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Original Article

Changes of inflammatory factors in patients after resection of lung adenocarcinoma with propofol and etomidate

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Abstract: Objective: This research was designed to investigate the changes of inflammatory factors in patients after resection of lung adenocarcinoma with propofol versus etomidate. Methods: A total of 104 patients who underwent resection of lung adenocarcinoma in our hospital were divided into a propofol group (group A, n=50) and an etomidate group (group B, n=54). The levels of CRP and IL-6 at different time points and the changes of blood gas indexes at 10 min before and after operation were observed in both groups. Their pain score and quality of life score were compared. Besides, we observed the wake-up time, tracheal extubation time and the incidence of adverse reactions. Results: The anesthesia recovery and tracheal extubation time in group B were shorter than those in group A (P<0.05). After 10-minutes of spontaneous breathing, PaO_2 and SaO_2 in group B were higher than those in group A (P<0.05), and $PaCO_2$ was lower (P<0.05); compared with group A. The incidence of adverse reactions and the levels of inflammatory factors in group B were lower than those in group A after operation (both P<0.05). The quality of life of patients in group B after operation was better than that in group A (P<0.05). There was no marked difference in VAS scores between groups. Conclusion: Etomidate has better anesthetic effect than propofol in lung adenocarcinoma resection, leading to better stabilization of the vital signs of patients and it also has higher safety.

Keywords: Propofol, etomidate, resection of lung adenocarcinoma, inflammatory factors

Introduction

Currently, lung cancer (LC) is the most common type of cancer. It is estimated that there are more than 2 million new cases every year in the world [1]. Lung adenocarcinoma is the main type of non-small cell lung cancer (NSCLC). About 50% of NSCLC is lung adenocarcinoma [2]. Patients with lung adenocarcinoma are often treated with surgery, chemotherapy or radiotherapy, among which surgery is the most important and effective treatment for those with early onset [3, 4]. Nevertheless, surgical treatment for lung adenocarcinoma patients will lead to a high incidence of pain, severe stress response, increased inflammation, decreased immune function and related pulmonary complications [5, 6]. If the patients' inflammation can't be suppressed well during the operation, it may form a cascade effect, resulting in the release of a large number of inflammatory factors, even systemic inflammatory response syndrome and lung injury [7].

Safety of anesthesia is a vital step in surgery, which can be determined by the influences on oxidative stress and inflammation of patients. Therefore, proper anesthesia methods and selection of anesthetic drugs often do not cause serious hemodynamic changes, abdominal pain and inflammation [8-10]. However, research has shown that different anesthesia methods in lung adenocarcinoma surgery will affect the immune function of patients [11]. Rybojad *et al.* [12] showed that immunosuppression can occur in lung cancer surgery, resulting in increased levels of immunosuppressive factor IL-10 and cancer antigens, which may reduce the survival time of patients.

Propofol and etomidate are two kinds of anesthetic drugs with outstanding clinical effects,

with high hemorheological stability and rapid recovery [13]. Propofol has an anti-inflammatory effect, and it has also been found to have anti-tumor effects in a variety of cancers [14]. Freeman *et al.* [15] used propofol to anesthetize mice modeled with breast cancer, and found that it could reduce postoperative lung metastasis. Etomidate also has a certain anti-inflammatory effect. Intravenous anesthesia with etomidate in rats with sepsis showed a marked decrease in serum TNF-α [16]. At the moment, there are only a few related studies on the comparison of the effects and influences of two anesthetics in lung adenocarcinoma resection.

The purpose of this experiment was to compare the application effects of propofol and etomidate in patients undergoing lung adenocarcinoma resection.

Materials and methods

Patient data

This research was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of our hospital. A total of 104 patients undergoing lung adenocarcinoma resection who were admitted to Hunan Provincial People's Hospital from July 2017 to August 2019 were regarded as the research subjects. Among them, 50 were anesthetized with propofol (34 males and 23 females), with an average age of (54.3 ± 6.8) years, while 54 were anesthetized with etomidate (34 males and 23 females), (54.3 ± 6.8) years old on average. All patients were informed about the study and signed an informed consent form.

Inclusion and exclusion criteria

Inclusion criteria were as follows: all patients were diagnosed with lung adenocarcinoma by imaging and pathological examination; the examination criteria were based on the diagnostic guidelines of European Society of Medical Oncology (ESMO) [17] for LC; those who met the indications for resection and were willing to undergo surgery; no new adjuvant treatment was given before operation.

Exclusion criteria were as follows: patients who were allergic to the drugs used in the process; those complicated with other severe inflammation, immunodeficiency diseases, other cardiovascular and cerebrovascular diseases; those with congenital liver and kidney defects.

Reagents and kits

Midazolam (Xuzhou Nhwa Pharmaceutical Group Co., Ltd., batch number: 2011005), sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., batch number: 1150719), rocuronium (Zhejiang Xianju Pharmaceutical Co., Ltd., batch number: 181004.2), propofol (Beijing Fresenius Kabi Pharmaceutical Co., Ltd., batch number: 16IF1533), etomidate (Jiangsu Nhwa Pharmaceutical Group Co., Ltd., batch number: 20141016), remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd., batch number: 614-1201), IL-6 ELISA kit (Abcam, UK, ab178013), CRP ELISA kit (Abcam, UK, ab260058).

Anesthesia methods

Group A received 0.1 mg/kg midazolam + 5 μg/kg sufentanil + 0.8 mg/kg rocuronium + 1 mg/kg propofol for anesthesia induction, while group B was given 0.1 mg/kg midazolam + 5 μg/kg sufentanil + 0.8 mg/kg rocuronium + 0.2 mg/kg etomidate. After muscle relaxation, patients were intubated and mechanically ventilated. The tidal volume was set to 10 mL/kg, and the respiratory rate was about 12 times/min, $PaCO_2$ was kept at about 40 mmHg. Group A received 0.1 mg/kg/min propofol plus 0.05-0.6 μg/kg/min remifentanil for anesthesia maintenance, while group B was given 15 μg/kg/min etomidate plus 0.05-0.6 μg/kg/min remifentanil.

Detection methods

A total of 6 mL venous blood from the elbow was collected from the non-intravenous infusion side before, 6 h, 12 h and 24 h after surgery, and centrifuged at 3,000×g for 10 min to separate the serum. The CRP and IL-6 levels were detected by ELISA. In the kit, 100 μl standard substance was added to the standard well, 100 μl sample was added to the sample well to be tested, and 100 μl biotinylated antibody working solution was added to each coated and incubated well. Afterwards, they were all coated and incubated 1 h at 37°C. After the plate was cleaned and patted dry, 100 μl enzyme conjugate was added into each well, coated and cultivated for 30 min at 37°C. After the plate was washed for 5 times, 90 μl chromogenic reagent was added. Next, it was incubated for 15 min under dark conditions at 37°C. Finally, 50 μl termination solution was added into each well. The optical density of

Table 1. Clinical baseline data table

	Group A (n=50)	Group B (n=54)	X^2/t	P
Gender			1.186	0.276
Man	39 (78.00)	37 (68.52)		
Woman	11 (22.00)	17 (31.48)		
BMI (kg/m^2)	21.35 ± 1.37	21.73 ± 1.53	1.330	0.186
Age (years)	54.3 ± 6.8	55.0 ± 7.4	0.501	0.617
Tumor diameter (cm)	2.8 ± 1.1	2.6 ± 1.0	0.971	0.334
ASA grade			0.641	0.423
I	28 (56.00)	26 (48.15)		
II	22 (44.00)	28 (44.00)		
Operation time (min)	170.42 ± 14.39	166.58 ± 13.92	1.383	0.170
Blood loss (ml)	201.34 ± 18.36	197.31 ± 15.49	1.213	0.228
Pathological typing			1.375	0.503
Adenocarcinoma in situ	9 (18.00)	10 (18.52)		
Microinvasive adenocarcinoma	6 (12.00)	3 (5.55)		
Invasive adenocarcinoma	35 (70.00)	41 (75.93)		
TNM staging			0.760	0.944
I^a	23 (46.00)	22 (40.74)		
I^b	15 (30.00)	19 (35.19)		
II^a	7 (14.00)	6 (11.11)		
II^b	3 (6.00)	4 (7.41)		
III^a	2 (4.00)	3 (5.55)		
Operation modes			0.276	0.871
Lobectomy	33 (66.00)	38 (70.37)		
Segmentectomy	7 (14.00)	6 (11.11)		
Wedge resection of lung	10 (20.00)	10 (18.52)		

each well was determined at a wavelength of 450 nm within 15 min.

Outcome measures

Main outcome measures were as follows: the CRP and IL-6 levels of the two groups were compared before operation, 6 h, 12 h and 24 h after operation; PaO_2, SaO_2 and $PaCO_2$ were measured before operation and after 10-minutes of spontaneous breathing; patients' pain was evaluated by VAS score, their quality of life was evaluated by QLQ-C30 scale; the VAS score and QLQ-C30 scale were compared after operation; the recovery and tracheal extubation time of both groups were observed; the adverse reactions of patients after the operation were recorded.

Statistical methods

Statistical analysis conducted in this research was carried out by SPSS 21.0. The counting data, marked by utilization rate (%), were analyzed through Chi-square test and expressed as X^2. The measurement data were represented by mean ± standard deviation (Means ± SD), and all data conformed to a normal distribution; repeated analysis of variance test was applied for comparison among three or more groups. Bonferroni test was used in back testing and expressed by F. A *P* value of <0.05 was regarded to be statistically remarkable.

Results

Comparison of baseline data between both groups

It was found that there was no marked difference between the two groups in gender, BMI, age, tumor diameter, ASA grade, operation time, blood loss, pathological type, TNM stage and operation mode (**Table 1**).

Comparison of inflammation at different time points

There was no marked difference in CRP and IL-6 levels between the two groups before oper-

Table 2. Inflammation levels of both groups in different time periods

Group	CRP (mg/L)				IL-6 (ng/L)			
	Before surgery	Six hours after surgery	Twelve hours after surgery	Twenty-four hours after surgery	Before surgery	Six hours after surgery	Twelve hours after surgery	Twenty-four hours after surgery
Group A (n=50)	5.50 ± 1.17	9.85 ± 1.82[a]	13.33 ± 2.03[ab]	11.32 ± 1.91[abc]	42.67 ± 5.48	95.42 ± 10.76[a]	158.58 ± 17.71[ab]	132.64 ± 15.48[abc]
Group B (n=54)	5.64 ± 1.24	8.21 ± 1.42[a]	11.04 ± 1.79[ab]	9.74 ± 1.53[abc]	43.84 ± 6.24	82.65 ± 9.94[a]	131.96 ± 28.48[ab]	113.84 ± 13.24[abc]
t value		0.275	9.681	8.476	0.622	11.318	8.540	0.622
P value		0.760	<0.001	<0.001	0.540	<0.001	<0.001	0.540

Note: a indicates marked difference compared with before surgery, b indicates marked difference compared with 6 h after surgery, and c indicates marked difference compared with 24 h after surgery.

ation ($P>0.05$). The levels increased at 6 h and 12 h after operation ($P<0.05$), and gradually rose at 24 h after operation. CRP and IL-6 in Group B were lower than those in Group A at 6 h, 12 h and 24 h after operation ($P<0.05$) (**Table 2**).

Blood gas analysis results of both groups

There was no obvious difference in PaO_2, SaO_2, $PaCO_2$ between both groups before operation ($P>0.05$). PaO_2 and SaO_2 after 10-minutes of spontaneous breathing decreased ($P<0.05$), while $PaCO_2$ increased ($P<0.05$). In the meantime, PaO_2 and SaO_2 in group B were higher than those in group A, while $PaCO_2$ in group B was lower than that in group A ($P<0.05$) (**Figure 1**).

Comparison of pain intensity and quality of life

There was no marked difference in VAS scores between the two groups after operation ($P>0.05$), but the average score of QLQ-C30 scale in group B after operation was higher than that in group A ($P<0.05$) (**Figure 2**).

Comparison of surgical data

By observing the surgical data of the two groups of patients, we found that the recovery and tracheal extubation time of group A were higher than those of group B ($P<0.05$) (**Figure 3**).

Comparison of adverse reactions

Adverse reactions such as confusion, drowsiness, nausea and vomiting and bradycardia occurred in patients after operation, and the total incidence in group A was higher than that in group B ($P<0.05$) (**Table 3**).

Discussion

The target of propofol is GABA receptors in the postsynaptic membrane of the hippocampus in the central nervous system. Etomidate is similar to propofol. Thus, we can selectively enhance GABA receptor activity. With higher cardiovascular stability, patients can quickly recovery after stopping the drug [18].

The main finding of this research is that etomidate can improve the inflammatory response of patients during lung adenocarcinoma resection compared with propofol. As far as we know, this is the first study to discuss the effects of etomidate and propofol on inflammation in patients undergoing lung adenocarcinoma resection. At the same time, the blood gas analysis results of patients were more stable, and their quality of life was high. Hence, the application of etomidate in lung adenocarcinoma resection can enhance the postoperative recovery of patients.

Surgery inevitably leads to inflammation due to tissue damage; patients with high levels of inflammatory factors may have systemic inflammatory response syndrome, which may further develop into sepsis and multiple organ dysfunction [19]. However, the inflammation associated with LC surgery may promote the recurrence of cancer, thus affecting the prognosis of patients, so that the inflammatory state is an independent factor that can directly affect the postoperative results [20, 21]. We also found that CRP and IL-6 in both groups increased at 6 h and 12 h after operation, and then decreased gradually at 24 h, which was due to the release of pro-inflammatory factors caused by the stimulation of operation, and then the body began to adjust gradually. However, the CRP and IL-6 levels of patients treated with etomidate were lower than those of propofol at 6 h, 12 h and 24

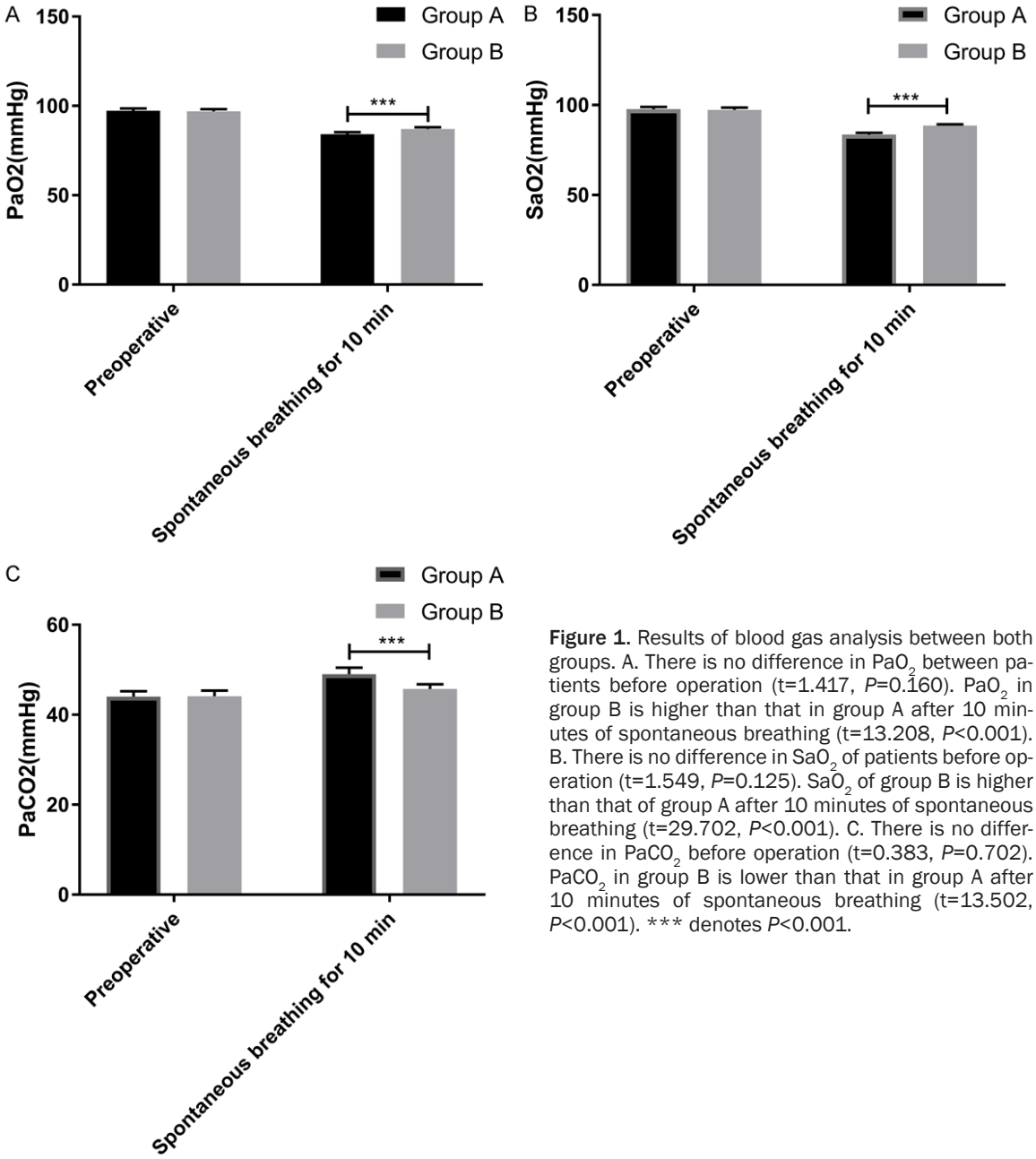

Figure 1. Results of blood gas analysis between both groups. A. There is no difference in PaO_2 between patients before operation (t=1.417, *P*=0.160). PaO_2 in group B is higher than that in group A after 10 minutes of spontaneous breathing (t=13.208, *P*<0.001). B. There is no difference in SaO_2 of patients before operation (t=1.549, *P*=0.125). SaO_2 of group B is higher than that of group A after 10 minutes of spontaneous breathing (t=29.702, *P*<0.001). C. There is no difference in $PaCO_2$ before operation (t=0.383, *P*=0.702). $PaCO_2$ in group B is lower than that in group A after 10 minutes of spontaneous breathing (t=13.502, *P*<0.001). *** denotes *P*<0.001.

h after operation. Inflammatory cytokines are involved in the occurrence of cancer and can promote deterioration, and they become the intermediary between inflammatory immune or non-immune cells and cancer cells. IL-6 and CRP, as pro-inflammatory factors, have also been shown in some studies to be prognostic indicators of lung adenocarcinoma after treatment. Compared with low-level patients, the survival rate of those with high-level IL-6 and CRP is reduced [22, 23].

Operation will affect patients' normal oxygenation [24]. We observed that PaO_2, SaO_2 and $PaCO_2$ in both groups were abnormal after operation, but the abnormal degree in patients using etomidate was less than that of those using propofol, indicating that etomidate had a high effect on improving oxygenation. Propofol can act on vascular smooth muscle or cause sympathetic nerve activity to weaken and cause vasodilation, which leads to hypotension. Etomidate cannot inhibit sympathetic

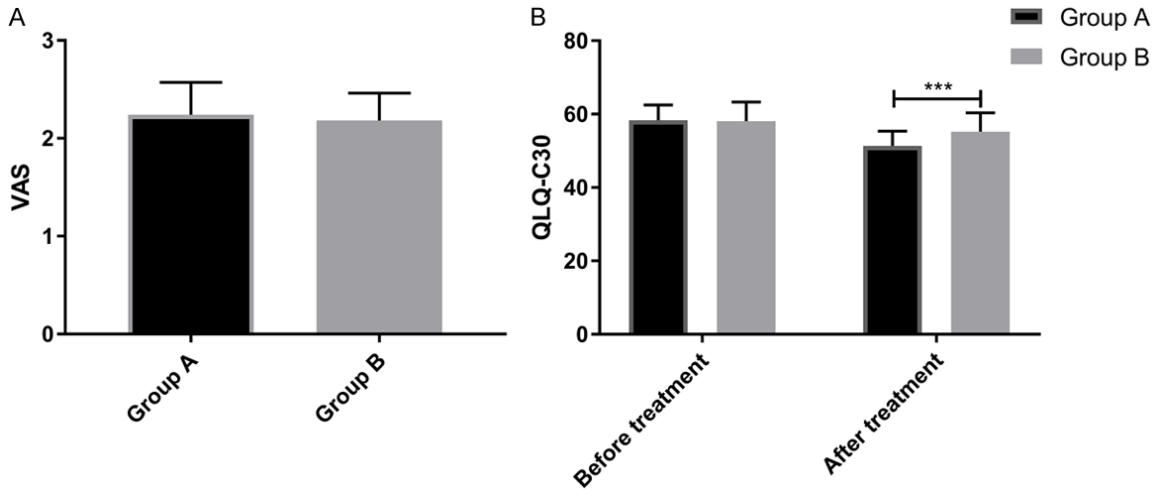

Figure 2. Comparison of pain intensity and quality of life between both groups. A. There is no difference in VAS scores of postoperative patients (t=1.002, *P*=0.319). B. There is no difference in the mean score of QLQ-C30 before operation (t=0.290, *P*=0.773), but the score in group B after operation is higher than that in group A (t=4.252, *P*<0.001). *** denotes *P*<0.001.

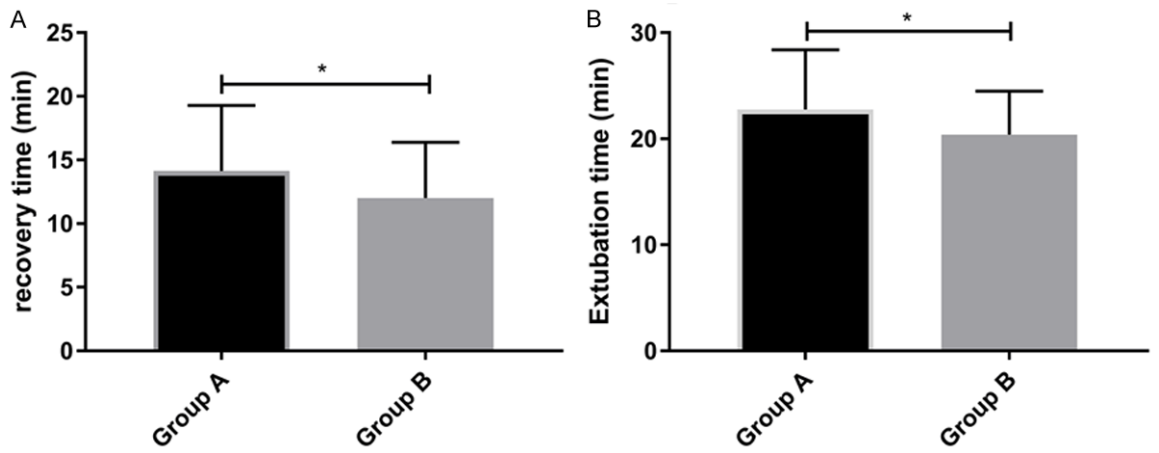

Figure 3. Comparison of surgical data between both groups. A. The recovery time of patients in group A is higher than that in group B (t=2.274, *P*=0.025). B. The time of tracheal extubation in group A is longer than that in group B (t=2.488, *P*=0.015). * denotes *P*<0.05.

Table 3. Adverse reaction table

	Group A (n=50)	Group B (n=54)	X^2	P
Confusion	3 (6.00)	1 (1.85)	4.125	0.042
Drowsiness	2 (4.00)	1 (1.85)		
Nausea and vomiting	4 (8.00)	2 (3.70)		
Bradycardia	3 (6.00)	0 (0.00)		
Total adverse reactions	12 (24.00)	4 (9.26)		

nerve tension and myocardial function, so it has good stability on cardiovascular function and hemodynamics [25, 26]. It has been mentioned that etomidate anesthesia takes effect quickly, and propofol has rapid action with metabolism in the liver, so the anesthesia maintenance time is short [27]. Research has verified that etomidate can provide shorter recovery and tracheal extubation time, but there is no obvious difference between these in VAS comparison. Different anesthesia schemes may produce different adverse reactions, immune and inflammatory outcomes for patients undergoing surgery, which will affect their quality of life [6]. There were 12

cases of adverse reactions in patients treated with propofol and 4 in those treated with etomidate. Meanwhile, patients using etomidate had higher quality of life after operation.

Nevertheless, there are some limitations in this study. Firstly, the impact of postoperative recovery of specific patients and the recurrence and prognosis in about 3-5 years has not been determined. Secondly, the specific mechanism of inflammation, oxygenation and lung-related effects caused by etomidate and propofol is vague; more *in vitro* and animal experiments are needed. Thirdly, the subjects of this research are patients with lung adenocarcinoma, so that further studies are needed for other types of NSCLC and the effects of small cell LC.

To sum up, the anesthetic effect of etomidate in lung adenocarcinoma resection is better than that of propofol. Etomidate can stabilize the vital signs of patients more effectively, with higher safety.

Disclosure of conflict of interest

None.

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