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

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## Informed consent form Part I Instructions for subjects

We are going to conduct a study "Effects of remimazolam tosilate on oxygenation and postoperative cognitive function in elderly patients undergoing thoracoscopic lobectomy". Your situation may be eligible for enrollment in the study, so we would like to invite you to participate in the study. This informed consent form will introduce to you the purpose, procedures, benefits, risks, inconvenience or discomfort of the study. Please carefully read the informed consent form before making a decision about whether to participate in the study. When the investigator explains and discusses the informed consent form to you, you can always ask questions and ask him/her to explain to you anything that you do not understand. You can make a decision after discussing it with family and friends, as well as with your doctor.

If you are currently participating in another clinical study, please inform your study physician or investigator.

The principal investigator of this study was affiliated with the First Affiliated Hospital of Kunming Medical University, and the sponsor/fundings of this study were the First Affiliated Hospital of Kunming Medical University and Beijing Zhongkang United Foundation.

Why was this study conducted?

About one in five people will develop cancer in their lifetime, and about one in nine men and one in 12 women will die from cancer, according to the American Cancer Society's 2024 Cancer Statistics report. Lung cancer is the most common cancer worldwide (accounting for 12.4% of new cases) and the leading cause of cancer death (18.7% of all cancer deaths), almost twice as high as the second leading cause of cancer-related death. At present, the treatment of early stage lung cancer is mainly based on surgical treatment. Early surgical treatment can reduce tumor recurrence and metastasis and improve survival rate of patients.

video-assisted thoracic surgery (VATS) has the advantages of minimal

operative wound, quick postoperative recovery and few complications, and has gradually replaced the traditional thoracotomy. VATS usually requires one-lung ventilation (OLV) of the non-operated lung using a double-lumen bronchial tube. Olv is a ventilation technique that separates the two ventilation pathways at the level of the carinal of the trachea in order to cause collapse of the operated lung lobe. In addition, the non-surgical lung lobe is protected from pollution, which is more conducive to the exposure of the surgical field and the reduction of the incidence of surgical complications [2]. During one-lung ventilation, various pathophysiological changes may occur due to mechanical injury, lung collapse, imbalance of lung ventilation and blood flow ratio, ischemia-reperfusion, etc., resulting in the release of a large number of inflammatory factors, local and systemic inflammatory responses, affecting perioperative oxygenation, and leading to hypoxemia and even lung injury. During OLV, lateral atelectatic lung, though not for Ventilation, but there is still blood flow, which leads to Ventilation/blood flow ratio (Ventilation/perfusion thewire, V/Q) disorders, leading to the proliferation in patients with pulmonary shunt, oxygenation decline to hypoxemia [4. Due to the influence of gravity, the ventilation and blood flow of patients are unevenly distributed, and the shunt volume reaches 40-50%. Finally, due to the gravity, the mediastinum and heart will move to the healthy lung, which will limit the ventilation of the ventilated lung, and the ventilation-blood ratio will also be imbalance, which will lead to the increase of the pulmonary shunt of the patient.

hypoxic pulmonary vasoconstriction (HPV) is a unique adaptive mechanism of pulmonary circulation, which can promote blood flow from hypoxic alveolar area to well-ventilated alveolar area, thereby improving V/Q imbalance [6]. When the alveolar partial pressure of oxygen is reduced,

HPV can be stimulated, which makes the pulmonary precapillary arterioles in the hypoxic area shrink, vascular resistance increases, blood flow decreases, and more blood flows to the well-ventilated alveolar area, thereby reducing the shunt in the lung. Many factors, such as anesthetic agents, acid-base imbalance, temperature, vasodilators, and pulmonary manipulation, may affect the HPV mechanism in the nonventilated lung. Alveolar hypoxia stimulates the production of A variety of vasoactive substances, such as the peptide endothelin, thrombinogen A, platelet activating factor, and leukotrienes, all of which have potent vasoconstrictive effects. 7 HPV is inhibited by many agents administered during anesthesia, and all volatile anesthetics inhibit HPV in a dose-dependent manner. Thus, inhibition of HPV is one of the major causes of hypoxemia during OLV. Oxygen delivery in anesthetized patients during OLA is complex and depends on hemoglobin, oxygen saturation, and cardiac output. Oxygen delivery must exceed oxygen consumption, or cellular hypoxia will occur. Hypoxemia associated with OLV is mainly attributed to shunting, which improves over time and remains fixed unless adjunctive measures are taken or two-lung ventilation is restored. Oxygen transport in the blood depends primarily on the hemoglobin concentration, the saturation of blood red protein, and the cardiac output. A reduction in either reduces oxygen delivery and may lead to target-organ dysfunction, increasing the risk of perioperative complications such as cognitive dysfunction, atrial fibrillation, renal failure, and pulmonary hypertension.

9-10 Meanwhile, hypoxemia in elderly patients increases the risk of perioperative complications such as cognitive dysfunction, atrial fibrillation, renal failure, and pulmonary arterial hypertension. Postoperative cognitive dysfunction (POCD) is a common cognitive deficit in elderly patients after surgery and anesthesia. Surgical trauma and

anesthesia-induced neuroinflammation are the main factors for the development of POCD. The occurrence of POCD prolongs the length of hospital stay, increases the incidence of postoperative complications and worsens the short-term quality of life in elderly patients. Therefore, more strict anesthesia methods and medications should be adopted to reduce the incidence of POCD. The mechanism of POCD is still unclear, but neuroinflammatory response is considered to be the key factor and initiating link. During surgery and anesthesia, the immune system is activated in a nuclear factor-kB (NF-KB) -dependent manner, releasing TNF-α and other inflammatory mediators, which cause damage to the blood-brain barrier and promote the migration of macrophages into the brain parenchyma, leading to cognitive dysfunction. Studies have shown that patients with evidence of POCD have elevated serum levels of peripheral inflammatory markers such as C-reactive protein, S100-β, and IL-6. Cerebral hypoperfusion caused by relatively large intraoperative hemodynamic fluctuations and the use of high-dose opioids during the perioperative period are also important causes of POCD. The risk of POCD is different in different hand procedures. POD occurs in 7-23% of patients who undergo open chest surgery. Aging is an irreversible change that occurs with the passage of time, which is mainly reflected in the insufficiency of organ function reserve, the decline of physical function and the reduction of tolerance to injury, which is easy to lead to POCD. The existing literature shows that advanced age is an independent risk factor for POCD, which is related to the decrease of brain volume and white matter integrity and the increase of blood-brain barrier permeability caused by aging. Therefore, how to improve the occurrence of postoperative delirium in elderly patients is an urgent problem to be solved.

Remimazolam tosilate, as A new ultra-short-acting benzodiazepine agonist, can reduce the excitability of nerve cells by acting on Y-aminobutyric

acid type A receptors, so as to achieve less movement and sedation. Remimazolam tosilate is metabolized by a non-specific esterase, the metabolite has no pharmacological effect, and it allows prolonged infusion without accumulation. It can provide rapid anesthesia and wakeup while stabilizing hemodynamics, and has a small inhibitory effect on respiration, so it is suitable for older patients with unstable peripheral circulation. Studies have shown that remimazolam tosilate can inhibit the release of pro-inflammatory factors, relieve neuropathic pain, reduce cerebral ischemia/reperfusion (I/R) injury, reduce oxidative stress and inflammation, and protect the liver, lung and brain to a certain extent, thereby helping to maintain the cognitive function of the brain.

Who will be invited to participate in the study?

Subjects accepted for the study should have the following conditions: (1) age 65 to 75 years undergoing elective thoracoscopic hand under general anesthesia

Surgical patients; (2)BMI18~30kg/m2; (3)ASA grade L-iii; (4) no drug contraindications;

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

How many people will participate in the study?

The study plans to recruit 150 subjects.

How was the study conducted?

Elderly patients undergoing elective thoracoscopic surgery under general anesthesia in the First Affiliated Hospital of Kunming Medical University from August 2025 to August 2026 were selected. Relevant examinations were completed before surgery, and patients who did not meet the inclusion criteria were excluded. The preoperative age, gender and American Society of Anesthesiologists classification were recorded. The patients were divided into three groups: R(remimazolam), P (propofol), C (remimazolam

+ propofol). Remimazolam group (group R): after intubation, the pump rate of remimazolam was maintained at 1-2 mg/kg/h until 10 minutes before the end of surgery. Propofol group (group P): after intubation, propofol was maintained at a pump rate of 4-10 mg/kg/h until 10min before the end of surgery. Remimazolam combined with propofol group (group C): after intubation, 0.3-1 mg/kg/h remimazolam + 3-6 mg/kg/h propofol was maintained until 10min before the end of surgery.

The following data were recorded: ① Oxygenation index (OI) and Shunt fraction (Qs/Qt) at each time point, before OLV (T1), 30 minutes after OLV (T2) and 60 minutes after OLV (T3); ② Cognitive function: cognitive function 30min after extubation and within 7 days after operation (at 1 day before operation, 30min and 7 days after operation, Montreal Cognitive Assessment scale (MoCA) was used to evaluate the patient's cognitive function, and the incidence of POCD at different time points after operation was counted). ② Intraoperative situations of patients: one-lung ventilation time, blood loss, infusion volume, remimazolam consumption, propofol consumption, remifentanil consumption, urine volume, blood loss, ephedrine consumption, atropine consumption, and hypoxemia. ③ Hemodynamic parameters: mean arterial pressure (MAP), heart rate (HR) and SpO2 were monitored before anesthesia induction (T0), immediately after tracheal intubation (T1), before one-lung ventilation (T2), at skin incision (T3), 60min of one-lung ventilation (T4) and immediately after extubation (T5). 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). Airway plateau pressure (Pplat) was recorded at each time point. Tidal volume (VT), positive end-expiratory pressure (PEEP), oxygenation index (OI), arterial partial pressure of oxygen (PaO2) and alveolar partial pressure of oxygen (PaO2) were recorded (PAO2),

central venous oxygen pressure (PcvO2), arterial oxygen saturation (SaO2), central venous oxygen saturation (ScvO2), alveular-arterial oxygen difference (DO2(A-a)), respiratory index (RI), Qs/Qt and lung dynamic compliance (Cdyn) were calculated. ⑤ Serological indicators: at T0, immediately after the end of operation (T6) and 24h after operation (T7), 4mL peripheral venous blood was collected from the patients, and the levels of serum central nervous system specific protein (S100 β ), interleukin-6 (IL-6) and interleukin-8 (IL-8) were detected by enzyme-linked immunosorbent assay (ELISA). The white blood cell count, the percentage of neutrophils, the percentage of lymphocytes, and C-reactive protein (CRP) in peripheral blood were detected. ⑥ Postoperative recovery: Ramsay sedation scale was used to evaluate the recovery at 2, 4, 12, and 24 hours after operation. VAS score was used to evaluate the pain at 2, 4, 12 and 24 hours after operation, and the number of patients with rescue analgesia after operation was recorded. The occurrence of postoperative adverse reactions such as restlessness, nausea and vomiting, dizziness, arrhythmia and drowsiness were recorded in each group. Pulmonary infection, respiratory failure and atelectasis were recorded within 1 week after operation.

Postoperative pulmonary complications were recorded. QOR-15 scale was used to evaluate the quality of postoperative recovery at 24 hours and 48 hours after operation. The length of postoperative hospital stay was recorded. Arterial blood gas analysis and central venous blood gas analysis were performed before OLV (T1), 30 minutes after OLV (T2), and 60 minutes after OLV (T3). MAP,HR, SpO2, airway plateau pressure, alveolar oxygen partial pressure, central venous oxygen partial pressure, arterial oxygen saturation, central venous oxygen saturation, alveolar-arterial oxygen partial pressure difference were recorded at the three time points, and the fractional flow fraction and lung dynamic compliance were

calculated. Finally, the collected data were statistically analyzed and compared.

How does participating in the study affect the subjects' daily life?

The procedures in this study were all completed during the hospitalization of the subjects, and the study will not bring you other adverse reactions after the operation. If you have any questions about the examination and procedure involved in the study, you can contact us for consultation. For your safety and to ensure the validity of the study results, you are not allowed to participate in any other clinical research on drugs and medical devices during the study period.

What are the risks and adverse effects of participating in this study?

The possible adverse reactions during the study included: (1) toxic reactions of anesthetic drugs; (2) local hematoma and pneumothorax caused by puncture; (3) airway obstruction and respiratory depression. Your research physician will monitor side effects during the trial. If you experience any side effects during the trial, it is vital that you report them to your study doctor right away. The study doctor may give you vasopressors, antihypertensive medications, or other medications to control side effects. If you or your study physician determines that you cannot tolerate these side effects, the study medication may be discontinued completely, and you may be withdrawn from the study.

Other Risks

If the research involves a questionnaire, state the psychological discomfort that may be caused, such as certain questions in the questionnaire may make you uncomfortable and you may refuse to answer. If the research involves personal privacy issues, please explain the possible harm. If you accidentally disclose personal private information, it may cause adverse effects on your work, study and life.

What are the possible benefits of participating in this study?

The benefits of participating in the study included providing intraoperative lung protection and more stable anesthesia support; There is no direct monetary benefit to you from participating in the study. However, we hope that the information gained from your participation in this study will benefit patients with your condition in the future.

Are there other treatment options if you do not participate in this study?

You may choose not to participate in this study without any adverse effect on your access to usual care. For your current health condition, the usual treatment is to apply other intravenous anesthetics empirically during the operation.

Are you required to participate in and complete this study?

Your participation in the study is entirely voluntary. If you do not want to, you can refuse to participate and this will not have any negative impact on your current or future health care. Even after you agree to participate, you can change your mind at any time and tell the investigator to withdraw from the study. You will not face discrimination or retaliation for withdrawing from the trial, and your access to normal medical services will not be affected. When you decide not to participate in this study, you are encouraged to inform your research doctor in time, and the research doctor can provide advice and guidance on your health condition. Participants were informed of the circumstances under which participation in the study would be discontinued according to the protocol discontinuation/withdrawal criteria, and the sponsor or regulatory authorities may terminate the study during the course of the study. In the event of premature termination of the study, you will be notified promptly, and your study physician will advise you on the next steps of treatment based on your health status. For subjects who drop out, we have a final follow-up plan for safety reasons, and you have the right to refuse. In addition to this, you are encouraged to return all unused study

medications to your study physician. If you withdraw, we may contact you again if new information is found that is relevant to your health and rights. After your withdrawal, you should make clear that no new data related to your withdrawal will be collected. Detailed instructions were provided to the subjects on how to handle the previously collected study data and those who withdrew due to adverse events.

The cost of participating in the study

There were no additional costs associated with the study, and the trial drugs or devices were included in the cost of the surgery and anesthesia. Study-related blood draws were funded by the sponsor.

Treatment of study-related injuries?

If your health is harmed as a result of participating in this study, please let the investigator know and we will take necessary medical action. The sponsor of this study, the First Affiliated Hospital of Kunming Medical University, will bear the medical expenses and provide financial compensation in case of study-related injuries in accordance with relevant Chinese regulations.

What do I need to do to participate in the study?

● Provide accurate past medical history and information about current medical conditions.

● Tell the study doctor about any health problems you have had during the study.

● Tell the study doctor about any new drugs, medications, vitamins, or herbs you took during the study.

● Do not take any medications or treatments, including prescription drugs and medicines (including vitamins and herbs) purchased over the counter at pharmacies, unless approved by the study doctor.

● Do not participate in other medical studies.

● Follow the directions of the researchers and study doctors.

● If you are not clear, you can ask at any time.

Will the subject's personal information be kept confidential?

If you decide to participate in this study, your participation in the study and your personal data in the study will be kept confidential. All your information will be identified by the study number rather than by your name. Information that can identify you will not be disclosed to members outside the research team unless your permission is obtained. All study members and study sponsors are asked to keep your identity confidential. Your files will be kept in locked filing cabinets for researchers' access only. To ensure that the study is carried out in accordance with the regulations, if necessary, members of the government administration or ethics committee are required to have access to your personal data at the research unit. No personal information about you will be disclosed when the results of this study are published.

Any new information relevant to the study?

We may learn new information about treatment during the course of the trial, and we will notify you promptly so that you can decide whether to continue in the study or withdraw.

Who should I contact if I have questions or difficulties?

If you have any questions related to this study, please contact the investigator doctor, and if you have questions related to the subjects' own rights and interests, please contact the Ethics Committee of the First Affiliated Hospital of Kunming Medical University.

## Part 2 Informed Consent signature page

Statement of informed consent of the subject

I have been informed of the background, purpose, procedures, risks and benefits of the study of the project "Effects of remimazolam tosilate on

oxygenation and postoperative cognitive function in elderly patients undergoing thoracoscopic lobectomy". I had ample time and opportunity to ask questions, and I was pleased with the responses. I was also told who to contact if I had questions or wanted further information. I have read this informed consent form and agree to participate in this study. I am aware that I may withdraw from the study at any time during the study without any reason. I was informed that I would be provided with a copy of this informed consent form, which included my signature and that of the investigator.

Subject's Signature: Date:

I confirm that the information in the informed consent has been correctly interpreted and that the subject and/or the subject's legal representative have understood the information. The subject voluntarily consented to participate in this study.

Fair Witness Signature: Date Period:

Investigator Notification Statement

I have informed the subject (and his legal representative) of the research background, purpose, procedures, risks and benefits of the project "Effects of remimazolam tosilate on oxygenation and postoperative cognitive function in elderly patients undergoing thoracoscopic lobectomy". I have given him/her enough time to read the informed consent, discuss with others, and answer his/her questions about the study. I have informed the subject of his/her contact information in case of problems;

I have informed the subject and her legal representative that she may withdraw from the study at any time during the study without any reason.

Investigator's Signature: Date: