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Influences of etomidate combined with propofol on cognitive function, inflammation and immunity in patients undergoing gastric cancer surgery

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ABSTRACT

This study examined how etomidate combined with propofol affected cognitive function, inflammation, and immunity in patients undergoing gastric cancer surgery. 182 gastric cancer patients treated in our hospital were enrolled and randomly divided into two groups, namely group A (anesthetized using etomidate) and group B (anesthetized using etomidate combined with propofol). Then the cognitive function, inflammation and immunity indicators were determined in the two groups. Compared with group A, group B exhibited shorter operation duration and hospital stay and smaller bleeding volume ($p<0.01$). At 3 d after the operation, group B had a higher Ramsay score, but a lower visual analogue scale (VAS) score than group A ($p<0.05$). Moreover, the mini-mental state examination (MMSE) score was lower in group A than that in group B ($p<0.01$). At the end of the operation, the heart rate (HR), mean arterial pressure (MAP) and saturation of pulse oxygen (SpO_2) were decreased to a great extent in both groups compared with those before anesthesia ($p<0.05$). Compared with those before anesthesia, the levels of immunoglobulin (Ig)M, IgG and IgA were lower in group A at the end of the operation and 1 and 3 d after the operation ($p<0.05$), but they were substantially higher in group B than those in group A ($p<0.05$). At the end of the operation and 1 and 3 d after the operation, the levels of the T-cell subset indicators decreases in group A were greater than those in group B ($p<0.05$). Etomidate combined with propofol has few influences on the immune and cognitive functions of gastric cancer patients and can effectively lower the expression levels of inflammatory factors in these patients.

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Introduction

People's health is seriously impacted by gastric cancer, a common malignant tumor (1). The mortality rate of gastric cancer is stubbornly high in China, and the people dying of this disease account for 23.02% of all cancer-related deaths (2). As the standard of living improves and constant changes in people's diet habits and working and rest modes, the incidence rate of gastric cancer is increasing. Studies have demonstrated that gastric cancer patients tend to be treated via surgery that can damage their immune system, producing negative effects on the treatment of gastric cancer. The choice of different anesthetic measures and agents has varying influences on the immune system of gastric cancer patients, and the use of improper anesthetic agents will cause surgical infections in patients. Therefore, it is vital to choose appropriate agents for anesthesia. Anesthetic means and agents can directly affect postoperative immune and cognitive functions to a certain degree (3). According to the findings in a study, during normal metabolism in the human body, there are few inflammatory cytokines secreted, while once the body gets injured or infected, numerous inflammatory factors will be produced, thereby inducing inflammatory responses. In severe cases, the patients will suffer from systemic inflammatory response syndrome (4). Several studies have reported that the stimulation by etomidate combined with propofol can have a certain impact on the immune function in the body of humans (5,6). Thanks to certain defects in the immune function of gastric cancer patients and drug effects, immunosuppressive responses often occur, such as great increases in the levels of immunosuppressive factors and abnormal declines in the levels of the pro-immune factors, to influence the postoperative immune functions in the patients. Another study has found that patients undergoing gastric cancer surgery often have such symptoms as mental confusion, declines in memory, attention and language abilities and intelligence and restlessness. The patients are particularly prone to cognitive confusion after the operation, with the incidence rate as high as 50%. Both etomidate and propofol can be used for mitigation, hypnosis and amnesia in patients. To investigate the effects of etomidate combined with propofol on cognitive function, inflammation, and immunity in patients undergoing gastric cancer surgery, the present study was conducted.

Materials and Methods

Study subjects

A total of 182 gastric cancer patients treated in the Affiliated Hospital of Nantong University from January to December 2018 were selected as the subjects of this study and randomly divided into group A (anesthetized using etomidate) and group B (anesthetized using etomidate combined with propofol). Group A (n=90) com-

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prised 56 males and 34 females, aged 36-62 years old and (45.2±8.2) years old on average and with a weight of 52-86 kg and a mean of (68.2±2.5) kg, while group B (n=92) consisted of 54 males and 38 females, aged 35-70 years old and (46.6±7.4) years old on average and weighing 50-82 kg and (67.8±3.1) kg on average. There were no statistically significant differences in the above comparable indicators between the two groups(p>0.05). Patients and/or guardians signed informed consent after the study was approved by the Affiliated Hospital of Nantong University.

Inclusion and exclusion criteria

Inclusion criteria: 1) patients with the indications related to the treatment of gastric cancer, 2) those definitely diagnosed with gastric cancer through pathological examination, 3) those with normal cognitive function, 4) those with normal coagulation function, and 5) those who and whose family members were informed of the present study and signed the consent. Exclusion criteria: 1) patients complicated with hypertension, diabetes or abnormalities in the immune system or coagulation function, 2) those who took sedatives, 3) those with hypoglycemia, or 4) those who disobeyed the medical advice.

Anesthetic method

Half an hour before surgery, all the patients were intramuscularly injected with 0.5 mg of atropine, and the venous channel was constructed, followed by infusion of Ringer solution for the maintenance of hemodynamic stability and recording of heart rate (HR), mean arterial pressure (MAP) and saturation of pulse oxygen (SpO_2). The anesthesia induction was performed using 2 mg/kg propofol,1 mg/kg vecuronium and 3 μg/kg fentanyl. After induction, the respiration of the patients was supported by the respirator. The infusion was conducted using the TCI-III dual-channel intravenous target-controlled infusion pump in both group A and group B at the rate that was adjusted based on the information of patients to ensure the cerebral state index (7) of 45-60, and it was terminated at 5 min before the operation was completed.

Observation indicators

At 6 d after the operation, the pain survey was performed in the two groups of patients with reference to the standard of visual analogue scale (VAS) that the pain feeling is gradually intensified from 0 to 10 points. We assessed cognitive function using the mini-mental state examination (MMSE) scale (8) as follows: the memory, concentration power, computing power and communication ability of the patients were evaluated. With the total score ranging from 0-30 points, an MMSE score below 23 points and lower than the basic value by over 2 points represents cognitive dysfunction. All the above detections were carried out at 1 d before operation and at 3 d after the operation.

Indicator detection

We measured serum levels of inflammatory factors using enzyme-linked immunosorbent assays (ELISA) according to the instructions; hypersensitive C-reactive protein (hs-CRP), IL-6, IL-8 and TNF-α were assessed. The HR, SpO_2 and MAP of the patients were measured. Immunoturbidimetry was employed to detect serum immunoglobulins (Igs) IgM, IgG and IgA, and the levels of T-cell subsets [the percentages of a cluster of differentiation (CD) 3-, CD4- and CD8-positive cells and the ratio of CD4-positive cells/CD8-positive cells)] were measured using a flow cytometer. The venous blood was drawn from the patients and sent to the Laboratory Department of the Affiliated Hospital of Nantong University for detecting the above indicators.

Statistical methods

SPSS 17.0 software was adopted for statistical analysis. Measurement data were presented as ($\overline{\chi}$±S) and compared using t-test, and enumeration data were analyzed using χ^2 test. p<0.05 represented that the difference was statistically significant.

Results

Comparisons of operation duration, bleeding volume and hospital stay between the two groups

Group B exhibited shorter operation duration and hospital stay and smaller bleeding volume than group A (p<0.05). (Table 1)

Comparisons of VAS and Ramsay scores between the two groups

At 3 d after the operation, the Ramsay score of patients in group B was higher than that in group A, while the VAS score was higher in group A than that in group B, with no statistically significant differences(p>0.05) (Table 2).

Table 1. Comparisons of operation duration, bleeding volume and hospital stay between the two groups ($\overline{\chi}$±S).

Group	Operation duration (min)	Bleeding volume (mL)	Hospital stay (d)
A	67.03±7.59	140.71±15.91	7.35±0.79
B	62.2±6.81	132.01±14.78	6.44±0.69
t	4.521	3.823	8.282
p	<0.001	<0.001	<0.001

Table 2. Comparisons of Ramsay and VAS scores between the two groups ($\overline{\chi}$±S, point).

Group	Ramsay score	VAS score
A	1.99±0.35	1.60±0.41
B	2.03±0.33	1.58±0.39
t	0.793	0.337
p	0.428	0.736

Comparisons of MMSE score and incidence of cognitive disorder between the two groups of patients

In the two groups of patients before surgery, there was no statistically significant difference in MMSE scores ($p>0.05$). At 3 d after the operation, the patients in group A had a lower MMSE score than those in group B ($p<0.05$), while there were fewer cases of cognitive disorder in group B (2 patients) than that in group A ($p<0.05$) (Table 3).

Comparisons of hs-CRP, IL-6, IL-8 and TNF-α between the two groups

The levels of inflammatory factors between the two groups were not statistically significant before surgery ($p>0.05$), and at 3 d after the operation, all the indicators declined remarkably in both groups and were lower in group B than those in group A ($p<0.05$) (Table 4).

Comparisons of HR, MAP and SpO_2 between the two groups at different time points

Compared with those before anesthesia, the HR, MAP and SpO_2 were decreased to a great extent in both groups at the end of the operation ($p<0.05$), while there were no statistically significant differences in the HR, MAP and SpO_2 in the two groups between at 1 and 3 d after the operation and before anesthesia ($p>0.05$). At all-time points, there was no statistically significant difference between the two groups in HR, MAP, and SpO2 ($p>0.05$) (Table 5).

Comparisons of Ig levels between the two groups at different time points

Compared with those before anesthesia, the indicators IgM, IgG and IgA were lowered notably in group A ($p<0.05$), while those in group B showed no statistically significant differences ($p>0.05$) at the end of the operation and at 1 and 3 d after the operation, but they were substantially higher than those in group A ($p<0.05$) (Table 6).

Comparisons of T-cell subsets between the two groups at different time points

At the end of the operation and 1 and 3 d after the ope-

Table 3. Comparisons of MMSE score and incidence of cognitive disorder between the two groups of patients ($\bar{\chi}$±S).

Group	MMSE at 1 d before operation (point)	MMSE at 3 d after operation (point)	Cognitive disorder (n)
A	28.77±4.01	24.51±3.06[ab]	10
B	28.62±4.33	26.96±3.68[a]	2
t	0.242	4.889	5.001
p	0.808	<0.001	0.025

Note: [a]$p<0.05$ vs. that in the same group before anesthesia and [b]$p<0.05$ vs. that in group B at 3 d after operation.

Table 4. Comparisons of levels of serum hs-CRP, IL-6, IL-8 and TNF-α between the two groups ($\bar{\chi}$±S, n=182).

Group	hs-CRP (mg/L)		IL-6 (ng/L)		IL-8 (ng/L)		TNF-α (μg/L)	
	At 1 d before operation	At 3 d after operation	At 1 d before operation	At 3 d after operation	At 1 d before operation	At 3 d after operation	At 1 d before operation	At 3 d after operation
Group	17.21±4.59	13.18±2.71[ab]	47.62±4.93	30.56±5.49[ab]	44.67±6.15	28.93±4.73[ab]	61.68±6.45	51.82±6.34[ab]
Group	16.92±5.83	7.26±4.95[a]	46.39±5.71	16.24±3.85[a]	43.59±5.92	17.46±3.56[a]	62.38±7.23	42.36±5.25[a]
t	0.372	9.977	1.554	20.411	1.207	18.513	0.688	10.972
p	0.711	<0.001	0.121	<0.001	0.228	<0.001	0.492	<0.001

Note: [a]$p<0.05$ vs. that in the same group before anesthesia and [b]$p<0.05$ vs. that in group B at 3 d after operation.

Table 5. Comparisons of HR, MAP and SpO_2 between the two groups at different time points.

Group	Indicator	Before anesthesia	At the end of operation	At 1 d after operation	At 3 d after operation
A (n=90)	HR (beat/min)	88.23±15.42	82.19±18.21[ab]	85.66±16.52	87.77±18.64
	MAP (mmHg)	106.52±16.53	100.36±18.32[ab]	102.09±15.35	105.28±18.74
	SpO_2 (%)	98.29±3.03	92.65±6.08[ab]	95.83±4.32	97.06±6.32
B (n=92)	HR (beat/min)	85.56±16.32	81.28±18.43[a]	88.41±18.74	88.87±16.64
	MAP (mmHg)	104.33±12.20	100.47±14.53[a]	103.79±15.36	104.52±16.52
	SpO_2 (%)	98.71±5.32	92.88±5.42[a]	96.03±4.53	97.92±6.30

Note: [a]$p<0.05$ vs. that in the same group before anesthesia and [b]$p<0.05$ vs. that in group B at the same time point.

Table 6. Comparisons of Ig levels between the two groups at different time points (g/L).

Group	Indicator	Before anesthesia	At the end of operation	At 1 d after operation	At 3 d after operation
A (n=90)	IgG	8.23±1.42	7.72±1.36[ab]	7.74±1.21[ab]	7.78±1.26[ab]
	IgA	1.12±0.28	0.93±0.22[ab]	0.91±0.23[ab]	0.96±0.21[ab]
	IgM	0.93±0.22	0.78±0.24[ab]	0.76±0.24[ab]	0.78±0.28[ab]
B (n=92)	IgG	8.26±1.43	8.12±1.16	8.16±1.14	8.18±1.32
	IgA	1.14±0.26	1.06±0.28	1.08±0.26	1.08±0.28
	IgM	0.91±0.21	0.86±0.22	0.84±0.23	0.86±0.22

Note: [a]$p<0.05$ vs. that in the same group before anesthesia and [b]$p<0.05$ vs. that in group B at the same time point.

Table 7. Comparisons of T-cell subsets between the two groups at different time points.

Group	Indicator (%)	Before anesthesia	At the end of operation	At 1 d after operation	At 3 d after operation
A (n=90)	CD3	60.81±7.62	52.84±6.63[ab]	53.23±5.88[ab]	53.84±6.45[ab]
	CD4	43.62±4.82	32.87±4.21[ab]	33.28±3.86[ab]	33.59±3.68[ab]
	CD8	28.67±2.83	23.44±2.62[ab]	22.63±2.43[a]	23.65±2.85[ab]
	CD4/CD8	1.55±0.26	1.35±0.18[ab]	1.25±0.19[ab]	1.37±0.24[ab]
B (n=92)	CD3	61.39±6.82	58.87±5.43[a]	58.37±6.26[a]	58.63±6.41[a]
	CD4	44.23±5.15	41.92±4.26[a]	42.12±4.67[a]	42.39±4.89[a]
	CD8	29.46±3.26	27.38±3.20[a]	27.24±3.37[a]	27.75±3.85[a]
	CD4/CD8	1.61±0.36	1.51±0.22[a]	1.41±0.23[a]	1.56±0.24[a]

Note: [a]$p<0.05$ vs. that in the same group before anesthesia and [b]$p<0.05$ vs. that in group B at the same time point.

ration, the T-cell subset indicators in both groups were obviously lower than those before anesthesia ($p<0.05$), but the decreases in group A were greater than those in group B ($p<0.05$) (Table 7).

Discussion

In radical gastrectomy, general anesthesia is mainly performed clinically, but it will cause abnormalities to various immune functions in the body so anesthesia and stress to surgery will have serious effects on gastric cancer patients (9-11). The selection of anesthetic agents is vital for patients, and less immunosuppressive ones are of great significance for the intraoperative safety, response and later recovery of gastric cancer patients. As general anesthetics commonly used in today's hospitals (12,13), both propofol and etomidate are characterized by rapid onset, short waking time and fast postoperative recovery, so they are more suitable for anesthesia. The present study, therefore, mainly investigated the influences of etomidate combined with propofol on cognitive function, inflammation and immunity in patients undergoing gastric cancer surgery, which is greatly valuable for alleviating the suffering of gastric cancer patients.

Postoperative cognitive dysfunction is mainly attributed to anesthetic agents in gastric cancer surgery, and the residues are able to spur abnormal activity in the central nervous system, inducing cognitive disorder in gastric cancer patients (14-16). The purpose of anesthesia is to mitigate the pain of patients based on the principle that the patients are made unconscious in the whole body or several sites to lower the difficulty in the surgical operations to some extent. Research has manifested that anesthetic agents are the main factor for cognitive disorders in patients, and another study demonstrated that different anesthetic agents and methods have varying influences on the cognitive function of gastric cancer patients. Propofol is a common agent for general anesthesia, which is characterized by convenient adjustment of anesthesia degree and fast recovery of consciousness. A study confirmed that (17) propofol can not only effectively mitigate the pain of patients to produce the anesthetic effect, but also improve their postoperative living quality. Likewise, etomidate has a sedative effect on patients, with the advantages of a higher level of safety and better efficacy. According to the results of this study, these two anesthetic agents can suppress the release of such inflammatory factors as IL-6, IL-8 and TNF-α, with the efficacies easy to be observed, namely promoting the postoperative recovery of patients and less affecting the immunity of patients. The reason may be that etomidate combined with propofol can resist inflammation and oxidation and weaken the gobbling ability of cells, thereby manipulating the immune system (18,19). So far, the influences of propofol and etomidate on immunity in patients undergoing surgery have rarely been reported in studies. The present study compared and analyzed the impacts of target-controlled infusion-based anesthesia using these two agents on patients undergoing radical gastrectomy. The influences of propofol and etomidate on humoral immunity in gastric cancer patients were first evaluated, and it was found that group A had obviously lower levels of IgM, IgG and IgA at each time point than that before anesthesia ($p<0.05$), and group B exhibited much smaller decreases in them than group A ($p<0.05$). Since T cells and their subsets are the main immune cells in the human body, the impacts of propofol and etomidate on the cellular immunity of gastric cancer patients were analyzed in this study as well. The results showed that compared with those before anesthesia, all the indicators of T-cell subsets obviously declined in both groups at each time point ($p<0.05$), and the decreases in them were greater in group A. Studies have manifested that surgery will repress the immune function in the body to different extents, thus probably heightening the risks of perioperative cell metastasis and postoperative incision infection. As such, selecting anesthetic agents is important for relieving immunosuppression and promoting postoperative recovery in patients. Etomidate is an intravenous sedative drug that can calm and hypnotize patients and make them forget and after continuous infusion, there are no massive residues in the patients. Studies have revealed that (20-25), the application of etomidate combined with propofol anesthesia has few effects on cognitive dysfunction in patients undergoing gastric cancer surgery, with a low incidence rate of postoperative adverse reactions, and this study confirms these findings.

In conclusion, etomidate combined with propofol can effectively lower the expression levels of inflammatory factors and has few effects on the immune and cognitive functions in gastric cancer patients.

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