BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-084469
Article Type:	Protocol
Date Submitted by the Author:	19-Jan-2024
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Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, PAIN MANAGEMENT, Randomized Controlled Trial

Feasibility and safety of esketamine hydrochloride adjunct to sufentanil for non-surgical patients under mechanical ventilation in ICU (The SENSATION trial): Study protocol for a multicentre, single-blind, randomised, controlled trial

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Abstract

Introduction: Pain is common in patients receiving mechanical ventilation in the intensive care unit (ICU). Intravenous opioids are recommended as the first-line therapy for pain management; however, opioids have adverse side effects. Thus, low-dose ketamine is recommended as an opioid adjunct to reduce opioid consumption, based on low-quality evidence, and esketamine is an alternative to ketamine with greater efficacy and fewer side effects. However, evidence on the use of esketamine in patients receiving mechanical ventilation is lacking; thus, this study investigated the feasibility and safety of esketamine as an adjunct to sufentanil for analgesic therapy in nonsurgical ICU patients under mechanical ventilation.

Methods and analysis: This ongoing multicentre, single-blind, randomised controlled trial was conducted in nine intensive ICUs in China. Overall,132 nonsurgical patients under mechanical ventilation will be randomly assigned to the standard care and S-ketamine groups in a 1:1 ratio. Patients in the standard care group received a minimal dose of sufentanil as the sole analgesic agent. Patients in the S-ketamine group received a minimal dose of sufentanil in addition to an esketamine infusion at a fixed rate of 0.2 mg/kg/h for analgesia. The primary outcome was the mean hourly sufentanil consumption during the treatment period.

Ethics and dissemination: This study was approved by the Ethics Committee of Chongqing University Cancer Hospital. The ethical approval document ID is

CZLS2022067-A. The results of this trial will be reported in peer-reviewed journals and presented at conferences.

Trial registration: The trial was registered in the Chinese Clinical Trial Registry (CHICTR) on April 20th, 2022 (ChiCTR2200058933).

Strengths and Limitations

Strength 1 ： This is a randomised, multicenter, controlled study aim at evaluate the feasibility and safety of esketamine as an adjunct to sufentanil for analgesic therapy in nonsurgical ICU patients under mechanical ventilation.

Strength 2: The study population was limited to nonsurgical patients, which helps reduce bias caused by postoperative pain.

Limitation 1: This was not a double-blind study; the study design could not completely avoid bias.

Limitation 2: The study population was limited to nonsurgical ICU patients under mechanical ventilation who did not require deep sedation or neuromuscular blockers, which may limit the generalisability of the results to other ICU patients.

Introduction

Pain is inevitable in mechanically ventilated patients in the ICU and is associated with poor outcomes. [1-3] Intravenous opioids are recommended as first-line therapy for pain management. [4] However, opioids have troublesome side effects, such as unexpected sedation, delirium, respiratory depression, and ileus. [5] A prior prospective cohort study demonstrated that adverse drug reactions in the surgical ICUs were mainly caused by opioids, which increased the length of ICU stay by 53.2%. [6] Furthermore, the use of opioids in nonsurgical ICU patients is associated with persistent opioid use. [7 8] There is a growing concern that new persistent opioid use may be contributing to the "opioid crisis". [9-11]

Current guidelines suggest that non-opioids should be used as adjuncts in ICU analgesia to reduce opioid consumption. [5] However, commonly used non-opioids, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), may aggravate pre-existing organ dysfunction in critically ill patients. [12-15] Acetaminophen-induced hypotension is common in critically ill patients, and acetaminophen hepatotoxicity is the leading cause of acute liver failure. [13 16] NSAIDs have a weak opioid-sparing effect but may increase the risk of AKI and gastrointestinal bleeding. [17-19] Nefopam has significant opioid-sparing effects; however, there is a risk of increased heart rate and mild decrease in mean arterial pressure in critically ill patients. [18 20] Moreover, nefopam is not available in many places outside Europe.

Ketamine is an N-methyl-D-aspartate (NMDA) receptor inhibitor with a short half-life and minimal adverse effects on the respiratory and circulatory systems and is used for anaesthesia and analgesia. Anaesthetic doses of ketamine can cause side effects, such as hallucinations and cognitive impairment, while low-dose ketamine has good analgesic effects with fewer side effects than anaesthetic doses of ketamine.[21] Based on the limited evidence obtained in surgical patients, the guidelines recommend the adjuvant use of low-dose ketamine to reduce opioid consumption.[5] However, the analgesic effect of ketamine in ICU patients under mechanical ventilation remains controversial, especially in nonsurgical patients.[22 23] Esketamine (S-ketamine) is a right-handed enantiomer of ketamine with three times the potency of R-ketamine and twice that of racemic ketamine.[24] Esketamine may reduce opioid consumption in patients outside the ICU and have fewer side effects than ketamine.[25-28] To our knowledge, there are no studies demonstrating the feasibility and safety of esketamine for analgesia in nonsurgical ICU patients under mechanical ventilation. This study was designed to assess whether esketamine can reduce opioid consumption and the associated clinical outcomes in nonsurgical ICU patients under mechanical ventilation.

Methods and analysis

Design

This is a multicentre, single-blind, randomised, controlled trial. The study design followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Supplementary Table S1). A flowchart of the study is shown in Figure 1. This is version 1.2 of the protocol from the 18th of May 2022.

Setting

This ongoing study is being conducted in the ICUs of tertiary hospitals, including Chongqing University Cancer Hospital, Jinling Hospital, Fujian Provincial Hospital, Longyan First Hospital Affiliated to Fujian Medical University, Linyi City People Hospital, and Jiangsu Province Hospital of Integrated Chinese and Western Medicine.

Eligibility criteria, recruitment, and informed consent

Inclusion criteria

1. Age between 18 and 70 years.

2. Non-surgical patients (defined as patients who have not undergone surgery above level 2 within one week).

3. Patients were intubated and mechanically ventilated within 12 hours and expected to require ventilation for longer than 48 hours.

Exclusion criteria

1. Pregnant or breast-feeding.

2. Medical condition prevented assessment of RASS and CPOT.

3. Contraindications to esketamine hydrochloride.

4. Contraindications to sufentanil, propofol, midazolam, or their excipients.

5. Require deep sedation (RASS≤-4) or continuous infusion of neuromuscular blocker or both.

6. Suspected or proven acute primary brain injury (traumatic brain injury, cerebral infarction, intracranial haemorrhage, spinal cord injury, hypoxic-ischaemic encephalopathy, hydrocephalus, or cerebral oedema).

7. Ejection Fraction <30%, cardiogenic shock, and acute myocardial infarction.

8. Endogenous creatinine clearance rate <30 mL/min.

9. End-stage liver disease (Child-Pugh grade C).

10. Require surgery or tracheotomy within 48 hours.

11. Ketamine or esketamine hydrochloride is required due to status epilepticus or other diseases.

12. History of drug or alcohol abuse or both.

13. Palliative care or expected to die within 48 h.

14. History of dementia or mental illness, or require psychotropic medication.

15. Refusal to sign the informed consent form.

16. Participating in clinical trials of other drugs, or having participated in other clinical trials within 30 days.

17. As determined by the clinician, does not require opioids for analgesia.

Recruitment and informed consent

Recruitment and informed consent were obtained once eligible patients were identified. The objectives, potential risks, and benefits of this trial will be presented to the patients or their surrogate decision-makers. Randomisation and study intervention will begin after obtaining written informed consent. If written informed consent cannot be obtained within 12 hours of intubation, randomisation and timely intervention may start when verbal consent is obtained from the patients or their surrogate decision-makers, and prospective written consent will be obtained.

Randomisation, allocation, and concealment

Permuted-block randomisation stratified by the study site was used in this trial. Block lengths ranging from four to eight were used. Random allocation was performed using Interactive Web Response Systems (IWRS). Eligible patients were randomly allocated in a ratio of 1:1 to the standard care and S-ketamine group. The investigators, treatment teams, and patients will not know the allocation until randomisation is completed to ensure allocation concealment.

Blinding

The grouping of interventions will be kept strictly confidential to patients until the results of the study are revealed. Several specialized personnel (blind assessors) will be established at each study site for CPOT and RASS assessments, and the study groupings will remain confidential to them. The treatment team will titrate the analgesics and sedatives according to the blind assessors' assessments, in accordance with this study protocol and their experience. In addition, the study grouping will maintain the confidentiality of the outcome assessors and the trial statisticians who analysed the data.

Interventions

Administration and dosage adjustment of analgesics

Standard care group

In the standard care group, a minimal dose of sufentanil is used as the sole analgesic for pain management. The recommended sufentanil loading dose is 0.1–0.5 μg/kg, with an initial dose of 0.3 μg/kg/h and a range of 0.15–0.7 μg/kg/h that can be adjusted at the discretion of the patient's treating physician. Sufentanil was titrated to the minimum dose required to maintain the analgesic goal. The analgesic goal is to maintain CPOT≤ 2. An intravenous bolus of sufentanil is allowed when there is a procedure or treatment ordered by a physician. CPOT will be reassessed every 2–4 hours, and the dose of sufentanil will be adjusted based on the CPOT assessment. Other analgesic measures (such as massage, music, and relaxation techniques) of the

standard care group will follow international guidelines and be determined by the treating physician. [5]

S-ketamine group

In the S-ketamine group, esketamine hydrochloride (Hengrui Pharmaceutical Co., Ltd.) was infused at a rate of 0.2 mg/kg/h in addition to the minimal dose of sufentanil for pain management. Sufentanil would be administered in the same manner as that in the standard treatment group, and esketamine hydrochloride will be administered within 1 h of randomisation. CPOT will be reassessed every 15–30 min after the administration of esketamine hydrochloride. If CPOT≤ 2, the dose of sufentanil will be reduced by 10%; if CPOT>2, the dose of sufentanil will be increased by 10%; repeat this process and titrate the dose of sufentanil to the minimum dose that can maintain CPOT ≤ 2. The esketamine hydrochloride dose will remain unchanged throughout the study period. Unless the patient remains over sedated when the administration of sufentanil and sedatives has stopped, esketamine hydrochloride will be reduced in a gradient of 0.05 mg/kg/h until the sedation goal is achieved. The analgesic goals and other analgesic measures in the S-ketamine group will be the same as those in the standard care group. The analgesic dosing algorithm for the S-ketamine group is shown in Figure 2.

Duration of the intervention

For the standard care group, the intervention will stop when the following events occur (whichever occurs first): 1) 72 hours after randomisation. 2) Analgesics are not required due to extubation or other medical reasons, as determined by the treatment team. 3) Patient dies. 4) Patient requires surgery or tracheotomy. 5) Patient requires deep sedation or neuromuscular blockers. 6) Treatment goals shift to palliative care.7) Severe adverse event occurred (see definition of the severe adverse event). 8) Patients or family members withdraw informed consent. 9) Unable to accurately assess CPOT and RASS scores due to changes in disease status. For the S-ketamine group, in addition to the criteria for the standard care group, the intervention will also be discontinued if the criteria for discontinuation of esketamine hydrochloride are met. The criteria for discontinuation of esketamine hydrochloride are shown in Supplementary Table S2.

Management of sedation, delirium, sleep disturbance, and immobility

The management of sedation will follow the guideline recommendations and will be the same in both groups, and the target RASS for both groups ranges from -2 to 1. Propofol is the sedative of choice, with midazolam as an alternative. Based on the recommendations of the guidelines and the widely accepted eCASH principle, a relevant sedation algorithm was established (Figure 3). The management of delirium, immobilisation, and sleep disturbance will follow the recommended guidelines.

Mechanical ventilation and weaning

Mechanical ventilation will be implemented according to practical guidelines. [29] Mechanical ventilation in patients with ARDS should follow the lung-protective ventilation strategy, including the use of lower tidal volumes (4–8 mL/kg predicted body weight) and lower inspiratory pressures (plateau pressure<30 cm H_2O). [30]

Weaning from mechanical ventilation will follow the practical guidelines for mechanical ventilation. [29] The specific processes include weaning screening, spontaneous breathing test (SBT), airway patency assessment, and airway protection ability assessment. Patients who pass the SBT with good airway patency and protection will be weaned off and extubated.

Other therapies

It is not recommended to use analgesics other than sufentanil and esketamine hydrochloride in either group. Acetaminophen and NSAIDs can be used as antipyretics; however, their use should be recorded in detail. Nutritional therapy in both groups needs to follow the recommendations of relevant guidelines and refer to the "Nutrition Support Process for Critically Ill Patients." [31 32] Treatment of the primary disease and comorbidities in both groups follows the corresponding guidelines and is determined by the medical team. Other symptomatic and supportive treatments determined by the patient's medical team may also be provided.

Follow-up

All subjects will be followed up for 28 days after randomisation or until the patient's death, whichever occurs first. The indicators involved in the study are evaluated and recorded according to the study schedule (Supplementary Table S3).

Data collection and management

A web-based database has been established for data collection, and the principal investigator and coinvestigator at each research site have access to a database. Data entered and modified by investigators at each research site are based on the original data. The accuracy and compliance of the data will be audited by the principal investigator and coordinating centre. Once errors or omissions are found, specific personnel are asked to clarify the data and make corrections. The principal investigator will hold a training session for all co-investigators involved in data collection before the commencement of the study to avoid inconsistencies in data collection. Range editing and value checking have been incorporated into the database to reduce data entry errors.

Outcomes measurements

Primary outcomes

The primary outcome is mean hourly sufentanil consumption during the treatment period, which is s defined as the time from randomisation to the end of the intervention. The study intervention will be stopped according to the pre-specified criteria described in section 2.5.2.

Secondary outcomes

1. The mean hourly consumption of sedatives during the treatment period.

2. The CPOT and RASS assessment every 4 hours during the treatment period.

3. The mean hourly consumption of sufentanil on the 5th day after randomisation.

4. The proportion of requiring frequent suctioning during the treatment period.

5. The proportion of uncontrolled agitation during the treatment period.

6. The SOFA score in the first 7 days after randomisation (in ICU).

7. The APACHE-II score of the 7th day after randomisation (in ICU).

8. Liver function, renal function, and myocardial enzyme in the first 3 days and the 7th day after randomisation (in ICU).

9. AGI score, enteral nutrition tolerance score, gastric residual volume, and intra-abdominal pressure in the first 7 days after randomisation (in the ICU).

10. Nutrition compliance rate on the 4th and 7th day after randomisation (in ICU).

11. The incidence of ICU delirium, the number of delirium days, and the proportion of psychotropic drugs used for delirium.

12. Ventilation-free day in 28 days.

13. Vasopressor-free day in 28 days.

14. Adverse events (AE), severe adverse events (SAE), and adverse events that may be related to the study drug.

15. Length of ICU stay in 28 days.

16. Length of hospital stay in 28 days.

17. 28-day mortality after randomisation.

Adverse events

Investigators and treatment teams will closely monitor possible and unexpected adverse events as well as severe adverse events during the trial. Adverse events (AEs) are defined as any untoward medical occurrence in a patient who received an investigational intervention. A serious adverse event is defined as any serious medical event that causes death, life-threatening conditions, prolonged hospital stay, persistent disability or dysfunction, or other unpredictable serious medical events. The causal relationship between the adverse events and the study drug will be classified as certain, probable, possible, unlikely, or uncertain. Any adverse events will be treated appropriately and recorded, and severe adverse events will be reported by the principal investigators.

Sample size calculation

Previous studies have shown that consumption of morphine in surgical intensive care unit patients after major abdominal surgery was reduced by 25% in 48 h (80 ± 37 mg

vs 58 ± 35 mg) when ketamine was administered with an initial dose of 0.5 mg/kg followed by a perfusion of 2 μg/kg/min during the first 24 h and 1 μg/kg/min in the following 24 h. [33] According to the single-centre data from Chongqing University Cancer Hospital, the mean hourly consumption of sufentanil in mechanically ventilated patients may be reduced by about 26% (0.23±0.10 μg/kg/h vs 0.17±0.09 μg/kg/h) when a dose of 0.2 mg/kg/h of esketamine hydrochloride adjunct to sufentanil. We conservatively anticipate that the mean hourly consumption of sufentanil will decrease by 20% when a dose of 0.2 mg/kg/h of esketamine hydrochloride adjunct to sufentanil is applied (μ1=0.94, μ2=0.75, σ=0.35), with a power of 90% and an α error of 0.05 (two-side), a sample size of 120 subjects is needed which calculated by software of PASS 11.0. This number was 60 in the standard group and 60 in the S-ketamine group. Considering the possibility of dropouts, a sample size of 132 study participants was planned (10% inflation), including 66 in the standard care group and 66 in the S-ketamine group.

Statistics analysis

The normality distribution of the variables was tested using the Shapiro–Wilk test. All numerical continuous variables will be presented by the mean ± standard deviation (SD) or medians ± interquartile ranges (IQR), according to whether they obey the normal distribution. Counting and Categorical variables will be presented as proportions, frequencies, or percentages. Normally distributed continuous variables

will be statistically analysed using Student's t-test, and non-normally distributed continuous variables will be statistically analysed using the Wilcoxon rank sum test. Counts and categorical variables will be statistically analysed using the chi-square test or Fisher's precision probability test. The P-values will be reported with two decimal points, all tests will be 2-sided, and p-values with a level of significance of <0.05 will be considered statistically significant.

Recruiting process

The trial was registered on 20 April 2022, and the first patient was randomised on 23 June 2022. To date, 55 patients have been randomised, and enrolment continues on schedule.

Discussion

Although the guidelines recommend the use of multimodal analgesia to reduce the adverse effects of opioids, only approximately one-third of mechanically ventilated ICU patients are administered nonopioids for pain management. [5 20] This partly relates to the adverse effects of currently used non-opioids and the lack of solid evidence; therefore, it is necessary to expand the analgesic arsenal and to provide stronger evidence. Esketamine has the potential to reduce opioid consumption. Several randomised trials that evaluated the analgesic effects of esketamine are ongoing outside the ICU. [34-36] Song, X et al. conducted a single-arm clinical study on esketamine in combination with remimazolam tosilate for analgesic sedation in

mechanically-ventilated ICU patients.[37] To our knowledge, this is the first parallel randomised trial to evaluate the feasibility and safety of esketamine as an opioid adjuvant for analgesia in critically ill patients under mechanical ventilation.

Previous studies have revealed that high-dose ketamine causes anaesthesia and is associated with side effects, such as hallucinations and delirium, whereas low-dose ketamine delivers promising analgesic effects and is less likely to cause side effects.[38] Ketamine was considered as low dose at an infusion rate of 0.1–0.5 mg/kg/h.[23 33 39 40] Esketamine is theoretically twice as potent as racemic ketamine.[25] Based on the abovementioned data, the fixed infusion rate of 0.2 mg/kg/h of esketamine hydrochloride was adopted in this study, which is similar to the dose selected by Song et al.[37]

Per the guidelines, carefully titrated analgesic dosing is important to balance the benefits and potential risks of opioid exposure.[5] In this study, the sufentanil dose was minimised to achieve the analgesic goal. Therefore, as in other studies, the mean hourly consumption of sufentanil was chosen as the primary outcome because it illustrates the analgesic effects of esketamine and reflects the potential benefits of reducing opioid consumption.[23 33 41] Since different analgesic drugs and analgesic measures may affect analgesic and sedative effects in addition to patient outcomes, analgesic effects, organ function, and other outcomes were included as secondary outcomes.[42 43] Opioid agonists (particularly u-opioid receptor agonists) are associated

with gastrointestinal motility dysfunction.[44] It has been demonstrated that ketamine-based anaesthesia reduces gastrointestinal inhibition compared to fentanyl-based anaesthesia, and food intake improves when analgesic sedation was switched to ketamine,.[45 46]; thus our study assessed whether esketamine had a similar effect. Finally, the adverse effects of ketamine in mechanically ventilated patients in the ICU are of great concern and controversial, and the common adverse effects of ketamine (such as delirium and increased secretions) were also included as secondary outcomes.[23 47]

The time window for randomisation and initiation of the intervention in this study was narrow enough to be in line with clinical practice and guidelines.[23 27 48 49] Given the short intervention period of the study, delayed administration of the study drug may lead to false-negative results; therefore, esketamine was required to be administered within 1 h after randomisation.

The following measures were taken to control for bias in this study: (1) Randomisation and allocation concealment. 2) The study population was limited to nonsurgical patients to avoid the impact of postoperative pain. 3) Patients with factors that may affect the drug response and analgesic evaluation were excluded. 4) The treatment team and scoring assessors were independent. The assessors were unaware of the study groupings, the treatment team adjusted the dosage based on the assessors' results, and all patients followed the same analgesic approach (using the minimum

dose of sufentanil to achieve the analgesic goal). 5) A dose adjustment algorithm was developed for the S-ketamine group to avoid bias caused by differences in analgesic modulation at different study sites. 6) The study protocol was discussed and trained to ensure that it was fully understood and strictly implemented by the researchers at each participating site.

This study had some limitations. First, this is not a double-blind study. Although efforts have been made to control bias, the single-blind design of the study could not completely avoid bias. Second, the study population was limited to nonsurgical ICU patients under mechanical ventilation who did not require deep sedation or neuromuscular blockers, which may limit the generalisability of the results to other ICU patients.

In conclusion, the results of this trial may reveal whether low-dose esketamine can reduce opioid usage in nonsurgical patients under mechanical ventilation and whether it is associated with clinical improvements.

Patient and public involvement

The patients and public were not involved in the design, conduct, reporting, or dissemination of this study.

Ethics and dissemination

This study was approved by the Ethics Committee of Chongqing University Cancer Hospital. The ethical approval document ID is CZLS2022067-A. The research sites obtained ethical approval from local ethics committees. The results of this trial will be reported in peer-reviewed journals and presented at conferences.

Funding

This study was supported by the Chongqing Joint Medical Scientific Research Project of Science and Health (grant no. 2020FYYX091) and Chongqing Science and Technology Committee (grant no. cstc2017shmsA130057). The study protocol was peer-reviewed by the funding bodies. The funding bodies had no role in the design of the study and will have no role in the data collection, analysis, interpretation, or writing of the manuscript.

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567

568 **Figure Legends**

569 **Figure 1：Trial flow chart.**

570

571 **Figure 2. Analgesics dosing algorithm of the S-ketamine group.**

572

573 **Figure 3. Sedation algorithm.**

574

575 ***Declarations***

576 **Authors' contributions：**

577 All authors were involved in the study design, and read and approved the final
578 manuscript. Yi Long, Donghuang Hong, Haibin Ni, Dandan Zhou, Tingfa Zhou,
579 Songwu Liu, Qian Liu, Rui Li are responsible for carrying out recruitment, managing
580 the treatment of the patients and collecting data. Yi Long , Lu Ke, and Zhengying
581 Jiang drafted the manuscript.

582 **Competing interests**

583 This study is supported by the Chongqing Joint Medical Scientific Research Project of
584 Science and Health and Chongqing Science and Technology Committee. But the

funding bodies has no influence on the study design, data analysis, or report. The investigators take full responsibility for the integrity and content of this paper.

Consent for publication

Not Applicable.

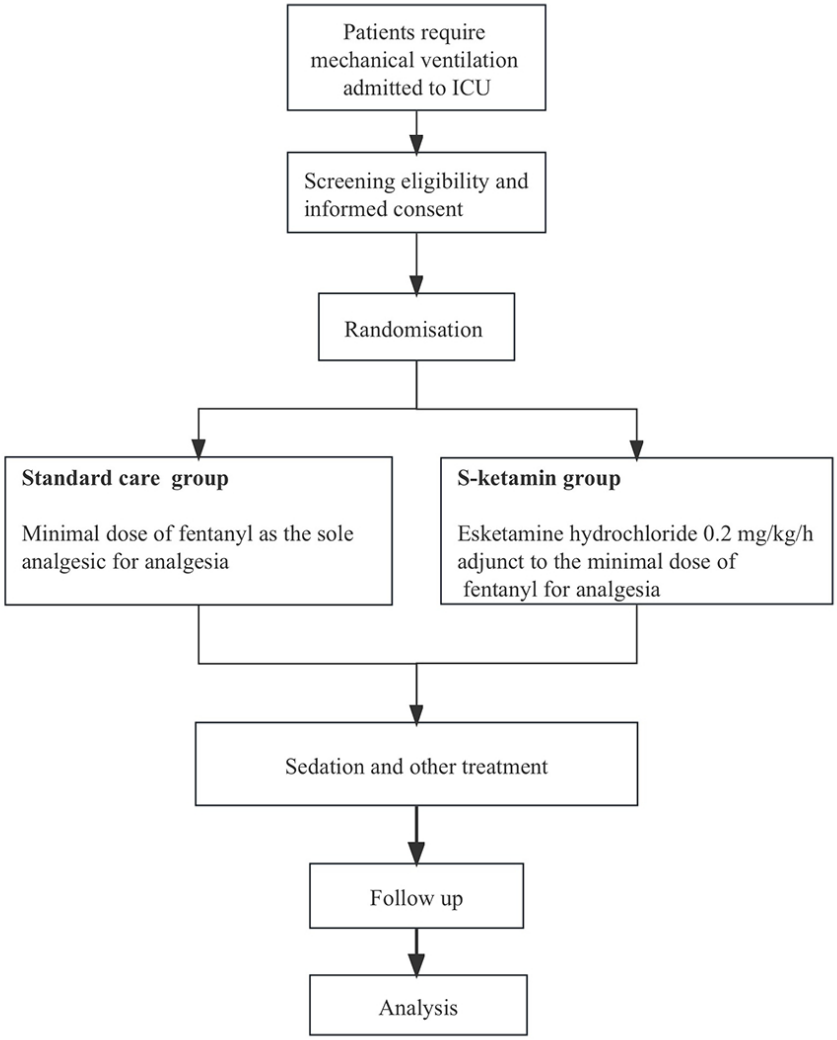

Figure 1 Flow chart of study.

Figure 1：Trial flow chart.

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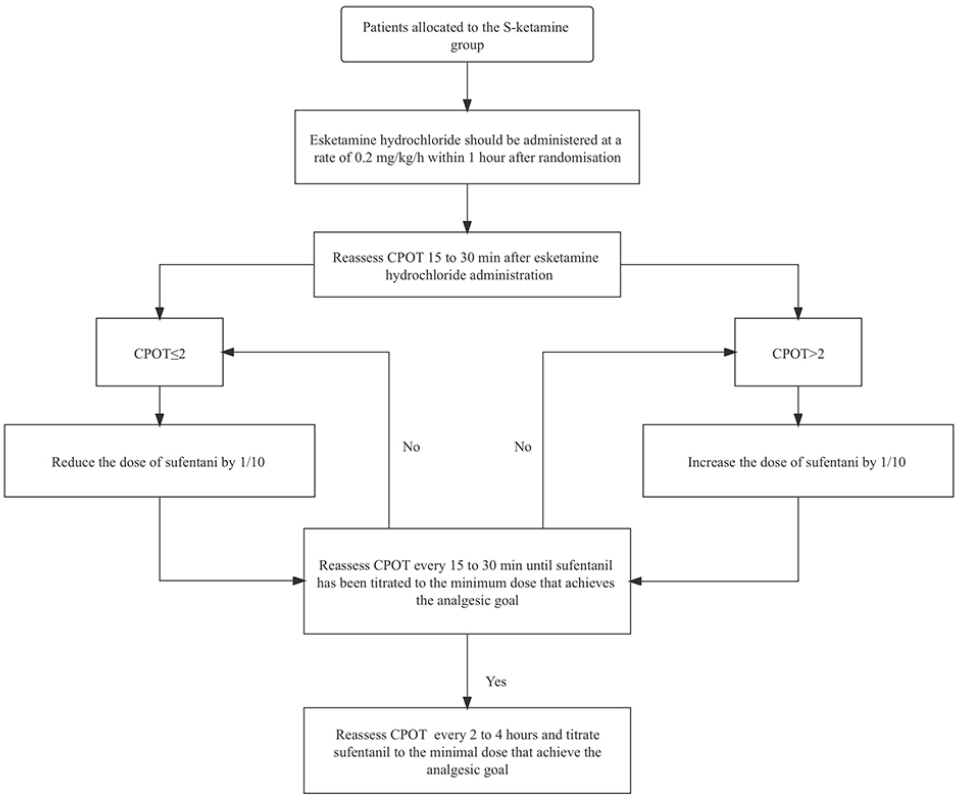

Figure 2 Analgesics dosing algorithm of the S-ketamine group.

Figure 2. Analgesics dosing algorithm of the S-ketamine group.

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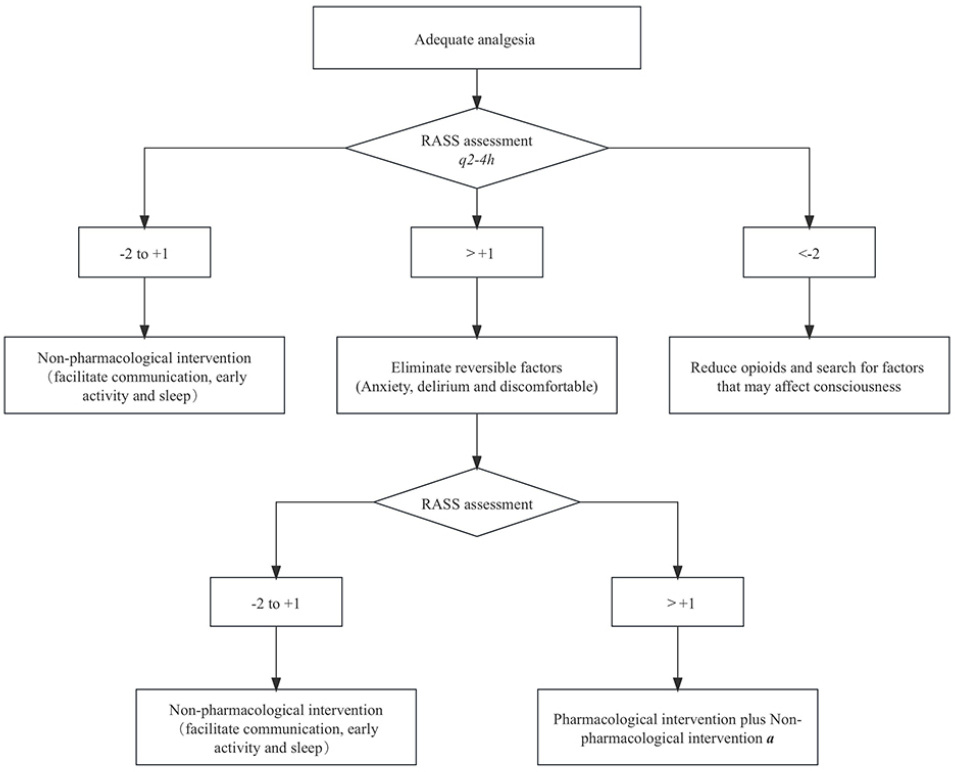

Figure 3 Sedation algorithm. ***a*** In this study, propofol was used as the preferred sedative, midazolam was used as the alternative sedative, and dexmedetomidine was not used as the main sedative.

Figure 3. Sedation algorithm.

82x76mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	page/line numbers
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/Line1-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3/Line48-49
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P6/Line 104
Funding	4	Sources and types of financial, material, and other support	P21/Line391-396
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P26/Line579-583 And P1/Line5-19
	5b	Name and contact information for the trial sponsor	P1/Line5-24
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P21/Line391-397
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Detail in aggrement
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4/Line63-P5/Lline95
	6b	Explanation for choice of comparators	P4/Line72 And P17 Line320-325
Objectives	7	Specific objectives or hypotheses	P5/Line96-98
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P5/Line100-P6/Line104
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P6/Line105-109
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P6/Line110-P8/Line139
Interventions	11a	Interventions for each group with and sufficient detail to allow replication, including how when they will be administered	P9/L164-P10/Line192
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P11/Line194-205
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P11/Line207-P12/Line231

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P13/L248-P15/L274
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Supplementary Table S3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P15/Line287-P15/Line302
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P8/Line141-147
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P8/Line149-151
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P8/Line150-154
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8/Line149-154
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P9/Line156-162

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P13/Line 240-246 And The handbook for researche
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P13/Line 233-235
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P13/Line237-240 And The handbook for researc
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P16/Line304-314
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P15/Line276-285
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P21/Line387-390
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8/Line142-147
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in informed consent form
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Detail in informed consent form
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P27/Line585-588
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Detail in aggrement
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Detail in informed consent form

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P9/L315-316
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Detail in informed consent form
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary Table S2: Criteria for discontinuation of esketamine hydrochloride

Event	Discontinuation criteria and management (esketamine hydrochloride)	Data processing
72 hours after randomization	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Patient or family member withdraw the informed consent	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Patient died	Stop esketamine hydrochloride infusion	Data will be included in the analysis
Analgesics are not required due to extubation or other medical reasons	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Require deep sedation or neuromuscular blockers	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Severe heart failure (EF<30%), cardiogenic shock or acute myocardial infarction	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the Electronic Data Collection System（EDC）	Follow up, data will be included in the analysis
Acute liver failure	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Renal dysfunction that probably caused by esketamine	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Require Surgery or tracheotomy	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Unable to accurately assess CPOT and RASS score	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Uncontrolled agitation (pulling off artificial airway, tubes or lines and combative behavior)	If it is related to esketamine hydrochloride, the infusion stops; if not, the infusion continues. Adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Uncontrollable hypertension (SBP≥180mmHg, DBP ≥100mmHg) lasting more than 3 hours		
Other sever adverse events that the treating team believes may be related to esketamine hydrochloride	Stop esketamine hydrochloride infusion, the adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis

Esketamine hydrochloride infusion should be discontinued when any of the events listed in the table occur, whichever occurs first, but

patient follow-up should continue.

Supplementary Table S3 : study schedule

Time point	-D1	D0	D1	D2	D3	D4	D5	D6	D7	D...	D28
Enrolment											
Eligibility screen	×										
Informed consent	×										
Allocation		×									
Intervention											
Intervention of the standard care group		×	×	×	×						
Intervention of S-ketamine group		×	×	×	×						
Assessment											
Baseline demographics	×										
Diagnosis	×										
Comorbidity	×										
Mechanically ventilation duration before randomization		×									
Cumulative dose of sufentanil before randomization		×									
SOFA score		×	×	×	×	×	×	×	×		
APACHE-Ⅱ score		×							×		
AGI and enteral nutritional tolerance score（daily）		×	×	×	×	×	×	×	×		
Gastric residual volume and intra-abdominal pressure （every 12 hours）		×	×	×	×	×	×	×	×		
Liver function, renal function, and myocardial enzymes		×	×	×	×				×		
RASS and CPOT（every 4 h）		×	×	×	×						
Cumulative dose of sufentanil		×	×	×	×		×				
Cumulative duration of sufentanil		×	×	×	×		×				
Cumulative dose of esketamine hydrochloride		×	×	×	×						
Cumulative duration of esketamine hydrochloride		×	×	×	×						
Cumulative dose of propofol, midazolam and dexmedetomidine		×	×	×	×						
Cumulative duration of propofol, midazolam and dexmedetomidine		×	×	×	×						
Require for frequent suctioning			×	×	×						
Uncontrolled agitation			×	×	×						
Nutrition implementation						×			×		
CAM-ICU and psychotropic drugs			×	×	×	×	×	×	×	×	×

used for delirium											
Adverse events, severe adverse events and adverse events that may related to study drug			×	×	×	×	×	×	×	×	×
Ventilation free day			×	×	×	×	×	×	×	×	×
Vasopressor free days			×	×	×	×	×	×	×	×	×
Length of ICU stay			×	×	×	×	×	×	×	×	×
Length of hospital stay			×	×	×	×	×	×	×	×	×
28-day mortality rate after randomization			×	×	×	×	×	×	×	×	×

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scores as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

BMJ Open

Efficacy and safety of esketamine hydrochloride adjunct to sufentanil for non-surgical patients under mechanical ventilation in the ICU (SENSATION trial): protocol for a multicentre, single-blind, randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-084469.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Aug-2024
Complete List of Authors:	Long, Yi; Chongqing University Cancer Hospital, Department of Critical Care Medicine Hong, Donghuang; Fujian Provincial Hospital, Department of Critical Care Medicine Ni, Haibin; Nanjing University of Chinese Medicine, Department of Critical Care medicine Zhou, Dandan; Nanjing University of Chinese Medicine, Department of Critical Care medicine Zhou, Tingfa; Linyi People's Hospital Liu, Songwu; Linyi People's Hospital Luo, Xiang; Fujian Medical University Affiliated Longyan First Hospital, Department of Critical Care Medicine Liu, Qian; Chongqing University Cancer Hospital, Department of Critical Care Medicine Li, Rui; Chongqing University Cancer Hospital, Department of Critical Care Medicine Jiang, Zhengying; Chongqing University Cancer Hospital Ke, Lu; Nanjing Jinling Hospital, Department of Critical Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia, Pharmacology and therapeutics
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, PAIN MANAGEMENT, Randomized Controlled Trial

Efficacy and safety of esketamine hydrochloride adjunct to sufentanil for non-surgical patients under mechanical ventilation in the ICU (SENSATION trial): protocol for a multicentre, single-blind, randomised controlled trial

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Abstract

Introduction: Pain is common in patients receiving mechanical ventilation in the intensive care unit (ICU). Intravenous opioids are recommended as the first-line therapy for pain management; however, opioids have adverse side effects. Thus, low-dose ketamine is recommended as an opioid adjunct to reduce opioid consumption, based on low-quality evidence. Esketamine is an alternative to ketamine with greater efficacy and fewer side effects. However, evidence on the use of esketamine in patients receiving mechanical ventilation is lacking; thus, this study investigates the efficacy and safety of esketamine as an adjunct to sufentanil for analgesic therapy in nonsurgical ICU patients under mechanical ventilation.

Methods and analysis: This ongoing multicentre, single-blind, randomised controlled trial is being conducted at six ICUs in China. 132 nonsurgical patients under mechanical ventilation will be randomly assigned to the standard care and S-ketamine groups in a 1:1 ratio. Patients in the standard care group received a minimal dose of sufentanil as the sole analgesic agent. Patients in the S-ketamine group received a minimal dose of sufentanil in addition to an esketamine infusion at a fixed rate of 0.2 mg/kg/h for analgesia. The primary outcome is mean hourly sufentanil consumption during the treatment period.

Ethics and dissemination: This study was approved by the Ethics Committee of Chongqing University Cancer Hospital (CZLS2022067-A). Participants are required to provide informed consent. The results of this trial will be reported in peer-reviewed journals and presented at conferences.

Trial registration: The trial was registered in the Chinese Clinical Trial Registry on April 20th,

2022, ChiCTR2200058933.

Strengths and limitations of this study

- This is a multicenter, randomised controlled trial to evaluate the efficacy and safety of esketamine as an adjunct to sufentanil for analgesic therapy in nonsurgical ICU patients under mechanical ventilation.
- The study population is limited to nonsurgical patients, which helps reduce bias caused by postoperative pain.
- The study is single-blind only.
- The study population is limited to nonsurgical ICU patients under mechanical ventilation who do not require deep sedation or neuromuscular blockers, which may limit the generalisability of the results to other ICU patients.
- The effect of esketamine on chronic pain and post-intensive care syndrome will not be assessed.

INTRODUCTION

Pain is inevitable in mechanically ventilated patients in the ICU and is associated with poor outcomes. [1-3] Intravenous opioids are recommended as first-line therapy for pain management. [4] However, opioids have troublesome side effects, such as unexpected sedation, delirium, respiratory depression, and ileus. [5] A prior prospective cohort study demonstrated that adverse drug reactions in the surgical ICUs were mainly caused by opioids, which increased the length of ICU stay by 53.2%. [6] Furthermore, the use of opioids in nonsurgical ICU patients is associated with persistent opioid use. [7 8] There is a growing concern that new persistent opioid use may be contributing to the "opioid crisis". [9-11]

Current guidelines suggest that non-opioids should be used as adjuncts in ICU analgesia to reduce opioid consumption. [5] However, commonly used non-opioids, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), may aggravate pre-existing organ dysfunction in critically ill patients. [12-15] Acetaminophen-induced hypotension is common in critically ill patients, and acetaminophen hepatotoxicity is the leading cause of acute liver failure. [13 16] NSAIDs have a weak opioid-sparing effect but may increase the risk of AKI and gastrointestinal bleeding. [17-19] Nefopam has significant opioid-sparing effects; however, there is a risk of increased heart rate and mild decrease in mean arterial pressure in critically ill patients. [18 20] Moreover, nefopam is not available in many places outside Europe.

Ketamine is an N-methyl-D-aspartate (NMDA) receptor inhibitor with a short half-life and minimal adverse effects on the respiratory and circulatory systems and is used for anaesthesia and analgesia. Anaesthetic doses of ketamine can cause side effects, such as hallucinations and cognitive

impairment, while low-dose ketamine has good analgesic effects with fewer side effects than anaesthetic doses of ketamine.[21] Based on the limited evidence obtained in surgical patients, the guidelines recommend the adjuvant use of low-dose ketamine to reduce opioid consumption.[5] However, the analgesic effect of ketamine in ICU patients under mechanical ventilation remains controversial, especially in nonsurgical patients.[22 23] Esketamine (S-ketamine) is a right-handed enantiomer of ketamine with three times the potency of R-ketamine and twice that of racemic ketamine.[24] Esketamine may reduce opioid consumption in patients outside the ICU and have fewer side effects than ketamine.[25-28] To our knowledge, there are no studies demonstrating the efficacy and safety of esketamine for analgesia in nonsurgical ICU patients under mechanical ventilation. This study was designed to assess whether esketamine can reduce opioid consumption and the associated clinical outcomes in nonsurgical ICU patients under mechanical ventilation.

METHODS AND ANALYSIS

Design

This is a multicentre, single-blind, randomised, controlled trial. The study design followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Supplementary Table S1). A flowchart of the study is shown in Figure 1. This is version 1.2 of the protocol, from the 18th of May 2022.

Setting

This ongoing study is being conducted in the ICUs of tertiary hospitals, including Chongqing University Cancer Hospital, Jinling Hospital, Fujian Provincial Hospital, Longyan First Hospital

Affiliated to Fujian Medical University, Linyi City People Hospital, and Jiangsu Province Hospital of Integrated Chinese and Western Medicine.

Eligibility criteria, recruitment, and informed consent

Inclusion criteria

1. Age between 18 and 70 years.

2. Non-surgical patients (Defined as not undergoing surgery classified as grade 2 or above in the "Management Measures for Surgical Grading in Medical Institutions" established by the Chinese Ministry of Health within one week).

3. Patients were intubated and mechanically ventilated within 12 hours and expected to require ventilation for longer than 48 hours.

Exclusion criteria

1. Pregnant or breast-feeding.

2. Medical condition prevented assessment of RASS and CPOT.

3. Contraindications to esketamine hydrochloride.

4. Contraindications to sufentanil, propofol, midazolam, or their excipients.

5. Require deep sedation (RASS≤-4) or continuous infusion of neuromuscular blocker or both.

6. Suspected or proven acute primary brain injury (traumatic brain injury, cerebral infarction, intracranial haemorrhage, spinal cord injury, hypoxic-ischaemic encephalopathy, hydrocephalus, or cerebral oedema).

7. Ejection Fraction <30%, cardiogenic shock, and acute myocardial infarction.

8. Endogenous creatinine clearance rate <30 mL/min.

9. End-stage liver disease (Child-Pugh grade C).

10. Require surgery or tracheotomy within 48 hours.

11. Ketamine or esketamine hydrochloride is required due to status epilepticus or other diseases.

12. History of drug or alcohol abuse or both.

13. Palliative care or expected to die within 48 h.

14. History of dementia or mental illness, or require psychotropic medication.

15. Refusal to sign the informed consent form.

16. Participating in clinical trials of other drugs, or having participated in other clinical trials within 30 days.

17. As determined by the clinician, does not require opioids for analgesia.

Recruitment and informed consent

The objectives, potential risks, and benefits of this trial will be presented to the patients or their

surrogate decision-makers. Randomisation and study intervention will begin after obtaining written informed consent. If written informed consent cannot be obtained within 12 hours of intubation, randomisation and timely intervention may start when verbal consent is obtained from the patients or their surrogate decision-makers, and written consent will be obtained later. The translated patient consent form is attached as a Supplementary File.

Randomisation, allocation, and concealment

Permuted-block randomisation stratified by the study site was used in this trial. Block lengths ranging from four to eight were used. Random allocation was performed using Interactive Web Response Systems (IWRS). Eligible patients were randomly allocated in a ratio of 1:1 to the standard care and S-ketamine group. Before being randomized, the choice of analgesic and sedative drugs and dose titration were determined by the patient's treatment physician. Since the randomization is done through IWRS, the investigators, treatment teams, and patients will not know the allocation until randomisation is completed. In this way, the allocation concealment is ensured.

Blinding

The grouping of interventions will be kept strictly confidential to patients until the results of the study are revealed. Several specialized personnel (blind assessors) will be established at each study site for CPOT and RASS assessments, and the study groupings will remain confidential to them. The treatment team will titrate the analgesics and sedatives according to the blind assessors' assessments, in accordance with this study protocol and their experience. In addition, the study

grouping will maintain the confidentiality of the outcome assessors and the trial statisticians who analysed the data.

Interventions

Administration and dosage adjustment of analgesics

Standard care group

In the standard care group, a minimal dose of sufentanil is used as the sole analgesic for pain management. The recommended sufentanil loading dose is 0.1–0.5 μg/kg, with an initial dose of 0.3 μg/kg/h and a range of 0.15–0.7 μg/kg/h that can be adjusted at the discretion of the patient's treating physician. Sufentanil was titrated to the minimum dose required to maintain the analgesic goal. The analgesic goal is to maintain CPOT≤ 2. An intravenous bolus of sufentanil is allowed when there is a procedure or treatment ordered by a physician. CPOT will be reassessed every 2–4 hours, and the dose of sufentanil will be adjusted based on the CPOT assessment. Other analgesic measures (such as massage, music, and relaxation techniques) of the standard care group will follow international guidelines and be determined by the treating physician. [5]

S-ketamine group

In the S-ketamine group, esketamine hydrochloride (Hengrui Pharmaceutical Co., Ltd.) was infused at a rate of 0.2 mg/kg/h in addition to the minimal dose of sufentanil for pain management. Sufentanil would be administered in the same manner as that in the standard treatment group, and esketamine hydrochloride will be administered within 1 h of randomisation. CPOT will be reassessed every 15–30 min after the administration of esketamine hydrochloride. If CPOT≤ 2, the dose of sufentanil will be reduced by 10%; if CPOT>2, the dose of sufentanil will be increased by

10%; repeat this process and titrate the dose of sufentanil to the minimum dose that can maintain CPOT ≤ 2. The esketamine hydrochloride dose will remain unchanged throughout the study period. Unless the patient remains over sedated when the administration of sufentanil and sedatives has stopped, esketamine hydrochloride will be reduced in a gradient of 0.05 mg/kg/h until the sedation goal is achieved. The analgesic goals and other analgesic measures in the S-ketamine group will be the same as those in the standard care group. The analgesic dosing algorithm for the S-ketamine group is shown in Figure 2.

Duration of the intervention

For the standard care group, the intervention will stop when the following events occur (whichever occurs first): 1) 72 hours after randomisation. 2) Analgesics are not required due to extubation or other medical reasons, as determined by the treatment team. 3) Patient dies. 4) Patient requires surgery or tracheotomy. 5) Patient requires deep sedation or neuromuscular blockers. 6) Treatment goals shift to palliative care.7) Severe adverse event occurred (see definition of the severe adverse event). 8) Patients or family members withdraw informed consent. 9) Unable to accurately assess CPOT and RASS scores due to changes in disease status. For the S-ketamine group, in addition to the criteria for the standard care group, the intervention will also be discontinued if the criteria for discontinuation of esketamine hydrochloride are met. The criteria for discontinuation of esketamine hydrochloride are shown in Supplementary Table S2.

Management of sedation, delirium, sleep disturbance, and immobility

The management of sedation will follow the guideline recommendations and will be the same in both groups, and the target RASS for both groups ranges from -2 to 1. Propofol is the sedative of choice, with midazolam as an alternative. Based on the recommendations of the guidelines and the widely accepted eCASH principle, a relevant sedation algorithm was established (Figure 3). The management of delirium, immobilisation, and sleep disturbance will follow the recommended guidelines.

Mechanical ventilation and weaning

Mechanical ventilation will be implemented according to practical guidelines. [29] Mechanical ventilation in patients with ARDS should follow the lung-protective ventilation strategy, including the use of lower tidal volumes (4–8 mL/kg predicted body weight) and lower inspiratory pressures (plateau pressure<30 cm H_2O). [30]

Weaning from mechanical ventilation will follow the practical guidelines for mechanical ventilation. [29] The specific processes include weaning screening, spontaneous breathing test (SBT), airway patency assessment, and airway protection ability assessment. Patients who pass the SBT with good airway patency and protection will be weaned off and extubated.

Other therapies

It is not recommended to use analgesics other than sufentanil and esketamine hydrochloride in either group. Acetaminophen and NSAIDs can be used as antipyretics; however, their use should be

recorded in detail. Nutritional therapy in both groups needs to follow the recommendations of relevant guidelines and refer to the "Nutrition Support Process for Critically Ill Patients." [31 32] Treatment of the primary disease and comorbidities in both groups follows the corresponding guidelines and is determined by the medical team. Other symptomatic and supportive treatments determined by the patient's medical team may also be provided.

Follow-up

All subjects will be followed up for 28 days after randomisation or until the patient's death, whichever occurs first. The indicators involved in the study are evaluated and recorded according to the study schedule (Supplementary Table S3).

Data collection and management

A web-based database has been established for data collection, and the principal investigator and coinvestigator at each research site have access to a database. Data entered and modified by investigators at each research site are based on the original data. The accuracy and compliance of the data will be audited by the principal investigator and coordinating centre. Once errors or omissions are found, specific personnel are asked to clarify the data and make corrections. The principal investigator will hold a training session for all co-investigators involved in data collection before the commencement of the study to avoid inconsistencies in data collection. Range editing and value checking have been incorporated into the database to reduce data entry errors.

Outcomes measures

Primary outcome

The primary outcome is mean hourly sufentanil consumption during the treatment period, which is defined as the time from randomisation to the end of the intervention. The study intervention will be stopped according to the pre-specified criteria described in section 2.5.2.

Secondary outcomes

1. The mean hourly consumption of sedatives during the treatment period.

2. The CPOT and RASS assessment every 4 hours during the treatment period.

3. The mean hourly consumption of sufentanil on the 5th day after randomisation.

4. The proportion of requiring frequent suctioning during the treatment period.

5. The proportion of uncontrolled agitation during the treatment period.

6. The SOFA score in the first 7 days after randomisation (in ICU).

7. The APACHE-II score of the 7th day after randomisation (in ICU).

8. Liver function, renal function, and myocardial enzyme in the first 3 days and the 7th day after randomisation (in ICU).

9. AGI score, enteral nutrition tolerance score, gastric residual volume, and intra-abdominal pressure in the first 7 days after randomisation (in the ICU).

10. Nutrition compliance rate on the 4th and 7th day after randomisation (in ICU).

11. The incidence of ICU delirium, the number of delirium days, and the proportion of psychotropic drugs used for delirium (a positive CAM-ICU assessment is considered as delirium).

12. Ventilation-free day in 28 days.

13. Vasopressor-free day in 28 days.

14. Adverse events (AE), severe adverse events (SAE), and adverse events that may be related to the study drug.

15. Length of ICU stay in 28 days.

16. Length of hospital stay in 28 days.

17. 28-day mortality after randomisation.

Adverse events

Investigators and treatment teams will closely monitor possible and unexpected adverse events as well as severe adverse events during the trial. Adverse events (AEs) are defined as any untoward medical occurrence in a patient who received an investigational intervention. A serious adverse event is defined as any serious medical event that causes death, life-threatening conditions, prolonged hospital stay, persistent disability or dysfunction, or other unpredictable serious medical events. The causal relationship between the adverse events and the study drug will be classified as certain, probable, possible, unlikely, or uncertain. Any adverse events will be treated appropriately and recorded, and severe adverse events will be reported by the principal investigators. We have not set up a study-specific DMC for this trial. Alternatively, we are required to submit adverse events without assignment information to the IRB once a year.

Sample size calculation

Previous studies have shown that consumption of morphine in surgical intensive care unit patients

after major abdominal surgery was reduced by 25% in 48 h (80 ± 37 mg vs 58 ± 35 mg) when ketamine was administered with an initial dose of 0.5 mg/kg followed by a perfusion of 2 μg/kg/min during the first 24 h and 1 μg/kg/min in the following 24 h. [33] According to the single-centre data from Chongqing University Cancer Hospital, the mean hourly consumption of sufentanil in mechanically ventilated patients may be reduced by about 26% (0.23±0.10 μg/kg/h vs 0.17±0.09 μg/kg/h) when a dose of 0.2 mg/kg/h of esketamine hydrochloride adjunct to sufentanil. We conservatively anticipate that the mean hourly consumption of sufentanil will decrease by 20% when a dose of 0.2 mg/kg/h of esketamine hydrochloride adjunct to sufentanil is applied (μ1=0.94, μ2=0.75, σ=0.35), with a power of 90% and an α error of 0.05 (two-side), a sample size of 120 subjects is needed which calculated by software of PASS 11.0. This number was 60 in the standard group and 60 in the S-ketamine group. Considering the possibility of dropouts, a sample size of 132 study participants was planned (10% inflation), including 66 in the standard care group and 66 in the S-ketamine group.

Statistics analysis

The primary comparative analysis will be based on the intention-to-treat (ITT) population, and secondary supportive analyses will be done on the PP population. The safety analysis will be performed on the safety population. Missing data will be handled by multiple imputations to evaluate the robustness of the primary endpoint analyses. The normality distribution of the variables was tested using the Shapiro–Wilk test. All numerical continuous variables will be presented by the mean ± standard deviation (SD) or medians ± interquartile ranges (IQR), according to whether they obey the normal distribution. Counting and Categorical variables will be presented as proportions,

frequencies, or percentages. Normally distributed continuous variables will be statistically analysed using Student's t-test, and non-normally distributed continuous variables will be statistically analysed using the Wilcoxon rank sum test. Counts and categorical variables will be statistically analysed using the chi-square test or Fisher's precision probability test. For the primary outcome, a generalized linear mixed model (GLMM) will be used to compare group differences. In the GLMM model, the mean hourly sufentanil consumption during the treatment period will be treated as the response variable following a gaussian distribution and the esketamine intervention as fixed effect and site as the random effect, and the identity link function will be used. Additionally, some prespecified variables were pre-planned as covariates, including age, gender, body mass index (BMI) and baseline Acute Physiology and Chronic Health Evaluation II (APACHE II). From this model, the difference of the mean hourly sufentanil consumption during the treatment period and its two-sided 95% CI for the group comparison will be estimated. For the secondary outcomes, the GLMM models were also used, and the identity-gaussian models will be used for continuous endpoints, and log-binomial models for categorical endpoints. If the above log-binomial regression model does not converge, the Mantel-Haenszel method will be used to calculate the RR and its 95% CI stratifying by the site. If the above continuous endpoints do not fulfill the normal distribution assumption of the models, data conversions (including log, reciprocal, and square root transformations) will be performed. The P-values will be reported with two decimal points, all tests will be 2-sided, and p-values with a level of significance of <0.05 will be considered statistically significant. No interim analysis was planned in our study.

Patient and public involvement

None.

Study status

The trial was registered on 20 April 2022, and the first patient was randomised on 23 June 2022. The planned end date for the study was originally 30 November 2023. However, due to various factors, the recruitment process was slower than expected. At the time of writing, 55 patients have been randomised, and enrolment is ongoing.

ETHICS AND DISSEMINATION

This study was approved by the Ethics Committee of Chongqing University Cancer Hospital (ethical approval document ID CZLS2022067-A). The research sites obtained ethical approval from local ethics committees. Participants are required to provide informed consent. The results of this trial will be reported in peer-reviewed journals and presented at conferences.

DISCUSSION

Although the guidelines recommend the use of multimodal analgesia to reduce the adverse effects of opioids, only approximately one-third of mechanically ventilated ICU patients are administered nonopioids for pain management.[5 20] This partly relates to the adverse effects of currently used non-opioids and the lack of solid evidence; therefore, it is necessary to expand the analgesic arsenal and

to provide stronger evidence. Esketamine has the potential to reduce opioid consumption. Several randomised trials that evaluated the analgesic effects of esketamine are ongoing outside the ICU. [34-36] Song, X et al. conducted a single-arm clinical study on esketamine in combination with remimazolam tosilate for analgesic sedation in mechanically-ventilated ICU patients. [37] To our knowledge, this is the first parallel randomised trial to evaluate the efficacy and safety of esketamine as an opioid adjuvant for analgesia in critically ill patients under mechanical ventilation.

Previous studies have revealed that high-dose ketamine causes anaesthesia and is associated with side effects, such as hallucinations and delirium, whereas low-dose ketamine delivers promising analgesic effects and is less likely to cause side effects. [38] Ketamine was considered as low dose at an infusion rate of 0.1–0.5 mg/kg/h. [23 33 39 40] Esketamine is theoretically twice as potent as racemic ketamine. [25] Based on the abovementioned data, the fixed infusion rate of 0.2 mg/kg/h of esketamine hydrochloride was adopted in this study, which is similar to the dose selected by Song et al. [37]

Per the guidelines, carefully titrated analgesic dosing is important to balance the benefits and potential risks of opioid exposure. [5] In this study, the sufentanil dose was minimised to achieve the analgesic goal. Therefore, as in other studies, the mean hourly consumption of sufentanil was chosen as the primary outcome because it illustrates the analgesic effects of esketamine and reflects the potential benefits of reducing opioid consumption. [23 33 41] Since different analgesic drugs and analgesic measures may affect analgesic and sedative effects in addition to patient outcomes, analgesic effects, organ function, and other outcomes were included as secondary outcomes. [42 43]

Opioid agonists (particularly u-opioid receptor agonists) are associated with gastrointestinal motility dysfunction. [44] It has been demonstrated that ketamine-based anaesthesia reduces gastrointestinal

inhibition compared to fentanyl-based anaesthesia, and food intake improves when analgesic sedation was switched to ketamine,.[45 46]; thus our study assessed whether esketamine had a similar effect. Finally, the adverse effects of ketamine in mechanically ventilated patients in the ICU are of great concern and controversial, and the common adverse effects of ketamine (such as delirium and increased secretions) were also included as secondary outcomes.[23 47]

The time window for randomisation and initiation of the intervention in this study was narrow enough to be in line with clinical practice and guidelines.[23 27 48 49] Given the short intervention period of the study, delayed administration of the study drug may lead to false-negative results; therefore, esketamine was required to be administered within 1 h after randomisation.

The following measures were taken to control for bias in this study: (1) Randomisation and allocation concealment. 2) The study population was limited to nonsurgical patients to avoid the impact of postoperative pain. 3) Patients with factors that may affect the drug response and analgesic evaluation were excluded. 4) The treatment team and scoring assessors were independent. The assessors were unaware of the study groupings, the treatment team adjusted the dosage based on the assessors' results, and all patients followed the same analgesic approach (using the minimum dose of sufentanil to achieve the analgesic goal). 5) A dose adjustment algorithm was developed for the S-ketamine group to avoid bias caused by differences in analgesic modulation at different study sites. 6) The study protocol was discussed and trained to ensure that it was fully understood and strictly implemented by the researchers at each participating site.

This study had some limitations. First, this is not a double-blind study. Although efforts have been made to control bias, the single-blind design of the study could not completely avoid bias. Second,

the study population was limited to nonsurgical ICU patients under mechanical ventilation who did not require deep sedation or neuromuscular blockers, which may limit the generalisability of the results to other ICU patients. Thirdly, the effect of esketamine on chronic pain and post-intensive care syndrome was not observed in this study. Nevertheless, recent investigations have indicated that ketamine might be associated with chronic pain.[50]

In conclusion, the results of this trial may reveal whether low-dose esketamine can reduce opioid usage in nonsurgical patients under mechanical ventilation and whether it is associated with clinical improvements.

Declarations

Contributors

All authors (YL, DH, HN, DZ, TZ, SL, XL, QL, RL, ZJ and LK) were involved in the study design. YL, DH, HN, DZ, TZ, SL, QL and RL are responsible for carrying out recruitment, managing the treatment of the patients and collecting data. YL, LK, and ZJ drafted the protocol and wrote the present protocol manuscript, and all authors (YL, DH, HN, DZ, TZ, SL, XL, QL, RL, ZJ and LK) have read and edited the manuscript and approved the submission of the final manuscript. YL is responsible for the overall content (as guarantor). The investigators take full responsibility for the integrity and content of this paper.

Competing interests

None declared.

Funding

This study was supported by the Chongqing Joint Medical Scientific Research Project of Science and Health (grant no. 2020FYYX091) and Chongqing Science and Technology Committee (grant no. cstc2017shmsA130057). The study protocol was peer-reviewed by the funding bodies. The funding bodies had no role in the design of the study and will have no role in the data collection, analysis, interpretation, or reporting of the results.

Consent for publication

Not applicable.

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FIGURE TITLES

Figure 1. Study flowchart

Figure 2. Analgesics dosing algorithm of the S-ketamine group

Figure 3. Sedation algorithm

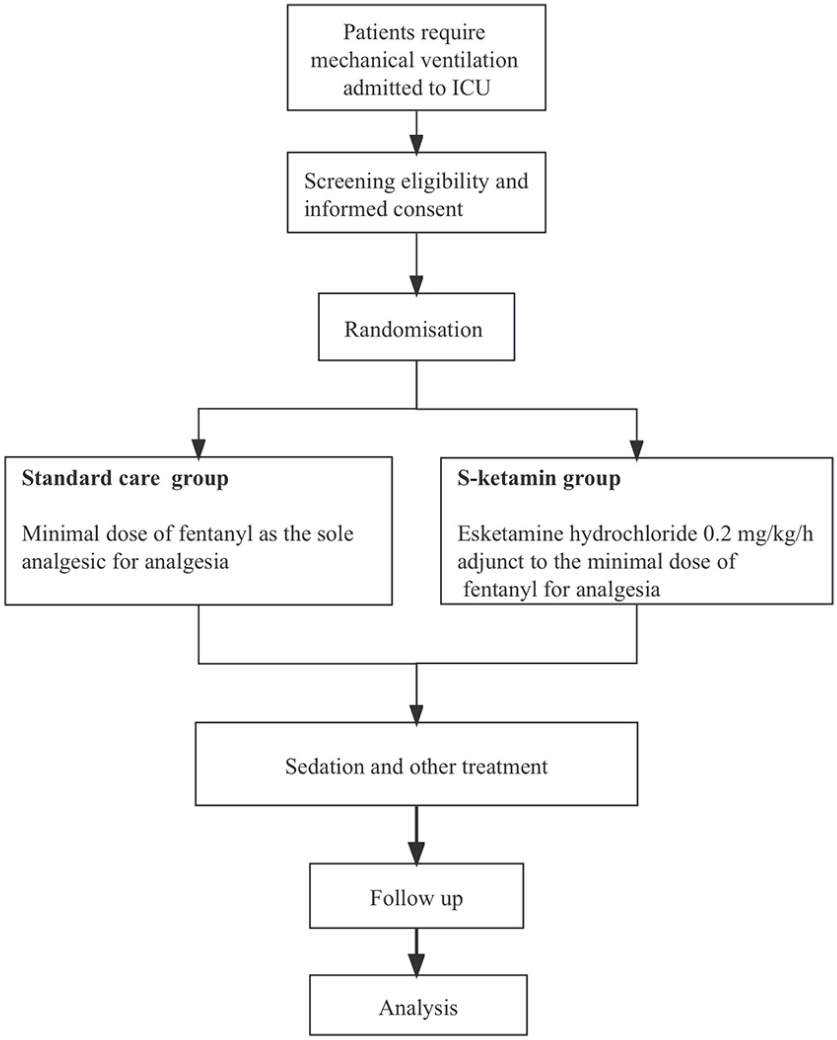

Figure 1 Flow chart of study.

Figure 1：Flow chart of study.

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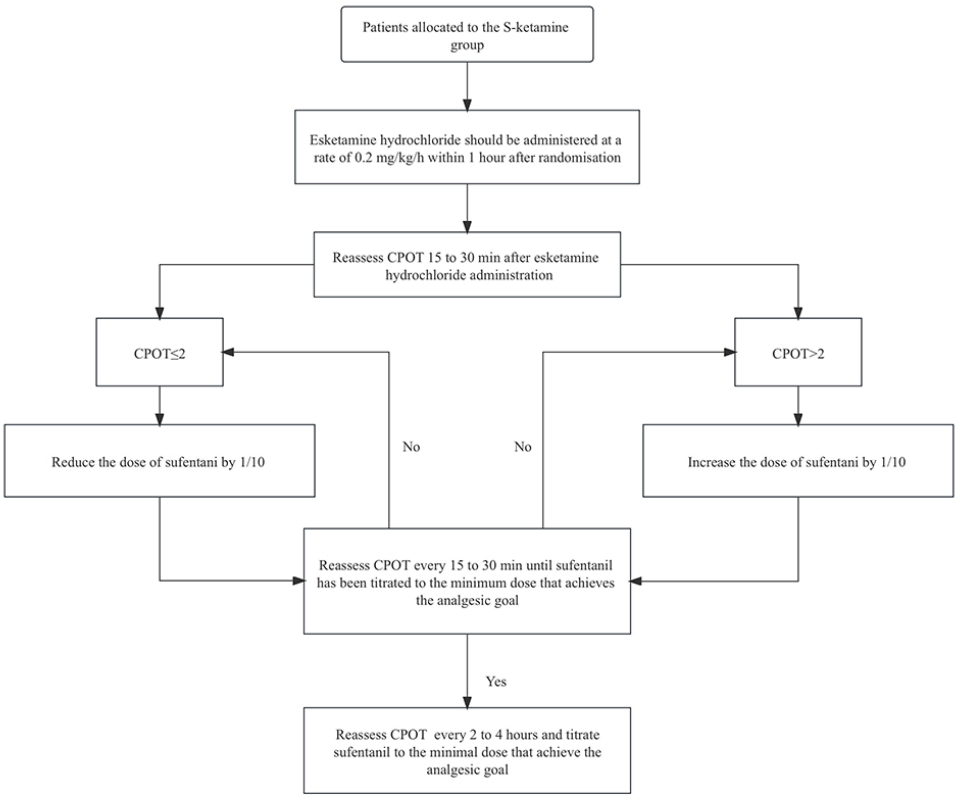

Figure 2 Analgesics dosing algorithm of the S-ketamine group.

Figure 2. Analgesics dosing algorithm of the S-ketamine group.

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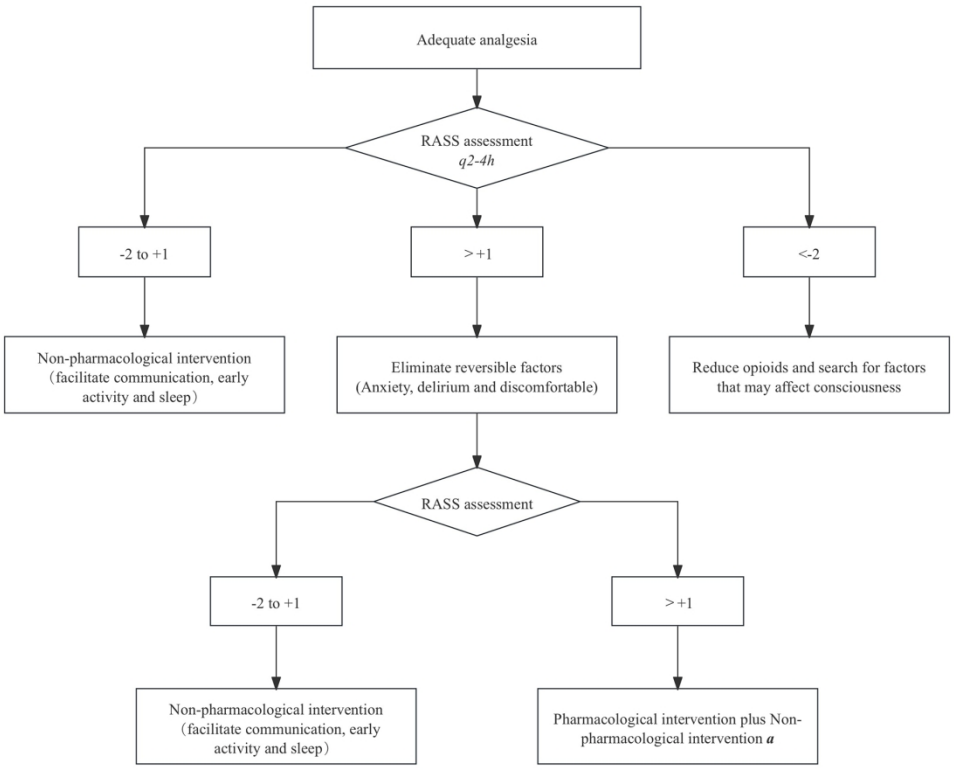

Figure 3 Sedation algorithm. ***a*** In this study, propofol (loading dose 5μg/Kg/min, maintenance dose 5-50μg/Kg/min) was used as the preferred sedative, midazolam (loading dose 0.01–0.05mg/Kg, maintenance dose 0.02–0.1 mg/Kg/h) was used as the alternative sedative, other sedatives include cycloprofen (loading dose 0.1mg/Kg, maintenance dose 0.3-0.8mg/Kg/h) and lorazepam (loading dose 0.02–0.04mg/Kg, maintenance dose 0.01–0.1mg/Kg/h), and dexmedetomidine (no loading dose, 0.2–0.7μg/Kg/h) was not recommended as the main sedative.

Figure 3. Sedation algorithm.

173x164mm (300 x 300 DPI)

Supplementary Table S1: SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	page/line numbers
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/Line1-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3/Line43-44
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	P6/Line 95-96
Funding	4	Sources and types of financial, material, and other support	P22/Line394-398
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1/Line5-17 and P21/Line378-383
	5b	Name and contact information for the trial sponsor	P1/Line5-8 and the registration information.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P22/Line395-399
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Detail in aggrement
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P5/Line60-P6/Lline90
	6b	Explanation for choice of comparators	P5/Line68-76 And P18 Line319-321
Objectives	7	Specific objectives or hypotheses	P6/Line87-90

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P6/Line93-96
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P6/Line98-P7/Line101
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P7/Line104-P8/Line131
Interventions	11a	Interventions for each group with and sufficient detail to allow replication, including how when they will be administered	P10/L158-P11/Line193
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P11/Line185-194
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P12/Line194-P13/Line218
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P14/L233-P15/L258
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Supplementary Table S3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P15/Line271-P16/Line284
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P9/Line133-138
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P9/Line142-144
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P9/Line143-149
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9/Line144-149
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P9/Line151-P10/156
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P13/Line 224-231 And The handbook for researchers
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P13/Line 220-222
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P13/Line225-231 And The handbook for researchers
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P16/Line286-P17/Line312
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P17/Line296-310
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P16/Line286-288

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P15/Line267-269
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P17/Line310-312
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	From P15/Line260-269
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P21/Line390-393
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P9/Line133-139
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in the ICF
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Detail in the ICF
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P21/Line385-388
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Detail in aggrement
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Detail in the ICF

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P21/L392-393
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary document-ICF
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary Table S2: Criteria for discontinuation of esketamine hydrochloride

Event	Discontinuation criteria and management (esketamine hydrochloride)	Data processing
72 hours after randomization	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Patient or family member withdraw the informed consent	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Patient died	Stop esketamine hydrochloride infusion	Data will be included in the analysis
Analgesics are not required due to extubation or other medical reasons	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Require deep sedation or neuromuscular blockers	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Severe heart failure (EF<30%), cardiogenic shock or acute myocardial infarction	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the Electronic Data Collection System（EDC）	Follow up, data will be included in the analysis
Acute liver failure	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Renal dysfunction that probably caused by esketamine	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Require Surgery or tracheotomy	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Unable to accurately assess CPOT and RASS score	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Uncontrolled agitation (pulling off artificial airway, tubes or lines and combative behavior)	If it is related to esketamine hydrochloride, the infusion stops; if not, the infusion continues. Adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Uncontrollable hypertension (SBP≥180mmHg, DBP ≥100mmHg) lasting more than 3 hours		
Other sever adverse events that the treating team believes may be related to esketamine hydrochloride	Stop esketamine hydrochloride infusion, the adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis

Esketamine hydrochloride infusion should be discontinued when any of the events listed in the table occur, whichever occurs first, but patient follow-up should continue.

Supplementary Table S3 : Study schedule

Time point	-D1	D0	D1	D2	D3	D4	D5	D6	D7	D...	D28
Enrolment											
Eligibility screen	×										
Informed consent	×										
Allocation		×									
Intervention											
Intervention of the standard care group		×	×	×	×						
Intervention of S-ketamine group		×	×	×	×						
Assessment											
Baseline demographics	×										
Diagnosis	×										
Comorbidity	×										
Mechanically ventilation duration before randomization		×									
Cumulative dose of sufentanil before randomization		×									
SOFA score		×	×	×	×	×	×	×	×		
APACHE-Ⅱ score		×							×		
AGI and enteral nutritional tolerance score（daily）		×	×	×	×	×	×	×	×		
Gastric residual volume and intra-abdominal pressure （every 12 hours）		×	×	×	×	×	×	×	×		
Liver function, renal function, and myocardial enzymes		×	×	×	×				×		
RASS and CPOT（every 4 h）		×	×	×	×						
Cumulative dose of sufentanil		×	×	×	×		×				
Cumulative duration of sufentanil		×	×	×	×		×				
Cumulative dose of esketamine hydrochloride		×	×	×	×						
Cumulative duration of esketamine hydrochloride		×	×	×	×						
Cumulative dose of propofol, midazolam and dexmedetomidine		×	×	×	×						

Cumulative duration of propofol, midazolam and dexmedetomidine		×	×	×	×						
Require for frequent suctioning			×	×	×						
Uncontrolled agitation			×	×	×						
Nutrition implementation						×			×		
CAM-ICU and psychotropic drugs used for delirium			×	×	×	×	×	×	×	×	×
Adverse events, severe adverse events and adverse events that may related to study drug			×	×	×	×	×	×	×	×	×
Ventilation free day			×	×	×	×	×	×	×	×	×
Vasopressor free days			×	×	×	×	×	×	×	×	×
Length of ICU stay			×	×	×	×	×	×	×	×	×
Length of hospital stay			×	×	×	×	×	×	×	×	×
28-day mortality rate after randomization			×	×	×	×	×	×	×	×	×

INFORMED CONSENT FORM

Patients and family members:

We invite you to participate in a multi-center clinical study sponsored by us. Before deciding whether to participate in this study, please read the following carefully. If you have any questions, you can further consult with the researcher or discuss with your relatives or friends.

TITLE OF STUDY:Feasibility and safety of esketamine hydrochloride adjunct to sufentanil for non-surgical patients under mechanical ventilation in ICU (The SENSATION trial): Study protocol for a multicentre, single-blind, randomised, controlled trial.

VERSION NUMBER OF PROTOCOL:1.2

VERSION NUMBER OF THE Informed Consent Form: ZQ 1.2
PRINCIPAL INVESTIGATOR: Yi Long

Part 1: Notice to Participants

WHY IS THIS STUDY BEING DONE?

Pain is common in patients receiving mechanical ventilation in the intensive care unit (ICU). Intravenous opioids are recommended as the first-line therapy for pain management. However, opioids have troublesome side effects, such as unexpected sedation, delirium, respiratory depression, and ileus. Current guidelines suggest that non-opioids should be used as adjuncts in ICU analgesia to reduce opioid consumption.However, commonly used non-opioids such as acetaminophen and NSAIDs also have potential adverse effects on critically ill patients. Low-dose ketamine is recommended as an opioid adjunct to reduce opioid consumption based on low-quality evidence, and esketamine is an alternative to ketamine with greater efficacy and fewer side effects. However, evidence on the use of esketamine in patients receiving mechanical ventilation is lacking. This study investigated the feasibility and safety of esketamine as an adjunct to sufentanil for analgesic therapy in nonsurgical ICU patients under mechanical ventilation.

WHAT WILL HAPPEN IN THE STUDY?

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. Neither you nor the study doctor will

choose what group you will be in. You will have an equal chance of being placed in either group.

Standard care group

In the standard care group, a minimal dose of sufentanil is used as the sole analgesic for pain management. Sufentanil was titrated to the minimum dose required to maintain the analgesic goal. The analgesic goal is to maintain CPOT≤ 2. CPOT will be reassessed every 2–4 hours, and the dose of sufentanil will be adjusted based on the CPOT assessment. Other analgesic measures (such as massage, music, and relaxation techniques) will follow guidelines and be determined by your treating physician.

S-ketamine group

In the S-ketamine group, esketamine hydrochloride (Hengrui Pharmaceutical Co., Ltd.) was infused at a rate of 0.2 mg/kg/h in addition to the minimal dose of sufentanil for pain management within 1 h of randomisation. After the start of ketamine infusion, the dose of sufentanil will be titrated according to the predetermined plan and the advice of your treating physician.

You will receive a maximum of 72 hours of study intervention and 28 days of follow-up. However, You can withdraw from this study at any time. If you decide to withdraw from this study, please let your doctor know.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We are not sure if you can benefit from the research yourself. The results of this study could help future patients with your condition.

WHAT ARE THE RISKS OF THE STUDY?

Any therapeutic agents have the potential for side effects. The possible side effects of ketamine hydrochloride include hallucinations, delirium, elevated intraocular pressure, thyroid dysfunction, respiratory depression, hypertension or hypotension, drug addiction, etc.There also may be other side effects that we cannot predict. These side effects are often manageable and reversible. You will be observed for side effects, and all medically appropriate efforts will be made to prevent and/or control them. If there are side effects that cannot be controlled or reversed, they may result in serious injury or death.

The treating physician will try to prevent and treat any potential harm caused by this study. If there is any discomfort or unexpected situation during the study, please inform your study doctor immediately, who will make a judgment and provide medical treatment.

There may be situations where any treatment may be ineffective, and the condition may continue to develop due to ineffective treatment or the combination of other diseases. This is a treatment risk that every patient will face, and even if they do not participate in this clinical study, the risks caused by treatment will still exist. During the research period, if the doctor finds that the treatment measures taken in this study are ineffective, the study will be terminated and other potentially effective treatment measures will be adopted.

WHAT ARE THE COSTS AND COMPENSATION?

Taking part in this study will not lead to added costs to you or your insurance company. The trial drug and related laboratory tests are included in the routine treatment cost. The sponsor will not pay for routine costs required during hospitalization. You will receive no payment for taking part in this study.

WHAT DO YOU NEED TO COOPERATE WITH?

Cooperate with relevant examinations and treatments.

Truthfully inform your doctor about your disease condition.

If you experience any unexpected discomfort during the research period, please inform your doctor promptly.

WHAT ABOUT CONFIDENTIALITY?

Only the medical information that will be collected from you if you take part in this study.The investigator and the ethics committee may have access to your medical records. No public report on the results of this study will disclose your personal identity. We will make every effort to protect the privacy of your personal medical information as permitted by law.

WHAT ARE MY RIGHTS?

Participation in the study depends entirely on your willingness. You may refuse to participate in the study or withdraw at any time during the study, which will not affect your treatment or other benefit.

Your treating physician may suspend your participation in this study at any time during the study, in your best interest. If you withdraw from the study for any reason, you may be asked about your use of the trial drug. You may also need a laboratory and physical examination. This is very good for protecting your health.

Any new information found during the study that may affect your willingness to continue participating in the study will be provided to you and a new informed consent form and request to sign to indicate your willingness to continue participating in the study.

CONTACT INFORMATION

If you have any concerns or questions about the study, or if any emergency occurs, please contact your doctor promptly.

Doctor's name:_____, telephone number: _____

If you have any questions about your rights and interests, you may contact Tang Xiaohua, the Ethics Committee of the Affiliated Cancer Hospital of Chongqing University, telephone number:023-65075696.

Part 2: STATEMENT of CONSENT and AUTHORIZATION

I have read the above introduction to this study and have the opportunity to discuss and ask questions about this study. All the questions I have raised have been answered satisfactorily.

I am aware of the possible risks and benefits of participating in this study and volunteer to participate in this study. I confirm that I have sufficient time to consider this and understand that:

- I can always consult my doctor for more information.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and interests will not be affected.

I am also aware that if I withdraw from the study, especially due to the medication, if I tell the doctor about the changes in my condition and complete the corresponding laboratory and physical examinations, it will be very beneficial to me and the whole study.

If I need to take any other medication due to the change in my condition, I will ask my doctor for his advice in advance or tell him the truth afterwards.

I agree with the relevant management, ethics committee or researchers to consult my research data.

I agree with □ or refuse□ to use my medical records, blood/urine/pathological examination specimens for studies other than this one.

I will obtain a copy of the signed and dated informed consent form.

I decided to consent to participate in this study.

Signature of the Patient/Patient's Legally Authorized Representative:_____

Date:_____

Signature of Witness to consent process:_____Date:_____

I have explained to the patient the details of the trial, including their rights and

possible benefits and risks, and gave them a copy of the signed informed consent form.

Signature of Investigator:_____Date:_____