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ORIGINAL RESEARCH

Effects of Esketamine Versus Remifentanil on Hemodynamics and Prognosis in Patients with Septic Shock Receiving Invasive Mechanical Ventilation: A Randomized Controlled Trial

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Background: Analgesics and sedatives may affect the hemodynamics of patients with septic shock and produce adverse reactions. The purpose of this study is to compare the hemodynamic effects and prognosis of esketamine and remifentanil in combination with propofol in patients with septic shock receiving invasive mechanical ventilation.

Methods: In this single-center, prospective, randomized, controlled pilot study, patients with septic shock in the intensive care unit (ICU) receiving invasive mechanical ventilation were randomized to receive esketamine or remifentanil in combination with propofol intravenously. The target Critical-Care Pain Observation Tool (CPOT) score was <3 points and Richmond Agitation and Sedation Scale (RASS) score was −2~0 points. The primary outcome was dosage of norepinephrine (mg/kg). Secondary outcomes included mechanical ventilation time(hours), dosage of propofol (mg/kg), intestinal dysfunction rate, ICU length of stay(days), hospital length of stay(days), hospital mortality and 28-day survival rate. We registered the study at ClinicalTrials.gov on 23/09/2022 (https://clinicaltrials.gov/study/NCT05551910).

Results: A total of 120 patients were enrolled in the study. Sixty patients were assigned to each group. The median dosage of norepinephrine of remifentanil group was 4.09(1.52,8.85) mg/kg while that of esketamine group was 1.72(1.01,3.97) mg/kg. The dosage of norepinephrine of esketamine group was less than that of remifentanil group(P=0.007). There were no significant differences between the two groups with respect to adverse event rate, intestinal dysfunction rate, dosage of propofol, mechanical ventilation time, ICU length of stay, hospital length of stay and hospital mortality(P>0.05). Kaplan-Meier survival analysis showed that there was no significant difference in 28-day survival rate between the two groups(P=0.225).

Conclusion: Esketamine may decrease the dosage of norepinephrine in patients with septic shock receiving invasive mechanical ventilation. It is beneficial for stabilizing hemodynamics and appears to be an effective and safe agent for patients with septic shock requiring invasive mechanical ventilation.

Keywords: septic shock, invasive mechanical ventilation, esketamine, remifentanil, norepinephrine

Background

Septic shock refers to sepsis with hypotension and blood lactate level of >2.0mmol/L that cannot be corrected by adequate fluid resuscitation.[1] Although the World Health Organization has declared the management of sepsis and septic shock to be a global health priority,[2] the high morbidity and mortality rates in intensive care units (ICUs) demonstrate that septic shock remains a major medical and economic problem worldwide.[3] Multiple organ dysfunction syndrome-(MODS) is the most dangerous consequence of sepsis, caused by septic shock and an unchecked inflammatory response. Mechanical ventilation is frequently initiated in patients with sepsis to maintain alveolar ventilation and arterial oxygenation.[4,5] Mechanical ventilation provides adequate respiratory support and reduces lung damage, and is one of

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the most commonly used life support measures in septic shock. The need for mechanical ventilation in septic shock patients is the result of multiple pathophysiological conditions that lead to impaired oxygenation and/or ventilation.[6]

Patients with invasive mechanical ventilation (IMV) often experience pain, agitation and delirium. The concept of early comfort using analgesia, minimal sedatives and maximal humane care(eCASH) proposed in 2016 aims to establish optimal patient comfort with minimal sedation as the default presumption for ICU patients in the absence of recognized medical requirements for deeper sedation.[7] The 2018 Pain, Agitation/sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruption) (PADIS) guideline in critically ill adults builds on this mission.[8] Opioids remain the mainstay of pain management in most ICU settings. Remifentanil is an ultra-short-acting μ-opioid receptor agonist, characterized by rapid onset (about 1 minute) and rapid metabolism (with a half-life of approximately 2–3 minutes). Its metabolism is not affected by liver or kidney function, making it widely used in ICUs for analgesia in mechanically ventilated patients. Particularly in situations where rapid adjustment of analgesic levels is needed, remifentanil is widely used due to its characteristics of rapid onset and metabolism. However, due to important safety concerns such as sedation, delirium, respiratory depression, intestinal obstruction, and immunosuppression, their side effects have been troubling clinicians and may prolong the length of stay (LOS) in the ICU and worsen post-ICU patient outcome. The guideline generally supports the use of multimodal pharmacotherapy as a component of an analgesia-first approach to spare/minimize opioid and sedative use and optimize analgesia and rehabilitation.[9]

Esketamine, an antagonist of the N-methyl-D-aspartate(NMDA) receptor antagonist, has twice the analgesic and anesthetic strength of ketamine.[10,11] Studies show it does not suppress breathing and maintains stable hemodynamics, preserving spontaneous respiration and lowering hypoxemia risk at sedative doses.[12] It also reduces propofol-induced hypotension and bradycardia while providing pain relief.[13] Additionally, esketamine-based opioid-sparing anesthesia decreases postoperative nausea/vomiting (PONV) and opioid needs.[14] Based on these studies, the combination of esketamine and propofol may improve the safety and comfort for patients with septic shock requiring analgesia and sedation. However, few studies have explored the application of esketamine in the analgesia and sedation of ICU patients with septic shock so far. Remifentanil has become an important analgesic drug in the ICU due to its ultra-short duration of action and controllability, but its hemodynamic risks need to be weighed in septic shock. Esketamine, on the other hand, has emerged as an alternative choice for analgesics due to its hemodynamic stability and multi-target action. Therefore, the purpose of this randomized controlled study is to compare the hemodynamic effects and prognosis of esketamine and remifentanil in combination with propofol in patients with septic shock receiving invasive mechanical ventilation.

Materials and Methods

Study Design and Ethics

The current study is a single-center randomized controlled clinical trial. The study was conducted from March 2023 to February 2024 in The First Hospital of Jilin University, Changchun, China. The enrolled patients were all from the ICU inpatients, including both medical and surgical patients. This study was approved by Ethics Committee of The First Hospital of Jilin University (22K019-001) and written informed consent was obtained from all subjects participating in the trial. For conscious patients, consent was obtained directly after detailed explanation by the attending physician. For unconscious patients, consent was provided by surrogates (eg, next of kin), and deferred consent was sought from the patients themselves if they regained decision-making capacity. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT05551910, Principal investigator: Yuting Li, Date of registration: 23/09/2022). The trial complied with the Declaration of Helsinki and the trial report complied with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Study Population

The inclusion criteria are: 1)Adults(≥18 years old); 2) Septic shock patients with invasive mechanical ventilation;3) Use norepinephrine (the only vasoactive drug) to maintain a target mean arterial pressure (MAP) of ≥ 65 mmHg;4) Body mass index(BMI) 18.5–23.9kg/m^2.

The exclusion criteria are:1) Pregnant or lactating women;2) Patients who are allergic to planned medication;3) Patients with poorly controlled hypertension, which refers to a resting systolic/diastolic pressure exceeding 180/100 mmHg;4) Patients with mental illness, chronic pain, seizures, elevated intracranial pressure, severe ischemic heart disease, bronchial asthma;5) Patients with severe coma who do not require analgesia or sedation;6) Other reasons that the researchers considered it inappropriate to participate in the study.

We used the Sepsis-3 definition to diagnose sepsis. The specific criteria included a Sequential Organ Failure Assessment (SOFA) score of ≥2, as well as clear evidence of infection. Patients with septic shock can be identified as clinical manifestations of sepsis with persistent hypotension requiring vasoactive medications to maintain MAP ≥65 mmHg and serum lactate level >2 mmol/L despite adequate fluid resuscitation.[1] The diagnosis was made by the ICU team, including attending physicians and critical care specialists. To ensure the accuracy of the diagnosis, we adopted a dual-diagnosis mechanism, where two doctors independently made the diagnosis and discussed and consulted with each other in case of disagreement. In addition, we regularly re-evaluated the patients' conditions to ensure the ongoing accuracy of the diagnosis. The data management team reviewed all diagnostic data to ensure their accuracy and integrity.

Randomization and Blinding

Patients who met the inclusion criteria and signed the informed consent forms were randomized into esketamine group or remifentanil group in a 1:1 ratio by opening consecutively numbered, sealed, opaque envelopes with computer-generated allocation. It is a single-blind trial as patients were blinded to allocation, but medical staff were not. This study is an exploratory study, and no experimental design of the above groups has been found in the previous stage, so the sample size is determined to be 120 cases according to the project period and the number of patients in the department.

In this study, to reduce the potential impact of individual differences among healthcare providers on the study results, we randomly assigned nurses and physicians to participate in patient care. Specifically, all healthcare providers involved in the study were randomly divided into several groups before the study began, with each group responsible for patient care during specific time periods. After patients were enrolled, they were randomly assigned to different care groups based on the order of their enrollment. The random assignment process was completed using a computer-generated random number table to ensure the randomness and fairness of the allocation.

Intervention

Esketamine group: The patient was given esketamine (50mg/2mL, Jiangsu Hengrui Pharmaceutical Co., Ltd., China), with an initial bolus of 0.5mg/kg followed by a continuous infusion of 0.5mg/kg/h, titrated by 0.15 mg/kg/h increments every two minutes based on the Critical-Care Pain Observation Tool (CPOT) targets.[15] The target CPOT score was <3 points, and the dosage of Esketamine was adjusted according to the CPOT score. CPOT scores are shown in Supplementary Table 1.

Remifentanil group: The patient was given remifentanil (1mg/ dose, Yichang Renfu Pharmaceutical Co., Ltd., China), with an initial bolus of 1ug/kg followed by a continuous infusion of 0.05–2ug/kg/min, titrated by 0.25 ug/kg/min increments every two minutes based on CPOT targets. The target CPOT score was<3 points. The dose of remifentanil was adjusted according to the CPOT score.

Both groups of patients received intravenous target controlled infusion of propofol (0.2g/20mL, Jiangsu Yingke Biopharmaceutical Co., Ltd., China) for sedation, with an initial bolus of 2mg/kg followed by a continuous infusion of 0.3–4.0 mg/kg/h, titrated by 1 mg/kg/h increments every two minutes based on Richmond Agitation and Sedation Scale (RASS) targets.[16] The target RASS score was −2~0 points. The dosage of propofol was adjusted based on the RASS score. Patients did not receive any other analgesics or sedative drugs, including those that might have been administered by other specialties.

In our study, the CPOT/RASS scores were completed by a team of ICU nurses who had undergone unified training. Although these evaluators were aware of the drug administration, they followed a standardized assessment procedure, which included the use of structured scoring sheets and regular calibration of inter-evaluator consistency. All evaluators underwent quality control through synchronous dual-person scoring.

Both groups of patients were administered norepinephrine to maintain blood pressure, with an initial dose of 20 μg/min followed by a continuous infusion of 4–8ug/min, titrated by 4 ug/min increments every two minutes to maintain MAP ≥65 mmHg.

Data Collection

The collected data included age, gender, body weight, the Acute Physiology and Chronic Health Evaluation (APACHE) II score based on the worst values obtained within 24 hours after the onset of septic shock, SOFA score, past medical history and sites of infection. In addition, procalcitonin(PCT), C-reactive protein (CRP), white blood cells(WBC), platelets(PLT), creatinine(CRE), liver function, lactate(Lac), oxygenation index(PaO_2/FiO_2) and MAP were also collected. Furthermore, We also collected mechanical ventilation time(hours), dosage of norepinephrine (milligrams per kilogram of body weight, mg/kg), dosage of propofol (mg/kg), the incidence of intestinal dysfunction [2012 European Society of Intensive Care Medicine (ESICM) acute gastrointestinal injury grade >I],[17] ICU length of stay(days), hospital length of stay(days), hospital mortality, 28-day mortality, and adverse event incidence (tachycardia, bradycardia, hypertension, hypotension, headache).

Outcomes

The primary outcome was dosage of norepinephrine (mg/kg). Secondary outcomes included mechanical ventilation time(hours), dosage of propofol (mg/kg), intestinal dysfunction rate, ICU length of stay(days), hospital length of stay(days), hospital mortality, 28-day mortality, and adverse event rate.

Statistical Analysis

SPSS 26.0 and R 4.2.1 were used for statistical analysis. Categorical data were expressed as percentages, and the Chi-square test or the Fisher's exact test was used for comparison between groups. Continuous data that conformed to a normal distribution were expressed as mean ±standard deviation(SD), and Student's *t* test was used for comparison between groups. Continuous data that did not conform to a normal distribution were expressed as median[interquartile range(IQR)], and group comparisons were performed using the Mann–Whitney *U*-test or the Kruskal–Wallis test. Kaplan-Meier survival analysis was used to analyze 28-day survival by comparing two groups of patients. $P<0.05$ was considered statistically significant.

Results

Cohort Characteristic

Totally 622 patients were screened, 120 subjects were enrolled and randomly assigned to either remifentanil group or esketamine group in a 1:1 ratio (Figure 1). The mean (±SD) age of remifentanil group was 66.48(±12.5) years and that of esketamine group was 66.22(±12.29) years. Among these included patients, 72 (60.0%) were male. The baseline patient characteristics were well balanced between the two groups (Table 1).

Primary and Secondary Outcomes

The clinical outcomes of the two groups are shown in Table 2. Primary outcome showed that the median (IQR) dosage of norepinephrine of remifentanil group was 4.09(1.52,8.85) mg/kg while that of esketamine group was 1.72(1.01,3.97) mg/kg. The dosage of norepinephrine of esketamine group was less than that of remifentanil group(P=0.007).(Figure 2).

Secondary outcomes showed that the median (IQR) dosage of propofol of remifentanil group was 11.00(8.00, 67.14)mg/kg while that of esketamine group was 10.72(1.00,45.87)mg/kg. There was no significant difference in the dosage of propofol between the two groups (P=0.072). (Figure 3A). The median (IQR) ICU length of stay of remifentanil group was 9.50 (5.25,11.75)days while that of esketamine group was 8.50(3.00,15.00) days. There was no significant difference in ICU length of stay between the two groups (P=0.298) (Figure 3B). The median (IQR) hospital length of stay of remifentanil group was 12.5 (5.75,29.75)days while that of esketamine group was 12.00(6.00,19.75) days. There was no significant difference in hospital length of stay between the two groups (P=0.549) (Figure 3C). The median (IQR) mechanical ventilation time of remifentanil group was 174.00(63.50,325.75) hours while that of esketamine group was 103.00(46.75,243.00) hours. There was no significant

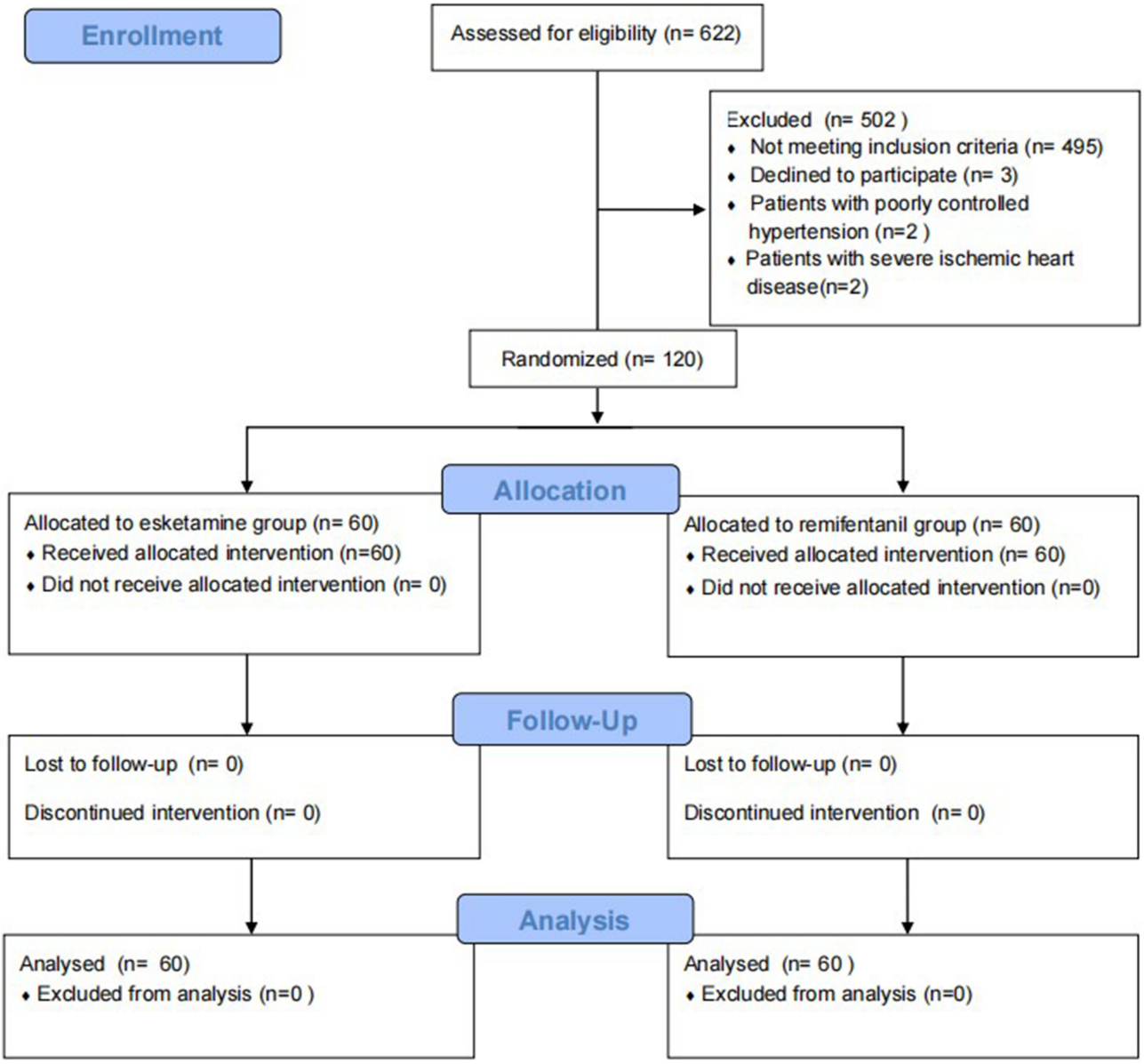

Figure 1 Flow diagram of included patients.

difference in mechanical ventilation time between the two groups (P=0.115) (Figure 3D). There was no statistically significant difference in secondary outcomes.

Kaplan-Meier survival analysis showed that there was no significant difference in 28-day survival rate between the two groups(P=0.225) (Figure 4). In addition, there were no significant differences between remifentanil and esketamine groups with respect to intestinal dysfunction rate (P=0.084) and hospital mortality (P=0.783). Regarding adverse events, the remifentanil group reported two cases (tachycardia, bradycardia), while the esketamine group reported three (tachycardia, bradycardia, hypotension). However, there was no statistically significant difference in the rate of adverse events between the two groups (P=1.000).

Discussion

This single-center randomized controlled study aimed to compare the hemodynamic effects and prognosis of esketamine and remifentanil in combination with propofol in patients with septic shock receiving invasive mechanical ventilation.

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Table 1 The Baseline Characteristics of Included Patients

Characteristic	Total Participants (n=120)	Remifentanil Group (n=60)	Esketamine Group (n=60)	P value
Male sex, n(%)	72(60.00)	37 (61.67)	35 (58.33)	0.709
Age (years), mean±SD	65.35±12.40	66.48±12.50	66.22±12.29	0.319
Weight (kg), median (IQR)	67.50 (60, 70)	65 (60, 70)	70 (60, 70)	0.756
APACHE II, median (IQR)	15 (12, 20)	15 (12, 21)	15 (12, 20)	0.973
SOFA, median (IQR)	6 (5, 10)	6 (5, 12)	6 (5, 8)	0.609
Past medical history, n (%)				
Hypertension	41(34.17)	18 (30.00)	23 (38.33)	0.336
Diabetes mellitus	27(22.50)	16 (26.67)	11 (18.33)	0.274
Coronary artery disease	12(10.00)	9 (15.00)	3 (5.00)	0.068
Cerebral infarction/hemorrhage	9(7.50)	6 (10.00)	3 (5.00)	0.488
Cancer	6(5.00)	4 (6.67)	2 (3.33)	0.675
Cirrhosis	1(0.83)	0 (0)	1 (1.67)	1.000
PCT(ng/mL), median (IQR)	15.00 (3.13, 63.00)	10.68 (1.80, 51.00)	22.50 (6.20, 73.60)	0.085
CRP(mg/L), mean±SD	187.33±107.23	175.38±108.21	199.27±105.79	0.224
WBC($\times10^9$/L), mean±SD	11.51±6.64	11.82±5.64	11.20±7.55	0.611
PLT($\times10^9$/L), mean±SD)	166.33±95.56	174.48±101.54	158.17±89.29	0.352
CRE(umol/L), median (IQR)	132.25 (78.88, 204.35)	139.95 (89.90, 204.35)	130.30 (76.73, 206.35)	0.548
AST(U/L), median (IQR)	47.50 (27.63, 119.08)	45.55 (28.50, 113.40)	51.85 (24.83, 124.10)	0.875
ALT(U/L), median (IQR)	24.60 (13.70, 68.70)	25.05 (14.04, 92.85)	23.35 (13.33, 65.80)	0.475
TBIL(umol/L), median (IQR)	15.40 (10.08, 22.48)	15.90 (9.83, 26.30)	15.00 (10.98, 21.75)	0.789
Lac(mmol/L), median (IQR)	2.40 (2.00, 3.30)	2.30 (1.80, 3.45)	2.55 (2.10, 3.30)	0.446
PaO_2/FiO_2(mmHg), mean±SD	227.75±104.74	217.74±99.55	237.77±109.60	0.297
MAP(mmHg), mean±SD	78.63±14.46	77.93±17.88	79.33±10.04	0.598
Site of infection, n (%)				
Pulmonary	38(31.67)	23 (38.33)	15 (25.00)	0.116
Genitourinary	1(0.83)	1(1.67)	0(0)	1.000
Intra-abdominal	65(54.17)	30(50.00)	35(58.33)	0.360
Skin/soft tissue infection	10(8.33)	3(5.00)	7(11.67)	0.186
Blood	4(3.33)	3(5.00)	1(1.67)	0.611
Biliary system	2(1.67)	0(0)	2(3.33)	0.476

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cells; PLT, platelets; CRE, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; Lac, lactate; PaO_2/FiO_2, oxygenation index; MAP, mean arterial pressure.

Table 2 The Clinical Outcomes of Included Patients

Clinical Outcomes	Remifentanil Group (n=60)	Esketamine Group (n=60)	P value
Dosage of norepinephrine(mg/kg), median (IQR)	4.09(1.52,8.85)	1.72(1.01,3.97)	0.007
ICU length of stay(day), median (IQR)	9.50(5.25, 11.75)	8.50(3.00,15.00)	0.298
Hospital length of stay(day), median (IQR)	12.5(5.75, 29.75)	12.00(6.00,19.75)	0.549
Dosage of propofol(mg/kg), median (IQR)	11.00(8.00, 67.14)	10.72(1.00, 45.87)	0.072
Mechanical ventilation time(h), median (IQR)	174.00(63.50,325.75)	103.00(46.75,243.00)	0.115
Intestinal dysfunction rate, n(%)	18(30.00)	10(16.67)	0.084
Hospital mortality, n(%)	8 (13.33)	7 (11.67)	0.783
28-day mortality, n(%)	30(50.00)	22(36.67)	0.141
Adverse event rate, n(%)	2(3.33)	3(5.00)	1.000

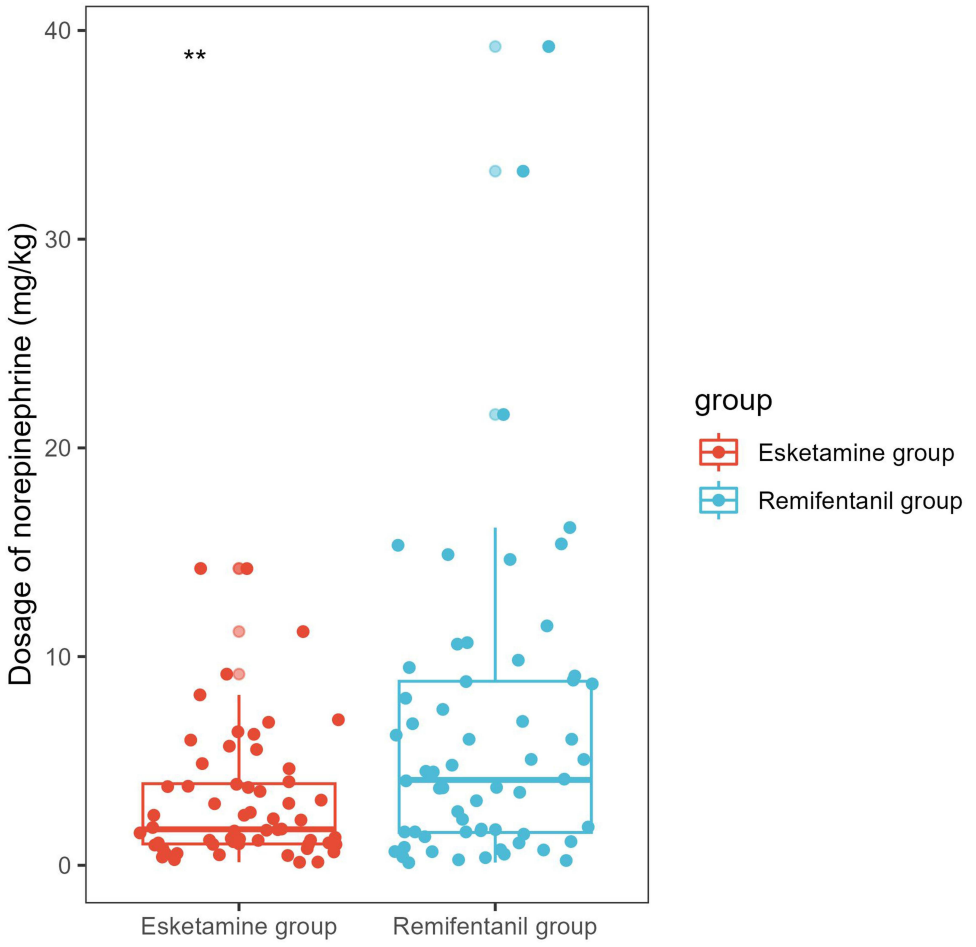

Figure 2 Dosage of norepinephrine.

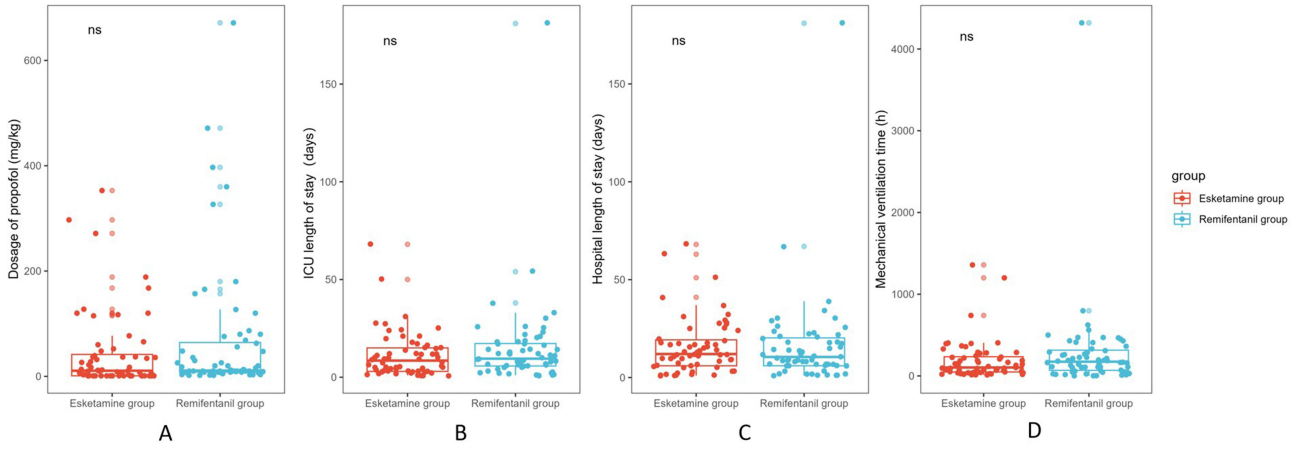

Figure 3 Secondary outcomes.

The results demonstrated that esketamine in combination with propofol can reduce the dose of norepinephrine compared with remifentanil. Vasopressors are the cornerstones of shock treatment.[18] Specifically, norepinephrine is used as first-line vasopressor therapy for septic shock.[19] Given the numerous side effects of high-dose norepinephrine, including

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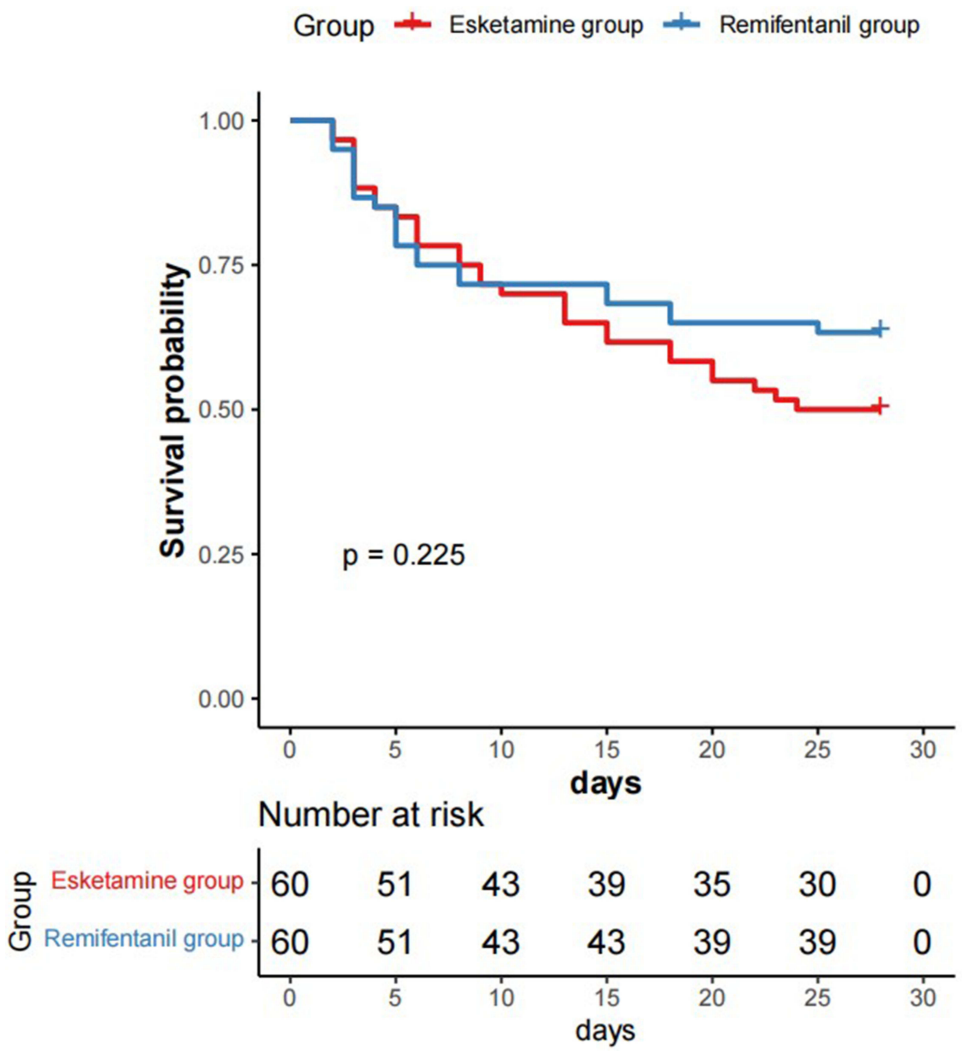

Figure 4 Kaplan-Meier curve of 28-day survival rate.

arrhythmia and tissue ischemia, there is an urgent need to reduce its requirements. In addition, some studies have revealed that the need for norepinephrine is one of the indicators of severity in patients with septic shock.[20–22]

Critically ill adults need sedation to reduce anxiety and stress and to facilitate invasive procedures and mechanical ventilation. Sedation indication, goal, pharmacology, and cost of acquisition are important determinants in the selection of sedatives. Propofol over benzodiazepines for sedation in critically ill, mechanically ventilated adults was recommended in the 2018 PADIS guideline because it can provide light sedation in patients experiencing or at risk of agitation due to its improved safety and efficacy profiles. However, propofol has side-effect profiles that include hypotension and bradycardia.[23,24] Due to the pathophysiology of septic shock, patients may be at increased risk of experiencing adverse effects and their associated sequelae when administered propofol.[25] Therefore, it is crucial to select analgesic drugs that can optimize the hemodynamics.

Esketamine, the newly marketed S-enantiomer of ketamine, has enhanced anesthetic effect[26] and reduced incidences of psychiatric side effects of ketamine.[27] The cardiovascular excitation effect of esketamine provides stable mean arterial pressure and heart rate without significant fluctuation.[28–30] Esketamine increases cardiac output in a dose-dependent manner and improves blood pressure stability and it decreases the incidence of hypotension.[31] As a result, esketamine provides better circulative stability and stable hemodynamics.[32] These results support our findings and suggest that analgesic therapy with esketamine is hemodynamically beneficial in patients with septic shock.

Furthermore, secondary outcomes demonstrated that there was no significant difference in adverse events between remifentanil and esketamine groups. Common side effects of esketamine include dissociation symptoms, dizziness, drowsiness, nausea and vomiting, elevated blood pressure, and increased heart rate, etc., but they are usually transient, mild, and self-limiting.[33–35] Researches have shown that a low dose of esketamine can reduce the incidence of anaesthesia-related side effects and has good analgesic effects, fewer adverse reactions, a short recovery time, and antidepressant effects.[36,37] Therefore, esketamine is safe and effective in the analgesic treatment of septic shock patients with invasive mechanical ventilation.

As an intravenous opioid, remifentanil is a short-acting μ-receptor agonist with fast metabolism and the mainstay of pain treatment in most ICUs.[38] However, eCASH emphasizes the need to reduce total opioid exposure in order to avoid adverse effects such as respiratory depression, feeding intolerance, constipation and ileus, withdrawal, tolerance, hyperalgesia, physical dependence and depression of the immune system. To date, there is a lack of relevant research comparing analgesic adverse reactions between esketamine and opioids specifically in septic shock patients. Our study, though preliminary, found no significant differences between the remifentanil and esketamine groups in terms of intestinal dysfunction rate, mechanical ventilation time, ICU length of stay, hospital length of stay, hospital mortality, and 28-day survival rate. Given the exploratory nature of our study, further research with larger, multi-center samples is required to validate our findings and clarify any potential differences in clinical outcomes and adverse reactions.

There are several limitations to our study. Firstly, it was conducted in a single center, limiting the generalizability of our conclusions. Secondly, the relatively small sample size of our study population was due to the exploratory nature of the research. Thirdly, the study was not blinded to nurses and physicians as the two analgesics had distinct physical appearances, although nurses and physicians were randomly involved in the care of all patients during their ICU stay. Fourthly, although we minimized bias through standardized training and quality control procedures, the awareness of patient medication by CPOT/RASS scorers may have influenced the assessment outcomes. Future studies may consider adopting a double-blind design to further control for information bias.

Conclusion

Compared to remifentanil, esketamine may decrease the dosage of norepinephrine in patients with septic shock receiving invasive mechanical ventilation. Esketamine is beneficial for stabilizing hemodynamics and appears to be an effective and safe agent for patients with septic shock requiring invasive mechanical ventilation. Further large-scale studies are still required to confirm these results.

Data Sharing Statement

The data presented in this study are available from the corresponding author on reasonable request.

Ethics

This trial was registered prior to patient enrollment at clinicaltrials.gov (NCT05551910, Date of registration: 23/09/2022). This study was approved by Ethics Committee of The First Hospital of Jilin University (22K019-001) and written informed consent was obtained from all subjects participating in the trial. The trial complied with the Declaration of Helsinki and the trial report complied with the CONSORT guidelines.

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Disclosure

The authors declare that there is no conflicts of interest. This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-4093328/v1.

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