days after operation

(Table 2, P<0.05), as the MMSE and MoCA scores of B group seven days after operation was appreciably lower than those of A group seven days after operation (Table 2, P<0.05) and the incidence of POCD in B group was higher than that in A group (Table 2, P<0.05).

Table 2 Cognitive score between two groups

Group	Case	MMSE score (point)		MoCA score (point)		POCD [n (%)]
		1d before	7d after	1d before	7d after	
A	40	23.72±1.68	22.07±1.45[a]	23.12±1.14	21.87±1.35[a]	4 (10.00)
B	40	24.15±1.59	20.36±1.38[a]	22.87±1.21	19.64±1.24[a]	11 (27.50)
t/χ^2		-1.176	5.403	0.951	7.694	4.021
P		0.243	0.000	0.344	0.000	0.045

Note: compared with one day before operation, [a]P<0.05.

Inflammatory factors

There was no prominent difference of TNF-α and IL-10 levels between the two groups one day before operation (Table 3, P>0.05), whereas the levels of TNF-α and IL-10 in both groups seven days after operation were dramatically higher than those one day before operation (Table 3, P<0.05). Relative to A group, TNF-α level in B group seven days after operation obviously elevated while IL-10 level reduced markedly (Table 3, P<0.05).

Table 3 Inflammatory factors between two groups

Group	Case	TNF-α (ng/mL)		IL-10 (ng/mL)	
		1d before	7d after	1d before	7d after
A	40	54.26±4.87	61.34±7.82[a]	46.24±8.66	66.34±7.23[a]
B	40	55.67±5.12	83.54±6.71[a]	45.50±7.17	58.28±6.95[a]
t		-1.262	-13.626	0.416	5.083
P		0.211	0.000	0.678	0.000

Note: compared with one day before operation, [a]P<0.05.

S-100β level

S-100β level of the two groups did not differ notably before anesthesia (Table 4, P>0.05). In contrast with before anesthesia, S-100β level of both groups after operation (immediately after operation and one day after operation) appreciably rose (Table 4, P<0.05), with S-100β level one day after operation lower that that immediately after operation (Table 4, P<0.05). In addition, patients in B group dramatically declined S-100β level when compared with A group immediately after operation and one day after operation (Table 4, P<0.05).

Table 4 S-100β level between two groups ($\bar{x}\pm s$, pg/mL)

Group	Case	Before anesthesia	Immediately after operation	One day after operation
A	40	132.24±31.65	257.64±51.49[a]	193.64±38.76[ab]
B	40	135.48±29.47	224.97±44.36[a]	151.46±29.69[ab]
t		-0.474	3.040	5.464

P	0.637	0.003	0.000

Compared with before anesthesia, [a]$P<0.05$; compared with immediately after operation, [b]$P<0.05$.

Discussion

The depth of sedation in operation greatly affects operation effect as well as physical and mental health of patients. Lighter sedation may affect manipulation of surgeons during operation or even wake the patients up during operationand further cause physical and mental traumas to them;whereas deeper sedation is unfavorable for postoperative recovery of patients and closely associated with the incidence of POCD.

MMSE is widely applied to evaluate cognitive function of the elder clinically, which is easy to operate and has a certain reliability. However, it holds a poor sensibility for diagnosis of MIC. As a POCD screening tool with high sensitivity and specificity, MoCA covers a broader range of cognitive domain than MMSE, so it is able to evaluate POCD of patients more effectively. Hence, this research assessed cognitive function of patients through the combination of MMSE and MoCA. The consequences exhibited that contrasted with A group, the MMSE and MoCA scores of B group with deeper sedation in seven days after operation were significantly reduced and the incidence of POCD was significantly increased in B group through calculating z value of MMSE and MoCA scores. Those findings implied that a low BIS(40 to 50) could effectively decline the probability of postoperative POCD. And the results that the anesthesia time, operation time, intraoperative blood loss and intraoperative urine volume did not differ obviously between the two groups suggested that different depths of sedation would not do notable harm to clinical indicators of patients.

TNF-α is a pivotal pro-inflammatory cytokine in the human body, fulfilling a critical indicative function on human inflammatory response examination. Previous studies have discovered that POCD had an intimate correlation with activation of postoperative neuroinflammation and the upregulations of various inflammatory factors like TNF-α, IL-1 and IL-6 were also confirmed in patients with POCD [4]. IL-10 is a member of anti-inflammatory cytokines involved in processes related to cerebral ischemia injury and repair, which can protect cranial nerve and inhibit a series of pro-inflammatory factors (IL-1β, IL-6 etc.) caused by craniocerebral injury. IL-10 helps to restore the stability of intracranial environment and realizes a crucial effect on prevention and treatment for cognitive dysfunction [5]. S-100β is one of the components of glia in intracytoplasm, regarded as a highly specific and sensitive evaluation index of brain injury. A previous report demonstrated that S-100β participated in regulation of inflammatory factor (IL-1β, TNF-α etc.) expression to influence on the interaction of neurons and glial cells, whose upregulation effectively implicated injury of human central nervous system [6]. In the study, both groups showed significantly elevated TNF-α and IL-10 levels after operation. In comparison with A group, TNF-α level was increased but IL-10 level was decreased in patients of B group after operation. Moreover, S-100β level in one day after operation was dramatically lower than immediately after operation but was higher than before anesthesia. And S-100 β level of B group was lower than that of A group whenever immediately or one day after operation. The similar consequences were obtained as well in former studies [7, 8], indicating that increased depth of sedation was able to upregulate levels of human inflammatory factors and repress expressions of relevant anti-inflammatory cytokines so as to raise the incidence of systemic inflammatory response of patients.

In conclusion, the maintenance of BIS at 40-50 through regulating sedation depth during operation in elderly patients with MCI under general anesthesia could effectively reduce the POCD incidence of MCI patients and mitigate the symptoms of systemic inflammatory response in patients.

Declaration of conflict-of-interest

The authors declare no conflict-of –interest.

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