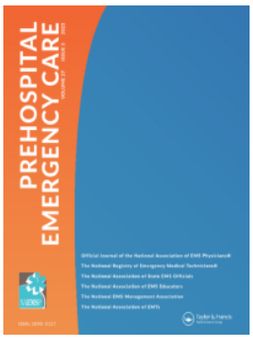

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Prehospital Treatment of Benzodiazepine-Resistant Pediatric Status Epilepticus with Parenteral Ketamine: A Case Series

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ABSTRACT

We report the initial six pediatric patients treated with ketamine for benzodiazepine-resistant status epilepticus in an urban, ground-based emergency medical services (EMS) system. Evidence for ketamine as a second-line agent for both adult and pediatric refractory seizure activity in the hospital setting has increased over the past decade. The availability of an inexpensive and familiar second-line prehospital anti-epileptic drug option is extremely desirable. We believe these initial data demonstrate promising seizure control effects without significant respiratory depression, indicating a potential role for ketamine in the EMS treatment of pediatric benzodiazepine-refractory seizures.

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Background

Seizures in children are a common reason for calls to emergency medical services (EMS). Rapid control of seizures is vital as airway compromise, morbidity, and mortality are high in cases of prolonged seizure activity (1). While the definition has evolved, a seizure that persists for greater than 5 min or two or more seizures with incomplete recovery between is termed status epilepticus (SE) (2, 3). In a recent large, randomized trial evaluating the efficacy of medications for seizure refractory to benzodiazepines, patients were eligible for enrollment if they had been treated with an acceptable cumulative dose of benzodiazepine for convulsions lasting longer than 5 min and continuing after the last dose of benzodiazepine; this working definition of refractory status epilepticus (RSE) was also used for the purpose of this protocol and in this review (3, 4). Previous studies have indicated that treatment failure is common with benzodiazepine-based treatment paradigms (4–9), and patients with RSE often warrant supplemental oxygenation and ventilatory support.

The incidence of SE in pediatric patients is estimated at 10.5–42 cases per 100,000, with 15–30% of these being refractory to conventional therapies (1). Additional second-line therapies are commonly added following benzodiazepine failure for RSE in the emergency department and hospital setting, including fosphenytoin, levetiracetam, and valproic acid. However, the use of these medications presents multiple challenges in the prehospital environment due to storage limitations and high cost. The potential for medication error may also increase related to the infrequency of use. Ketamine has also been studied, as a third-line option, in this subset of RSE patients, and while robust data are still lacking to describe its use, at least one randomized trial is underway (10).

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) antagonist with anticonvulsant properties. Both bench studies and *in vivo* studies have suggested that ketamine could be an effective antiepileptic given this mechanism of action (11–13). This is particularly important in the context of other studies suggesting the downregulation of γ-aminobutyric acid (GABA) receptors in cases of prolonged or refractory seizures, thereby limiting the ability of benzodiazepines to terminate seizure activity (14, 15). Prehospital and hospital treatment of SE and RSE with intravenous (IV) or intramuscular (IM) ketamine have been described as a therapy for treating benzodiazepine-resistant SE (16–20).

Unlike the common second-line agents used in the hospital, ketamine safety and efficacy are well-described in EMS systems for multiple indications, including analgesia, airway management, and control of agitation. Paramedic education now commonly includes instruction in its use, including its known risks and potential benefits. Thus, many paramedics across the United States have experience with the medication, making it a natural choice for implementation for RSE (21). In the prehospital setting, ketamine is also advantageous as a potential therapy, given its shelf stability at room

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temperature and broad therapeutic index. In this case series, we report our experience using parenteral ketamine in the prehospital setting for seizures refractory to initial therapy with benzodiazepines.

Setting

This case series summarizes the initial six patients treated under a previously approved and implemented EMS protocol. Harris County Emergency Service District 11 Mobile Healthcare (HCESD11 MHC) is a ground-based EMS agency in Greater Houston that employs approximately 250 emergency medical technicians, advanced emergency medical technicians, and paramedics. In a service area encompassing 171 square miles, HCESD11 MHC responds to more than 65,000 annual 9-1-1 calls for service. These six patients were treated between September 1, 2021 and March 15, 2022. The protocol was initiated on September 1, 2021, and all patients <12 years old treated with ketamine for RSE during the study period were included in the analysis. All patients were delivered to specialty children's hospital emergency departments. This study was approved by the Baylor College of Medicine institutional review board with a waiver of informed consent (H-51787).

Training/Protocol

This case series was undertaken as part of a continuous quality improvement (CQI) process of a previously implemented protocol (Figure 1). A 1-h lecture review of ketamine pharmacology in relation to its various prehospital uses including RSE was included for all EMS clinicians during their initial onboarding. Emphasis was placed on the service's requirement for thorough patient monitoring following ketamine administration, including continuous pulse oximetry, waveform end-tidal capnography ($EtCO_2$), and three-lead cardiac monitoring. This mandatory education program occurred for all service employees preceding the data collection period for this case series.

All electronic prehospital care reports were queried, as using ketamine for RSE electronically triggered a CQI audit, including a complete review of the EMS chart. Data were abstracted using deidentified EMS and hospital electronic records.

The EMS RSE protocol allows for 2 mg/kg IV or 4 mg/kg IM of ketamine to be given in cases where seizure persists following maximum midazolam dosing. The pediatric midazolam dose is 0.2 mg/kg, which can be administered *via* IV, IM, intraosseous (IO), or intranasal (IN) routes, with an upper limit of 5 mg total. Depending on the child's weight, this 5 mg maximum dose may be given in single or multiple doses. Rapid IM midazolam administration is encouraged and preferred. Additional medication administration was left to paramedic judgment. A pediatric age-based medication dose assistance application (the Handtevy system – Pediatric Emergency Standards, Davie, FL) was used in all cases. Exclusion criteria included known hypersensitivity to ketamine. Along with demographics and standard EMS times, data on all antiepileptic medication administered, associated airway support (before and after ketamine administration), and seizure symptom progression were collected from the prehospital care record. Hospital emergency department (ED) data collected included actual patient weights, the recurrence of seizure activity in the ED, the occurrence of ED intubation, the rate of hospital and pediatric intensive care unit (PICU) admission, and hospital length of stay, if applicable.

Case Series

Case #1

An 18-month-old female with a past medical history of seizures, prescribed home diazepam, presented to EMS actively seizing with an oxygen saturation of 25% on room air. Paramedics described "convulsions" and "foamy oral secretions" initially. Seizures had started approximately 7 min before EMS arrival, and the child was given 2.5 mg rectal diazepam by the family immediately. The EMS crew provided supplemental oxygen immediately, and midazolam (0.16 mg/kg) IM was administered 4 min after their arrival. An IV was established, and transport was initiated, during which "convulsions" recurred following a brief period of apparent absence. At that time, 2 mg/kg of IV ketamine was given 35 min following the initial midazolam dose. Following ketamine administration, a brief period of assisted ventilation using a bag-valve-mask (BVM) was required due to "irregular respirations" and hypercarbia ($EtCO_2$ 70 mmHg), which stabilized 6 min later, and assisted ventilation was discontinued. The patient also received 2.5 mg nebulized albuterol and 6 mg IV dexamethasone during transport due to documented wheezing. No hypoxic episodes were noted following ketamine administration. ED arrival was 13 min post ketamine administration, by which time BVM ventilations were no longer needed. The patient had no further reported seizures in the ED, was not intubated, and was discharged home without hospital admission.

Case #2

A 23-month-old female with known seizure history, on maintenance levetiracetam, presented to EMS with no initial tonic-clonic movement. Upon transfer to the ambulance, paramedics noted "disconjugate gaze, right-hand twitching, and trismus" concerning for seizure activity. Midazolam (0.2 mg/kg) intranasally (IN) was administered 5 min after EMS arrival on scene. Another 0.2 mg/kg IM dose was given 10 min following the first. Following the initial IN dose of midazolam, continuous $EtCO_2$ monitoring and oxygen by non-rebreather mask were initiated. The patient exhibited seizure activity throughout, with the development of "irregular respirations," prompting the initiation of BVM ventilation. Seven minutes after the second midazolam dose, 4.1 mg/kg IM ketamine was administered. Following ketamine, the seizure activity appeared to have subsided as "trismus relaxed, and respirations normalized." Thus, BVM

ventilations were discontinued. The time from ketamine administration to ED arrival was 22 min. No additional medications were given during prehospital care, and no hypoxia or hypercarbia was noted following ketamine administration. The patient had no further seizures documented while in the ED, was not intubated, and was discharged home without hospital admission.

Case #3

A 21-month-old female with no seizure history presented to EMS "actively seizing." The child had an initial temperature of 39.8 °C. IV access was obtained, and oxygen was administered at 10 Lpm starting 2 min after arrival. This was followed by two doses of IV midazolam (0.17 mg/kg) 5 and 10 min after patient contact. "Seizure activity continued," and 1.7 mg/kg IV ketamine was given 8 min following the second dose of midazolam, which "terminated the seizure." The patient was then placed on continuous waveform capnography for the duration of transport. No additional seizure activity was noted during the 34-minute transport to the ED. The patient received a 20 mL/kg crystalloid fluid bolus during transport; no other medications were given. No hypoxic or hypercarbic episodes were noted following ketamine administration. The patient had no additional ED seizure activity reported and was not intubated. She was admitted to the hospital and had a 19-h hospitalization without PICU requirements.

Case #4

A 3-year-old female with a history of seizures, on levetiracetam, presented to EMS after seizing for approximately 15 min before EMS arrival. The patient presented with agonal respirations and an oxygen saturation of 46% on room air. Supplemental oxygen and capnography were immediately applied. Seizure activity resumed as "jerking of the arms and face" with "clenched teeth" were noted on paramedic patient examination. Three doses of midazolam were administered (0.1 mg/kg each) over the course of 21 min. The first midazolam dose was given IM; additional doses were given IV. Assisted BVM ventilation was required following midazolam with an $EtCO_2$ value of 90 mmHg and oxygen saturation of 80%. Seizure activity persisted for 10 min following the third dose of midazolam, and 2.5 mg/kg IV ketamine was given, after which no further abnormal motor activity was noted. Ventilation was assisted for an additional 10 min, at which point $EtCO_2$ and oxygen saturation normalized. A 20 mL/kg crystalloid bolus was given en route; no other medications were administered. The patient arrived at the ED 18 min after ketamine administration. The patient did experience additional reported ED seizure activity; however, she was not intubated. She was admitted to the PICU and had a 2-day hospital stay. Formal education was provided to the crew in follow-up regarding proper midazolam dosing and progression to ketamine for RSE.

Case #5

A 4-year-old female with a history of seizures, on levetiracetam and diazepam, presented to EMS actively seizing for nearly an hour despite receiving two 10 mg doses of rectal diazepam from her parents. The paramedics noted "tonic-clonic seizure activity" and "vomiting" upon arrival. An IV was established, and 0.16 mg/kg midazolam was administered 3 min after patient contact. Seven minutes later, the child was still seizing, and 1.6 mg/kg of ketamine was administered IV. Seizure activity ceased following ketamine. Vital signs, including continuous pulse oximetry and $EtCO_2$, were normal throughout the prehospital encounter. No additional medications were given while en route to the ED. The patient arrived at the ED 19 min after ketamine administration. The patient had no additional ED seizure activity reported and was not intubated. She was admitted to the hospital and had a 2-day length of hospitalization without PICU requirements (Table 1).

Case #6

A 10-year-old ventilator-dependent female with a history of seizures, on levetiracetam and diazepam, presented to EMS actively seizing for over an hour despite 30 mg rectal diazepam and an unknown quantity of levetiracetam before EMS arrival. The initial medications were given by her parents an hour before calling 9-1-1. Paramedics bypassed additional benzodiazepines in favor of 3.0 mg/kg of IV ketamine, which was administered 8 min after EMS arrival. There were no signs of ongoing seizure activity following the administration of ketamine. The first documented prehospital oxygen saturation was 70%, obtained 11 min following ketamine administration. Vital sign data are missing prior to ketamine. $EtCO_2$ values and oxygenation consistently improved throughout the EMS encounter, with no hemodynamic instability noted. The patient was transported on her home ventilator due to parental request. A 20 mL/kg fluid bolus was administered during transport; no other medications were given. The patient arrived at the ED 53 min after ketamine administration with an oxygen saturation of 93% on 10 liters of oxygen with an $EtCO_2$ value of 31 mmHg. The patient had no additional ED seizure activity reported. She was admitted to the PICU and had a 3-day hospital stay.

Discussion

In this case series of pediatric patients with SE refractory to benzodiazepines, ketamine appeared to be effective. All six patients were observed to have cessation of motor signs associated with seizure activity by paramedics in the field. These findings are consistent with other prehospital and hospital data, which suggest that ketamine is effective at terminating seizure activity in RSE, although robust evidence is still lacking (16–20). However, some data suggest that earlier administration may lead to better outcomes, further highlighting the potential utility of ketamine administered in the prehospital setting (9). Ketamine may offer an additional

	MEDICINE REFERENCE	KETAMINE	Page 1 of 2 Last Revision: 10/31/2022

Pharmacologic Class:

- Ketamine is an NMDA receptor antagonist that produces a rapid-acting dissociative effect and has limited cardiovascular or respiratory side effects. Ketamine is unique for its ability to provide, analgesia, and amnesia safely and simultaneously.
- Amnesia induced by ketamine is on the same order as that induced by midazolam

Indications:

- Dissociative Sedation for violent or agitated patients requiring medical intervention and transport
- Rapid Sequence Intubation (Induction and continued sedation)
- Pain
- Seizure activity refractory to benzodiazepine administration

Contraindications:

- Known Hypersensitivity
- Pregnancy
- For the nebulized route, the patient must be able to hold the breath actuated nebulizer

Dosing

Adult	Pediatric
▪ Pain Management 0.3mg/kg IV/IO ○ Mix in 100ml Saline ○ Infuse over 15 minutes ○ Pump not required ○ No repeat dose OR ○ 1mg/kg nebulized ○ **MUST USE BREATH ACTUATED NEBULIZER** ○ Add saline for total volume of 5mL ○ No repeat dose ▪ Dissociative 2mg/kg IV/IO or 4mg/kg IM ○ Violence, Undifferentiated agitation, and Intubation ○ May repeat PRN q 5 minutes ▪ Continued sedation (post advanced airway management) 4mg/kg/h ○ Mix 500 mg in 100 mL Saline ○ **MUST USE IV PUMP** OR ○ 2mg/kg IV/IO or 4mg/kg IM bolus	▪ Pain Management ○ 1mg/kg nebulized ○ **MUST USE BREATH ACTUATED NEBULIZER** ○ Add saline for a total volume of 5mL ○ No repeat dose ▪ Pain Management IV/IO ○ **CONTRAINDICATED** ▪ Dissociative 2mg/kg IV/IO or 4mg/kg IM ○ Same as Adult ▪ Continued sedation (post advanced airway management) ○ Same as Adult ○ **MUST USE IV PUMP** ▪ Status epilepticus (refractory to benzodiazepines x2) ○ Same as Adult

Figure 1. HCESD11 ketamine medication reference.

advantage in that it induces a plane of anesthesia sufficient to terminate seizure activity while also maintaining protective airway reflexes and spontaneous ventilation, thus sparing the need for advanced airway management (22). This may be desirable, particularly in the prehospital environment, given the inherent challenges of pediatric advanced airway management.

The challenges surrounding the proper estimation of patient weight and dosing of medications in the ED and by EMS, including discrepancies between recommended and administered doses, are well established (23–26). In this series, we observed similar variations in both midazolam and ketamine doses, further highlighting this as a critical area for education, training, and quality improvement in EMS. In

Table 1. EMS demographics and vital signs.

Case	Age/Sex	Actual Weight (kg)	Seizure Hx	Home AEDs	EMS IV (Y/N)	Initial EMS Pulse (BPM)	Initial EMS BP (mmHg)	Initial EMS SpO_2	Initial EMS $EtCO_2$ (mmHg)	Final EMS Pulse (BPM)	Final EMS BP (mmHg)	Final EMS SpO_2	Final EMS $EtCO_2$ (mmHg)	EMS scene interval (min)	EMS transport interval (min)
1	18 mo/F	12	Y	D	Y	197	121/61	25%	70	159	101/86	100%	46	30	18
2	23 mo/F	12	Y	L	N	131	87/52	97%	49	130	98/62	99%	46	14	30
3	21 mo/F	12	N	NA	Y	187	88/62	100%	44	144	92/65	99%	45	30	22
4	3 yo/F	14	Y	L	Y	147	112/71	46%	81	109	100/68	98%	21	32	23
5	4 yo/F	21	Y	L,D	Y	128	93/67	100%	31	135	116/55	100%	31	12	17
6	10 yo/F	27	Y	L,D	Y	183	79/32	70%	28	130	90/47	93%	31	24	37

AED = anti-epileptic drugs, D = diazepam, L = levetiracetam.

the ESD11 protocols, paramedics are directed to administer midazolam and ketamine based on patient age at 0.2 mg/kg IM or IV and 2 mg/kg IV or 4 mg/kg IM, respectively, using the Handtevy system. Given the known limitations associated with prehospital pediatric medication administration, the actual midazolam and ketamine doses administered in this case series varied in an expected and grossly acceptable prehospital range. Patient #6 did receive a 3.0 mg/kg IV ketamine dose, which is 1 mg/kg over the protocol amount. She was a 10-year-old, chronically ill, underweight, ventilator-dependent patient for whom the age-based, app-assisted estimated weight was well over her actual. This case highlights the need to confirm the dose assistance method prior to medication administration, especially in the extremes. Formal education related to dose assistance variability was provided during the next service-wide mandatory education session following this call. Despite some ketamine doses falling outside of prescribed ranges, these doses appear to have been safe. All patients maintained airway patency and hemodynamic stability following ketamine administration, consistent with prior evidence suggesting a wide, safe therapeutic range for ketamine (27). This does not minimize the vital importance of ongoing training for prehospital personnel in time-sensitive, high-risk/low-frequency presentations such as pediatric RSE and in weight-based medication administration situations for pediatric patients in general. In this series, we also observed that paramedics rightly recognized instances in which a prescribed benzodiazepine, such as diazepam, had been administered before their arrival and proceeded to administer ketamine for persistent seizure activity. While home benzodiazepine administration was not specifically described or defined within ESD11 protocols, we feel these considerations were valid and clinically sound.

A frequent concern associated with ketamine use is the development of post-administration hypoxia or ventilatory failure. In this series, three patients received assisted ventilation by BVM; however, only patient #1 required airway support escalation following ketamine administration. The others required BVM before ketamine secondary to RSE. One chronically ventilator-dependent patient remained mechanically ventilated, and two patients did not require ventilatory assistance. Additionally, while patient #1 did require brief BVM assistance following ketamine, this was ceased before ED arrival, and the patient was discharged home without admission. No instances of worsened hypercarbia following ketamine administration were noted, lending support to the concept that paramedics can readily identify and intervene in cases that require support to maintain ventilation or oxygenation. Case #6 was hypoxic following ketamine administration, but the administration was much earlier in the patient care episode, secondary to multiple diazepam doses administered before EMS arrival (Table 2). It is possible that the hypoxia was ketamine-related. However, the patient is chronically ventilator dependent and had been in RSE for more than 1 h before EMS arrived. The hypoxia was likely multifactorial and related to chronic comorbidities, RSE, and pharmacologic interventions. The oxygen saturation improved during EMS care with no

Table 2. Patient care course.

Case	Rectal Valium PTA	EMS Midazolam #1	Time to Dose #1 (min)	EMS Midazolam Dose #2	Time to Dose #2 (min)	EMS Midazolam Dose #3	Time to Dose #3 (min)	EMS Ketamine Dose	Time to Ketamine Dose (min)	Hypoxia Post Ketamine	EMS Airway Support	EMS Seizure Cessation	Ketamine to ED (min)
1	0.2 mg/kg	0.16 mg/kg IM	4	NA	NA	NA	NA	2mg/kg IV	35	N	BVM post-ketamine	Y	13
2	N	0.2 mg/kg IN	5	0.2 mg/kg IM	15	NA	NA	4.1 mg/kg IM	22	N	BVM pre and post-ketamine	Y	22
3	N	0.17 mg IV	5	0.17 mg/kg IV	10	NA	NA	1.7 mg/kg IV	18	N	None	Y	34
4	N	0.1 mg/kg IM	8	0.1 mg/kg IM	20	0.1 mg/kg IM	29	2.5 mg/kg IV	37	N	BVM pre and post-ketamine	Y	18
5	0.9 mg/kg	0.16 mg/kg IM	3	NA	NA	NA	NA	1.6 mg/kg IV	10	N	None	Y	19
6	1.1 mg/kg	NA	NA	NA	NA	NA	NA	3.0 mg/kg IV	8	Y	Chronic Vent	Y	53

Table 3. ED and hospital encounter characteristics.

Patient #	1	2	3	4	5	6
ED Intubation	N	N	N	N	N	N/A
Additional ED Seizure	N	N	N	Y	N	N
Admit (Y/N)	N	N	Y	Y	Y	Y
PICU (Y/N)	N/A	N/A	N	Y	N	Y
Hospital LOS	N/A	N/A	19hrs	2d	2d	3d

hemodynamic instability. Given the small cohort and retrospective nature of this report, it is not possible to identify whether these patients required BVM ventilation due to ketamine administration or because of prolonged seizure activity. Finally, no patients treated with prehospital ketamine for RSE required intubation during EMS care or following ED arrival, suggesting that in this critically ill subset of seizure patients, ketamine may be able to decrease advanced airway management rates. Larger studies are needed to confirm this hypothesis.

Previous studies have demonstrated a high failure rate for parenteral midazolam and diazepam for RSE in the prehospital setting (6). In the hospital setting, large, randomized trials have shown that standard antiepileptics have a similarly high failure rate (4). Treatment for status epilepticus in the prehospital environment is further limited to fast-acting benzodiazepines, as antiepileptic drugs commonly found in the ED, such as levetiracetam or fosphenytoin, are rarely available in the field (28). Ketamine, however, appeared effective at terminating pediatric seizures in this critically ill population refractory to benzodiazepines. Only one patient had additional seizure activity reported after transfer of care to the pediatric ED (Table 3).

Limitations

The small number of patients treated and the single-service nature of protocol use and data collection limit generalizability. Data were also collected from EMS and hospital charts and narrative review only. Real-time monitor data were unavailable. Lastly, continuous EEG monitoring is not currently possible in the prehospital setting, limiting the ability of paramedics to fully rule out subclinical status epilepticus.

Conclusions

This case series suggests both the safety and efficacy of ketamine for the treatment of prehospital pediatric RSE. While the total number of patients treated was small, they were critically ill, with half being significantly hypoxic, receiving prehospital BVM airway management and two-thirds requiring hospital admission. Advanced airway management, however, was not performed by EMS clinicians or in the emergency department. Larger, prospective, randomized trials are needed. These preliminary findings suggest that ketamine is worthy of further investigation as a therapy for treating RSE in pediatric patients in the prehospital setting.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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