

# Ketamine sedation in critically ill patients: Past, present and future

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Sameer Sharif<sup>1,2,3</sup>, Jay Prakash<sup>4</sup>, Bram Rochwerf<sup>2,3</sup>

<sup>1</sup>Department of Medicine, Division of Emergency Medicine, McMaster University, Hamilton, ON, <sup>2</sup>Department of Medicine, Division of Critical Care, McMaster University, Hamilton, ON, <sup>3</sup>Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, <sup>4</sup>Department of Critical Care Medicine, Rajendra Institute of Medical Sciences, Ranchi, India

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**Address for correspondence:** Dr. Sameer Sharif,  
237 Barton St East, 2<sup>nd</sup> Floor McMaster Wing, Room 252, Hamilton General Hospital, Hamilton,  
ON L8L 2X2, Canada.  
E-mail: sameer.sharif@medportal.ca

When it comes to sedation modalities for patients in the intensive care unit (ICU), the available options have not immensely increased over the past 60–70 years.<sup>[1]</sup> The first drugs used to sedate critically ill patients came from anaesthesia and included agents used for both general anaesthesia and short-term sedation during regional anaesthesia.<sup>[2]</sup> The Food and Drug Administration approved ketamine, a derivative of phencyclidine, in 1970 after it was first identified in 1965. Still, adverse effects, including an intense and prolonged emergence delirium, limited its use.<sup>[3]</sup> Ketamine has historically been referred to as a ‘dissociative anaesthetic’, a term that describes how distinct brain regions are ‘dissociated’ from one another when simultaneously activated (such as the hippocampus and frontal cortex) or suppressed (such as the thalamus).<sup>[4]</sup> Ketamine functions as an N-methyl-D-aspartate (NMDA) receptor antagonist, an advantageous mechanism compared to other agents, providing analgesia and anaesthesia.<sup>[5]</sup> In addition, it has sympathomimetic properties thought to be secondary to a reduction in catecholamine reuptake and interacts with the mu, kappa and delta opioid receptors.<sup>[5]</sup>

Fast forward to the present, ketamine is used to induce anaesthesia in operating rooms, as an analgesic agent in perioperative and postoperative patients, as well as in patients experiencing chronic pain.<sup>[6]</sup> Ketamine

maintains relatively stable haemodynamics and has less impact on respiratory drive than other induction agents. Hence, it is frequently used in critically ill patients to ease endotracheal intubation.<sup>[7]</sup> In the emergency department and ICU setting, ketamine has been used for severe agitation (intramuscular dosing at 5 mg/kg),<sup>[8]</sup> delayed sequence intubation<sup>[9]</sup> and procedural sedation.<sup>[10,11]</sup> Ketamine is also sometimes used in the ICU as a continuous infusion in the management of refractory status epilepticus<sup>[12]</sup> and severe bronchospasm.<sup>[13]</sup>

While transient bolus dosing of ketamine in the emergency department and operating room is well established and supported by the literature, there is not much data examining its use as a continuous sedative in the ICU.<sup>[14]</sup> The coronavirus disease 2019 pandemic was a tipping point for many ICU clinicians, providing an impetus to broaden their selection of continuous sedatives owing to the high sedation needs of these patients and the international drug shortages that forced the consideration of non-traditional sedation agents, including ketamine.<sup>[15]</sup> A prior survey of intensivists in Canada found that while ICU clinicians may consider ketamine infusions for severe asthma, acute respiratory distress syndrome and refractory pain, its use is not widespread and concerns about increased delirium limit it.<sup>[16]</sup> Surveys in other countries, including Germany and the USA, have not only

demonstrated consistent findings but also indicated that there is increased interest in the use of ketamine for wider ICU-based indications.<sup>[16-18]</sup> Another potential explanation for this increase in ketamine interest in the ICU setting may be the increasing number of emergency physicians and anaesthesiologists training in critical care, a group of physicians with a reputation for being more comfortable with this drug and its use in the acute setting.<sup>[19]</sup>

While sparse, data examining the efficacy and safety of using ketamine in the ICU is increasing. A recent scoping review examining continuous ketamine infusion for sedation of mechanically ventilated adults in the ICU found nine eligible prospective randomised studies.<sup>[20]</sup> These randomised studies were all small, with sample sizes ranging from 25 to 160 patients, ketamine infusion doses ranging from 0.06 to 4.9 mg/kg/h and duration of infusion ranging from 9 h to 8 days.<sup>[20]</sup> Of these nine studies, only two were blinded, leading the authors to conclude that currently there exists a lack of high-quality, well-designed studies investigating the use of a continuous ketamine infusion in the ICU. These conclusions were echoed in two recent systematic reviews and meta-analyses on ketamine use in critically ill patients.<sup>[20,21]</sup> Interestingly, one also found that ketamine may decrease the need for other sedatives<sup>[22]</sup> and the other found that it may decrease delirium.<sup>[21]</sup> That being said, based on the existing low-quality data that we do have, ketamine appears to be safe and well-tolerated in critically ill patients.<sup>[20-22]</sup>

Given this renewed interest in ketamine, future studies need to focus on its use as a continuous infusion in critically ill patients. Specifically, significant uncertainty regarding the frequency and seriousness of ketamine emergence reactions and their impact on long-term outcomes persists. How will ketamine use impact delirium? On one hand, an increase in emergence reactions may increase delirium, while on the other, evidence shows that ketamine use may reduce delirium.<sup>[21,22]</sup> Given the increasing frailty of the ICU population and their proclivity for developing delirium, this remains a significant concern that must be addressed before ketamine is used more widely. Given the sympathomimetic effects of the drug, there is also uncertainty in how it may affect haemodynamics or potentially impact vasopressor use or frequency of arrhythmias in critically ill patients. To address some of these concerns, randomised controlled trials are needed to explore the use of ketamine as an adjunctive

infusion in mechanically ventilated critically ill patients. We expect that in the near future, we will have insight into the efficacy and safety of ketamine as a continuous sedative, which will inform its application in critically ill patients in the years to come.

## ORCID

Sameer Sharif: <https://orcid.org/0000-0002-3346-0308>

Jay Prakash: <https://orcid.org/0000-0002-5290-3848>

Bram Rochweg: <https://orcid.org/0000-0002-8293-7061>

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