Four good reasons to choose ketamine in the emergency department. A case series and literature review

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Abstract

Ketamine is a fast-acting N-methyl-D-aspartate (NMDA) receptor antagonist that can be used in a range of clinical scenarios in the pre-hospital setting and emergency department (ED). When compared with other anesthetic agents, ketamine has many unique properties, such as the ability to produce dose-dependent analgesic and anesthetic effects with a wide margin of safety. Ketamine may be used in the ED for sedation, pain management, and acute agitation treatment in the cases of benzodiazepine (BDZ)-resistant alcohol withdrawal syndrome (AWS) and substance use disorder. To highlight the efficacy and safety of ketamine, we reviewed the literature, starting with a description of four different cases of patients who presented to our ED and were treated with ketamine.

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Highlights

- *Ketamine is a fast-acting NMDA receptor antagonist with a dose-dependent effect but with a very broad action on different receptor sites.*
- *Ketamine can be safely used by emergency clinicians for procedural sedation, and pain management, including pain unresponsive to opioids, neuropathic pain, opioid-induced hyperalgesia, and rapid agitation control in benzodiazepine-resistant alcohol withdrawal syndrome and substance use disorder.*
- *Other indications include hyperactive delirium with severe agitation, acute life-threatening refractory asthma, refractory status epilepticus, sedation during non-invasive ventilation, and palliative sedation in the end-of-life.*
- *The most common routes of administration are intramuscular and intravenously.*
- *Caution must be maintained in patients with severe and uncontrolled hypertension and/or persistent cardiovascular diseases.*
- *Absolute contraindications to ketamine administration are pregnancy, hepatic porphyria, and the first three months of life.*

Case Reports

We briefly present four cases of patients who were admitted to the ED of Guglielmo da Saliceto Hospital, Piacenza, Italy, and treated with ketamine for four different causes.

Case #1

As a result of acute alcohol withdrawal syndrome (AWS), a 48-year-old man developed delirium tremens with tachycardia, hypertension, diaphoresis, agitation, and hallucinations while recovering in our observational unit. He was immediately treated with benzodiazepines, using delorazepam 5 mg intravenous (IV) and midazolam 5 mg bolus IV, followed by a continuous infusion of midazolam without benefits. A diagnosis of benzodiazepine-resistant AWS was

made, and ketamine was started at a sub-dissociative dose of 0.5 mg/kg/h IV with complete symptom management.

Case #2

A 29-year-old man was found agitated on the street as a result of an alcohol and substance use disorder. He was sent to our ED with a diagnosis of severe BDZ-resistant psychomotor agitation after being treated with midazolam (15 mg IM plus 10 mg IV) by the emergency medical service. In the ED, ketamine was started at a dissociative dose of 1 mg/kg/h IV, with optimal symptom management.

Case #3

A 51-year-old woman with a history of obesity and bipolar disorder was brought to our ED by the police for psychotic delirium. She was immediately treated with ketamine at a dissociative dose of 5 mg/kg IM with immediate sedation. When the patient was dissociated, delorazepam 5 mg IV was infused, and she was transferred to the psychiatric inpatient clinic.

Case #4

A 50-year-old man with surgical monokidney presented to our ED complaining of renal colic. Despite receiving massive doses of morphine IV (3 consecutive boluses of 0.1 mg/Kg IV), he continued to suffer intense pain (NRS 10/10). Ketamine was given intravenously at an analgesic bolus dose of 0.2 mg/kg, which provided immediate pain relief. Except for patient 4, who experienced moderate anxiety, which was treated immediately and successfully with midazolam 2 mg IV, none of the patients experienced side effects.

Discussion

Ketamine is a stereoselective non-competitive antagonist of the ionotropic receptor of NMDA that reduces calcium ion influx through this channel and therefore prevents neuronal activation required for conscious state,[1] resulting in a non-competitively block of the opening of glutamatergic channels, mainly in the prefrontal cortex and hippocampus. However, the analgesic effects of ketamine are diverse and multifaceted, with effects on dopaminergic, adrenergic, serotoninergic, opioid, and cholinergic receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr) and on spinal GABA interneurons: ketamine modulates the reuptake of serotonin, dopamine, and norepinephrine, causing a paradoxical increase in glutamate with stimulation of the descending inhibitory pathways, and having an antidepressant action caused by actions on several levels.[2]

It was first synthesized by Calvin Stevens of the Parke-Davis Pharmaceutical Company in 1962 (Ann Arbor, Michigan) while searching for an alternative to the potent hallucinogenic agent phencyclidine,[3] and later, it was approved by the FDA as an anesthetic agent in 1970.[4]

Ketamine is unique among drugs for its ability to produce different effects, from analgesic to dissociative, depending on the dosage[2] (Tables 1 and 2). Its potential benefits are evident in

Table 1. Dosages and effects of ketamine in adults.

	Adult dose
Analgesia	• 0.15-0.3 mg/kg IV/IO (slow push), followed by 0.15-0.3 mg/Kg/h IV/IO (continuous infusion) • 0.5 mg/kg IM, repeat 0.3 mg/kg after 45 min • 1 mg/Kg IN
Procedural sedation	• 1-2 mg/kg (IV/IO)
Dissociative dose	• 1-2 mg/Kg IV/IO • 5 mg/Kg IM (max single/cumulative dose 500 mg) Maximum volume of administration: - Deltoid: 2 mL - Lateral thigh: 4-5 mL - Gluteal: 5 mL
Sub-dissociative dose	• 0.5-0.7 mg/kg IV/IO

IV, intravenous. IO, intraosseus. IM, intramuscular.

Table 2. Dosages and effects of ketamine in pediatrics.

	Pediatric dose (aged > 6 months)
Analgesia	Intravenous/Intraosseous • 0.15-0.33 mg/kg slow push • Maximum single dose 20 mg • Repeat every 2-3 minutes to a total cumulative dose of 0.6 mg/kg Intramuscular • 0.5 mg/kg • May repeat 0.3 mg/kg at 45 min Intranasal • 1.5 mg/kg • May repeat 1 mg/kg at 20 min • Maximum single dose 100 mg
Procedural sedation	See adult dosing guidelines and follow a weight-based dosing regimen

patients suffering from depression,[5,6] pain,[7] status epilepticus,[8] alcoholism,[9] and substance abuse disorders,[10] hyperactive delirium with severe agitation,[11] but it may also be useful in treating severe acute pain in the presence of hemodynamic instability, such as pre-hospital trauma,[12] and for sedation during non-invasive ventilation alone or combined with other drugs.[13–16]

Drug characteristics

Ketamine is a highly lipophilic drug with a rapid and large steady-state volume of distribution.[1,17] Acting as an antagonist on NMDA receptors, it can reverse the enhanced pain sensitivity that is frequently present in major trauma or surgical injury and increases the anti-nociceptive effects of conventional opioid and nonsteroidal anti-inflammatory drugs, but ketamine can also interact with several other receptors, including μ, κ and δ opioid receptors, that contributes to its analgesic effects. In addition, ketamine can inhibit muscarinic and nicotinic receptors, L-type calcium and sodium channels current, adrenergic and serotonin receptors, and dopaminergic D_2 receptors,[1] and it can have anti-inflammatory effects by decreasing IL-6, TNF alpha, CRP, and NO synthase levels, particularly in the post-operative setting.[2]

Metabolism

Ketamine undergoes liver metabolism via the cytochromes CYP2B6 and CYP3A4, producing the active metabolite (R, S)-norketamine, which has psychoactive properties and anesthetic effects. The major metabolic pathway is *N*-demethylation. Depending on the expression of P450 enzymes,[18,19] the metabolism of ketamine varies individually.

Absorption, distribution, and excretion

After being metabolized in the liver, ketamine is rapidly distributed into highly perfused tissues with an immediate passage through the central nervous system,[20,21] crossing the blood-brain barrier. Since ketamine is very lipid-soluble and has a relatively low protein binding (ranging from 10% to 50%),[22] it has a large volume of distribution (3-5 L/kg).

Ketamine has a faster onset of action but a shorter half-life:[2,20] its onset of action is 2-3 min, with a duration of effect ranging from 5-30 minutes.[23] Therefore, for prolonged activity sometimes continuous infusions may be required. Due to its quick onset and short duration of action with only slight cardio-respiratory depression, ketamine is a preferred drug for short-term surgical procedures, especially in children.[24]

Duration of action and bioavailability may vary depending on the route of administration.[25] Ketamine can be administered via almost any route depending on the intent. Bioavailability largely depends on the route of administration.[1] It showed a limited bioavailability after oral, sublingual, and rectal administration, because of the first-pass effect.[26] After oral administration, bioavailability is 16-29%, the action onset typically occurs within 20-30 min, and the duration of effect is between 60 and 90 min. The most common routes of administration are intravenous (IV) and intramuscular (IM)[27] with bioavailability higher and rapid achievement of maximum plasma concentrations.[28] When administered intravenously, the bioavailability is 100% and the onset of action typically occurs within 1-2 min, and anesthesia lasts for approximately 20-60 min. After IM injection, bioavailability is 93%, and maximum effect is achieved within 5-10 min and typically lasts for 30-120 min. IM administration is used in emergency cases of uncooperative and agitated patients and neonates, even if intranasal (IN) is less invasive in children and easier in critically ill patients.[29] IN administration for analgesic purposes is a good alternative to IV administration for its rapid systemic absorption and because it bypasses first-pass hepatic metabolism,[30] especially in children.[6,31] IN administration shows a bioavailability of 35-50%, an analgesic effect with the onset of action within 10 min, a time-to-peak effect of 10-14 min, and a duration of up to 60 min.[2]

Elimination of ketamine and metabolites is performed by the kidneys,[17] thorough the conversion of ketamine and norketamine to 6-hydroxynorketamine and 5,6-dehydronorketamine,[18,32] both inactive free and glucuronidated hydroxylated derivatives, which are more water-soluble compounds to facilitate urinary excretion. Due to its shorter half-life, no dosage adjustment is required for patients with impaired renal function.[33]

Clinical settings

In the pre-hospital setting, ketamine is particularly effective in the treatment of trauma patients who have hemodynamic instability or head injuries because of its favorable cardiovascular characteristics of stimulating the central sympathetic system and inhibiting neuronal catecholamine uptake,[20] increasing blood pressure and cardiac rate but not intracranial pressure.[34,35] Ketamine is safe in head trauma, and the myth of this contraindication has been overcome: its action of increasing intracranial pressure is entirely negligible, and its neuroprotective action due to blockade of NMDAr neurons with glutamate-induced inhibition of neural edema prevails.[36–38] In the ED, ketamine plays an important role in procedural sedation, in the management of acute and chronic pain, and in acute agitation in the case of BDZ-resistant acute AWS,[39] and substance-use disorder,[10] but also in psychotic delirium[40] or hyperactive delirium with severe agitation,[11] as reported in our experience.

AWS is a potentially life-threatening condition that requires immediate treatment to avoid progression to delirium tremens.[41] The withdrawal symptoms vary from hallucinations and seizures to delirium tremens. Although BZDs have been considered first-line agents for the prevention and/or the treatment of AWS, lowering mortality and symptoms, they are associated with respiratory depression, and some patients may experience BZD-resistant alcohol withdrawal.[39,42] The first case report of this manuscript depicts a male patient who is still agitated and hyperdynamic after receiving large doses of BZD. As demonstrated by the case, ketamine at a sub-dissociative dose becomes an attractive agent for the treatment of BZD-resistant AWS, with earlier resolution of delirium tremens, not inducing respiratory depression and preserving the patient's protective reflexes and vital functions.[43] Ketamine, as an NMDA antagonist, stimulates the GABA receptors and inhibits the NMDA-glutamate receptors, miming the action of alcohol and reducing alcohol cravings.[44] According to Garel *et al*.,[45] ketamine can help to manage both AWS and substance use disorder by reducing withdrawal symptoms, promoting abstinence, and decreasing cravings in alcohol and cocaine use disorders.[46] Jones *et al*.[10] also demonstrated that ketamine may play a therapeutic role in enhancing long-term complete abstinence from alcohol and cocaine. In the position paper of the American Academy of Emergency Medicine, ketamine is mentioned in the list of medications for treating agitation in patients with alcohol intoxication, alcohol withdrawal, and alcohol use disorder in the Eds.[42] According to the authors, for agitated patients who are uncontrollably violent with concern for immediate harm to self or others, or if there is a concern for an immediately life-threatening medical condition whose diagnosis and management is hindered by agitation, dissociative-dose ketamine (4-5 mg/kg IM or 1-2 mg/kg IV)

should be considered. These patients require procedural sedation-level care with an airway-capable clinician available and vigilant attention paid to ventilation until dissociation resolves or the patient is intubated.[42]

In the case of BDZ-resistant psychomotor agitation, psychiatric disorders, or hyperactive delirium with severe agitation, as in cases 2 and 3, ketamine becomes an important alternative for the acute management of agitation at a dissociative dose of 2 mg/kg IV or 5 mg/kg IM.[11,40] The optimal management strategy for these patients includes immediate IM administration and rapid sedation, followed by airway protection, supportive measures, and cooling of hyperthermic patients. Ketamine has a rapid onset of action (30 sec IV, 2-15 min IM),[11] a short transit time, and a safety profile for its ability to maintain airway reflexes, as demonstrated in case 3, in which our patient maintained spontaneous respiration after receiving a high dose of ketamine. For these reasons, ketamine can be considered the ideal first-line medication for hyperactive delirium in the pre-hospital or ED setting.

Even if ketamine has a well-known effect on the NMDA receptors, it is involved in multiple other pathways like opioid receptors, nicotinic and muscarinic receptors, and dopamine receptors, with an analgesic activity.[47,48] Opioids are considered the cornerstone for the treatment of severe pain, but the analgesic dose of ketamine (0.15-0.3 mg/kg bolus, followed or not by 0.15-0.3 mg/kg/h continuous infusion) is an attractive option.[17] Ketamine is a safe and effective non-opioid alternative for a variety of painful conditions, like acute, chronic, oncologic, and refractory pain.[49] The use of ketamine for the treatment of acute pain can have opioid-sparing effects without increasing sedation,[4,50] especially in patients at risk of opiate-related respiratory failure (such as those with obstructive sleep apnea) since it can provide adequate analgesia without compromising the cardiorespiratory drive.[51]

In case 4, ketamine was administered intravenously at an analgesic dose of 0.2 mg/kg, providing rapid pain relief, after a massive dose of morphine (3 consecutive boluses of 0.1 mg/Kg IV). In chronic pain, the NMDAR is upregulated in the dorsal horn of the spinal cord, enhancing signal transmission in the pain circuitry and leading to chronic pain. Ketamine may be able to block this sensitization and briefly relieve chronic pain.[52] It is also interesting how the combination of ketamine with midazolam or propofol ("ketofol") or dexmedetomidine ("ketadex") can be extremely useful and safe for sedation and pain relief in intensive care patients, especially during sepsis, cardiovascular instability,[21] and non-invasive ventilation.[13–16]

When treating patients who have refractory pain, particularly those who are nearing the end of their lives (EoL) and have uncontrolled pain, emergency clinicians should remember to use ketamine as a painkiller and/or sedative agent. As reported by Serra *et al.*,[53] ketamine (IV: 0.1-0.3 mg/kg bolus; 0.1-0.3 mg/kg/h via continuous infusion) may have a role in the management of pain unresponsive to opioids, in neuropathic pain, in opioid-induced hyperalgesia, and could also have a future role in palliative sedation in the EoL.[54]

Ketamine shows also potential as a bronchodilator for pediatric patients with acute asthma exacerbation and has emerged as a treatment option for pediatric patients with acute asthma exacerbation who do not respond to standard therapy as a temporizing measure to prevent mechanical ventilation.[55,56] In the review by Garner *et al.*,[57] the authors outline strategies for the assessment and management of patients with acute life-threatening asthma focusing on those requiring admission to the ICU and they suggest using ketamine or propofol as sedative agents for non-invasive mechanical ventilation because of their potential bronchodilation properties. Finally, ketamine is useful to treat refractory status epilepticus by antagonizing NMDA receptors and inhibiting glutamatergic transmission.[58]

Adverse events, drug-drug interactions, and contraindications

Although ketamine is generally considered safe, it can cause different dose-dependent side effects and are most observed at doses above 0.35 mg/kg (especially at doses between 0.4 and 0.7 mg/kg).[2] At lower doses it can cause dreamy thinking, alterations of speech, hearing and seeing, muscular discoordination, disorientation, anxiety, disinhibition, euphoria, seeing the world differently, and irrational behavior;[2,59] higher doses can cause great difficulty in moving, seizures, nausea, and vomiting; extreme doses can produce complete dissociation from reality and loss of consciousness, hallucinations, out-of-body experiences, and so-called "near-death experiences" or the "K-hole". These side effects can be well controlled by benzodiazepines,[60] such as diazepam, bromazepam, or midazolam, and they usually disappear within 30 min after the first dose, especially at high doses, or after the start of a continuous infusion.[2] Nausea and vomiting can be adequately controlled with ondansetron.

Other side effects are sialorrhea (treated with atropine 0.5 mg IV) and very rarely laryngospasm.[61] Laryngospasm occurs more frequently and with greater severity in pediatric patients. In one meta-analysis, adults have an incidence of 4.2 per 1000. Children up to the age of 9 years have an incidence of 17 in 1000 cases. Children between 3 and 6 months have an incidence three times greater.[62] Laryngospasm is a life-threatening condition that requires prompt recognition and treatment to avoid morbidity and mortality. Since ketamine-associated laryngospasm seems to be idiosyncratic and without evidence of correlation with age, dose, or other clinical variables, emergency clinicians administering ketamine must be prepared for its rapid identification and management.[63] A unique case of opisthotonos has been reported after the administration of 250 mg intramuscular ketamine by paramedics in a 24-year-old male patient with a history of schizophrenia to control severe agitation.[64] Opisthotonos was completely solved after intravenous midazolam (2 consecutive boluses of 2.5 mg IV) and probably related to the sub-dissociative dose.

No medical deaths from ketamine are reported in the literature, probably due to the very wide therapeutic range of ketamine. The lethal dose of ketamine is about 60 mg/kg.[48]

Ketamine inhibits the reuptake of catecholamines leading to a modest increase in blood pressure and heart rate, through sympathetic activation.[65] Even if the stimulation of cardiac output is considered an advantage in the case of a hypotensive patient,[66] and It usually does not impair airway maintenance and spontaneous respiration, caution must be maintained in patients with severe and uncontrolled hypertension and/or persistent cardiovascular diseases.[4,26,50] ECG monitoring before and, if necessary, during administration is recommended, as is blood pressure monitoring before and, at intervals during treatment.

Ketamine administration is contraindicated in the first three months of life,[17] during pregnancy,[49] and in patients affected by hepatic porphyria.[67]

Conclusions

Our experience confirms that ketamine is a safe drug that can be used for multiple purposes. Our case studies cover a variety of

indications for ketamine in the ED, such as treating delirium tremens in cases of AWS at a sub-dissociative dose, controlling psychomotor acute agitation due to substance use disorder or psychotic delirium at a dissociative dose, and managing pain as a valid opioid alternative. All of the patients were successfully treated by emergency clinicians, avoiding fatal outcomes in the case of BDZ-resistant AWS, and ensuring good pain control in the other cases. As a result, we strongly recommend emergency clinicians consider ketamine as a valid option for pain management and acute agitation treatment in cases of alcohol withdrawal syndrome and substance use disorders.

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