



Ketamine Use in Adults with Critical Illness

Key Articles

Hurth KP, Jaworski A, Thomas KB, Kirsch WB, Rudoni MA, Wohlfarth KM. *The Reemergence of Ketamine for Treatment in Critically Ill Adults. Crit Care Med.* 2020;48(6):899-911.

Background

- Ketamine is a well-known anesthetic used in the Emergency Department for procedural sedation for decades
- It is an attractive medication due to its short-acting sedative, analgesic, and dissociative properties.
- Ketamine's unique pharmacology also may have significant anti-inflammatory and antidepressant effects which are not yet fully understood but make it an attractive medication for the critically ill.
- The goal of this review will not be to discuss the more familiar uses of ketamine which include RSI and for procedural sedation but rather frame it with respects to specific disease states.
- **Worth noting: Tables in this paper are extremely helpful and worth reviewing the summaries for individual study data, medication doses, and indications.**

Pharmacokinetics and dynamics

- Ketamine acts as a noncompetitive inhibitor of NMDA (N-methyl-D-aspartate) receptors in the brain.
 - Onset of action: 30 seconds (IV) and 3-4 minutes (IM)
 - Duration of action: 5-10 minutes (IV) and 12-25 minutes (IM)
 - Primarily metabolized by the liver and excreted in the urine.
- **Ketamine acts on:**
 - **NMDA receptors** are responsible for awareness and memory, but also have a significant role in the sensation of pain.
 - **GABA receptors**, which are responsible for agitation or sedation, can be either antagonized or enhanced – which is why benzodiazepines are often given in conjunction with ketamine.
 - **Catecholamine receptors** are stimulated through reuptake blockade, which is the reason for ketamine's favorable hemodynamic profile compared to anesthetics with negative hemodynamic effects.
- PEARL: Despite the sympathomimetic potential, ketamine's myocardial depressant effects can be unmasked in states of catecholamine depletion (e.g., acute heart failure) resulting in hypotension and bradycardia.

POTENTIAL USES FOR KETAMINE

Acute Pain Management

- **Rationale:** Ketamine may be an ideal adjunctive treatment in mechanically ventilated patients since it can reduce opioid requirements without any negative hemodynamic effects.
- In the authors' review, the most evidence was found for ketamine's use as an adjunct analgesic, however most published data are retrospective studies.
- **Evidence:** 3 studies were identified to find sub-dissociative doses of ketamine (<1 mg/kg/hr) significantly reduce opioid and propofol requirements in intubated patients.
- Commonly reported adverse effects include tachycardia, nystagmus, and agitation. This is likely due to the unpredictable effect on GABA receptors.
- **Clinical interpretation:** Data is largely retrospective (level 3 evidence) but appears ketamine may reduce opioid requirements but should be reserved as an adjunctive agent for refractory situations.

Status Asthmaticus

- **Rationale:** Ketamine causes bronchodilation by increasing circulating catecholamines, inhibiting vagal tone, and relaxing smooth muscle in the large airways.
- **Evidence:** Only one randomized control trial identified, which evaluated the safety and efficacy of ketamine in *non-intubated* adults with acute asthma exacerbation.
 - Pt's were randomized to 0.2 mg/kg IV bolus plus infusion at 0.5 mg/kg/hr vs. placebo; NOTE: Significant dysphoria identified after bolus so the initial dose was decreased to 0.1 mg/kg IV.
 - Result: Improved peak flow, asthma severity score, reduced respiratory rate and FEV1, but it was NOT statistically significant.
- **Clinical interpretation:** Data is sparse, with only 1 well conducted trial. The authors could not recommend routine use for status asthmaticus.

Alcohol Withdrawal Syndrome

- **Rationale:** Ketamine has a mechanism of action similar to ethanol by blocking NMDA receptors, which is a site of action uncommonly used in AWS management. **Given the high doses of benzodiazepines** often required for severe alcohol withdrawal and significant benzodiazepine side effects, ketamine is an attractive alternative for this disease.
- **Evidence:** Two studies reported the use of ketamine as an adjunct to symptom triggered BZD use in the ICU. 1 study had no effect, a 2 studies used a higher infusion doses (0.15 up to 3 mg/kg/hr continuous infusion) which significantly reduced total Ativan requirements, ICU length of stay, and likelihood of intubation compared to traditional symptom based strategy.
- **Clinical interpretation:** Although ketamine appears to be a safe option, evidence pool is still too small to recommend routine use as a BZD adjunct in EtOH withdrawal.

Status Epilepticus

- **Rationale:** Refractory status epilepticus has been found to cause decreased GABA receptor sensitivity to commonly used treatments including phenytoin, benzodiazepines, and phenobarbital as early as 30 minutes after seizure onset. NMDA receptor upregulation has been identified in status epilepticus, which raises the possibility that Ketamine may be useful in refractory seizures.
- **Evidence:** One multicenter study identified which trialed ketamine in refractory SE on seizure control.
 - The treatment endpoints were somewhat ambiguous, where “possible response” was defined by the permanent control of SE within 24 hours of starting ketamine.
 - 1/3 of patients were “possible responders”, and it appeared that those started earlier on ketamine had a shorter duration of SE.
- **Risks:** The authors of the review raised the risk of ketamine’s effect on ICP while managing refractory status epilepticus, but there is data support that this is likely a myth in terms of adverse side effects of ketamine.
- **Clinical application:** It may be reasonable to consider ketamine in the management of refractory SE, especially in patients with hemodynamic depression from conventional treatment.

Acute Agitated Delirium

- **Rationale:** Ketamine may be a desirable treatment option given its rapid onset and duration of action.
- **Evidence:** One prospective, observational study compared Ketamine to BZD or haloperidol in 98 patients found less agitation 5, 10, and 15 minutes using a 6-point agitation scale in those receiving ketamine.
 - The authors identified 3 retrospective studies do exist, which suggest similar findings as the prospective study above.
- **Risks:** High intubation rates after ketamine administration have been reported however this may be more due to provider practice rather than a true adverse effect. Doses given ranged from 2 mg/kg IV to > 5mg/kg IM
- **Clinical application:** There appears to be a higher adverse event rate in critically ill adults compared to ED/prehospital patients, but could be considered until further prospective data are available.

Summary

- There appears to be an emerging role for Ketamine use in critically ill patients.
- Data is still limited but its role looks to largely be adjunctive as opposed to using it as a primary treatment.
- Evidence is the most robust for adjunctive analgesia in the intubated patient, but could also be considered in the critically ill asthmatic and seizure patient.
- Beware of high doses in the patient with excited delirium as there have been reports of increased need for intubation after administration.