Research Theme: The Impact of Tosylate Remimazolam on Oxygenation and Postoperative Cognitive Function in Elderly Patients Undergoing Thoracoscopic Lobectomy

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Test name	The Impact of Tosylate Remimazolam on Oxygenation and Postoperative Cognitive Function in Elderly Patients Undergoing Thoracoscopic Lobectomy
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I. Research Background

According to the cancer statistics report released by the American Cancer Society in 2024, about one in five people will develop cancer in their lifetime, and about one in nine men and one in twelve women will die from cancer. Lung cancer is the most common cancer worldwide (accounting for 12.4% of all new cases), and it is also the leading cause of cancer deaths (accounting for 18.7% of all cancer deaths), almost twice the second leading cause of cancer deaths. At present, the main treatment for early-stage lung cancer is surgical treatment. Early surgical treatment can reduce the recurrence and metastasis of tumors and improve the survival rate of patients.

Video-assisted thoracic surgery (VATS) has the advantages of small operation wound, quick postoperative recovery and few complications. Currently, it has gradually replaced the traditional thoracotomy. VATS usually requires one-lung ventilation (OLV) on the non -surgical side of the lung using a double-lumen bronchial catheter. One-lung ventilation refers to a ventilation technique that separates the two ventilation pathways at the level of the tracheal carina, with the aim of causing the surgical side of the lung lobe to collapse and protecting the non-surgical side of the lung lobe from contamination. At the same time, it is more conducive to the exposure of the surgical field and reduces the incidence of surgical complications During one-lung ventilation, various pathophysiological changes may occur due to mechanical injury, lung collapse, imbalance of the ventilator-blood flow ratio in the lungs, ischemia-reperfusion, etc., leading to the release of a large amount of inflammatory factors, local and systemic inflammatory responses, affecting perioperative oxygenation, and causing hypoxemia or even lung injury. During the OLV process, although the collapsed lung is not ventilated, blood still flows through it. This can lead to an imbalance in the Ventilation/perfusion ratio (V /Q), resulting in an increase in intrapulmonary shunt and a decrease in oxygenation, which in turn causes hypoxemia. Secondly, thoracic surgeries are generally performed in a lateral position. Due to the influence of gravity, the distribution of ventilation and blood flow in patients is uneven, with the maximum shunt volume reaching 40-50%. Finally also causes longitudinal partition by gravity, the heart to move to the contralateral lung, make limited ventilation side lung ventilation, airway will also appear, blood flow ratio, leads to increase in patients with pulmonary shunt.

Hypoxicpulmonary vasoconstriction (HPV) is a unique adaptive mechanism of the pulmonary circulation, which can promote the flow of blood from hypoxic alveolar areas to well-ventilated alveolar areas, thereby improving V/Q dysregulation. When the partial pressure of oxygen in the alveoli decreases, it can trigger HPV, causing the small arteries before the capillaries in the hypoxic area of the lungs to contract, increasing vascular resistance and reducing blood flow. As a result, more blood flows to the well-

ventilated alveolar area, thereby reducing the shunt within the lungs. Many factors such as anesthetic drugs, acid-base imbalance, temperature, vasodilators and pulmonary operations may all affect the HPV mechanism in non-ventilated lungs. Alveolar hypoxia stimulates the production of various vasoactive substances, such as peptide endothelin, thromboxane A, platelet activating factor and leukotrienes, all of which have strong vasoconstrictive effects. Many drugs used during the anesthesia period can inhibit HPV. All volatile anesthetics inhibit HPV in a dose-dependent manner. Therefore, the inhibition of HPV is one of the main reasons for hypoxemia during OLV. The oxygen delivery of anesthetics during OLA is very complex and depends on hemoglobin, oxygen saturation and cardiac output. The oxygen delivery volume must exceed the oxygen consumption; otherwise, cellular hypoxia will occur.

Hypoxemia related to OLV is mainly attributed to shunt, shunt will improve over time. Unless auxiliary measures are taken or bilateral lung ventilation is restored, shunt will remain fixed. The oxygen transport mainly depends on the concentration of the hemoglobin in the blood, hemoglobin saturation degree and output. The reduction of any one of them will decrease oxygen delivery and may lead to target organ dysfunction, increasing the risk of complications such as cognitive dysfunction, atrial fibrillation, renal failure and pulmonary hypertension in patients during the perioperative period [9-10].

Epidemiological investigations have found that approximately 50% of elderly people worldwide have undergone at least one surgical treatment. POCD is one of the common postoperative complications. Compared with younger patients, the risk of adverse reactions in patients over 60 years old is significantly higher, and about one quarter of patients may develop POCD. With the increase of age, the number of brain neurons decreases, neurotransmitters change, the ability to regulate cerebral blood flow reduces, liver and kidney functions decline, the clearance of anesthetic drugs decreases, intraoperative blood loss increases, and postoperative infections all lead to a significant increase in the incidence of POCD in elderly patients [12].POCD is acute and reversible. The current pathogenesis remains unclear. Elderly patients are an independent risk factor for POCD. Other risk factors include low education level, prolonged anesthesia time, postoperative co-infection, previous cerebral vascular disease or cognitive decline, etc. Early prevention can significantly reduce postoperative cognitive impairment in elderly patients. With the prolongation of postoperative recovery time, the decline in cognitive function in most patients can gradually alleviate or disappear, while in a small number of patients, it may persist and progressively worsen [13].

Thoracic surgery can promote the production of pro-inflammatory factors and reactive oxygen species (ROS) due to intense hemodynamic fluctuations and the occurrence of hypoxemia, leading to the proliferation of glial cells in the brain. Increased oxidative stress

and inflammation injury will destroy the function of endothelial cells, lead to the blood-brain barrier (BBB) permeability increases, nerve vascular decouple and cerebral blood flow decreases, nutrient transport and toxic product removal was damaged and eventually lead to white matter damage, nerve degeneration and cognitive obstacle [14].

In order to improve hemodynamic stability and the occurrence of hypoxemia during thoracoscopic surgery in elderly patients and thereby improve postoperative cognitive dysfunction, more rigorous anesthesia methods and medications should be adopted to reduce the incidence of hypoxemia and POCD. At present, the application of drug intervention is a hot topic in the research on improving hypoxemia and postoperative cognitive dysfunction during thoracoscopic surgery for OLV.

Remimazolam, as a short-acting γ -aminobutyric acid (GABA)-A receptor agonist with rapid onset and metabolism, has metabolites that have almost no pharmacological activity, reducing the risk of drug accumulation. At the same time, it has obvious hemodynamic and respiratory stability. Remimazolam has the advantages of rapid onset, fast metabolism, no dependence on liver and kidney functions, no accumulation, and less impact on circulatory function. It is very suitable to be used as a sedative drug during anesthesia induction and maintenance in elderly patients [15-17]. At present, most of the research on remimazolam at home and abroad focuses on short surgeries and outpatient painless gastroscopy and colonoscopy, etc. There is a lack of relevant research on the application of remimazolam in the perioperative period of elderly patients. Liao et al. [18] found that remimazolam and dexmedetomidine are equally beneficial in reducing the incidence of early postoperative POCD in elderly patients undergoing radical gastrectomy for gastric cancer. The underlying mechanism is to reduce the occurrence of inflammatory responses.Previous studies have shown that remimazolam is used for general anesthesia induction and maintenance for elderly patients undergoing thoracoscopic lobectomy can alleviate brain injury in the elderly and thereby reduce the incidence of POCD [19]. However, whether remiazolam can reduce the occurrence of POCD by improving interpulmonary oxygenation during one-lung ventilation in elderly patients undergoing thoracoscopic lobectomy has not been studied at home or abroad so far.

This project mainly explores the effects of remiazolam mesylate on oxygenation and intrapulmonary shunt in elderly patients during one-lung ventilation after thoracoscopic surgery, as well as its impact on postoperative cognitive dysfunction. To clarify the application advantages of remimazolam toluenesulfonate in thoracoscopic surgery for elderly patients, and to provide new clinical application references for improving oxygenation during one-lung ventilation and postoperative cognitive dysfunction in elderly patients undergoing thoracoscopic surgery.

and pulmonary dynamic compliance (Cdyn) were calculated. ④ Serological indicators: 4mL of peripheral venous blood was collected from the patient immediately after the operation (T6) and 24 hours after the operation (T7). The serum central nervous system specific protein (S100β) was detected by enzyme-linked immunosorbent assay (ELISA).Levels of interleukin-6 (IL-6) and interleukin -8 (IL-8). The white blood cell count, the percentage of neutrophils, the percentage of lymphocytes and C-reactive protein (CRP) in the peripheral blood of the patients were detected. ⑤ Postoperative recovery: The Ramsay sedation classification was used to assess the awakening status at 2, 4, 12, and 24 hours after the operation. The pain conditions at 2, 4, 12 and 24 hours after the operation were evaluated by VAS score, and the number of cases of postoperative remedial analgesia in each group of patients was recorded. Record the occurrence of postoperative adverse reactions such as restlessness, nausea and vomiting, dizziness, arrhythmia and drowsiness in each group of patients; Record the occurrence of postoperative pulmonary complications such as pulmonary infection, respiratory failure and atelectasis within one week after the operation; The postoperative recovery quality of patients was evaluated by the QOR-15 scale at 24 hours and 48 hours after the operation. Record the duration of the patient's postoperative hospital stay. Finally, the collected data will be statistically analyzed and compared.

III. Research Design

1.selective cases：

1.1 Inclusion criteria for cases：

1) Patients aged 65 to 75 years who are scheduled to undergo thoracoscopic surgery under general anesthesia

2)BMI18~30 kg/m2;

3) ASA is classified into grades I to III;

4) There are no contraindications to the relevant drugs;

5) Both the patients and their families agreed to participate in this study and signed the informed consent form.

1.2 exclusion criteria：

6) Patients with severe sinus bradycardia (heart rate <50 beats per minute) and atrioventricular block;

7) Respiratory tract infection and the use of non-steroidal anti-inflammatory drugs or hormone drugs within two weeks before the operation;

8) People with central nervous system and mental disorders;

9) In the past half year, I have taken anticholinergic drugs, anticonvulsants, anti-anxiety drugs, antidepressants, etc;

10) Severe liver and kidney dysfunction and immune system diseases, uncontrolled hypertension and diabetes;

11) History of preoperative radiotherapy and chemotherapy;

12) Patients with communication barriers who are unable to cooperate to complete the test.

1.3 Exclusion Criteria:

13) Patients with OLV<60 minutes or those who are converted to thoracotomy;

14)Intraoperative blood loss >1000ml;

15)(3) Patients transferred to the ICU after surgery;

2. Test Method

2.1Anethesia method

MAC(Monitored Anesthesia Care) monitoring anesthesia management technique.

2.2 Experimental Subjects

The patients were randomly divided into 3 groups according to the random number table method:

Remimazolam group (Group R): After intubation, remimazolam was maintained at a pump rate of 1-2 mg/kg/h until 10 minutes before the end of the operation.

Propofol group (Group P): After intubation, propofol was maintained at a pump rate of 4-10mg/kg/h until 10 minutes before the end of the operation.

Remimazolam combined with propofol group (Group C): After intubation, remimazolam at a dose of 0.3-1mg/kg/h and propofol at a dose of 3-6 mg/kg/h were maintained until 10 minutes before the end of the operation.

2.3 Preoperative Preparation

One day before the operation, the patient was visited to have a comprehensive and detailed understanding of the patient's current physiological and pathological conditions, as well as to assess the patient's cardiopulmonary function before the operation. The application of remimazolam mesylate in anesthesia was also explained to the patient. Explain the precautions for the hand surgery, and fast for 8 hours and refrain from drinking for 6 hours. Sign the informed consent form for anesthesia and the "Informed Consent Form" for the clinical trial.

2.4 Basic Preparations Before Anesthesia

2.4.1 Basic vital signs monitoring and item preparation

After the patient entered the room, their vital signs were routinely monitored using a multi-functional monitor. Including Heart rate (HR), Pulse rate (PR), Electrocardiograph (ECG), Saturation of pulse oximetry (SpO_2) Prepare emergency medicines: atropine 0.5mg, epinephrine hydrochloride 1mg, ephedrine 30mg; prepare a set of general anesthesia induction drugs: etomidate, fentanyl, cisatracurium; prepare a set of tracheal intubation tools: video laryngoscope, double-lumen bronchial catheter, sputum suction tube; Open the peripheral venous channel and fully inhale oxygen at an oxygen flow rate of 6 L/min.

2.4.2 Invasive operations

Under local anesthesia, radial artery puncture and catheterization (heparin water flushing) was selected, and invasive arterial blood pressure (IABP) was monitored.

2.5 Anesthesia induction and maintenance

After the pre-anesthesia preparations were completed, anesthesia induction began. After 3 minutes of mask inhalation of pure oxygen, the three groups were successively given fentanyl 3-5μg/kg, etomidate 0.4 mg/kg, and cisatricurium 0.15 mg/kg. After mask controlled oxygen inhalation for 5 minutes, after the relaxation of the mandibular muscles and anesthesia induction, a double-lumen endobronchial tube (DLT) was inserted to ensure good alignment. The anesthesia machine was adjusted to volume-controlled ventilation, and the respiratory parameters were adjusted: the tidal volume was regulated by 6-8 ml/kg and the respiratory rate was maintained to keep the end-expiratory CO_2 partial pressure at 35-45

mmHg. After the anesthesia stabilizes, a retrograde puncture and catheterization of the internal jugular vein is performed. The puncture point beside the thyroid cartilage is determined. After disinfection and laying a towel, the puncture is performed and a catheter is placed. The catheter is fixed with sutures and fluid replacement is carried out during the operation. Anesthesia maintenance: Total intravenous anesthesia was used during the operation. Intravenous anesthetics were continuously pumped according to the groups. Group R: Remimazolam was maintained at a pumping rate of 1-2mg/kg/h. Group P: Propofol was maintained at a pump speed of 4-10mg/kg/h. Group C: Maintained with remimazolam at a dose of 0.3-1mg/kg/h and propofol at a dose of 3-6 mg/kg/h. All three groups were combined with remifentanil at 6-12 μg/kg/h, and the drug pumping speed was adjusted to maintain the BIS value at 40-60. Thirty minutes before the end of the operation, 0.15 mg/kg dezocine was administered. The infusion of remimazolam and propofol was stopped 10 minutes before the operation, and remifentanil was stopped 5 minutes before the operation.

2.6 Anesthesia Completed

After the anesthesia ended, all patients underwent lung recruitment for 30 seconds after bilateral lung ventilation was restored. The patient was sent to the PACU with a tube. After spontaneous breathing, muscle strength and consciousness were restored, sputum was suctioned and the tube was removed. The patient will be returned to the ward after assessment by the PACU physician.

3. Data collection

3.1 General Condition of the Patient

Age, gender, ASA classification, BMI, surgical method, surgical side, preoperative basic lung function

3.2 Intraoperative condition of the patient

One-lung ventilation time, blood loss, infusion volume, dosage of remimazolam, dosage of propofol, dosage of remifentanil, urine volume, blood loss, dosage of ephedrine, dosage of atropine, occurrence of hypoxemia

3.3 Cardiovascular responses of patients at all times during the perioperative period

Record the heart rate, mean arterial pressure and pulse oxygen saturation of the patient at the time of entering the room (TO), before OLV (T1), 30 minutes after OLV (T2), 60 minutes after OLV (T3), before extubation (T4), and 5 minutes after extubation (T5).

3.4 Intraoperative blood gas analysis:

All patients underwent arterial blood gas analysis and central venous blood gas analysis before OLV (T1), 30 minutes after OLV (T2), and 60 minutes after OLV (T3). Record the Pplat, VT, PEEP, OI, PaO_2, PAO_2, $PcvO_2$, SaO_2, $ScvO_2$, $(A\text{-}a)DO_2$, RI at these three moments, and calculate Qs/Qt and Cdyn.

3.5 Serological indicators

4mL of peripheral venous blood was collected from the patients at the time of entering the room (TO), before extubation (T4), and 24 hours after the operation (T6). The levels of serum central nervous system specific protein (S100β) and interleukin-6 (IL-6) were detected by enzyme-linked immunosorbent assay (ELISA). Detect the white blood cell count, the percentage of neutrophils, the percentage of lymphocytes, and C-reactive protein (CRP) in the peripheral blood of the patients.

3.6 Postoperative Follow-up:

Postoperatively, Ramsay sedation scale was used to assess the recovery at 2, 4, 12 and 24 hours after surgery; VAS score was used to evaluate the pain at 2, 4, 12 and 24 hours after surgery. The number of cases requiring rescue analgesia in each group was recorded. The occurrence of postoperative adverse reactions such as restlessness, nausea and vomiting, dizziness, arrhythmia and drowsiness was recorded. The occurrence of PPCs such as pulmonary infection, respiratory failure and atelectasis within one week after surgery was recorded. The QOR-15 scale was used to assess the postoperative recovery quality at 24 and 48 hours after surgery. The postoperative hospital stay of patients was recorded.

PPCs can be diagnosed if any of the following conditions are met, in accordance with the European Perioperative Clinical Outcome (EPCO) standards jointly issued by the European Society of Anaesthesiology and the European Society of Intensive Care Medicine: (1) Pulmonary infection, suspected respiratory system infection and treated with antibiotics, and at least one of the following is met: new or changed sputum, new or progressive pulmonary infiltration shadow, fever, total white blood cell count > 12×109/L. (2) Respiratory failure, PaO_2 < 60 mmHg when breathing air, PaO_2/FiO_2 < 300 mmHg or SpO_2 < 90%, requiring oxygen therapy. (3) Pleural effusion confirmed by imaging. (4) Atelectasis confirmed by imaging. (5) Pneumothorax confirmed by imaging. (6) Bronchospasm, new wheezing heard and requiring treatment with bronchodilators. (7) Aspiration pneumonia: acute lung injury after aspiration of gastric contents.

Iv. Statistical Analysis

Data analysis was conducted using SPSS 27.0 statistical software. Normally distributed measurement data were expressed as mean ± standard deviation, and the comparison between groups was performed using the independent sample t-test; non-normally distributed measurement data were expressed as median and interquartile range [M(IQR)], and the comparison between groups was conducted using the Wilcoxon rank sum test. Count data were expressed as cases (%), and the comparison between groups was performed using the x^2 test or Fisher's exact probability method. A P value < 0.05 was considered statistically significant.

The main endpoint of this study is the oxygenation index measured at 60 minutes (T3) during OLV. According to the literature, the oxygenation index of patients when they are breathing pure oxygen in both lungs and are in a state of good oxygenation is generally

between 350 and 400 mmHg. After switching to OLV, the oxygenation index drops to 150 to 200 mmHg. Therefore, any change in the oxygenation index within 50 mmHg during OLV is not clinically significant. Thus, 50 mmHg is set as the cutoff value for the disadvantage. That is, in this study, if the oxygenation index of the study group is lower than that of the control group at T4, but the difference in oxygenation indices between the two groups is within 50, then the ventilation strategy of the study group is not inferior to that of the control group in improving intraoperative oxygenation. Taking the type I error probability $\alpha = 0.025$ and the type II error probability $\beta = 0.20$, power value 0.80; using SPSS 27.0 software, the sample size for each group was calculated to be 38. Considering a 20% dropout rate and withdrawal rate, the final required sample size for each group was 50.

V. Management of Experimental Data of Subjects

1. Strictly follow the provisions of Article 1034 of the Civil Code: The personal information of natural persons is protected by law; Article 1038 stipulates: Information processors shall not disclose or tamper with the personal information they have collected and stored. Without the consent of the natural person, they shall not illegally provide the personal information to others. Protect the privacy of the subjects and prevent it from being leaked.
2. Strictly implement the provisions of Article 62 of the "Injury Liability Law": Medical institutions and their medical staff shall keep patients' privacy confidential; Article 22 of the "Physician Practice Law" stipulates: Physicians in their professional activities should care for, protect and respect patients, and safeguard their privacy.
3. The personal information of the participants is strictly confidential. The patient data will be identified by the study number rather than the patient's name. Information that can identify the patient's identity will not be disclosed to members of the research team other than the authorized personnel.
4. All research participants and the research sponsors were required to keep the patients' identities confidential. The patients' files will be stored in locked filing cabinets and can only be accessed by the researchers.
5. To ensure that the research is conducted in accordance with the regulations, when necessary, members of the government management department or the ethics committee may, as per the regulations, access the personal information of the patients at the research institution. When the research results are published, no personal information of the patients will be disclosed.

Vi. Feasibility Analysis

1.This project has obtained some preliminary research data. The scientific questions raised by the project are based on the research work that has been discovered and published. This ensures the smooth implementation of the project from both the research concept and the foundation of previous studies.

2. Regarding the hospital, the First Affiliated Hospital of Kunming Medical University is a large-scale comprehensive hospital that integrates medical treatment, teaching, research, and cadre health care. It has abundant patient resources and sufficient medications.

3. In terms of department construction, the Anesthesiology Department of the First Affiliated Hospital of Kunming Medical University is a key clinical specialty in Yunnan Province, the Anesthesia Quality Control Center of Yunnan Province, the Anesthesiology Research Center of Yunnan Province, the location of the Anesthesiology Professional Management Committee of Yunnan Hospital Management Association, a resident physician training base, and a dominant development discipline of the hospital.