Study Protocol

project name	Comparison of the effects of esketamine-induced intubation versus conventional induced intubation in ICU patients: a single-center, randomized clinical trial
Scheme number	ZJC202203
version number	V2.0
Version date	2023.5.31
Principal investigator	Zhang Jiancheng
Professional department	Department of Critical Care Medicine

Study design

The trial was registered before enrollment on clinicaltrials.gov (NCT05464979) on July 14, 2022. This single-center, prospective, randomized, controlled pilot study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (2022-0351-01), and it conforms to the provisions of the 1964 Helsinki Declaration. Written informed consent was obtained from all patients or surrogates.

Patients selection and randomization

The inclusion criteria were age ≥ 18 years, no use of sedatives within the half-life of their elimination before inclusion. To be included, a signed informed consent was mandatory. In non-consenting patients, a medical witness or legal guardian signed a provisional informed consent form. The exclusion criteria were as follows: (1) age < 18 years; (2) allergic to esketamine or midazolam; (3) patients requiring endotracheal intubation without sedative medication such as those in cardiac arrest, those neurologically obtunded, or those

requiring awake intubation; (4) patients with suspected increased intracranial pressure; (5) bradycardia (heart rate (HR) below 50 beats/min) or atrioventricular block; (6) untreated or undertreated patients with hyperthyroidism; (7) chronic nephrosis; (8) severe chronic liver disease (child-Pugh: Grade C); (9) alcohol or opioid dependence, mental illness, or severe cognitive impairment; (10) pregnant or breastfeeding; and (11) lack of informed consent. Upon meeting the criteria for inclusion in the study, the patient was randomized to group esketamine or group midazolam/fentanyl. Randomization was performed by a coin toss (patients received esketamine for induction when the coin fell with the number up).

Study interventions

The study was double-blind, and the drug injectors, data analyzers, and patients (or surrogates) were not aware of the treatment groups they received. The person in charge of randomization dispenses the induction agents. Dispensers were not involved in the subsequent experimental process.

The use of analgesics and sedatives prior to study enrollment was discontinued. In group esketamine, esketamine was administered for induction. In group midazolam/fentanyl, a combination of midazolam and fentanyl citrate were prepared to be mixed in a syringe in the same volume as esketamine to avoid the drug injectors knowing the grouping. The doses of induction medications for individual patients were permitted to adjust for individual patients as believed clinically appropriate. Both groups were given roccuronium bromide before intubation. Sufentanil citrate combined with remimazolam besylate was administered intravenously to sustain a Critical-Care Pain Observation Tool (CPOT) score 0 and a Richmond Agitation and Sedation Scale (RASS) score between -3 and 0 following intubation. Before induction, monitors were applied: continuous electrocardiograph (ECG), continuous pulse oximetry, invasive blood pressure monitor through a 20-G radial arterial catheter connected to a pressure transducer placed at the level of the heart. Invasive blood pressure measurements were achieved by Progetti (PG M9500, Italy) monitor. Tachycardia (HR > 100 beats/min) and hypotension (systolic blood pressure < 90

mmHg) could be controlled by intravenous esmolol hydrochloride or vasopressors during and after induction. The stopping criteria were the occurrence of adverse events (e.g., drug allergy, severe neuropsychiatric symptoms, requirement for surgical airway as well as acute interventions for cardiovascular collapse such as cardiopulmonary resuscitation with chest compressions). Patients were followed up for 28 days after randomization.

Data collection

Data was obtained from the hospital's electronic medical records, vital signs monitor, nurse records, and laboratory findings. All data were checked by two researchers.

We collected data on age, sex, body mass index, and comorbidities (smoking and drinking history, cardiovascular and cerebrovascular diseases, chronic respiratory disease, chronic hepatopathy, chronic nephrosis, endocrine, nervous system diseases, autoimmune diseases, and malignant tumor). The acute physiology and

chronic health evaluation (APACHE II) score , Glasgow coma scale (GCS) score, sepsis-related organ failure assessment (SOFA) score, suspected or proven sepsis (known or suspected infection with SOFA score ≥ 2), and presence of shock (patients with blood pressure maintained via infusions of vasopressor prior to start of study drug) at randomization, as well as the main cause of ICU admission and the reasons for emergency intubation were recorded. The vital signs (peripheral arterial oxygen saturation (SpO2), HR, mean arterial pressure (MAP)) before induction, during induction, during intubation, and five time points after intubation (1 min, 5 min, 10 min, 30 min, and 60 min) were collected. The duration of ventilation support, ICU length of stay, and 28-day survival after randomization were recorded.

Outcomes

The primary outcomes were the effects of rapid sequence induction using esketamine or midazolam/fentanyl on HR and MAP at various designated time points as specified. Secondary outcomes included: the duration of invasive ventilator support, length of ICU stay, and 28-day

mortality. The safety outcomes included: hypotension (systolic blood pressure < 90 mmHg), dose of vasopressors, tachycardia (HR > 100 beats/min), dose of β-blocker esmolol, and cardiotonic treatment.

Statistical analysis

Based on a previous study, the mean arterial pressure immediately before endotracheal intubation in the esketamine group was 89 ± 14 mm Hg. We calculated a conservative sample size that could detect a mean difference of 10% (i.e. 8.9 mmHg) between study groups. Using PASS 15.0 software, a sample size of 40 patients (20 patients per group) was needed to have a study power of 80% and alpha error of 0.05. The number was increased by 10% to be 44 patients per group to compensate for possible dropouts.

Continuous data points were expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)). Statistical significance in differences between independent groups were calculated using either the Student's t test or the Mann-Whitney U-test, depending on the distribution. Categorical data are expressed as number

(percentage (%)). The Chi-square was applied to test differences between groups for their statistical significance. Proportional hazard ratios with 95% confidence interval (CI) were calculated using Mantel-Haenszel test, and Kaplan–Meier curves were depicted to compare the length of ICU stay and the cumulative incidence of mortality 28 days after randomization. There were no missing values for the variables examined in the statistical analysis. Analyses were conducted using IBM SPSS Statistics (Version 20) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA). All tests were two-sided, and a p-value of < 0.05 was considered statistically significant.