Informed consent

project name	Comparison of the effects of esketamine-induced intubation versus conventional induced intubation in ICU patients: a single-center randomized clinical trial
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Principal investigator	Zhang Jiancheng
Professional department	Department of Critical Care Medicine

Address: No.1277, Jiefang Avenue, Wuhan city, Hubei Province, 430000Tel.: 027-85726375 E-mail:whunionlunli@126.com

Honorific:

You will be invited to participate in a clinical study of "esketamine induced intubation and conventional induced intubation in ICU patients: single center randomized clinical trial (zhang)", the following describes the study background, purpose, methods, benefits during the study, and your rights, please read carefully before participating in the clinical study. The information provided to you by this informed consent form can help you decide whether to participate in this clinical study. If you have any questions, please ask the investigator responsible for the study to ensure that you fully understand the relevant content. Whether you participate in this study is voluntary, and if you agree to participate in this clinical study, please sign the statement in the informed consent form.

This study has been approved by the Medical Ethics Committee of the Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology.

1. Research background

Endotracheal intubation is one of the important measures for respiratory management in critically ill patients. Intubation performed in an intensive care unit (ICU) is usually an emergency situation. Pathophysiological changes such as shock, respiratory failure, and metabolic acidosis can significantly increase the occurrence of adverse events during intubation. There is still a lack of effective, safe and satisfactory intubation drugs in critically ill patients. Esketamine has strong analgesic, sedation and anesthetic effects, and was approved for clinical use by the National Medical Products Administration (NMPA) in 2019. The study showed that esketamine has no significant effect on body metabolism, endocrine system, liver, kidney, intestinal function and coagulation function. In terms of drug metabolism, esketamine has high bioavailability and short half-life, and patients wake up faster and more comfortable. It not only provides stable hemodynamic advantages during endotracheal intubation, but also fights the respiratory inhibition caused by opioids. In addition, esketamine also has antidepressant and anti-inflammatory effects. However, the effect and safety of its intubation in ICU patients have not been reported yet.

2. Purpose of research

The purpose of this study is to study the efficacy and safety of esketamine in tracheal intubation in ICU patients by comparing the effects of esketamine with midazolam in ICU patients, in order to provide an important theoretical basis for the safe and effective use of esketamine in tracheal intubation in ICU patients.

3. Who can participate in this study

The subjects in this study were all adult patients admitted to the comprehensive ICU of Huazhong University of Science and Technology from 1st June 2022 to June 30,2024.

- Inclusion criteria: age 18 years, not using sedative drugs still in the elimination half-life before inclusion in the study, consulting the patient or his family members, and agreeing to participate in this trial.
- Exclusion criteria: age <18 years, allergy to esketamine or midazolam; patients requiring endotracheal intubation without sedation, such as cardiac arrest, neurological dysfunction or awake intubation; patients with suspected elevated intracranial pressure; bradycardia (heart rate (HR) below 50 times / min) or atrioventricular block; untreated or undertreated hyperthyroid patients; chronic kidney disease; severe chronic liver disease (child-Pugh: Grade C); alcohol or opioid dependence, mental illness or severe cognitive impairment; pregnancy or lactation; lack of informed consent.

4. Research profile

This study is a single-center, randomized clinical trial. We will be in strict accordance with the inclusion and exclusion criteria into ICU need endotracheal intubation of adult patients, comparing esketamine intubation and conventional intubation of hemodynamic process and within 60 minutes after intubation changes, and collect before intubation venous blood 5 tube and artery 1 tube (2ml), venous blood sent to union medical hospital affiliated to huazhong university of science and technology laboratory detection blood routine, liver and kidney function + C reaction protein, myocardial enzyme, BNP, coagulation function, arterial blood in ICU detection of arterial blood gas. This study also needs to evaluate the pre-intubation APACHEII score and SOFA score, use of vasoactive drugs within 1 hour after intubation, number of intubation attempts, duration of mechanical ventilation support included in the study, 28-day hospital mortality, and the safety of esketamine.

4.1. Study visits and procedures

4.1.1 Research treatment

You will receive standard treatment and care appropriate for your own condition, based on which you will receive esketamine induced intubation or routine induced intubation. If you decide to participate in this study and have signed the informed consent form, you will be asked to perform the following study visits.

4.1.2. Screening period

This study will begin when you attend the screening visit. The purpose of the screening visit is to confirm that you meet the requirements for participation in this study. During the study screening period, you will need to complete the following processes and assessments. If your screening results do not meet the requirements of this study, then the study doctor will explain why to you and discuss other treatment options with you.

- ✧ Demographic data
- ✧ History of previous disease
- ✧ ICU diagnosis was performed
- ✧ vital sign
- ✧ And 12-lead ECG, chest X-ray / CT examination
- ✧ APACHEII Score, and the SOFA score
- ✧ Laboratory tests: blood routine, liver and kidney electric + C reactive protein, coagulation, BNP, myocardial enzyme, arterial blood gas
- ✧ Survival status assessment
- ✧ ICU admission assessment
- ✧ Confirmation of the inclusion / exclusion criteria

4.1.3. Baseline assessment

If you are qualified, your physical condition will be checked and randomized by coin toss half an hour before formal esketamine induced intubation or routine induced intubation. The specific processes and assessments include:

- ✧ vital sign
- ✧ APACHEII Score, and the SOFA score
- ✧ Laboratory tests: blood routine, liver and kidney electric + C reactive protein, coagulation, BNP, myocardial enzyme, arterial blood gas

4.1.4. Stage of therapy

Based on the randomization results, you will be assigned to the esketamine intubation

group or the regular intubation group.

During this period, you will also need to undergo the following tests and assessments, and to ensure your health, if necessary, your study doctor may require you to complete examinations other than the process and assessments.

- ✧ Vital signs (1 min, 5 min, 10 min, 30 min, 60 min before induction, during induction, during intubation and after intubation)
- ✧ APACHEII Score, SOFA score (before intubation)
- ✧ Laboratory tests: blood routine, liver and kidney electric + C reactive protein, blood coagulation, BNP, myocardial enzyme, arterial blood gas (before intubation)
- ✧ Type of and associated dose of vasoactive drugs (before and within 1 hour after intubation)
- ✧ Try the number of intubations
- ✧ Survival status assessment (once every 24 hours)
- ✧ ICU admission assessment (every 24 hours)
- ✧ Adverse events and serious adverse events

4.1.5. Follow-up period

At the end of the study drug infusion, you will also have 3 prescribed follow-ups over the next 25 days, each of which may include all or part of the process and evaluation. If you are discharged during this period, the staff of the research team will contact you by telephone to understand your health status and medical conditions. To protect your health, if necessary, your study doctor may ask you to complete examinations outside of the prescribed procedures and assessments.

- ✧ Time of mechanical ventilation support (after inclusion in the study)
- ✧ ICU and in-hospital mortality rates (28 days after inclusion in the study)
- ✧ Remission rate (90 days after study inclusion)

4.1.6. Study treatment terminated

If you decide to interrupt or terminate treatment, tell your study doctor or study staff. If you do not comply with the study procedures, the study group or the Regulatory Department will terminate the study. Even if you wish to continue the study, your study doctor may ask the study doctor to continue the study at any time during the study. If you are told to withdraw from the study, your study doctor will explain the reason for the withdrawal. The study doctor will ask you to return to the site to complete the end visit and discuss other treatment options after withdrawal from the study.

5. **Biological sample collection**

In this study, 5 tubes of peripheral venous blood and 1 tube of arterial blood (2ml per tube) will be extracted before intubation, in which venous blood will be sent to the Laboratory of Union Hospital, Tongji Medical College of Huazhong University of Science and Technology for blood routine, liver and kidney function + C reactive protein, myocardial enzyme, BNP, and coagulation function. Artery blood will be tested for arterial blood gas in ICU.

6. Detection, preservation, and destruction of the biological samples

Human biological samples usually refer to human body fluids (such as urine, blood, saliva, bile, gastric juice, lymph, and other secretions of organisms, etc.), hair, muscles, and some tissues and organs (such as thymus, pancreas, liver, lung, brain, stomach, kidney, etc.), and various microorganisms. Biological samples are of great significance to improving the level of human health care and promoting the development of biotechnology. Biological samples were collected as blood and sent for testing immediately after collection or in 4℃ refrigerator within 2 hours. If the remaining plasma specimens are not used for future studies after the study, they will be submitted to the designated units for centralized incineration after high temperature and high pressure treatment.

7. **Obligations of subjects**

Subject obligation: You are voluntary throughout the study. If you decide not to participate in this study, it will not affect the other treatment you should receive. If you decide to participate, you will be asked to sign this written informed consent form. You have the right to withdraw from the trial at any stage of the trial without discrimination or unfair treatment, and your corresponding medical treatment and rights and interests will not be affected.

matters need attention:

- As a subject, you or your guardian should provide true information about your medical history and current physical condition;
- Tell the study doctor about any discomfort the subject has found during the study;
- Do not take restricted drugs, food, etc., as already informed by the doctor;
- Tell the study doctor whether the subject himself has recently participated in other studies, or is currently participating in other studies.(Explain the taboos or restricted activities that the subjects should cooperate with during the trial, such as no food or medicine, pay attention to contraception, no driving, no drinking,

etc. Should cooperate with the matters, such as paying attention to the special requirements of taking medicine, etc.）

8. Possible study risks of participating in this study

8.1. **Risk of esketamine injection**

Esketamine was approved for clinical use in 2019 and is currently used mainly in combination with sedatives (e. g., propofol) or alone for the induction and administration of general anesthesia.allergic reactions and allergic reactions, mental symptoms (awakening reactions, hallucinations, irritability, anxiety, and disorientation, etc.), neurological diseases (tonic-clonic contraction, similar spasm (increased muscle tone), nystagmus, etc.), ocular symptoms (blurred vision, diplopia, and increased intraocular pressure), heart diseases (increased blood pressure and heart rate, temporary tachycardia, arrhythmia, and bradycardia), respiratory and circulatory disorders (increased pulmonary vascular resistance and mucus secretion, increased oxygen consumption, laryngeal spasm and temporary respiratory depression), and gastrointestinal diseases (nausea and vomiting And increased salivary secretion, etc.), etc. Esketamine also has a good anti-inflammatory effect, which may outweigh the disadvantages, and adverse reactions are closely monitored during the study. If the adverse reaction during the study may be caused by esketamine, its use should be suspended, and actively symptomatic treatment in accordance with the medical routine, dynamic observation and clinical determination whether esketamine is directly caused.

8.2. **Risks and discomfort of the study procedures (such as blood collection, biopsy, ECG, CT, etc.)**

Risk of blood drawing: This study will obtain the study specimens through peripheral vein and arterial blood collection, using disposable vacuum vessel collection, disposable needle, performed by trained professional medical staff, which is the same as the routine blood collection process in the hospital and carries no additional risk. A few people may have temporary discomfort and / or blue, more short time can subside spontaneously.

Risk of indwelling needle: This study needs to open a special venous access, which is routinely used in the same way for intravenous administration, and may cause infection, manifested as local red, swelling, heat, pain, or systemic infection, such as fever, chills, etc.

8.3. Risk of subjects in reproductive age

Because the study drug esketamine can rapidly cross the placenta, increasing the fetal muscle tone, it is prohibited in pregnant women. Therefore, women of childbearing age should first exclude pregnant women before participating in the clinical trial, and identify the possible impact stages of no family planning during the clinical trial and after the end of the trial. In drug metabolism esketamine bioavailability (up to 93%), short half-life (continuous infusion of 79 minutes), rapid metabolism, metabolism, endocrine system, liver, kidney, intestinal function, coagulation function and reproductive ability have no significant effect, so after the test does not affect the pregnancy of childbearing age.

8.4. Unknown risk

Eesketamine was approved by the national drug administration (NMPA) for clinical use in 2019, has been relatively sufficient basic research, animal experimental research, but esketamine still has potential unknown risks, these risks may come from the side effects of esketamine itself, may be due to the differences of individual patients. All drugs carry a potential risk of allergic reactions and can be life-threatening if not properly treated. If you have any of the following allergies: difficulty breathing, and a swollen face, mouth, lips, gums, tongue, or neck, you should immediately receive medical attention and contact your study doctor. Other allergic reactions include skin rashes, hives, and blisters.

Regardless of whether these symptoms are caused by the study drug, it is very important to inform all the symptoms and reactions of the study doctor.

9. Possible benefits of participating in this clinical study

This study is a randomized controlled trial with a scientific design and enrollment is not artificially controlled. Once you are enrolled in the clinical trial, you may receive esketamine induced intubation or conventional induced intubation. If esketamine induced (esketamine + rokuronium) intubation, because esketamine has strong analgesia, sedation and anesthesia, can get good intubation effect, while esketamine also has sympathetic activity and anti-inflammatory and antidepressant effect, can stabilize hemodynamics, reduce the use of vasoactive drugs, reduce systemic inflammatory factors, improve the effect of anxiety and depression symptoms, so that you benefit, and your participation may also benefit ICU patients

need intubation in the future. With conventional induction (midazolam + fentanyl + rocuronium) intubation, you will still benefit from a good intubation effect.

10. **Without this study, I have no other alternative treatments**

You may choose not to participate in this study and receive other medication, and your study doctor will provide guidance on your other treatment options depending on your specific circumstances.

11. How to deal with the study-related damage occurring

The study drug is a marketed drug, and the expected adverse reactions will be treated according to the medical routine. If the adverse reactions or injuries are directly related to the study drug, the research group will compensate in accordance with the relevant national laws and regulations. However, the research group will not pay fees not related to this study.

12. Is there any compensation for participation in clinical trials?

If you incurred costs related to the study and increased costs during the study, you will be compensated in RMB.

13. **What do I have to pay for it?**

- We select subjects in the principle of fairness and rationality, and will never charge you fees related to the study or increases due to the study.
- After inclusion in this study, the cost of your esketamine use (calculated at 91.8 yuan / dose) will be borne by the investigator. In addition, you need to receive testing before intubation including arterial blood gas (102 yuan / time), blood routine (27 yuan / time), coagulation function (220 yuan / time), liver and kidney function + electrolyte + C reactive protein (204 yuan / time), BNP (104 yuan / time), myocardial enzyme (56 yuan / time), electrocardiogram (50 yuan / time) and vital signs monitoring (150 yuan / hour), the cost shall be borne by the investigator.
- If you have any adverse events due to the use of the study drug (esketamine) during the study, the research group will provide active treatment free of charge and compensate you according to the relevant national laws and regulations.

- The usual treatment and examinations required for other diseases will not be free of charge.

14. **What will be done with the new clinical research information?**

If there is new information that may affect your continued participation in this trial, the investigator will inform you or your guardian. Know the information and progress related to this study.

15. Which conditions may terminate the clinical studies

Due to the termination of this clinical study: If subjects have adverse events or serious adverse events or other conditions (e. g., drug allergy, severe neuropsychiatric symptoms, arrhythmia, increased blood pressure, increased intracranial pressure, increased intraocular pressure, laryngospasm, respiratory depression, severe gastrointestinal symptoms, etc.), it is not suitable to continue the study.

16. The possible duration of the participation in this study?

If you agree to participate in this study, 90 days after study inclusion is the duration of this study.

17. How many people will participate in this study?

The project team has initially decided to include 80 patients.

18. **Privacy and confidentiality**

If you decide to participate in this study, your participation in the trial and your personal data during the trial are kept confidential. All information will be kept confidential to you, and your blood specimen will be identified by the study number rather than your name. Information that can identify you will not be disclosed to members of the research team without your permission. All study members were asked to keep your identity confidential. After the study, your medical records will be kept in the comprehensive ICU file cabinet of Union Hospital and locked. The data will be kept for at least 5 years for the researchers only. To ensure that the study is conducted in accordance with the regulations, if necessary, members of the government administration or the ethics review committee may access your personal data at the study site as required.

19. **The right to voluntarily choose to participate and withdraw from the study**

You may choose not to participate in this study or withdraw from the study at any notice without any medical discrimination or retaliation, and any medical treatment and interests will not be affected.

If you require any other diagnosis / treatment, or if you fail to comply with the study plan, or for any other reasonable reason, the Investigator may terminate your continued participation in this study.

20. How to get help in the study

When there are questions about trial information, research progress and rights of subjects, as well as any discomfort and damage related to the trial, you can contact the investigator Zhang Jiancheng, telephone number 13554105815 (24h), or contact the ethics committee of the center: Medical Ethics Committee of Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, telephone number: 027-85726375.

Subjects stated that

I have read this informed consent form carefully, I have the opportunity to ask questions and all questions have been answered. I understand that participation in this study is voluntary, I may choose not to participate in this study, or withdraw at any time after notifying the investigator without discrimination or retaliation, and any of my medical treatment and interests will not be affected.

If I need any other diagnosis / treatment, or if I do not adhere to the study plan, or for other reasonable reasons, the investigator may terminate me in this clinical study.

I voluntarily agree to participate in this clinical study, and I will receive a signed copy of the "informed consent form".

Subject name (in block letters): Contact telephone number:

Subject signature: Date: Date_____ _____

If the subject cannot sign the informed consent due to incapacity or other reasons, or if the subject is a minor, it shall be signed by his guardian.

Name of the guardian (in block letters): Contact telephone number:

Signature of the guardian: Date: Date

Relationship with the subject:

Subject should not sign the informed consent form:

If the subject or his guardian cannot read, it is signed by an impartial witness.

Name of impartial witness (kai kai): Contact number:

Signature of the impartial witness: Date: Date

The researchers statement

I have accurately informed the subject of the informed consent form and answered the questions, and the subject has volunteered to participate in this clinical study.

Investigators name (block letters): Contact number:

Investigator signature: Date: Date

Address: No.1277, Jiefang Avenue, Wuhan city, Hubei Province, 430000Tel.: 027-85726375 E-mail:whunionlunli@126.com