Effects of Propofol and Sevoflurane on Cellular Immune Function and Postoperative Complications in Patients with NSCLC Undergoing Surgery

Haijing Zhu (✉ 826165713@qq.com )
Guangxi Cancer Hospital and Guangxi Medical University Affiliated Cancer Hospital
https://orcid.org/0000-0003-3470-7840

Shenglin Pei
Guangxi Cancer Hospital and Guangxi Medical University Affiliated Cancer Hospital

Menghua Ge
Guangxi Medical University

Hongmeng Lan
Guangxi Medical University

Manyu Fu
Guangxi Medical University

Linghui Pan
Guangxi Cancer Hospital and Guangxi Medical University Affiliated Cancer Hospital

Research Article

Keywords: propofol, sevoflurane, NSCLC, cellular immune function, complication

Posted Date: December 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1180850/v1

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Abstract

Objective

We explore the effects of propofol and sevoflurane on the immunity and postoperative complications of patients undergoing thoracosopic NSCLC radical surgery.

Methods

61 patients were selected. They were divided into two groups. Patients take the same drugs for induction of anesthesia. Propofol was used for maintenance of anesthesia in Group P. Sevoflurane was used for another group. Hemodynamics and related anesthesia doses and laboratory data were recorded during the perioperative period. Immune Function, postoperative complication rate were evaluated in two groups.

Results

Comparisons of MAP and HR under anesthesia in patients, Group P were more smoothly than Group S at OLV 1h and TLV 30min. The recovery time and extubation time were significantly longer in the Group S than Group P. NEU: Group P were significantly lower at T3. LYM : Group P were significantly higher at T1 and T2. CD8+ : Group P were significantly higher at T1, T2 and T3. NK cells were significantly higher in Group P at T3. CD4+/CD8+: Group P were significantly lower at T2 and T3. The incidence of pleural effusion: Group P were significantly higher at T3. The postoperative hospital stays were significantly shorter in the Group S.

Conclusions

Propofol anesthesia has more stable hemodynamics and better resuscitation effect. The immune system of patients in the perioperative period was suppressed to varying degrees after surgery, and the propofol group was less severe than the sevoflurane group. However, the postoperative hospital stay depends more on whether postoperative complications occur.

Preface

Most patients are accompanied by changes in immune function and inflammation during the perioperative period, and most of them are characterized by suppressed immune function and significant inflammation. This result is influenced by many factors, such as the patient's basic preoperative condition, the duration of the operation, the site involved in the operation, the use of perioperative anesthetics, allogeneic blood transfusion, etc. [1]. During the perioperative period, lymphopenia leads to many possible complications in patients, such as sepsis and postoperative lung infections [2]. In patients with malignant tumors, postoperative immune function and inflammatory response imbalance may also
increase the risk of tumor metastasis [3]. Immune function suppression and severe inflammation have a negative impact on the short-term and long-term postoperative results of lung cancer patients [4].

Minimally invasive surgery: Video-assisted thoracoscopic lobectomy plus regional lymphatic dissection is the most preferred option for patients with stage I–IIIA non-small cell lung cancer [5–6]. In the perioperative period of lung cancer patients, it is very important to prevent pulmonary complications, such as pneumonia, pulmonary edema, pleural effusion, etc., ensure oxygenation, and maintain hemodynamic stability (especially during one-lung ventilation). Propofol and sevoflurane are widely used in surgical anesthesia for patients with thoracic lung cancer. Propofol, an ultra-short-acting sedative intravenous anesthetic, has the advantages of high plasma clearance, quick and complete postoperative recovery. Sevoflurane is a high-efficiency, non-flammable anesthetic gas with the advantages of low distribution coefficient and high anesthesia efficiency. The immune function and complication rate of those in perioperative lung cancer patients has not been determined yet. This research focuses on the effects of propofol or sevoflurane on CD3+, CD4+, CD8+, NK cells, B cells, CD4+/CD8+ and the release of cytokines IL-1β and TNF-α in the blood during the perioperative period. To explore the effects of two anesthetics on perioperative liver and kidney function and postoperative pulmonary complications in NSCLC patients.

**Materials And Methods**

This is a randomized, prospective trial. The trial has been approved by the Ethics Committee of the Guangxi Medical University Affiliated Tumor Hospital (license number: KY2018010). This trial has been registered in the Chinese Clinical Trial Registration Center (Registration Number: ChiCTR1800020425), and all patients in the group were signed an informed consent form. The trial began in May 2019 at Guangxi Medical University Affiliated Tumor Hospital and lasted for 6 months. A total of 80 patients with elective lung cancer VATS were enrolled. According to the different anesthetic drugs, all subjects were divided into two groups: those who used propofol for anesthesia maintenance were Group P; those who used sevoflurane were Group S.

We learnt about the basic information and disease conditions of the patients 1 to 2 days before the operation, and screened the proposed patients according to the selection and exclusion criteria. Inclusion criteria: 35-70 years old, no gender limit; BMI 18-30 kg/m2; ASA grade I-III; the patient was clinically diagnosed as primary lung cancer (or pathological evidence) before surgery and planned to undergo thoracic cavity Endoscopic radical resection of lung cancer. Exclusion criteria: patients with ASA grade IV or requiring emergency surgery; recent history of chemotherapy or radiotherapy (≤ 8 weeks), recent history of using steroids or opioids or alcohol or abuse of illegal drugs; severe heart disease, or respiratory disease; secondary cancer or lung metastasis; liver and kidney function impaired before surgery.

Withdrawal criteria: intraoperative change to thoracotomy; intraoperative blood loss greater than 400mL or allogeneic blood transfusion; severe anesthesia accidents and complications; postoperative pathological types suggest non-cancerous nodules or small cell lung cancer, or tumor stage IIIB~IV stage
(refer to AJCC 8th edition lung cancer TNM staging standard); refusal to follow-up; patient refuses to follow-up or requests withdrawal.

The research team has 10 people. Among them, there are 2 people in the project design group, whose main tasks are project design, data search, registration, and supervision. Two people in the evaluation group (both with a professional title of diagnostic imaging or above) work on postoperative chest X-ray and B-ultrasound evaluation. There is 1 person in the data group, whose main work is the collection, sorting and statistical analysis of case data. There are 3 people in the anesthesia group (attendant doctor or above and at least 5 years of clinical work). The main work is to implement anesthesia according to the plan and record relevant data during anesthesia. The experimental group consists of 2 people. The main task is to complete the laboratory lymphocyte subtype detection and cytokine measurement.

Anesthesia plan

The age, gender, BMI, smoking history, ASA classification, lung function, preoperative complications, etc. of all patients were recorded before surgery. The patient appropriately increased the amount of exercise, learnt the correct way of expectoration, etc. to exercise lung function, and fasted for 8 hours before surgery. The patient was injected with penehyclidine 0.01 mg/kg into the contralateral deltoid muscle 30 minutes before anesthesia. After entering the room, the patient opened the right internal jugular vein under local anesthesia, established invasive continuous arterial blood pressure (IBP) in the contralateral radial artery, and monitored the electrocardiogram, pulse oximetry (SPO2), bispectral index (BIS), ventilator parameters, access volume, etc. The patient was given mask oxygen 10 min before induction, and the oxygen flow was 4-6L/min. Both groups were given intravenous injection of midazolam 0.05mg/kg, fentanyl 3µg/kg, and propofol 2mg/kg for induction of anesthesia. When the BIS value is less than 60, give cis-atracurium 0.2mg/kg and assist ventilation with a face mask. After 2 minutes of denitrication and oxygen supply, the anesthesiologist used a video laryngoscope to intubate a double-lumen endotracheal tube, connected the anesthesia machine to mechanical ventilation and adjusted parameters (tidal volume, frequency, oxygen flow, etc.). The same experienced anesthesiologist used bronchoscopy to assist in the alignment of the dual-lumen tube. The P group used propofol 4-6mg/kg/h in the anesthesia maintenance; the S group used sevoflurane 1.5-2.5 MAC value in the anesthesia maintenance. Both groups of patients were treated with constant rate infusion of remifentanil 0.1-0.2µg/kg/min for analgesia, and cis-atracuramide 2µg/kg/min for muscle relaxation. The dosage of propofol and sevoflurane were adjusted according to the BIS value to maintain it between 48±6.

In all cases, mechanical ventilation used lung protective ventilation strategy (LPVS). According to the method of Emmanuel Futier and other researchers, the tidal volume was adjusted to 6ml/kg, the frequency was 12-20 times/min, the PEEP was 5cmH2O, and the oxygen flow was 1 to 2L/min during one-lung ventilation. When the duration of a single lung exceeded 30 minutes, the two lungs were manually drummed once, and the pressure was maintained at 30 cmH2O for 30 seconds [7]. PETCO2 was maintained at 30-40 mmHg, PIP<35cmH2O, and SPO2 was maintained at more than 90%. Manage infusions were accorded to clinical routines. In hypertensive patients, control the systolic blood pressure.
≤160mmHg and diastolic blood pressure ≤90mmHg before operation. During anesthesia, maintain blood pressure within ±20% of the basic value, and heart rate fluctuations at 60-100 bpm.

After the operation, the patient returned to the supine position, added fentanyl 1 to 2 ug/kg, stopped the intravenous infusion of propofol or closed the sevoflurane volatilization tank. After sputum suction, replaced the single-lumen tube and manually expand the lung 1 to 3 times until there was no continuous gas overflow in the closed drainage bottle of the chest cavity. All patients were sent to the ICU for resuscitation. When the patient resumed spontaneous breathing, take off the ventilator and observe, it was regarded as the time to wake up. The patient shaked hands vigorously, lifted the head away from the bed for more than 5 seconds, the swallowing and cough reflexes are restored, the blood gas analysis results excluded the possibility of acute respiratory failure (PaO2>50mmHg and PaCO2<50mmHg), fully suction sputum in the trachea, and sucked out oral secretions. Pre-extubation of the tracheal tube was regarded as the time of extubation.

Blood sample collection and content determination

Blood samples were collected immediately after each patient entered the operating room (T0). T1, T2, and T3 collect two tubes of peripheral venous blood with 2ml, and placed them in the tubes containing heparin and EDTA-K2 anticoagulant. The former used flow cytometry (FCM) to analyze lymphocyte subsets within 24 hours at room temperature. The latter was collected and stored at 4°C, and centrifuged horizontally (3000r/min, 10min, 4°C) within 4h, the plasma was separated and stored in a -80°C refrigerator. The plasma will measure the cytokines IL-1β and TNF-α.

The plasma levels of IL-1β and TNF-α were measured by enzyme-linked immunosorbent assay (ELISA) using a kit (CUSABIO, China), and the average of the two measurements was taken as the final concentration.

We use an extracorporeal flow cytometer to analyze the lymphocyte subsets in the blood. FMC is a technology that can simultaneously detect and analyze multiple physical and biological properties of a single particle, and quantify it, at the same time, it can sort specific groups.

In the clinical test data of patients, T0, immediately after surgery (Ta), T1, T2, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and endogenous creatinine clearance (Ccr) would be recorded. When the observed index was greater than the upper limit of normal for two or more consecutive times, the function was considered impaired. Record the chest X-ray and body temperature at T3 to evaluate the patient's pulmonary complications. Evaluated the incidence of pulmonary complications were based on clinical characteristics, such as pulmonary infection (axillary temperature ≥38°C, white blood cell count>11.0×10⁹/L or <4.0×10⁹/L, sputum is purulent secretion or clear microorganisms Evidence of medical infection, and abnormal shadows of lungs were confirmed by radiology); pleural effusion (drainage bottle drainage is greater than 300ml/day or B-ultrasound shows pleural fluid volume is greater than 300ml or chest X-ray shows blunt costophrenic angle), etc. All images
were jointly read and recorded by two attending physicians engaged in imaging diagnosis, including lung inflammation, pleural effusion, and pneumothorax.

Statistical analysis

The SPSS 25.0 software package was used for data analysis. Two independent sample t-test analysis (for example: age, BMI, etc.) were used for comparison between groups of data conforming to normal distribution; measurement data were expressed as mean ± standard deviation (x ± s). Grade data were compared using chi-square test analysis (for example: gender, bleeding volume, etc.), and less than 5 cases were analyzed by Fisher's exact probability method (for example: incidence of hypertension, pneumonia, etc.). Repeated measurement data (for example: NK cell, B cell change trend) used repeated measurement analysis of variance. A p-value of less than 0.05 was considered a statistically significant difference. Prism 8 (GraphPad Software, Inc., San Diego, CA, USA) was used for graph analysis.

Results

80 patients were enrolled in this study, none of them had serious anesthesia complications such as intraoperative awareness, severe intraoperative hypoxemia, severe postoperative nausea and vomiting, etc. A patient had an intraoperative bleeding of 700ml and received a postoperative allogeneic blood transfusion; 8 patients postoperative pathology showed non-cancerous nodules; 2 patients postoperative pathology showed small cell lung cancer; 2 patients postoperative pathological staging showed NSCLC IV stage; 3 patients lacked postoperative chest imaging data; 2 patients actively asked to withdraw from the study; 1 patient was transferred to hospital for severe fungal pneumonia after surgery. Excluding the above 19 patients, 61 patients were enrolled in this study, including 30 in Group P and 31 in Group S (Figure 1).

There was no statistically significant comparison of the general data of two groups before surgery (p>0.05) (Table 1)

Table1 General condition of the patient before surgery(n=61)
| Item                                | Group P (n=30) | Group S (n=31) | Credibility interval (p < 0.05) |
|-------------------------------------|----------------|----------------|-------------------------------|
| Age (years)                         | 55.23±7.01     | 55.48±8.52     | 0.90                          |
| Sex (male/female)                   | 15/15          | 18/13          | 0.53                          |
| BMI                                 | 22.72±2.64     | 22.79±2.86     | 0.92                          |
| ASA I/II                            | 7/23           | 8/23           | 0.82                          |
| Smoking history (>10 years/none)    | 10/20          | 10/21          | 0.93                          |
| Pulmonary lobule (L/R)              | 11/19          | 14/17          | 0.80                          |
| FEV1 (L)                            | 2.21±0.56      | 2.19±0.47      | 0.83                          |
| FEV1/FVC (%)                        | 81.90±5.71     | 82.74±7.53     | 0.63                          |
| Hypertension                        | 4(13%)         | 3(10%)         | 1.00                          |
| Diabetes                            | 2(7%)          | 2(6%)          | 1.00                          |
| ALB (g/L)                           | 38.59±1.85     | 39.09±2.15     | 0.33                          |

Comparing the two groups of patients, the recovery time and extubation time of the Group P were significantly shorter than Group S (p < 0.05); the postoperative hospital stay in the Group P was significantly longer than Group S (p < 0.05). There was no statistically significant difference between the remaining item groups (p > 0.05) (Table 2).

Table 2 General condition of patients during operation and after operation (n=61)
| Item                                | Group P n=30 | Group S n=31 | Credibility interval | p \( <0.05 \) |
|-------------------------------------|--------------|--------------|---------------------|---------------|
| Duration of anesthesia min          | 220.01±40.47 | 207.74±32.01 | 0.19                |               |
| Duration of operation min           | 184.33±40.36 | 172.90±33.78 | 0.24                |               |
| Duration of OLV min                 | 158.17±39.69 | 148.23±33.43 | 0.29                |               |
| Propofol dosage mg                  | 94.41±13.21  | 94.72±12.67  | 0.30                |               |
| Maintenance medication mg           |              |              |                     |               |
| Remifentanil                        | 1.49±0.47    | 1.33±0.42    | 0.19                |               |
| Cisatracurium                       | 28.67±7.98   | 26.13±4.42   | 0.13                |               |
| OLV 1h PIP cm H2O                   | 22.81±2.93   | 22.62±3.33   | 0.78                |               |
| OLV 1h PaO2 mm Hg                   | 98.07±2.54   | 98.82±0.91   | 0.13                |               |
| OLV 1h BIS                          | 45.95±5.21   | 47.23±5.04   | 0.14                |               |
| Input-output ml                     |              |              |                     |               |
| Infusion volume                     | 1345.01±159.93 | 1387.10±155.44 | 0.30               |               |
| Bleeding volume 50/≤50%             | 9/21         | 7/24         | 0.51                |               |
| Urine volume                        | 278.33±152.39 | 267.74±122.85 | 0.77               |               |
| Duration of recovery min            | 67.13±39.53  | 86.29±29.69  | 0.03 \(^a\)         |               |
| Duration of cupping min             | 113.83±52.09 | 142.74±41.43 | 0.01 \(^a\)         |               |
| Duration of postoperative hospital stay d | 9.53±2.30   | 8.29±1.35    | 0.01 \(^a\)         |               |
| Pathological stage II/II,III        | 22/8         | 20/11        | 0.58                |               |
| Maximum tumor diameter cm           | 2.41±1.19    | 2.53±1.37    | 0.26                |               |
| Invasive adenocarcinoma yes/no      | 19/11        | 20/11        | 0.92                |               |

Hemodynamic effects: There were no patients with malignant arrhythmia and severe hypotension or hypertension during the operation in this study. MAP change results: comparing OLV 1h and TLV 30min between groups, Group P was significantly higher than Group S (p<0.01); comparison within groups: There was a statistically significant difference between T0 and skin incision, OLV 30min, and OLV 1h in Group P (p<0.01). There was a statistically significant difference between T0 and skin incision, OLV 30min, OLV 1h, and TLV 30min in Group S (p<0.01)(Figure 2). HR change results: In the comparison between groups: at the time of OLV 1h and TLV 30min, Group P was significantly lower than Group S (p<0.01); comparison within groups: There was a statistically significant difference between T0 and
intubation, skin incision, and OLV 1h in Group P (p<0.05); There was a statistically significant difference between T0 and the time of skin incision in Group S (p<0.05) (Figure 3).

Cellular immune function: NEU change results: comparison between groups: Group P was significantly lower than Group S at T3 (p<0.01); comparison within groups: compared with T0, NEU in both groups at T1~T3 was significantly increased (p<0.01)(Figure 4). LYM change results: comparison between groups: T1, T2, Group P was significantly higher than Group S, (p<0.05); comparison within groups: LMY at T1, T2 was significantly lower than T0 (p<0.01), the two groups recovered to the preoperative level at T3 (Figure 5).

CD3⁺ change results: There was no significant statistical difference between the groups; within the group comparison: at T1 and T2, in the both groups it was significantly lower than T0 (p<0.01), and at T3 it was restored to the preoperative level. CD4⁺ change results: There was no significant statistical difference between the groups; within the group comparison: at T1 in the both groups CD4⁺ were significantly lower than T0 (p<0.01), and at T3 it was restored to the preoperative level. CD8⁺ change results: comparison between groups: at T1, T2, and T3, in Group P it were significantly higher than Group S (p<0.05); intra-group comparison: no significant difference in group P; comparison between at T2, T3 and T0 in Group S it was significantly reduced (p<0.05). NK cell change results: comparison between groups, Group P's NK cell was significantly higher than Group S at T3 (p<0.05); intra-group comparison: in Group P, it was significantly higher at T1 then T0, T3 was significantly lower than T0 (p<0.01); T1 in Group S was significantly higher than T0, T3 which was significantly lower than T0 (p<0.01). B cell change results: There was no significant statistical difference between groups; comparison within groups: T1, T2, and T3 in both grops all increased significantly compared with T0 (p<0.05).

The results of the above lymphocyte subtype changes are shown in Table 3.

CD4⁺/CD8⁺ change: comparison between groups: group P was significantly lower than group S at T2 and T3 (p<0.01); comparison within groups: group P was significantly lower at T1 than at T0 (p<0.05); The S group was significantly higher at T2 and T3 than at T0(p<0.05) (Figure 6).

Among the 61 patients included in this study, 42 of NSCLC were in stage I, and 19 were in stage II and III. Observation of stage I patients after intervention with different anesthetic drugs (the number of patients in stage II and III is small and will not be analyzed temporarily). Analyze the cellular immune function of patients in stage I in propofol (Group P I stage) or sevoflurane (Group S I stage) after anesthesia (Table 4).

CD3⁺ change results: There is no significant statistical difference between the groups; comparison within the groups: PI stage group and SI stage group are significantly lower than T0 at T1 and T2 (p<0.01), and return to preoperative at T3 Level. CD8⁺ change results: comparison between groups: the PI phase group was significantly higher than the SI phase group at T1, T2 and T3 (p<0.05); within the group comparison: no significant difference was seen in the PI phase group; The SI stage group was significantly lower at T2
and T3 than T0 (p<0.05); the SI stage group showed a downward trend at T1, T2, and T3 (Figure 7).

Results of NK cell changes: There was no significant statistical difference between groups; comparison within groups: The PI stage group was significantly higher at T1 than at T0, T3 was significantly lower than T0 (p<0.01); T1 in the SI stage group was significantly higher than T0, and T3 was significantly lower than T0 (p<0.01); The percentages of the two groups at T2 and T3 showed a downward trend (Figure 8). Results of B cell changes: There was no significant statistical difference between groups; within-group comparison: T1, T2, and T3 time points of PI phase group and SI phase group were significantly increased compared with T0 (p<0.05); The percentages of the two groups of T1, T2, and T3 all showed an upward trend (Figure 9).

| Group P | Group S | Group P | Group S | Group P | Group S | Group P | Group S | Group P | Group S |
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| T0      | 68.0±6.88 | 65.49±9.46 | 36.67±6.03 | 39.56±7.04 | 22.29±6.56 | 21.06±5.17 | 12.68±4.06 | 12.12±3.92 | 14.73±4.26 | 15.35±5.13 |
| T1      | 56.82±8.39 | 55.71±11.29 | 27.02±6.72 | 29.02±8.97 | 21.73±6.34 | 17.57±7.87 | 17.62±4.09 | 15.78±5.27 | 16.14±4.55 | 17.15±4.69 |
| T2      | 59.95±7.07 | 59.85±8.12 | 34.07±6.55 | 35.73±7.98 | 19.78±5.82 | 15.74±6.57 | 13.67±4.79 | 12.63±5.41 | 18.88±5.52 | 18.31±3.40 |
| T3      | 63.79±8.08 | 67.22±9.12 | 38.49±7.41 | 40.93±10.99 | 21.17±7.59 | 16.53±5.57 | 8.99±3.34 | 6.99±3.06 | 20.63±6.01 | 20.79±6.33 |

Note: The difference between the groups was statistically significant, *p<0.05

| Group P | Group S | Group P | Group S | Group P | Group S | Group P | Group S | Group P | Group S |
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| T0      | 67.55±5.21 | 66.64±8.22 | 37.52±6.44 | 39.18±6.92 | 22.62±7.01 | 20.11±4.34 | 13.22±4.36 | 12.16±3.94 | 14.93±4.03 | 15.46±3.79 |
| T1      | 55.97±6.67 | 55.32±10.79 | 26.52±6.35 | 28.16±9.74 | 22.05±6.58 | 17.85±6.53 | 18.56±4.97 | 16.31±5.55 | 16.23±4.64 | 16.77±5.07 |
| T2      | 59.22±6.42 | 60.17±7.36 | 34.63±6.79 | 36.85±7.37 | 20.49±4.95 | 17.19±4.52 | 13.77±4.02 | 12.96±4.93 | 18.79±5.26 | 19.05±4.46 |
| T3      | 63.53±8.34 | 66.39±8.57 | 39.46±8.04 | 44.39±10.14 | 21.86±8.39 | 16.62±5.27 | 9.02±3.58 | 7.38±3.38 | 20.29±6.43 | 20.06±4.30 |

Note: The difference between the groups was statistically significant, *p<0.05

Effect of cytokine secretion: TNF-α change results: comparison between groups, T2 and T3, the increase in group S was more significant than that in group P (p<0.05); comparison within groups: comparison between group P and group S before operation, all time points were significant Increase (p<0.01) (Figure 10). IL-1β change results: Compared between groups, there was no significant difference between group P and group S at each time point, (p>0.05); comparison within groups, comparison between group P and group S before operation, all time points were significant Increase (p<0.05) (Figure 11).

Changes in liver and kidney function and the incidence of pulmonary complications after surgery: In this study, one patient developed iatrogenic severe fungal pneumonia on the second day after surgery. After treatment, it was deemed that our hospital did not have the treatment conditions such as extracorporeal artificial membrane lung. The patient was transferred to another hospital for continued treatment. This case was withdrawn from the study. None of the remaining patients had any serious complications such as liver and kidney failure, severe pneumonia.
The creatinine value of S group patients at T1 was significantly higher than that of P group, but the high value was still in the physiological range. There were 8 patients in the P group and 8 patients in the S group with AST > 40U/L at T1. The 16 patients (26%) returned to normal after the AST at T2 (Table 5). Preoperative chest CT of the two groups of patients showed local lesions, and the remaining lung lobes and trachea and bronchi were not abnormal. The lung conditions of the two groups of patients were observed on the 7th day after surgery. There was no significant difference in the incidence of fever, pneumonia on the affected side, pneumothorax on the affected side and other pulmonary complications (p > 0.05). Some (11.5%) patients on the affected lung inflammation can last for 7 days or even longer. The incidence of pleural effusion in the affected lung in the P group was significantly higher than that in the S group (p < 0.05) (Table 6).

| Item                  | Group P (n=30) | Group S (n=31) | p        |
|-----------------------|----------------|----------------|----------|
| Fever ≥ 38°C          | 14/43%         | 13/42%         | 0.80     |
| Pneumonia             | 3/10%          | 4/13%          | 1.00     |
| Hydrothorax           | 28/93%         | 22/71%         | 0.04     |
| Pneumothorax          | 18/60%         | 16/52%         | 0.61     |

Note: The difference between the groups was statistically significant. a, p < 0.05. *Ta was for the end of the operation.

Discussion

In our study, the surgical procedures of all patients were completed by the same group of thoracic surgeons, reducing the influence of surgical-related factors. There were no statistically significant differences in the length of operation, cumulative time of one-lung ventilation, and intraoperative blood loss between the two groups (Table 2). In addition, we also excluded patients with small cell lung cancer and stage IV NSCLC, patients with intraoperative bleeding greater than 400ml or allogeneic blood transfusion. Many studies have shown that perioperative infusion of allogeneic blood severely inhibits the immune function of patients [8–10]. During the induction of anesthesia, in order to protect the air
quality in the operating room, referring to the induction method of Elisena De Conn et al., the two groups of patients were sedated with propofol, and the difference in the induction dose was not statistically significant (Table 2) [11]. BIS monitoring is always used during anesthesia to reduce the incidence of intraoperative awareness. All patients were transferred to ICU for resuscitation after operation, and were sent to the thoracic surgery intensive care unit after awake extubation observation. In this experimental anesthesia, there were no cases of intraoperative awareness, malignant arrhythmia, severe hypotension or hypertension, and refractory hypoxemia. There were no deaths during the second operation or hospitalization within 2 weeks after surgery. This experimental plan is feasible reliable.

**Effects of two anesthetics on hemodynamics during perioperative period**

The operation position of the patients in this study was the folding knife position on the contralateral side. Most of the operation time is one-lung ventilation, Maintaining stable hemodynamics is more conducive for patients to tolerate the stress response caused by surgery. Propofol is an ultra-short-acting sedative intravenous anesthetic, which takes effect within 10 seconds of a head-to-arm circulation. It has the advantages of high plasma clearance, quick and complete recovery after surgery. In this study, the MAP and HR of the P group were more stable than those of the S group, and the recovery time and extubation time were shorter than those of the S group. The results were similar to those of Braz MG et al. Compared with sevoflurane, propofol can maintain a more stable anesthesia and improve the quality of recovery [12].

**Effects of two anesthetics on patients' immune function during perioperative period**

The immune system plays an important role in the body's defense function. It can be divided into cellular immunity, humoral immunity, and cytokine secretion. The three regulate and influence each other in a complete body, with cellular immunity as the mainstay. NSCLC patients cause a strong stress response during the perioperative period, which reduces the secretion of cytokines and weakens the cellular immune function through the neuroendocrine pathway, which affects the dynamic balance of the body's environment, thereby affecting postoperative recovery [13]. In the case of low immune function or continuous suppression, the body's defense against invasion by bacteria, viruses, fungi, etc., decreases. For NSCLC patients, immune suppression can even promote tumor recurrence and metastasis [14]. Many studies have shown that the preoperative immune function of NSCLC patients is lower than that of normal people, the tolerance of surgery and anesthesia is poor, and most anesthetics have a suppressive effect on the immune function [15]. Our randomized controlled trial showed that the two groups of patients undergoing thoracoscopic radical NSCLC surgery under general anesthesia had a significant decrease in LYM at T1 and a significant increase in NEU. The secretion of pro-inflammatory factors IL-1β and TNF-α at T1 was significantly higher than that at T0. Both groups of patients had different degrees of immunosuppression and inflammatory reactions after surgery. In this study, the LYM levels of the two groups of patients at T3 basically recovered to the preoperative level. NEU, IL-1β and TNF-α decreased compared with T1 time point, but still did not decrease to the preoperative secretion level. The patient's body still has inflammation, which may be related to surgical trauma, anesthetics, etc. [16–17]
Propofol can increase the expression of CD28 on CD4+, thereby enhancing the activation of T helper cells. However, there is no evidence that propofol has a direct effect on T cells [18]. Kushida et al. found that injection of propofol in mice can enhance the activity of cytotoxic T cells (CTL) and significantly inhibit tumor growth, which indicates that propofol may be beneficial to the anti-tumor immunity of mice [19]. Ren et al. proved that propofol stimulated the perioperative anti-tumor and anti-infection immunity of patients with NSCLC lobectomy, and promoted the activation and differentiation of peripheral CD4+ [20]. Loop et al. reported that isoflurane and sevoflurane induce T lymphocyte apoptosis and affect immune regulation by increasing the activation of caspase-3 and increasing the permeability of mitochondrial membranes [21]. Although many studies have shown that propofol has potential benefits over volatile drugs in cancer surgery, the study by Lim JA et al. indicated that during anesthesia, NK and CTL cell counts, including breast cancer cells, and cancer cells in terms of apoptosis rate, propofol is not superior to sevoflurane [22]. There are many studies on propofol and sevoflurane on postoperative cellular immune function, but the exact results are still inconclusive.

Many studies have shown that CD8+ infiltrated in tumors plays an important role in anti-tumor immune response. The infiltration of CD8+ high-expressing T cells in tumors helps to improve the clinical outcome of cancers including NSCLC [23–24]. NK cells constitute the first line of defense against microbial infections and cancer development. They can quickly kill tumor cells and control cancer development through perforin and granzyme and/or link death receptor-mediated pathways [25–28]. In this study, the perioperative cellular immunity related indexes LYM T1 and T2 in Group P were significantly higher than Group S. CD8+ and NK cells were significantly higher in Group P at T3 than in Group S; CD4+/CD8+ in Group P was significantly lower than Group S at T2 and T3. Patients in Group P can activate the immune regulatory system earlier, and its effect is more pronounced in patients with stage I NSCLC. Propofol may increase the long-term prognosis such as anti-tumor recurrence and metastasis.

During the perioperative period, NK cells T2 and T3 showed a downward trend. Although the role of NK cells in the control of primary tumors in metastatic immune monitoring is still controversial, a large number of circulating NK cells or tumor infiltrating NK cells are associated with gastrointestinal stromal tumors, gastric cancer, colorectal cancer, kidney cancer, and The metastasis of prostate cancer patients is negatively correlated, which has been confirmed in clinical manifestations. Similarly, in cancer patients with metastatic disease or risk of metastasis, the high expression level of NK cell activation receptors or the improvement of NK cell toxicity are associated with a good prognosis [29]. Conditions such as mechanical squeeze and increased permeability of blood vessels during surgery give tumor cells or tissues the opportunity to enter the circulatory system. The body’s NK cells are reduced, and tumor cells are monitored during the perioperative period. This may be one of the risk factors for perioperative tumor metastasis. As time increases during the perioperative period, the percentage of B cells is on the rise. After B lymphocytes are stimulated by antigens, they can proliferate and differentiate into plasma cells to synthesize antibodies and play the role of humoral immunity. It is an important sign of inflammation. Research by Takahashi R et al. showed that IL-35 secreted by regulatory B cells promotes pancreatic tumors in KC-IL1β mice by inducing B cells expressing PD-L1 (inhibiting CD8+ activity). In promoting the
progression of aggressive malignant tumors, B cell-mediated inflammation may play an important role [30]. Studies with regulatory phenotype B cells (Bregs) have shown that Breg infiltration can promote tumor progression [31–32]. Whether B-cell-mediated inflammation plays a role in accelerating the progression of lung cancer and other cancers requires detailed B-cell subtype specific analysis and large-scale prospective clinical trials.

IL-1β is an inflammatory factor, which is widely involved in various pathological injuries such as destruction of human tissue cells and edema. IL-1β can activate macrophages and neutrophils through IL-1R signal to make them proliferate and activate, and promote inflammation [33]. In this study, there was no significant difference in IL-1β between the two groups of patients during the perioperative period, and it cannot be ruled out that it is related to the small sample size. TNF-α is a type of tumor necrosis factor, which is mainly produced by activated macrophages, NK cells and T lymphocytes. It can directly participate in the damage and apoptosis of lung tissue cells, and it can also accelerate downstream monocyte neutrophils. The speed of cell recruitment will ultimately promote the occurrence and development of infection [34–35]. Studies have shown that propofol can inhibit the inflammatory response of the central nervous system caused by the Hif-1α/VEGF/VEGFR-2/ERK signaling pathway activated by TNF-α[36]. Compared with group S, TNF-α was reduced at T2 in group P, and the absolute number of neutrophils was decreased compared with group S. Propofol may reduce the secretion of TNF-α, reduce the degree of neutrophil recruitment and reduce inflammation.

The influence of two anesthetics on postoperative complications

After postoperative liver function is impaired, the peak of AST appears within 6 hours to 3 days after surgery. There were 8 cases in group P and 8 cases in group S with AST>40U/L at T1. The 16 patients (26%) returned to normal after reexamination at T2. The creatinine value at T1 in group S was significantly higher than that in group P, but the value was still within the physiological range. Two anesthetics, propofol and sevoflurane, have little effect on liver and kidney function, and can be safely used for patients with normal liver and kidney function before surgery. Some clinical studies have explored the regulatory effects of sevoflurane and propofol on lung inflammation during OLV. The results of Potočnik et al. showed that sevoflurane suppressed the local alveolar inflammatory response in patients receiving OLV, and reduced the release of inflammatory mediators such as IL-6, resulting in better clinical results in thoracic surgery [37]. A recent meta-analysis by Sun et al. also showed that inhaled anesthetics may be superior to propofol in thoracic anesthesia OLV. The levels of TNF-α, IL-6 and IL-8 in the inhalation anesthesia group were lower, the total number of pulmonary complications in this group was less and the patient's hospital stay was significantly shortened [38]. In this study, the incidence of lung inflammation was 10% in P group and 13% in S group 7 days after operation. The P value was greater than 0.05, and there was no statistical difference.

The secretion and absorption of fluid in the pleural cavity are in a state of dynamic balance. When this dynamic balance is broken, excessive pleural fluid will be produced and pleural effusion will be formed. Surgical wounds of patients with lung cancer are classified as Type II incisions. The production of pleural
effusion provides a natural "petri dish" for pathogens and increases the chance of infection. Thoracic drainage tubes are routinely indwelled after lung cancer surgery. Patients with a large number of pleural effusions will delay the removal of chest tubes or risk re-puncture and drainage. Postoperative chest tube removal is delayed, pain and pleural friction will affect the patient's recovery of respiratory function and getting out of bed. The inhalation anesthetic sevoflurane has been shown to reduce lung permeability by up-regulating connexin after ischemia-reperfusion. Research by Huang et al. showed that sevoflurane prevents LPS-induced rupture of the HMVEC-L monolayer by inhibiting RhoA/ROCK-mediated VE-cadherin signaling pathway, thereby reducing the permeability of lung tissue and reducing pleural effusion[39 ]. In this study, the incidence of pleural effusion on the affected side at T3 in group S was lower than that in group P. The use of sevoflurane can reduce the incidence of pleural effusion on the affected side, which may be related to the mechanism of sevoflurane to reduce lung tissue permeability and reduce exudation. The prolonged hospital stay of patients in group P may be related to the higher incidence of pleural effusion. This conclusion needs to be verified by a larger case study.

There are still some limitations in our research. First of all, we lack the most powerful imaging evidence for postoperative chest complications—chest CT. Considering factors such as cost and repeated high-dose radiation in a short period of time, we chose chest X-rays for observation. Secondly, the relatively short follow-up time limits our observation of long-term complications and even tumor recurrence and metastasis caused by the immune effects of propofol and sevoflurane on NSCLC patients. Finally, our study may have insufficient diagnostic evidence for postoperative complications in NSCLC patients. We did not use the guidelines for hospital-acquired pneumonia/ventilator-associated pneumonia issued by the Chinese Society of Respiratory Diseases in 2018 for evaluation [40]; we did not detect biomarkers that are strongly related to pulmonary complications. Our next goal is to conduct further large-scale, long-term trials to evaluate the effects of propofol and sevoflurane anesthesia on the long-term prognosis of NSCLC patients.

**Conclusion**

During anesthesia, the hemodynamics of propofol is more stable, and the anesthesia resuscitation is better than sevoflurane anesthesia. The immune system of patients in the perioperative period was suppressed to varying degrees after surgery, and the propofol group was less severe than the sevoflurane group. However, the postoperative hospital stay depends more on whether postoperative complications occur.

**Declarations**

Ethics approval: This study has been approved by the Ethics Committee of Guangxi Medical University Affiliated Tumor Hospital (NO. KY2018010).

Data Availability: The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Conflicts of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments: We thank all the patients for taking part into the study. Our team is grateful to Professor Linghui Pan for his design and guidance of this study. This study was supported by grants from the Guangxi Medical and Health Appropriate Technology Development and Application Project in 2019 (NO. S2019043).

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Figures

(1) 35-70 years old, no gender limit;
(2) BMI 18-30 kg/m²;
(3) ASA grade I-III;
(4) the patient was clinically diagnosed as primary lung cancer (or pathological evidence) before surgery;
(5) planned to undergo thoracic cavity Endoscopic radical resection of lung cancer.

8 patients postoperative pathology showed non-cancerous nodules;
2 patients postoperative pathology showed small cell lung cancer;
2 patients postoperative pathological staging showed that NSCLC stage IV;
1 patient had an intraoperative bleeding of 700ml and received a postoperative allogeneic blood transfusion;

3 patients lacked postoperative chest imaging data;
2 patients actively asked to withdraw from the study;

Patient analysis
(n=61)

P group
(n=30)

S group
(n=31)

We have recorded the patient's general condition before surgery, intraoperative surgical anesthesia related indicators, postoperative visits and laboratory data.

Figure 1

Flow chart
Figure 2

Changes of MAP in patients during anesthesia

Figure 2

Changes of MAP in patients during anesthesia
Figure 3

Changes of HR in patients during anesthesia

Figure 4

Changes of NEU in patients during perioperative period
Figure 5
Changes of LYM in patients during perioperative period

Figure 6
Changes of CD4+/CD8+ in patients during perioperative period

Figure 7
The trend of CD8+ cell in the patients of stage I during perioperative period
Figure 8
The trend of NK cell in the patients of stage I during perioperative period

Figure 9
The trend of B cell in the patients of stage I during perioperative period
Figure 10

Changes of TNF-α in patients during perioperative period

Figure 11

Changes of IL-1β in patients during perioperative period
Figure 12

The above 4 pictures were all chest X-ray imaging data on the 7th day after the operation.

Note: A (left lung) picture of the patient is assessed as having no pleural effusion on the affected side, B (left lung) and C (right lung) pictures show a small amount of pleural effusion on the affected side, and D (left lung) picture shows a moderate amount of pleural effusion.