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REVIEW ARTICLE

Expert Consensus on the Clinical Utilization of Ketamine and Its Isomers in Intensive Care Units

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Abstract
Analgesia and sedation are important treatment strategies in the intensive care unit (ICU). Due to the opioid crisis, opioid-sparing medications become the focus of clinical studies. Ketamine and its isomers (mainly esketamine) are intravenous anesthetics that possess sedative, analgesic, and anesthetic effects, which have recently attracted the attention of critical care physicians. However, the application of ketamine/esketamine in ICU is limited and inexperienced. Experts from the Critical Care Medicine Professional Committee of the Chinese Research Hospital Association drafted this consensus based on the current clinical evidence to provide recommendations for the application of ketamine/esketamine in different fields of critical care, including sepsis and septic shock, endotracheal intubation, neurocritical care, respiratory critical care, post cardiac surgery care, burn and depression in ICU. Meanwhile, this expert consensus also appeals for more high-quality clinical trials to facilitate more reasonable guidelines in this area.

Keywords Ketamine · Intensive care unit · Expert consensus

1 Introduction

Critically ill patients frequently encounter significant stress stemming from unfamiliar environments, severe illness, invasive medical procedures, concerns regarding their prognosis, and the fear of death. These stressors often culminate in patient anxiety, which can exacerbate their condition and affect treatment outcomes. Consequently, analgesia and sedation emerge as pivotal therapeutic strategies for managing critically ill patients [1]. The 2018 "Guidelines for Analgesia and Sedation in Adult ICU Patients in China" recommended that analgesia be administered prior to sedation in ICU patients. For non-neuropathic pain, opioid analgesics are the recommended first-line treatment, often used in conjunction with non-opioid analgesics to facilitate lower dosages and mitigate associated adverse effects, such as nausea and vomiting. Commonly utilized non-opioid analgesics encompass ketamine, non-steroidal anti-inflammatory drugs (NSAIDs), nefopam, gabapentin, and others [2]. Ketamine, in particular, has garnered increased attention within the ICU setting.

Ketamine, derived from phencyclidine (N-1-phenycyclohexy- piperidine, PCP), is an intravenous anesthetic renowned for its sedative, analgesic, and anesthetic properties. Its mechanisms of action primarily involve modulation of N-methyl-D-aspartate (NMDA) receptors, opioid receptors, monoamine receptors, acetylcholine receptors, sodium ion receptors, and calcium ion receptors, collectively imparting analgesic, sedative, bronchospasm-alleviating, anti-inflammatory, and neuroprotective effects. Ketamine may evoke central nervous system adverse effects, such as hallucinations and nightmares, but these phenomena are dose-dependent. A meta-analysis revealed that the incidence of

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psychiatric adverse reactions with low-dose ketamine (single intravenous dose of 0.25-1 mg/kg, continuous infusion of 0.12–0.3 mg/kg/h) for postoperative acute pain treatment was 5% (187/3614), which was not significantly higher than the placebo group (4%, 122/2924) [3].

Ketamine exists as a racemic mixture comprising equal proportions of levorotatory and dextrorotatory ketamine. Among these enantiomers, the analgesic and sedative potency of D-ketamine (S-ketamine, Esketamine) surpasses that of ketamine by a factor of two and four times, respectively. Esketamine boasts a higher clearance rate and more rapid elimination, resulting in swifter recovery and fewer adverse effects on the nervous system, including reduced respiratory secretions [4]. Low doses of esketamine can achieve equivalent anesthetic and analgesic effects as ketamine [5], rendering it a widely employed option in clinical practice. Presently, only ketamine and esketamine are utilized in ICU settings; therefore, when referring to ketamine and its isomers in this article, we primarily encompass ketamine and esketamine. The mechanisms and pharmacological effects of ketamine/esketamine are detailed in Table 1.

Previous investigations have elucidated that ketamine/esketamine possess the capability to mitigate opioid-induced hyperalgesia [6] and facilitate the reduction of opioid dosages [7]. Specifically, esketamine exhibits effectiveness in countering opioid-induced respiratory depression [8], inducing relaxation in bronchial smooth muscle, and prevent bronchospasm [9, 10]. Furthermore, ketamine/esketamine possess mild circulatory stimulation effect [11], and help to maintain the hemodynamics stability when administered in conjunction with propofol [12]. The combined use with benzodiazepines also enhances the stability of circulation and respiration [13]. A comparative analysis between ketamine hydrochloride injection and esketamine hydrochloride injection is presented in Table 2.

Given the increasing potential utilization of ketamine/esketamine in the ICU and the ongoing debates surrounding their application, the Critical Care Medicine Professional Committee of the Chinese Research Hospital Association has undertaken the task of formulating a consensus document. This consensus, based on prevailing clinical evidence, aims to provide valuable guidance for the judicious use of ketamine/esketamine in the ICU.

Question 1. Utilization of Ketamine/Esketamine in Sepsis and Septic Shock.

Rationale Sepsis and septic shock pose formidable challenges in critical care, prompting guidelines to advocate for appropriate analgesia and sedation in mechanically ventilated septic patients [14]. Conventional agents like opioids, propofol, and benzodiazepines can induce vasodilation, exacerbate tissue hypoperfusion, and lead to respiratory depression, thereby contributing to adverse clinical outcomes [15, 16]. In contrast, ketamine/esketamine exhibit the ability to modulate vascular tone without causing significant respiratory depression. Additionally, they stimulate the secretion of catecholamines [17] and the release of glucocorticoids [18, 19], reducing the reliance on vasoactive drugs [20]. An exploratory prospective open-label study comparing the hemodynamic effects and the requirement for other analgesics and sedatives in septic shock patients undergoing mechanical ventilation with early ketamine administration revealed a decrease in the dosages of norepinephrine and vasopressin, as well as reduced demand for fentanyl and other sedatives [21].

Opinion 1: It is reasonable to consider the use of ketamine/esketamine as adjunctive agents for analgesia and sedation in patients with sepsis and septic shock.

Question 2: Utilization of ketamine/esketamine in endotracheal intubation of critically ill patients.

Rationale Critically ill patients often require emergency endotracheal intubation, a procedure that can potentially induce hypotension following the administration of analgesic and sedative agents. Ketamine/esketamine, known for their analgesic and sedative properties, also possess vasomodulatory and anticholinergic effects, rendering them well-suited for facilitating emergency endotracheal intubation. A prospective, randomized, controlled, multicenter clinical study, published in The *Lancet* in 2009, conducted

Table 1 Targets and pharmacological actions of ketamine and esketamine

Opposing actions		Stimulatory effects	
Targets	Pharmacological Actions	Targets	Pharmacological Actions
NMDA Receptors	Anesthesia/sensory suppression, Analgesia/inhibition of hyperpathia, Neuroprotection, Amnesia	Opioid Receptors (μ, κ, δ)	Analgesia
Voltage-Gated Sodium Channels	Local anesthesia/ Decreased sympathetic activity	AMPA Receptors	Antidepressant
L-Type Voltage-Gated Calcium Channels	Negative cardiac inotropy/ Airway smooth muscle relaxation	$GABA_A$ Receptors	Anesthesia
HCN Channels	Hypnosis		
Potassium Channels	Analgesic effects on neuropathic pain		

Table 2 Comparative Analysis of Ketamine Hydrochloride Injection and Esketamine Hydrochloride Injection

	Ketamine hydrochloride injection	Esketamine hydrochloride injection
Main Ingredients	Racemic mixture of S-(+)-ketamine and R-(-)-ketamine	S-(+)-ketamine
Indications	In Mainland China (China): As the anesthetic agent for various superficial, minor surgical, diagnostic procedures of uncooperative children, and general anesthesia in combination with other anesthetic agents Abroad: 1. As the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation; 2. For the induction of anesthesia prior to the administration of other general anesthetic agents; 3. As a supplement to other anesthetic agents	In China: Used for the induction and maintenance of general anesthesia in combination with other anesthetic agents (such as propofol) Abroad: 1. Used for induction and maintenance of general anesthesia, if possible, in combination with other anesthetic agents; 2. Used as a supplement for local anesthesia; 3. Used for anesthesia and analgesia in emergency medical care; 4. Used for tracheal intubation in combination with muscle relaxants in the state of persistent asthma when other specific measures have failed; 5. Used for analgesia during mechanical ventilation (tracheal intubation)
Dosage and Administration	In China: 1. General anesthesia induction: 1–2 mg/kg administered intravenously to adults, and up to 1–2 mg/min (equivalent to 10–30 μg/kg) through continuous infusion for maintenance; 2. Analgesia: Adults receive an initial dose of 0.2–0.75 mg/kg intravenously over 2–3 min, followed by continuous infusion at a rate of 5–20 μg/kg/min. 3. Basic anesthesia: There is significant variation among clinical individuals. For pediatric patients, the intramuscular dose is 4–5 mg/kg, with an additional 1/2 to 1/3 of the initial dose if necessary Abroad: 1. Anesthesia induction: Intravenous route: Initially, 1 to 4.5 mg/kg administered slowly (over a period of 60 s). Alternatively, administer a dose of 1 to 2 mg/kg at a rate of 0.5 mg/kg/min. Intramuscular route: Initially, 6.5 to 13 mg/kg.; 2. Anesthesia maintenance: Increments of one-half to the full induction dose may be repeated as needed. Adjust the dose according to the patient's anesthetic needs and whether an additional anesthetic agent is employed. 3. Supplement to other anesthetic agents: The regimen of a reduced dose of ketamine supplemented with diazepam can be used to produce balanced anesthesia by combination with other agents	In China: General anesthesia: 0.5 mg/kg intravenous injection administered for anesthesia induction, and 0.5 mg/(kg·h) administered through continuous infusion for anesthesia maintenance. For patients with multiple injuries or poor physical condition, the dose should be reduced Abroad (corresponding to the above indications): 1. General anesthesia: The dosage for anesthesia induction is 0.5–1 mg/kg by intravenous injection or 2–4 mg/kg by intramuscular injection. If needed, half of the initial dose can be administered for anesthesia maintenance, usually every 10–15 min. Alternatively, continuous infusion at a dose of 0.5–3 mg/(kg·h), with a reduced dose for patients with multiple injuries or poor physical condition. 2. As a local anesthetic supplement agent: Administer a dose of 0.125–0.25 mg/(kg·h) by intravenous infusion as needed. 3. For analgesia in emergency medical care, intramuscular injection at a dose of 0.25–0.5 mg/kg or slow intravenous injection at a dose of 0.125–0.25 mg/kg. 4. For tracheal intubation in the state of persistent asthma, intravenous injection of 0.5–1 mg/kg of this drug, with a maximum dose of 2.5 mg/kg if necessary. 5. For analgesia during artificial ventilation (intensive care patients with tracheal intubation), a rapid injection of 0.25 mg/kg is usually administered, followed by continuous infusion of 0.2–0.5 mg/(kg·h) (up to a maximum of 1.5 mg/(kg·h)) while administering benzodiazepines

a comparative analysis of the prognostic impact of ketamine and etomidate as induction agents for emergency intubation. This study discovered that employing ketamine (2 mg/kg) as a single-dose induction agent significantly reduced the incidence of adrenal insufficiency compared to etomidate, implying that ketamine was both safe and effective for initiating emergency endotracheal intubation in critically ill patients [22]. Furthermore, a prospective, randomized, controlled, single-center clinical study conducted in 2022 demonstrated that the utilization of ketamine (1–2 mg/kg) as an induction agent for emergency endotracheal intubation resulted in a higher 7-day survival rate in comparison to the etomidate group (85.1% vs 77.3%) [23]. Esketamine, notable for its ability to dilate bronchial smooth muscles without

histamine release, emerges as a suitable option for emergency induction in patients experiencing asthma attacks and acute-phase chronic obstructive pulmonary disease (COPD) [24].

Opinion 2: Ketamine/esketamine can be effectively employed as induction agents for anesthesia in critically ill patients undergoing emergency tracheal intubation.

Question 3. Utilization of ketamine/eskeamine in Neurocritical Care.

Rational Neurocritical care patients necessitate the preservation of adequate cerebral perfusion to minimize the risk of secondary injuries and vigilance against intracranial hypertension. Appropriate analgesia and sedation are essential for reducing cerebral oxygen consumption, enhancing brain tissue tolerance to hypoxia. Severe traumatic brain injuries, subarachnoid hemorrhages, and intracerebral hemorrhages can provoke cortical spreading depolarization (CSD), which stands as an independent risk factor for poor neurological prognosis [25]. The mechanisms underlying CSD are primarily linked to excitotoxicity from amino acids, intracellular Ca^{2+} overload, and heightened production of oxygen free radicals. Beyond providing analgesia and sedation, ketamine/esketamine can also serve as nonspecific antagonist of NMDA receptor channels, mitigating neuronal cell damage triggered by increased glutamate production during cerebral ischemia/hypoxia, and demonstrating potential neuroprotective effects [26].

In a retrospective analysis of 115 patients with traumatic brain injury, ketamine was found to significantly reduce the occurrence of CSD in comparison to other sedative medications [27]. Additionally, Burgoinet et al. [29] observed that the combination of ketamine and midazolam did not adversely affect intracranial pressure and cerebral perfusion pressure when compared to sufentanil and midazolam in patients with severe traumatic brain injury requiring mechanical ventilation [28]. Moreover, elevated ketamine concentrations did not yield adverse hemodynamic effects in severe traumatic brain injury patients [29]. Subsequent investigations have further indicated that, in contrast to fentanyl, esketamine does not elavate the risk of intracranial hypertension [30]. Meta-analysis findings also suggest that the use of ketamine does not increase the likelihood of adverse events in patients with acute brain injuries [31].

Opinion 3: Ketamine/eskeamine may be considered as adjunctive agents for analgesia and sedation in patients with acute brain injuries.

Question 4. Utilization of Ketamine/eskeamine in Respiratory Critical Care.

Rational Ketamine/esketamine have been explored for their potential benefits in respiratory critical care due to their effects on vascular tone, airway dilation, modulation of catecholamine concentrations, catecholamine reuptake inhibition, regulation of calcium ion channels, and anticholinergic properties. Numerous studies have investigated the use of ketamine in patients with respiratory failure caused by severe asthma and chronic obstructive pulmonary disease (COPD). These studies have reported various outcomes.

A retrospective study demonstrated that ketamine administration led to a reduction in peak airway pressure, a decrease in $PaCO_2$, and an increase in PaO_2 at 15 min and 2 h after administration in patients with severe asthma-related respiratory failure [32].

A prospective study compared ketamine to fentanyl in patients with respiratory failure due to severe asthma or COPD, concluding that ketamine did not increase the occurrence of adverse events [33].

Miller et al. conducted a review of 20 clinical studies involving mechanically ventilated patients receiving ketamine for sedation. Their findings suggested that ketamine did not significantly affect hemodynamic parameters such as blood pressure, vascular tone, and heart rate. Moreover, ketamine improved hypercapnia and reduced the need for bronchodilators [34].

Co-administration of ketamine was shown to reduce the need for other sedatives and analgesics, enabling quicker achievement of sedation goals [35].

In a prospective, randomized, controlled exploratory study, which was to evaluate the impact of co-administered ketamine on the duration of mechanical ventilation and hemodynamics, the results showed no significant increase in mechanical ventilation duration or adverse effects on hemodynamics [36].

A retrospective study involving severe and critically ill patients with COVID-19 found that ketamine was associated with lower mortality (50% vs 72%) and improved safety compared to other sedatives [37].

Furthermore, as bronchoscopy becomes increasingly common in ICU, researches have explored the safety and efficacy of ketamine in this context. A prospective study comparing ketamine to fentanyl in adult bronchoscopy examinations found that ketamine was as safe and effective as fentanyl [38]. A review article highlighted that the hemodynamic impact of combining ketamine with bronchoscopy was less pronounced than that of other sedative drugs, with no statistically significant difference in awakening time [39].

Opinion 4: It is recommended to consider the use of ketamine and esketamine for adjunctive analgesia and sedation in mechanically ventilated patients, especially those with hemodynamic instability.

Opinion 5: Ketamine and esketamine are recommended as suitable options for providing adjunctive analgesia and sedation during painless bronchoscopy.

Question 5. Utilization of ketamine/esketamine in patients after cardiac surgery.

Rational Ketamine/esketamine have been shown to increase cardiac output in healthy adults [40, 41].

Additionally, in critically ill surgical patients, these agents have the potential to reduce oxygen consumption, which is particularly relevant in the postoperative period [42]. Ketamine has demonstrated its effectiveness in reducing the need for inotropic drugs, decreasing the incidence of myocardial infarction, and shortening the time to extubation in patients undergoing coronary artery bypass graft surgery [43]. Moreover, ketamine has been found to alleviate postoperative inflammatory reactions and reduce C-reactive protein [44, 45]. This anti-inflammatory effect could be particularly valuable in cardiac surgery patients. Ketamine has also been associated with a decreased incidence of postoperative delirium, a common concern in the post-cardiac surgery setting [46]. In patients undergoing coronary artery bypass graft surgery, esketamine has demonstrated benefits, including increase patient satisfaction with analgesia and reduce the incidence of postoperative nausea, vomiting, and shivering [47, 48].

Opinion 6: It is advisable to consider the use of ketamine and esketamine for adjunctive analgesia and sedation in patients undergoing cardiac surgery, particularly those involving cardiopulmonary bypass.

Question 6. Utilization of ketamine and esketamine in critically burned patients.

Rational Burn pain represents a distinct category of pain resulting from damage to the skin, mucosal membranes, and even deeper tissues, often accompanied by compromised structural integrity following burn injuries. This condition leads to various detrimental consequences, such as damage to exposed skin nerve, localized or systemic persistent inflammatory reactions, secondary wound swelling, heightened skin tension, ischemia, and hypoxia. The pain experienced by burn patients is exceptionally intense and immediate, typically peaking within 2–3 days post-injury. Furthermore, the diagnostic and therapeutic procedures performed during the later stages of burn recovery, such as dressing changes and functional exercises, frequently induce severe procedural pain. Given these circumstances, burn patients frequently require substantial doses of analgesic medications.

Critically ill burn patients experience a distinctive set of challenges, including significant plasma-like fluid exudation, reduced effective circulating blood volume, and persistent inflammatory responses. These factors often lead to the development of hypovolemic shock and distributive shock, ultimately resulting in inadequate perfusion of vital organs and the onset of multiple organ dysfunction, including respiratory and circulatory impairments. It is noteworthy that traditional opioid analgesics may exert adverse effects on respiration and circulation.

Ketamine and esketamine exhibit a unique pharmacological profile that makes them particularly valuable in the management of burn pain. Intravenous administration of sub-anesthetic doses of ketamine (typically 0.4–0.6 mg/kg) or esketamine (usually 0.2–0.3 mg/kg) can effectively provide analgesia and sedation without significantly inhibiting respiratory function. Notably, a retrospective study evaluating the efficacy and safety of analgesic drugs for procedural pain in burn patients has demonstrated that ketamine surpasses opioid analgesics in terms of both effectiveness and safety [49].

Opinion 7: It is recommended to consider ketamine or esketamine as adjunctive agents for analgesia and sedation during wound dressing changes in critically burned patients.

Question 7. Utilization of ketamine/esketamine in ICU patients with depressive symptoms.

Rational Patients admitted to ICUs often experience mental health challenges, including varying degrees of anxiety and depression. These psychological disturbances can be attributed to a range of factors, including the severity of their medical condition, the unfamiliar and highly intensive care environment, and the invasive medical treatments they undergo [50, 51]. Importantly, individuals with severe illnesses and complex medical conditions requiring prolonged ICU care are particularly susceptible to depression. Moreover, research has indicated that critically ill patients who also suffer from depression tend to have a higher mortality [52]. A prospective study conducted in the United Kingdom revealed that approximately 40% of ICU patients exhibited symptoms of depression [53]. Traditional antidepressant treatments typically require an extended duration to produce therapeutic effects and may not be suitable for ICU patients.

In 2000, Berman et al. introduced the concept that ketamine can produce a rapid therapeutic response in the context of depression [54]. Ketamine is believed to enhance excitatory glutamate transmission, promote the release of brain-derived neurotrophic factors, stimulates synaptic plasticity, and exerts antidepressant effects [55]. A retrospective analysis conducted by Giri et al. showed that continuous infusion of sub-anesthetic doses of ketamine (typically at doses of 0.5 mg/kg and 0.75 mg/kg) in the ICU setting can lead to improvement in depressive symptoms among critically ill patients with depression. As such, ketamine appears to offer significant advantages in the treatment of depression in ICU patients [56].

Moreover, the prevalence of depression tends to be higher among ICU patients with cancer, and individuals with a history of chronic depression are at greater risk of experiencing severe relapses. Thangathurai et al. conducted a study that highlighted the potential benefits of intravenous administration of ketamine (at doses ranging from 6 to 10 mg/h), along with fentanyl (20–30 μg/h) and desipramine (10–25 mg/d), in ameliorating depressive symptoms in ICU patients with cancer-related depression. This suggests that ketamine may be a valuable therapeutic option for managing depression in critically ill cancer patients [57].

Opinion 8: The use of ketamine/esketamine may be considered as an adjunctive therapy for ICU patients presenting with depressive symptoms.

2 In Summary

Ketamine/esketamine offer a unique combination of sedation and analgesia, acting through distinct receptors and pathways, with minimal impact on hemodynamics. Importantly, they do not increase intracranial pressure or inhibit respiratory rate. Furthermore, these agents have the potential to reduce the requirement for opioids and mitigate opioid-induced hyperalgesia. Additionally, there is emerging evidence suggesting possible neuroprotective properties associated with their use. Consequently, the future applications of ketamine and esketamine in critical care settings hold significant promise.

Despite these promising attributes, it is essential to acknowledge that the current body of evidence remains limited. To establish the safety and efficacy of ketamine and esketamine in the treatment of depressive symptoms among ICU patients, there is a clear need for large-scale, high-quality clinical studies. These investigations will be vital in confirming their therapeutic potential and guiding their appropriate utilization in critically ill individuals.

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Declarations

Conflict of Interest All authors declare no conflicts of interest.

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