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Literature Review

Ketamine Efficacy for Management of Status Epilepticus: Considerations for Prehospital Clinicians

Nikhil C. Williams, NRP, FP-C, C-NPT [1,*], Lindsey A. Morgan, MD [2,3], Jonathan Friedman, BSN, RN, CCRN [4], Jeffrey Siegler, MD, NRP, FAEMS [5]

[1] UVA Health System, Medical Transport Network, Charlottesville, VA
[2] Department of Neurology, Division of Pediatric Neurology, University of Washington, Seattle, WA
[3] Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA
[4] Special Operations Medic Coalition, Kinston, NC
[5] Department of Emergency Medicine, Washington University School of Medicine, St Louis, MO

A B S T R A C T

Current first-line therapies for seizure management recommend benzodiazepines, which target gamma-aminobutyric acid type A channels to stop the seizure activity. However, seizures may be refractory to traditional first-line therapies, transitioning into status epilepticus and becoming resistant to gamma-aminobutyric acid type A augmenting drugs. Although there are other antiseizure medications available for clinicians to use in the intensive care unit, these options can be less readily available outside of the intensive care unit and entirely absent in the prehospital setting. Instead, patients frequently receive multiple doses of first-line agents with increased risk of hemodynamic or airway collapse. Ketamine is readily available in the prehospital setting and emergency department, has well-established antiseizure effects with a favorable safety profile, and is a drug often used for several other indications. This article aimed to explore the utilization of ketamine for seizure management in the prehospital setting, reviewing seizure pathophysiology, established treatment mechanisms of action and pharmacokinetics, and potential benefits of early ketamine use in status epilepticus.

Seizures are a common occurrence both prehospital and in the emergency department; yet, clinical management can be challenging. Currently, the Centers for Disease Control and Prevention reports an estimated prevalence of 3.4 million Americans with epilepsy and an annual incidence of 150,000 people. Notably, this estimate does not account for first-time or provoked seizures, which do not meet criteria for epilepsy. Thus, seizure management strategies are fundamental for prehospital and emergency room clinicians. Convulsive status epilepticus is defined as continuous seizures lasting 5 minutes or longer or repeated seizures within 5 minutes without a return to the patient's baseline condition.[1] Refractory seizures, also defined as established status epilepticus (SE), are seizures that persist or return after the administration of antiseizure medications such as benzodiazepines. Although these definitions are not mutually exclusive, they share common treatment considerations. Additionally, SE has 2 time points: t1 and t2, which for convulsive status epilepticus is 5 minutes and 30 minutes, respectively. T1 involves either a failure of the mechanisms that would normally terminate a seizure or the initiation of mechanisms responsible for prolonging a seizure. T2 involves the time at which long-term consequence may occur as the result of neuronal death, neuronal injury, or altered network function (all of which have highly negative effects on morbidity).[2]

For convulsive seizures, whether continuous or refractory in nature, there is an ongoing imbalance between inhibition and excitation. Left untreated these persistent seizures may lead to a self-sustaining and pharmacoresistant state of seizure activity. Once patients have reached a self-sustaining imbalance, there is additional risk for glutamate-induced neuronal necrosis, which will result in inflammation; the inflammation can then become an independent propagator of

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*Address for correspondence: Nikhil C. Williams NRP, FP-C, C-NPT, 1205 Stoney Ridge Rd, Charlottesville, VA 22903.

E-mail address: nw3xd@uvahealth.org (N.C. Williams).

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seizure activity.[3-6] Early termination of seizure activity is imperative to prevent these propagating effects. SE requires a rapid and complex treatment progression, with protocols recommending a benzodiazepine first-line. Routinely, it is seen that prehospital protocols advise an additional 1 or 2 doses of first-line treatment but do not detail further pharmacologic measures for antiseizure therapy past first-line treatment because of a known lack of prehospital second-line options. Han et al[7] found across 33 state emergency medical services recommendations for the management of prehospital seizures, only 2 designated a second-line option. Furthermore, Ramgopal et al[8] examined nearly 300,000 pediatric transports for seizure; only ~27,000 received a benzodiazepine. Of those 27,000, only 13 were given levetiracetam, 2 were given phenytoin/fosphenytoin, and there was no mention of phenobarbital. This lack of second-line options is problematic given SE often requires treatment past first-line benzodiazepines. Drugs such as phenytoin, levetiracetam, and valproic acid are frequently recommended second-line therapies yet are seldom found in the prehospital setting. An alternative second-line treatment option is ketamine despite its absence in national and international guidelines.[7-13] Ketamine has well-established antiseizure properties, is frequently carried by prehospital clinicians, and boasts a favorable safety profile.[14-17] Furthermore, prehospital clinicians are familiar with the drug. These factors create a unique opportunity to use a readily available medication in an effort to more rapidly control SE.

Seizure Pathophysiology

For a seizure to occur, there must be an imbalance between excitatory glutamatergic and inhibitory GABAergic influences or an inadequacy of one or the other.[18,19] Some potential causes are a congenital syndrome/malformation, hypoxia, traumatic injury, and hypoglycemia.[5,16,19-22] Once an imbalance or inadequacy is present, aberrant neurologic activity that would otherwise be suppressed can emerge. This manifests itself as a sudden burst of unfocused and desynchronized neuronal activity, which may be generalized or focal. As the seizure persists, there is a synchronization of neuronal activity, and abortive treatment becomes increasingly challenging. The longer a seizure persists, the more imbalanced the excitatory and inhibitory influences become. As neurons continuously depolarize due to persistent seizure activity, extracellular glutamate concentrations increase, and gamma-aminobutyric acid (GABA) receptors internalize, leading to less effective gamma-aminobutyric acid type A (GABA-A) augmentation (pharmacoresistance) because of persistent inhibitory imbalance.[18,23,24] This may cause the seizure to become self-sustaining and refractory in nature. Furthermore, a complex series of inflammatory processes will begin, which cause independent propagation of seizure activity outside of the original imbalance.[1,3,4,14,25] The combination of these factors makes it imperative that seizures be controlled as early as possible.

Conventional Seizure Management

As noted, SE management begins with the administration of a benzodiazepine, a GABA-A channel augmenting medication.[13,19,26-28] Benzodiazepine agents cause GABA-A channels to open more frequently, allowing more chloride anions to enter the postsynaptic neuron, thereby lowering the overall charge and inhibiting depolarization. Unfortunately, not every seizure responds to GABA-A augmenting drugs. Second-line therapies are recommended because they address other points of the neural pathways to terminate the seizures.[1,20,21,26,27,29] Phenytoin and fosphenytoin primarily act on fast (voltage-gated) sodium channels. These drugs will primarily prolong the refractory period of these channels, during which they experience delayed depolarization and subsequently cause less glutamate release into the synaptic cleft.[30,31] Levetiracetam's mechanism of action is poorly understood, but its antiseizure effects are well established. The most observed evidence of levetiracetam's mechanism lies in SV2A proteins, which influence glutamate, ultimately influencing glutamate's availability in the synaptic cleft.[32-35] Valproate, to include valproic acid and sodium, works by increasing the concentration of GABA via the reduction of degradation, thereby modulating the firing of frequency of ion channels.[36] Like benzodiazepines, barbiturates, such as phenobarbital, act on GABA-A receptor channels to move chloride, specifically by prolonging the length a GABA-A receptor remains open. Propofol is not universally recommended as a second- or third-line medication, but because of the unique resource limitations of prehospital care, many transport guidelines use anesthetic dosing of propofol to manage SE given its established antiseizure effects.[1,27,37] Propofol acts primarily on GABA-A channels, has effects on voltage-gated sodium and calcium channels, and has minor effects as a N-methyl-D-aspartate (NMDA) agonist.[38-40] Of note, at high doses, propofol acts as a GABA-A agonist, and, given as either a bolus or infusion, propofol has established antiseizure effects.[1,28,38] Of these second-line medications, levetiracetam offers equivalent broad-spectrum coverage for SE to phenytoin/fosphenytoin.[31,32] In Figure 1, we can observe where these different medications work in respect to synaptic physiology. Despite multiple second-line medication options, the rate of successful seizure control across all recommended second-line medications is roughly 50% to 60%.[41-43]

Prehospital Challenges

As demonstrated, drugs that augment the inhibitory pathway alone may not be sufficient independently but may be more successful when combined synergistically with a medication that addresses the excitatory pathway. The challenge for prehospital care, in addition to logistic factors, often comes down to limited pharmacologic options. Most prehospital clinicians will have access to a single first-line antiseizure therapy, typically midazolam or lorazepam.[7,8,12,13,44,45] Although there is ample room for agency medical director discretion, most national guidelines recommend the administration of a first-line medication followed by identifying and treating possible reversible causes (such as hypoglycemia). These guidelines also recommend that prehospital clinicians administer repeat doses of first-line medications without need for online consult.[13] At this point, a prehospital clinician will likely be directed to contact online medical direction if seizures persist for benzodiazepine-refractory SE. There is a wide range of variability in protocols based on state guidelines and agency medical direction preference.[7] Although early termination of seizures via benzodiazepines is correlated with a reduction in intubations, repeat administrations of benzodiazepines are not without concern. A chief concern when administering benzodiazepines is loss of airway protection and adequate ventilation. Increasingly, more SE patients are intubated in the prehospital and emergency department settings, a trend not perceived in the intensive care setting.[46,47] It is difficult to attribute a direct cause to this trend given the lack of prehospital data, but it is clear that patients receiving medication in the prehospital setting are intubated more frequently than patients who do not receive any medication.[47] Given the risk of respiratory depression and the lack of other available medication options, many prehospital agencies are conservative in their dosing and direction for repeat administration of their first-line drug, often resulting in the administration of benzodiazepine agents outside of expert recommended methods and doses.[12,13,44] Administering benzodiazepines too liberally can lead to respiratory failure; yet, overly conservative administration can lead to poorly controlled seizures that certainly lead to airway collapse. Although measures like waveform capnography may assist prehospital clinicians in this decision making, there remains a lack of options in the event benzodiazepines fail to control seizures. This creates a unique prehospital challenge—management of actively

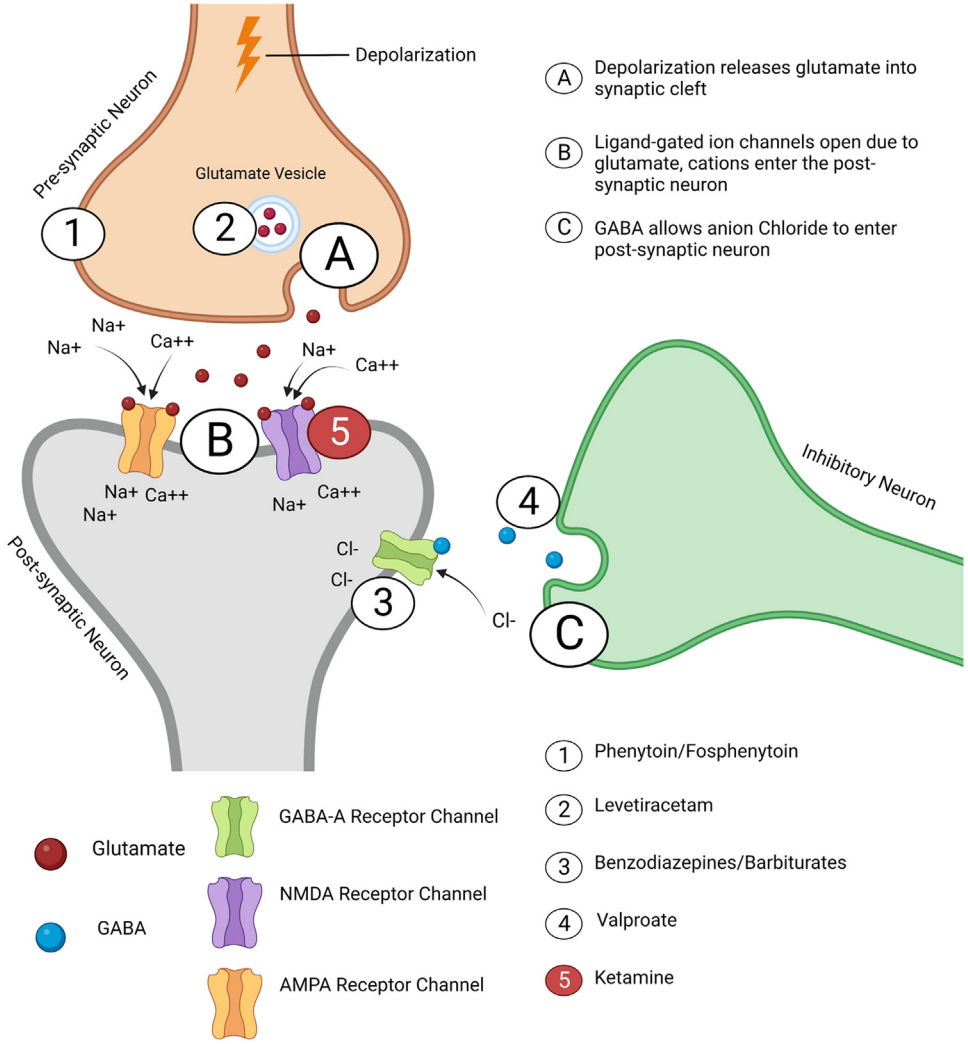

Figure 1. A depiction of antiseizure medication mechanisms of action on neuronal pathways. Created with BioRender.com.

seizing patients after guideline-recommended resources are exhausted.

Thirty-day mortality due to SE increases based on the duration of seizure and patient age, with a more than 30% increase in mortality after 1 hour of seizure activity.[48-50] The average ambulance response time in the United States is 7 minutes, with a median time of 14 minutes in rural settings and up to 30 minutes for 1 in 10 rural patients.[51] Scene times can often be greater than 10 minutes if a patient must be carried from their home or stabilized before moving. Transport times are subjective to traffic conditions, regional resources, and destination; therefore, they are difficult to quantify. In actively seizing patients, every minute is important, particularly with a lack of escalating medication resources.

The route of medication administration may also influence treatment. Intravenous (IV) access is challenging in an actively convulsing patient, and established second-line therapies are only available via an IV line. A unique benefit of ketamine is its ability to be given intramuscularly (IM). Frequently, upon arrival at the emergency department, actively seizing patients receive further doses of benzodiazepines before escalation to a second-line medication independent of prehospital intervention, likely reflecting a combination of need for IV placement and a limited rapid access to second-line treatment.[52,53] Access to second-line therapy in the prehospital setting may mitigate further treatment delays in the emergency department.

Ketamine Efficacy

Ketamine is a noncompetitive NMDA receptor agonist and short-acting anesthetic with dissociative and hallucinogenic properties.[54] In the seizing patient, it primarily acts by binding to NMDA channels on the postsynaptic neuron preventing the NMDA ligand-gated ion channels from opening (Fig. 1). This in turn prevents an influx of cations into the postsynaptic neuron, creating strong antiseizure effects.[1,14] Thus, it directly influences the excitatory pathway by closing off a channel that otherwise allows more positive charge into the postsynaptic neuron, which decreases propagation of action potentials. It is readily available on most ambulances, and clinicians have education on the drug itself and understand the overall safety profile, thereby providing an opportunity for ongoing escalation of treatment for seizing patients.

The evidence for ketamine's treatment of seizures dates back over 20 years and is largely composed of observational and retrospective data.[1,14,25,29,55-62] In addition to the acknowledged antiseizure effects, some data suggest additional neuroprotective qualities.[6,25,59] A 2020 study (N = 68) performed in an intensive care unit setting showed a significant decrease in seizure burden in refractory status epilepticus (RSE) across 81% of enrolled patients, with 63% of these patients having total cessation of seizure activity after ketamine administration.[56] A prehospital study from 2020

showed a 93% cessation of seizure activity in benzodiazepine refractory patients (N = 16). This study used a single bolus of ketamine after an initial benzodiazepine failed to control the seizures.[61] More recently, a 2022 study (N = 69) performed in infants and children found that ketamine infusion for RSE terminated seizures in 32 patients (46%), reduced them in 19 patients (28%), and had no effect in 18 patients (26%). Of these 69 patients, 3 patients (4%) who experienced seizure reduction also experienced minor adverse effects of delirium (n = 1) and hypertension (n = 2) within 12 hours of administration.[25] Evidence has continued to emerge demonstrating ketamine's effectiveness in RSE, but it is still often delayed until multiple other medications have failed.[62] Some hospitals in the United States have begun to adopt the use of ketamine in their treatment guidelines for RSE (ie, SE persisting after first- and second-line therapies have failed). Specifically, children and infants seem to be at the forefront of these guidelines because other anesthetic options such as propofol are contraindicated in children because of the risk for propofol infusion syndrome.[25,39,63]

Dosing

The dosing range of ketamine has been well studied and documented across multiple specialties, allowing a better perspective to analyze dosing for the treatment of seizures. Ketamine has unique effects across 3 dosing ranges: dissociative, subdissociative, and pain control. Dissociative dosing of ketamine, also referred to as anesthetic dosing, is given most frequently at a range of 1 to 4.5 mg/kg intravenously, with an average of 2 mg/kg intravenously needed to maintain 5 to 10 minutes of sedation.[54] Subdissociative dosing of ketamine is generally avoided in the prehospital setting because of unpredictability of patient response in an uncontrolled setting and a lack of clinical application within the prehospital scope. Partially dissociative dosing ranges from 0.4 to 0.8 mg/kg intravenously.[28,54] Patients who have already received a dissociative dose of ketamine may receive a partially dissociative dose as a follow-up to a dissociative dose to maintain desired sedation levels.[28] Pain control dosing of ketamine is administered at 0.1 to 0.3 mg/kg intravenously. Notably, all IV ketamine dosing ranges should be based on ideal body weight.[54] Currently, the literature suggests that anesthetic dosing of ketamine ensures NMDA receptors are adequately saturated, thereby decreasing the movement of cations into the postsynaptic neuron.[14,57] Ketamine is lipid soluble, allowing it to rapidly distribute in the body and reach maximum effects, so both bolused loading doses and infusions have been explored. However, because controlled trial data are not yet available, variance is present across the recommended methodology.[14]

For seizures, data exist supporting either the administration of a single bolus after refractory seizures to benzodiazepines as well as a bolus followed by an infusion with concurrent electroencephalography to guide ongoing management.[14,27,29,54-61] Across available prehospital and emergency department literature, a single bolus dose has been the most used. In the prehospital setting, an initial dose of 1 to 2 mg/kg intravenously may be reasonable followed by close monitoring with cardiopulmonary monitoring including waveform capnography.[14,55,61] Ongoing clinical seizures may benefit from an infusion of ketamine, which many prehospital pump systems could accommodate. However, there is a paucity of literature to support this route in the prehospital setting because infusions have primarily paired with electroencephalography for in-hospital management of super-refractory seizures.[14,25,29,59] Ketamine is also acceptable to administer IM, providing an option for escalating therapy when IV access is delayed. Intramuscular dosing of ketamine for seizure management of up to 3 mg/kg IM has been studied in the prehospital setting and shows no major difference in outcomes compared with 1 mg/kg intravenously up to 100 mg in small trials.[61] It is important to note that although ketamine is recommended for RSE, the current available literature does not recommend routine administration for second-line therapy in the presence of other established measures.[1,14,58]

Safety

Ketamine has an overall favorable safety profile, especially when considering hemodynamic and respiratory concerns. Unlike many antiseizure agents, ketamine does not cause respiratory depression or routine sympathetic blunting. Ketamine can cause short periods of apnea when administered rapidly, but when administered via infusion or a controlled bolus, this adverse effect is easily avoided.[54,64-68] Furthermore, ketamine has adrenergic effects via the release of endogenous catecholamines, influencing cardiovascular tone and sometimes resulting in an increase of blood pressure, making it a frequent drug of choice in hemodynamically compromised patients.[52] Importantly, although ketamine is noted to have advantages, it is not without risk. Ketamine can be associated with hypotension via acute myocardial depression when administered in large doses or when administered to catecholamine-depleted patients.[52,67] Some data further demonstrate ketamine to be associated with more instances of hypotension than other agents such as etomidate; however, these data are prone to selection bias and remain unclear.[17,69,70] Overall, although ketamine is generally not associated with negative outcomes in many patients, those who are catecholamine depleted or in shock states are at risk of negative side effects, warranting substantial caution with use. When compared with repeated administration of other antiseizure medications such as benzodiazepines, barbiturates, and propofol, ketamine may be preferable because of its decreased likelihood of compromising hemodynamic and respiratory stability including intubation.[17,46,49,50,71] It is possible that ketamine not only may reduce/stop seizures but also may mitigate unwanted side effects associated with other antiseizure medications, thus decreasing the need for respiratory support or intubation.

Ketamine for SE in Children and Neonates versus Adults

Ketamine also has evidence for use in neonates, but because of potentially neurotoxic effects, caution is indicated.[1,6,16,25] In children and neonates, ketamine continues to present a favorable safety profile. Given that propofol is contraindicated in children and neonates, ketamine may be a preferable alternative in the event of exhausted recommended options within the prehospital setting. Furthermore, neonates are a particularly dynamic patient population who may benefit from ketamine administration because GABA acting drugs may cause an efflux of the anion chloride from the postsynaptic neuron rather than the influx expected in mature neurons.[21,25] Currently, despite the lack of prospective data and randomized controlled trials, the popularity of ketamine administration for refractory seizures in children and neonates seems to be rising in popularity.[25,63]

Conclusion

Although there is a lack of prospective studies and randomized controlled trials specific to ketamine's use in SE, particularly early in the treatment course, there is an abundance of data that demonstrate a favorable safety profile, high sensitivity, and high specificity for the management of RSE. The data are currently insufficient to create formal recommendations for standardized practice and primarily hold only level 3 quality. With respect to resource-limited environments, ketamine has merit because of its antiseizure profile but not necessarily more benefit than other more established agents such as valproic acid, levetiracetam, and phenytoin/fosphenytoin. Still, the safety profile of ketamine creates an argument for the consideration of earlier use, particularly if other options are unavailable. Prehospital clinicians have a fundamental understanding of the medication and frequently use it

for a variety of conditions, allowing for a natural expansion into SE treatment without causing a training burden. Ultimately, although there is increasing evidence to consider ketamine in the early treatment of SE, higher-quality evidence is needed before routine recommendations can be made.

Declaration of Competing Interest

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Nikhil C. Williams: Conceptualization, Methodology, Visualization, Investigation, Writing – Original Draft. **Lindsey Morgan:** Validation, Investigation, Writing – Review & Editing. **Jonathan Friedman:** Writing – Review & Editing. **Jeffrey Siegler:** Writing – Review & Editing, Supervision.

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