

Ketamine for Acute Pain Management and Sedation

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TOPIC Ketamine is beneficial in clinical settings ranging from procedural sedation to the treatment of chronic pain. This article describes the clinical benefits of ketamine for treatment of acute pain and for sedation of patients undergoing mechanical ventilation.

CLINICAL RELEVANCE Ketamine causes analgesic and amnestic effects by noncompetitive inhibition of the *N*-methyl-*D*-aspartate receptor and activation of the opioid μ and κ receptors. Unlike other sedatives, ketamine provides analgesia and amnesia without causing hypotension or respiratory depression. Several studies have elucidated the clinical benefits of ketamine. The use of ketamine has extended beyond critical care areas such as the operating room and intensive care units. Nurses must be familiar with optimal clinical scenarios, monitoring parameters, and contraindications of ketamine.

PURPOSE To highlight the clinical utility and pharmacological properties of ketamine through a literature review. Current studies of ketamine in acute pain and sedation management are summarized.

CONTENT COVERED This narrative review describes pharmacological properties, dosing strategies, administration considerations, and adverse effects of ketamine. (*Critical Care Nurse*. 2020;40[5]:e26-e33)

Ketamine use has gone beyond the operating room and is becoming more common in acute care. Ketamine induces rapid sedation and analgesia through dual mechanisms mediated by noncompetitive inhibition of the *N*-methyl-*D*-aspartate receptor and activation of the opioid μ and κ receptors.¹⁻³ Because of its high lipophilicity, ketamine has a rapid onset, with effects potentiated within 30 to 40 seconds. The effects of ketamine are largely dependent on the dose. Doses greater than 1 mg/kg induce sedative effects that can create a dissociative state in which patients appear awake but are best described as insentient.³ Lower doses, 0.1 to 0.3 mg/kg, have less prominent central nervous system effects and provide more analgesia.^{1,2} Other favorable characteristics of ketamine include bronchodilation, cardiac output preservation, and increased blood pressure. Ketamine also has minimal effects on bowel motility, respiratory drive, and airway reflexes.¹⁻⁵

Ketamine has been shown to be an effective adjunct to traditional opioid therapy. Its opioid-sparing effects are useful for the treatment of acute pain in the emergency department and postoperative areas. In addition to analgesia, ketamine can provide amnesia and sedation.^{1,2} Unlike other agents, ketamine produces analgesia and sedation without causing hypotension or respiratory depression. Ketamine is therefore well suited for patients with respiratory and hemodynamic instability. Pharmacokinetic

Table Pharmacokinetic properties and adverse effects of sedatives and analgesics commonly used in the intensive care unit²⁻¹⁰

	Ketamine	Midazolam	Propofol	Dexmedetomidine	Fentanyl
Mechanism of action	NMDA antagonist and opioid μ agonist	GABA _A agonist	GABA _A agonist	α_2 Receptor agonist	Opioid μ agonist
Onset	30 s	1-5 min	~ 30 s	5-10 min	~ 10 s
Half-life	2.5 h	3-11 h	1-7 h	~ 2 h	2-6 h
Accumulation with prolonged infusion	No	Yes	Yes	No	Yes
Anesthetic/ hypnotic	Yes	Yes	Yes	No	No
Analgesic effects	Yes	No	No	Yes	Yes
Associated delirium	+	+++	++	-	++
Respiratory depression	-	+++	+++	-	++
Adverse effects and considerations	Hypertension, tachycardia, apnea with rapid administration, excessive secretions, psychomimetic effects (eg, vivid dreams, hallucinations), bronchodilation	Hepatically metabolized to an active metabolite that may accumulate with renal failure; accumulates in fat stores	Hypotension, bradycardia, PRIS (lactic acidosis, arrhythmias, cardiac arrest), pancreatitis, hypertriglyceridemia; accumulates in fat stores	Hypotension, bradycardia, dry mouth	Constipation, skeletal-muscle rigidity; accumulates in fat stores

Abbreviations: +++, strong association; ++, moderate association; +, theoretical concern; -, no association; GABA, γ -aminobutyric acid; NMDA, *N*-methyl-D-aspartate; PRIS, propofol infusion syndrome.

properties and adverse effect profiles of analgesics and sedatives commonly used in critical care can be found in the Table for comparison.

The 2013 guidelines for management of pain, agitation, and delirium mentioned ketamine as an option but provided no recommendations on its appropriate use.⁵ In the updated 2018 guidelines for managing pain, agitation/sedation, delirium, immobility, and sleep disruption, the Society of Critical Care Medicine recommended ketamine as an adjunct to opioids for postsurgical pain management in adults in critical care.¹¹ This update was published just months after the American Society of Regional Anesthesia and Pain Medicine released guidelines for ketamine use for acute and chronic pain.^{12,13} Since then, more literature has been published describing subanesthetic doses in the intensive care unit (ICU) to facilitate mechanical ventilation.

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As ketamine use continues to expand, nurses within acute care settings must become more familiar with its administration, monitoring, and pharmacokinetic properties. This review describes pharmacological properties, dosing strategies, administration considerations, and the adverse effect profile of ketamine for the treatment of acute pain and treatment of patients receiving mechanical ventilation.

For this review we queried the PubMed and MEDLINE electronic databases. The search query included combinations of the following terms: *critical care, intensive care, acute pain, emergency department, and ketamine*. The initial search was restricted to English-language articles and studies in humans. The query focused on articles that described the use of ketamine for the treatment of acute pain or facilitation of mechanical ventilation in the ICU.

Evidence for Ketamine for the Treatment of Acute Pain

Bolus Dosing

The vast majority of the literature describing ketamine use for acute pain is in the postoperative setting, with the emergency department setting becoming more common. Low-dose boluses of ketamine (0.1-0.3 mg/kg) have been shown to reduce pain scores and opiate consumption when used as an adjunct to opiate therapy in acute pain treatment.^{9,14,15} Clinical benefits can last up to 2 hours

after a single administration.¹⁵ Compared with lower doses, a dose of 0.3 mg/kg has been found to be more effective in reducing pain scores.⁹ However, higher doses are associated with more frequent minor adverse events.^{9,14}

Continuous Infusion

Evidence suggests that ketamine infusions can reduce hyperalgesia in the postoperative setting.^{10,16-18} Infusions of ketamine are well tolerated, significantly reduce pain scores, and increase postoperative pain control while decreasing opioid consumption in a variety of general surgical and orthopedic procedures.^{6,10} In 2 studies, bolus doses of 0.5 mg/kg of ketamine followed by continuous infusions of 0.12 to 0.36 mg/kg/h (2-6 µg/kg/min) of ketamine for 48 hours reduced the cumulative dose of morphine and decreased patient nausea.^{16,17} Intraoperative infusions of ketamine reduced opiate consumption in the 24 hours following total knee replacement.¹⁷ The use of ketamine was also associated with a prolonged time until the first dose of opiates.^{16,17} Ketamine use in conjunction with opioid therapy can improve pain control in patients undergoing surgical procedures. The growing evidence has led to the recom-

mendation

Continuous infusions can reduce consumption of opiates and concomitant sedatives. to use ketamine as an analgesic adjunct to reduce opioid consumption in adults after surgical procedures.¹⁶ The doses of ketamine have not been consistent among studies, but administration of ketamine as a perioperative bolus followed by a continuous infusion appears to be most effective in controlling postoperative pain.^{10,16,17}

Although ketamine was effective in many of the surgical trials, some studies showed that ketamine had no benefit when compared with placebo for controlling postoperative pain.^{19,20} Most available literature seems to demonstrate that a low dose ranging from 0.02 to 0.1 mg/kg/h (0.3-1.7 µg/kg/min) is safe for adjunctive analgesia for up to 48 hours. However, higher doses can be safely administered when sedation is indicated in critically ill patients.^{4,21-23}

Clinical Application

For the treatment of acute pain, short (10- to 15-minute) infusions of 0.3 mg/kg intravenous ketamine are becoming more common and provide appropriate analgesia while

potentially reducing the risks associated with more rapid intravenous administration. Continuous infusions can be used as adjunctive therapy to lower opioid requirements in patients after surgical procedures. Because of the minimal impact on respiratory and hemodynamic systems, continuous ketamine infusion is an appealing therapeutic option and can potentially be used in non-ICU telemetry patient care.

Evidence for Ketamine as a Sedative or Analgesic in Critical Care Units

Utility as Adjunct Sedation

No randomized trials have compared ketamine with conventional modes of sedation and analgesia in critically ill patients. At low doses (but typically higher than doses for acute pain), ketamine can provide sedative and analgesic effects and can be used as adjunctive therapy.³ Subanesthetic doses ranging from 0.03 to 0.24 mg/kg/h (0.5-4 µg/kg/min) are reported to be effective for sedation. In small analyses and case reports, ketamine was shown to decrease agitation and the use of concomitant sedatives and antipsychotics while facilitating mechanical ventilation liberation.⁷ There is growing consensus that ketamine may be a reasonable option to help decrease agitation, manage pain, and facilitate opioid and benzodiazepine withdrawal in critically ill patients.

In a study of trauma patients requiring mechanical ventilation, ketamine reduced the amount of concomitant sedatives and analgesics needed. Decreases in morphine equivalents and propofol dosing requirements were associated with the initiation of ketamine infusions.²¹ Doses of 0.03 to 0.06 mg/kg/h (0.5-1 µg/kg/min) have proven to be effective in reducing the number of sedative infusions within 24 hours needed to treat patients receiving mechanical ventilation.²² Ketamine infusions were also found to be associated with a significant increase in goal sedation scores in comparison with the 24-hour period preceding the infusion.^{21,22} Patients requiring mechanical ventilation in medical ICUs needed slightly higher doses than did trauma patients. Ketamine doses of 0.04 to 2.5 mg/kg/h (0.7-41.7 µg/kg/min) for a median duration of 2.8 days resulted in lower sedative and analgesic doses after the initiation of ketamine.²² These findings support the theory that ketamine can be safely used as an adjunctive agent for sedation and analgesia in patients receiving mechanical ventilation.^{4,7,21,22}

Ketamine has also been used as monotherapy for sedation, but minimal literature supports this strategy. Monotherapy may be reasonable for patients who can tolerate light sedation or short durations of mechanical ventilation. If ketamine is used as the sole agent, higher doses will be needed to effectively treat patients receiving mechanical ventilation. Ketamine is typically initiated at 0.06 to 0.12 mg/kg/h (1-2 µg/kg/min), with sedative effects seen in doses ranging from 0.6 to 1.2 mg/kg/h (10-20 µg/kg/min).²³ If targeted sedation is not achieved in that range, consider bolus doses of additional sedatives or analgesics before adding continuous infusions.

Ketamine is often used in conjunction with another continuous infusion to provide optimal sedation in patients undergoing mechanical ventilation. The question then becomes which agent to replace in an analgesia-based sedation protocol. The available evidence does not clearly delineate the answer. Ketamine is commonly treated as a sedative medication and used with analgesic medications such as fentanyl. However, the appropriate dose of ketamine as an adjunctive agent is inconclusive largely because of varying dosing strategies to achieve desired results. The use of different units of measure (milligrams per kilograms per hour vs micrograms per kilograms per minute) causes a wide variation in doses. Total daily doses for a 70-kg patient can vary significantly from 2016 mg (1.2 mg/kg/h [20 µg/kg/min]) to 4704 mg (2.8 mg/kg/h [46.7 µg/kg/min]), depending on institution standards. Further studies are needed to determine the most appropriate dosing scheme for the critically ill, but actual body weight is typically used. Although evidence is lacking, dose adjustments may be warranted in the morbidly obese. Because ketamine is a highly lipophilic compound, prolonged exposure to high doses could lead to toxicity.²⁴

Clinical Application

Monotherapy with ketamine in patients receiving mechanical ventilation is not well described in the literature. It is reasonable to use ketamine in conjunction with other agents to reduce sedative requirements. According to the evidence, initiation of continuous infusion of ketamine at 0.06 mg/kg/h (1 µg/kg/min), with increases of 0.03 mg/kg/h (0.5 µg/kg/min) every 15 minutes to goal sedation or a maximum dose of 1.2 mg/kg/h (20 µg/kg/min), is a reasonable strategy.²¹ Special populations may require higher doses, but the risks and benefits should

be assessed because higher doses may induce a dissociative state that may worsen delirium. Patients should be frequently monitored for adverse effects such as hypertension, tachycardia, altered mental status, and increased agitation.

Routes and Rates of Ketamine Administration

Ketamine can be administered through intravenous, intramuscular, or intranasal routes. The route of administration may limit the dose of ketamine on the basis of concentration and volume. Most of the available literature describes intravenous administration, which is the most ideal route for the treatment of acute pain and provision of sedation in adult populations.²² Intravenous administration is the fastest route of administration to provide therapeutic doses for acute pain and sedation. However, the rate of infusion is associated with adverse effects. Ketamine is recommended to be administered slowly because rapid administration may result in brief apnea and an enhanced cardiovascular response.²³ Motov et al²⁵ conducted a prospective, randomized, double-blinded, double-dummy trial to compare the clinical effects of 5-minute intravenous push and 15-minute intravenous infusion of low-dose ketamine to treat acute pain.

Ketamine can be safely used as an adjunctive agent for sedation and analgesia in patients receiving mechanical ventilation.

No significant difference in the analgesic effect was seen, but significant differences were found in the adverse effect profile and level of sedation. Patients receiving a 5-minute intravenous push had higher rates of feelings of unreality and more severe adverse effects. Administration by 5-minute push was also associated with a deeper level of sedation. The level of central nervous system disturbance appears to be higher with rapid administration than with slower infusion.²⁴ Administration of ketamine over 15 minutes has demonstrated similar efficacy, with minimal risk for adverse effects.²⁴

Ketamine Adverse Effects

Although ketamine has been reported to be safe and well tolerated, adverse events such as hypertension, tachycardia, decreased cardiac output, secretions, bronchodilation, and changes in mental status have been reported.^{1,26} The most well-known concern for ketamine

is its mind-altering effect. Ketamine can provoke a state similar to schizophrenia because of its *N*-methyl-D-aspartate antagonism. This unique dissociative state is characterized by a feeling of detachment from reality and impaired cognitive function. In addition, ketamine can cause transient increases in positive and negative symptoms of schizophrenia, dissociative symptoms, and manic symptoms. These symptoms may be present at the time of administration but usually disappear within 60 minutes of administration.²⁷ The incidence of these adverse effects can be reduced by maintaining a quiet environment while administering ketamine.²⁷ Central nervous system effects are seen more often in patients who receive doses greater than 2 mg/kg per dose, receive a high rate of infusion (> 40 mg/min), or have a preexisting psychiatric condition.¹⁵ Other psychotomimetic effects include feelings of intoxication, increased confusion, lowered inhibition, and perceptual disturbances.^{1,27} Although these effects are usually temporary, they can be significantly distressing for patients. Ketamine should be used cautiously in patients with recent myocardial infarction, malignant hypertension, tachyarrhythmia, heart failure, and cardiogenic shock because it will increase cardiac demand and output.²

The psychotomimetic properties of ketamine are a trademark adverse effect typically seen when patients emerge from a dissociative state. Because of the timing of

Current evidence does not link sustained ketamine infusions with delirium.

symptom onset, this occurrence is termed the emergence phenomenon. Patients may experience floating sensations; vivid, pleasant dreams; nightmares; hallucinations; and delirium.^{28,29} These symptoms have been associated with female sex, large doses, and rapid drug administration.²⁹ Evidence suggests that concomitant medications can decrease the severity of these events. Pre-medication with oral clonidine 90 minutes before surgery reduces the incidence and severity of nightmares attributed to anesthesia induction with ketamine. This benefit may be limited clinically with subanesthetic ketamine doses because of different dosing schemes, rates of administration, and onset of action of oral clonidine. Studies of clonidine use with subanesthetic ketamine doses are required before this practice can be recommended.³⁰

Intravenous benzodiazepines such as diazepam and midazolam have a fast onset and have been shown to

reduce psychological manifestations during emergence and attenuate the hemodynamic response to ketamine.²⁸ Propofol has also been used as an adjunctive agent to reduce the psychotomimetic effects of ketamine; this combination is called ketofol.³¹ By administering both agents together, individual dose-dependent adverse effects are attenuated while clinical efficacy is maintained.³² Lemoel et al³² conducted a double-blind randomized controlled trial to evaluate the adverse effect profile of ketofol (1:1 ratio of ketamine to propofol) compared with ketamine for emergency procedural sedation. Adverse events were reduced by 22.4% with use of the ketamine-propofol combination.³² However, dosing and efficacy may be in question because a significant number of patients required more than 2 doses of ketofol to achieve the predetermined level of sedation before the procedure.^{32,33} Although studies have shown the efficacy of ketofol, its use is not recommended or considered standard of care at this time.

Despite the extensive use of ketamine, controversy regarding its neurological effects remains. The known psychological disturbances and hallucinations associated with ketamine theoretically increase a patient's risk for developing delirium. This concern is significant because delirium puts patients at greater risk for negative outcomes in the ICU. This apprehension has not been validated in the literature, and rates of delirium-free days are similar for ketamine-based infusions and for nonbenzodiazepine sedatives.³³ Avidan et al²⁰ assessed the intraoperative use of ketamine at 0.5 mg/kg and at 1 mg/kg as a single dose after anesthesia induction. The incidence of delirium did not differ between the ketamine and placebo groups, but patients who received ketamine experienced more hallucinations and nightmares.²⁰ Further studies are necessary, but the current evidence does not link sustained ketamine infusions with delirium. Reports have also suggested that ketamine exhibits neurotoxicity and impairs neurogenesis in animal and in vitro models.^{34,35} However, concentrations required to cause neuronal death greatly exceed typical anesthetic concentrations.³⁶ The clinical significance of dose-dependent neuronal toxicity should be questioned because these concentrations are difficult to achieve, especially when using ketamine for acute pain and sedation. Randomized controlled studies are required to elucidate the true significance and incidence of neurotoxicity because the available evidence is limited to bench and animal studies.

Physiological tolerance may occur in individuals who have undergone repeated procedures requiring anesthesia with ketamine. Case reports have documented analgesia, anesthesia, and psychoactive tolerance with repeated doses of ketamine and illicit drug use. Potential dependence through chronic or repetitive ketamine use is a concern, but reports of abuse are minimal.^{1,2,25,37} A study evaluating healthy participants receiving subanesthetic doses of ketamine for a 6-month period found no instances of cravings or abuse, suggesting that low-dose ketamine is less likely to produce dependence.³⁸

Conclusion

Ketamine can be used in various settings and strategies to manage patients' sedative or analgesic needs. No standard unit of measure is currently used to describe ketamine infusion rates; various studies report infusion rates in milligrams per kilogram per hour or micrograms per kilogram per minute. The dose can significantly differ according to the rate used, potentially leading to errors in administration. With increasing use of ketamine, patient scenarios that require balancing the benefits and risks of ketamine will arise. The lowest tolerable dose via short or continuous infusion is recommended to avoid adverse effects such as apnea and excessive sedation. Caution should be exercised in patients with a history of cardiac ischemia, coronary artery disease, or acute cardiogenic shock because ketamine can increase blood pressure, heart rate, and cardiac output and may worsen their condition. Nurses should also be mindful of central nervous system disturbances, delirium, or severe agitation in patients receiving ketamine. Dose reduction or adjunctive medication boluses should be considered. Anticholinergic medications may be warranted if patients develop excessive secretions.

Although more comparative studies are needed to support the widespread use of ketamine in critically ill patients, ketamine can be considered a potential option for the treatment of pain and agitation. Ketamine has both sedative and analgesic properties, is generally well tolerated, and has minimal effects on respiratory drive, which is an appealing profile for managing pain and sedation in patients in the ICU. Additional data are needed to determine the effects of ketamine on pain control, level of sedation, opiate consumption, and patient outcomes including delirium occurrence, duration of mechanical ventilation, and length of ICU stay. **CCN**

Financial Disclosures
None reported.

See also

To learn more about pain management, read "Evidence-Based Strategies for the Prevention of Chronic Post-Intensive Care and Acute Care-Related Pain" by Bérubé in *AACN Advanced Critical Care*, Winter 2019;30(4):320-334. Available at www.aacnconline.org.

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- Low-dose boluses of ketamine (0.1-0.3 mg/kg) have been shown to reduce pain scores and opiate consumption when used as an adjunct to opiate therapy in acute pain treatment.
- Infusions of ketamine are well tolerated, significantly reduce pain scores, and increase postoperative pain control while decreasing opioid consumption in a variety of general surgical and orthopedic procedures. Ketamine is recommended as an analgesic adjunct to reduce opioid consumption in adults after surgical procedures.
- For the treatment of acute pain, short (10- to 15-minute) infusions of 0.3 mg/kg intravenous (IV) ketamine are becoming more common and provide appropriate analgesia while potentially reducing the risks associated with more rapid IV administration.
- Ketamine has been shown to decrease agitation and the use of concomitant sedatives and antipsychotics while facilitating mechanical ventilation liberation. Ketamine may be an option to help decrease agitation, manage pain, and facilitate opioid and benzodiazepine withdrawal in critically ill patients.
- Ketamine is often used in conjunction with another continuous infusion to provide optimal sedation in patients undergoing mechanical ventilation. However, the appropriate dose of ketamine as an adjunctive agent is inconclusive largely because of varying dosing strategies to achieve desired results.
- Although evidence is lacking, dose adjustments may be warranted in the morbidly obese. Because ketamine is a highly lipophilic compound, prolonged exposure to high doses could lead to toxicity.
- Ketamine can be administered through IV, intramuscular, or intranasal routes. The route of administration may limit the dose of ketamine on the basis of concentration and volume.
- Ketamine is recommended to be administered slowly because rapid administration may result in brief apnea and an enhanced cardiovascular response.
- Although ketamine has been reported to be safe and well tolerated, adverse events such as hypertension, tachycardia, decreased cardiac output, secretions, bronchodilation, and changes in mental status have been reported. The most well-known concern for ketamine is its mind-altering effect. Ketamine can cause transient increases in positive and negative symptoms of schizophrenia, dissociative symptoms, and manic symptoms.
- Patient scenarios that require balancing the benefits and risks of ketamine will arise. The lowest tolerable dose via short or continuous infusion is recommended to avoid adverse effects such as apnea and excessive sedation. Caution should be exercised in patients with a history of cardiac ischemia, coronary artery disease, or acute cardiogenic shock because ketamine can increase blood pressure, heart rate, and cardiac output and may worsen their condition. Nurses should also be mindful of central nervous system disturbances, delirium, or severe agitation in patients receiving ketamine. **CCN**

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