

Prehospital Emergency Care

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ipec20

Prehospital Ketamine Administration in Benzodiazepine Refractory Status Epilepticus: A Case Series Review

Joseph D Finney, Margaret Kowalski, Jinli Wang, Michael Perlmutter, Jordan Anderson, Jeffrey Siegler, Bridgette Svancarek, Robert Silbergleit, Fahd A. Ahmad & Casey Patrick

To cite this article: Joseph D Finney, Margaret Kowalski, Jinli Wang, Michael Perlmutter, Jordan Anderson, Jeffrey Siegler, Bridgette Svancarek, Robert Silbergleit, Fahd A. Ahmad & Casey Patrick (07 Apr 2025): Prehospital Ketamine Administration in Benzodiazepine Refractory Status Epilepticus: A Case Series Review, Prehospital Emergency Care, DOI: 10.1080/10903127.2025.2486302

To link to this article: https://doi.org/10.1080/10903127.2025.2486302

Accepted author version posted online: 07 Apr 2025.

Submit your article to this journal

Article views: 42

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at https://www.tandfonline.com/action/journalInformation?journalCode=ipec20

Check for updates

Prehospital Ketamine Administration in Benzodiazepine Refractory Status Epilepticus: A Case Series Review

Joseph D Finney, MD[a,b,*] 0000-0002-5106-6435, Margaret Kowalski[c], MD, Jinli Wang, MS[d] 0000-0003-0757-136X, Michael Perlmutter, MD[e] 0000-0002-9710-1523, Jordan Anderson, NRP[f] 0009-0004-6148-9492, Jeffrey Siegler, MD[b] 0000-0001-5936-443X, Bridgette Svancarek, MD[b], Robert Silbergleit, MD[g] 0000-0001-5919-6835, Fahd A. Ahmad MD, MSCI[h] 0000-0003-4101-2430, Casey Patrick, MD, FAEMS[i,j] 0000-0002-3272-7138

[a]Department of Pediatrics, Washington University in St. Louis, Saint Louis, MO
[b]Department of Emergency Medicine, Washington University in St. Louis, Saint Louis, MO
[c]Department of Pediatrics, Saint Louis Children's Hospital, Saint Louis, MO
[d]Center for Biostatistics and Data Science, Washington University in Saint Louis, Saint Louis, MO
[e]Department of Emergency Medicine, Hennepin County Medical Center Minneapolis, MN
[f]Harris County Emergency Services District #11 Mobile Healthcare, Spring, TX
[g]Division of Pediatric Emergency Medicine, Department of Pediatrics, Washington University in St. Louis, Saint Louis, MO
[h]Department of Emergency Medicine, University of Michigan, Ann Arbor, MI
[i]Montgomery County Hospital District, Conroe, TX
[j]Department of Emergency Medicine, Baylor College of Medicine, Houston, TX

***Corresponding Author:** Joseph D Finney, Department of Pediatrics, Washington University in St. Louis, Department of Emergency Medicine, Washington University in St. Louis, Saint Louis, MO, 660 S. Euclid Avenue, MSC 8116-0043-09, St. Louis, MO 63110, josephfinney@wustl.edu.

Accepted Manuscript

Abstract

OBJECTIVES: Benzodiazepines are the treatment for seizures in prehospital settings, but fail in up to 40% of cases, leading to benzodiazepine refractory status epilepticus (BRSE). Early treatment of BRSE is essential to prevent neurological damage and death. Ketamine, an N-methyl-D-aspartate receptor antagonist used by emergency medical services (EMS) for a variety of indications, has potential as a safe, effective prehospital treatment for BRSE. However, safety and efficacy data for early treatment of patients with seizures are limited.

METHODS: We retrospectively analyzed patients treated by EMS clinicians with ketamine for BRSE at a single urban ground-based EMS system between September 1, 2021, and December 1, 2023. Ketamine dose and route, patient characteristics, and airway interventions are described. Data were gathered from EMS records.

RESULTS: Forty-two patients aged 8 months to 79 years, were included. Ketamine was administered intramuscularly in 22 with an average dose of 3.3 mg/kg, and intravenously or intraosseous in 20, with an average dose of 2.2 mg/kg. Ketamine stopped seizures in 38 patients (90.5%). Transient hypoxia occurred in 9 patients (22%). Respirations were supported with bag-valve-mask ventilation in 13 patients (31%), a supraglottic airway in three (7%), and one patient was endotracheally intubated (2.4%).

CONCLUSIONS: Ketamine appears safe and effective for prehospital treatment of BRSE. Monitoring and intervention for respiratory complications appears necessary, but rates of these complications are consistent with expected rates from seizures and appropriate benzodiazepine dosing. These findings support ketamine's use in EMS for BRSE. Larger prospective studies are needed to confirm safety and efficacy.

Keywords: Ketamine, Benzodiazepine refractory status epilepticus, EMS, seizures, status epilepticus, prehospital

Accepted Manuscript

INTRODUCTION

Seizures account for approximately 5-8% of all emergency medical services (EMS) encounters and carry a significant risk of morbidity and mortality (1). Among adults, the mortality associated with status epilepticus (SE) is 26%; among children, it is up to 3% (2-4). Seizures lasting greater than 30 minutes are associated with an overall mortality rate of 19% (5). Rapid resolution of seizures is essential to prevent progression to SE and the development of refractory SE resulting in irreversible neurologic insult with cardiovascular and respiratory complications (6). Unfortunately, the overall survival from SE has changed little over the last 30 years in both children and adults (7). In the prehospital setting, the first-line standard of care treatment for seizure is benzodiazepines (8). However, up to 40% of adult and pediatric patients do not respond to an appropriate dose of a benzodiazepine, referred to as benzodiazepine refractory status epilepticus (BRSE) (9, 10). Prehospital treatment for BRSE is generally limited to repeated benzodiazepine dosing and searching for reversible causes (11, 12).

Current second-line treatments with levetiracetam, valproate, or fosphenytoin are only effective in stopping SE in about 50% of patients with BRSE and are not generally available in the prehospital setting (13, 14). In a survey of EMS protocols, only 2 of 33 (11%) publicly available state EMS protocols included recommendations for the treatment of seizures that continue after initial treatment with a benzodiazepine (15). The lack of second-line treatment options in the prehospital setting is multifactorial but includes the cost and challenges associated with modifying the EMS formulary. As a result, few patients receive a second-line medication prior to hospital arrival despite recurrent or persistent seizure activity. This is especially true in pediatric seizure management. Ramgopal et al. reviewed the National Emergency Medical Services Information System (NEMSIS) and found only a very small proportion of children received a second-line antiseizure medication (ASM) in the field (11). Shah et al., found that a significant percentage of children have recurrent or ongoing seizures upon EMS arrival to the emergency

Accepted Manuscript

department. They performed a retrospective cross-sectional study of pediatric prehospital seizure patients and found that 29% of patients had persistent or recurrent seizure activity on emergency department (ED) arrival (7, 12). In light of the high frequency and mortality of prolonged seizures associated with BRSE and the lack of evidence-based prehospital treatment options, there is an urgent need to identify a safe, effective, and practical prehospital treatment for BRSE.

Ketamine offers a pharmacologic alternative to traditional second-line ASMs. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with antiseizure properties first identified in 1975. During prolonged seizures, gamma-aminobutyric acid type a (GABAa) receptors, the primary receptor target for benzodiazepines, decrease in number over time, making it less likely that these medications will be effective in terminating seizure activity as the duration of status epilepticus increases (10, 16-20). Conversely, NMDA receptors are up regulated in prolonged seizures, providing a potential therapeutic target for the use of ketamine to terminate seizures in the context of BRSE. In the last decade, there has been a growing body of evidence describing the safety and efficacy of ketamine as an ASM, including prospective in-hospital trials in adult, pediatric, and neonatal intensive care units (21-26). Case series, case reports, and retrospective reviews have suggested that ketamine may be effective in treating BRSE in the prehospital setting as well.[27-30]

Ketamine has become increasingly familiar and available to EMS clinicians as it is used for various indications in the prehospital setting, including rapid sequence intubation, procedural sedation, analgesia, and agitation.[27, 31-37] Ketamine offers several desirable qualities for use in the prehospital setting, including relative preservation of cardiovascular and respiratory stability when used for procedural sedation, agitation, pain, and rapid sequence intubation. Preliminary data suggest this may also be true when used to treat BRSE (21, 28, 38). Additionally, ketamine

Accepted Manuscript

is shelf-stable at room temperature and at extremes of temperature (39, 40). Ketamine is characterized by a very broad therapeutic index and can be delivered through multiple routes, including intramuscular (IM), intravenous (IV), intraosseous (IO), and intranasal (IN) (41, 42). Considering the growing list of attributes, ketamine has been added to primary paramedic-level education over the last decade (43, 44). Its use for the treatment of seizures is also increasing over time (45, 46).

However, despite the potential advantages of ketamine, and its increasing popularity, there is still little clinical evidence to inform its use in the prehospital treatment of BRSE (47). As part of a quality assurance effort in a single-ground urban EMS system, we implemented a new clinical EMS seizure treatment protocol incorporating the use of ketamine after the administration of 2 appropriately dosed benzodiazepines. We reviewed all encounters where ketamine was administered for BRSE.

METHODS

Study design and setting

The Baylor College of Medicine (Houston, Texas, USA) Institutional Review Board approved this retrospective chart review with a waiver of informed consent (H-51787). Harris County Emergency Service District 11 Mobile Healthcare (HCESD11 MHC) is a ground-based EMS agency in Greater Houston that employs approximately 250 EMS clinicians, including paramedics, Advanced Emergency Medical Technicians (AEMTs), and Emergency Medical Technicians (EMTs). In a service area encompassing 171 square miles, HCESD11 MHC responds to more than 65,000 annual 9-1-1 calls for service. Paramedics have delayed sequence intubation (DSI), supraglottic airway placement (SGA), and bag-valve-mask (BVM) ventilation capabilities.

Accepted Manuscript

Clinical Protocol

On September 1, 2021, HCESD11 MHC updated its standard clinical protocol for the treatment of patients with seizures to include the option of ketamine for the treatment of BRSE (Figure 1). The protocol directs paramedics to administer 2 mg/kg IV or 4 mg/kg IM of ketamine in encounters where seizure persists following maximum midazolam dosing. The pediatric midazolam dose is 0.2 mg/kg, which can be administered via IV, IM, IO, or IN routes, with an upper limit of 5 mg total. The adult midazolam dose is 5 mg IV or 10 mg IM with the ability to repeat once in five minutes if seizure activity persists. Rapid IM midazolam administration is encouraged and preferred as the first-line treatment of prehospital seizures. Additional medication administration was left to paramedic judgment. A pediatric age-based medication dose assistance application (The Handtevy System - Pediatric Emergency Standards, Davie, FL, USA) was used in all pediatric encounters. The only protocol exclusion criteria included known hypersensitivity to ketamine.

EMS clinician training on the new protocol included a mandatory hour-long education program on ketamine pharmacology and administration during initial onboarding. Emphasis was placed on the service's existing requirement for robust patient monitoring, including continuous pulse oximetry, waveform end-tidal capnography ($EtCO_2$), and 3-lead cardiac monitoring.

Case Review

A review initially performed as part of quality assurance, including all runs between September 1, 2021, and December 1, 2023. All electronic prehospital care reports (ePCR) were queried for those receiving ketamine with a paramedic impression of seizure. Two expert reviewers (one paramedic and one EMS physician) independently abstracted data. All encounters of ketamine administration for BRSE also electronically triggered a real-time continuing quality improvement (CQI) audit. Data were abstracted using the deidentified EMS ePCR.

Accepted Manuscript

All cases of ketamine use for BRSE during the study period were included in the analysis. For purposes of case ascertainment, BRSE was defined as a paramedic's impression of ongoing or recurrent seizure activity after administration of two doses of a benzodiazepine. Based on chart review, patients were excluded if ketamine was administered for an indication other than seizure treatment, including pain, intubation induction, or agitation. Study population selection is shown in Figure 2. All data were collected from EMS records. Emergency Department and hospital outcome data were not included.

We reviewed data on patient characteristics, treatment, seizure termination, and safety. Patient characteristics included demographics, prior seizure history, relevant home medications, and vital signs (before and after intervention). Treatment data included benzodiazepine and ketamine dose, route of administration, and timing. Seizure termination was determined by paramedic observed response documented in the narrative section of the patient chart. Safety data included any documented episodes of hypoxia defined as a pulse oximetry reading <90%, any use of BVM ventilation, SGA device insertion, or endotracheal intubation.

Statistical analysis

Descriptive statistics were used to summarize the data. Means and standard deviations were reported for continuous variables, while counts and percentages were reported for categorical variables. Missing data were not imputed. Analyses were performed using SAS software, version 9.4 (SAS Institute).

Accepted Manuscript

RESULTS

Patient characteristics

There were 736 9-1-1 activations for impressions related to seizure, including 58 patients with documentation of ketamine administration. Of those, three had the medication drawn up and prepared but not administered, and 13 patients received ketamine for an indication other than seizure. Therefore, 42 patients met the inclusion criteria and are described in this analysis in Table 1.

Eighteen (42.9%) were pediatric and 24 (57.1%) were adult patients. The mean age was 44.8 years for adults and 6.7 years for children. The youngest patient was 8 months old. There were 31 (73%) female patients. Thirty-three (78.5%) patients had a known seizure diagnosis, and 28 of those 33 (84.8%) were on home seizure medications. One patient had a vagal nerve stimulator for treatment of seizures. Eight patients with a known history of seizures had received a rescue medication prior to EMS arrival.

Treatment

Initial ketamine doses were administered IM in 47.6% (20/42) of encounters and IV in 47.6% (20/42) of encounters. Two patients received ketamine through the IO route (4.8%, 2/42). The median doses were 3.3 mg/kg for IM and 2.2 mg/kg for IV. Between patient variability in dose was observed with IM dosing ranging from 1.3 to 4.4 mg/kg and IV dosing ranging from 1.6 to 4.4 mg/kg. However, 35/42 (83%) of patients received ketamine doses within 20% of the protocol dose. Five adult and two pediatric patients received incorrectly high or low doses. The dose was incorrectly low in five cases of IM administration and incorrectly high in two cases of IV administration. Two patients received two doses of ketamine, and one received two doses followed by an IV infusion. Four patients received only ketamine from EMS. Three of those

Accepted Manuscript

patients received two doses of benzodiazepine prior to EMS arrival. In those instances, EMS administered only ketamine without additional doses of benzodiazepine. Six patients received ketamine after receiving only one dose of a benzodiazepine.

Efficacy

Ketamine terminated clinically evident seizures in 38 (90.5%) patients. Thirty-five (92%) stopped seizing after a single dose, including three that failed benzodiazepines prior to EMS arrival. Four patients received only ketamine by EMS and seizures were terminated in all cases. Regarding route of administration, IM ketamine was successful in 20/22 (91%), IV in 17/18 (94%), and IO in 1/2 (50%) as shown in Table 1. Three patients received multiple doses of ketamine. However, in all these cases, only the first dose of ketamine was for seizure management. The additional doses were to facilitate airway placement and subsequent sedation, not seizure treatment. There were four patients, two adults and two children, who either continued to have seizures or had seizure recurrence after the administration of ketamine while in the care of EMS. Per protocol, repeat dosing of ketamine for refractory seizure was not allowed. The first patient was a 15-year-old male on three home ASMs. He had successful seizure termination after a single IM ketamine dose, but his seizure activity restarted 35 minutes later during a 50-minute transport. The second patient was a 46-year-old female on three home ASMs who was actively seizing for 15 minutes prior to EMS arrival. She received two doses of IM midazolam prior to IO ketamine. She was subsequently intubated for airway protection in the setting of refractory SE and did not experience hypoxia. This patient also had a prolonged transport time of 51 minutes. The third patient was a 5-year-old female with a history of a febrile seizure. She received two doses of IV midazolam followed by a single dose of IV ketamine without resolution of seizure activity. This patient did not experience hypoxia or receive an airway intervention. The fourth patient was a 60-year-old female with one home ASM who continued to have seizure activity after two doses of IM midazolam and one dose of IM ketamine. The ketamine was under-dosed

Accepted Manuscript

in this case by greater than 20%. This patient had no airway intervention or hypoxia after ketamine. In each of the other cases, the ketamine dose administered was within 20% of the protocol dose.

Safety

Transient hypoxia occurred in nine (22%) patients, six children and three adults. All patients with hypoxia had a known history of seizures. Seven of the nine (78%) patients with hypoxia received two doses of midazolam prior to ketamine administration. Two patients with hypoxia received multiple benzodiazepines prior to EMS arrival and received only ketamine from EMS. Respirations were supported by BVM ventilation alone in 13 patients, SGA placement in three, and endotracheal intubation in one (any respiratory support in 18/42, 43%). One additional patient was chronically ventilator dependent. Five of the 13 with BVM only and one with SGA placement, received support because of hypoxia.

In one patient, an SGA was placed for reported apnea following the administration of ketamine IV. In the one patient who was endotracheally intubated, the indication was respiratory failure after two doses of midazolam but prior to ketamine administration. It was unclear from the chart data and narrative if the ketamine was given for refractory SE or for intubation induction, so the patient was kept in the final data set. This patient was a 46-year-old female with a known history of refractory seizures and had required intubation for respiratory failure during a previous encounter. The indication for respiratory support could not be determined in other cases but was likely in response to subjective perceptions of respiratory depression, sedation, or dissociation.

DISCUSSION

In this case series of 42 patients from a single EMS agency, ketamine was effective in treating

Accepted Manuscript

clinically evident BRSE in over 90% of cases. This report expands upon the previous description of six children in the HCESD11 MHC system treated with ketamine for seizures (28). The observed effectiveness of ketamine was also consistent with another recently published large case series of prehospital ketamine use by EMS clinicians in 65 adults and 16 children with seizures over a 7-year period in a Palm Beach County EMS system in Florida. They reported seizure termination in 94% of cases (30, 48). However, there are differences in both the dose and administration process. Our protocol was weight-based dosing depending on route of administration regardless of age whereas their study was fixed dosing for adults and weight-based in pediatrics. Also, our protocol was for push dose ketamine whereas their study was an infusion in a carrier fluid. Despite these variations between studies, efficacy is similarly high in both our study and in the Palm Beach County study. These very high reported rates of efficacy for ketamine in these case series compare favorably to the only clinical trial data of second line anticonvulsants in the prehospital setting. In the SAMU Keppra trial 136 patients were randomized to clonazepam plus levetiracetam or clonazepam plus placebo in France (49). In that trial only 79% of patients had termination of seizures with no significant difference between treatment groups. The observed rates of seizure termination with ketamine in these prehospital case series also compares favorably to the 50% response rate observed in the emergency department treatment in patients with BRSE with any of three conventional second line anticonvulsants (levetiracetam, valproate, or fosphenytoin) in the ESETT study (13).

Safety in our case series was also comparable to that expected in patients treated for BRSE in the prehospital setting. In our study, hypoxia was an uncommon side effect, occurring in only nine patients. Our low rate of hypoxia is consistent with Scheppke et al who reported no episodes of hypoxia following ketamine administration albeit with some gaps in documentation of oxygen saturation and vital signs (30). Hypoxia is frequently observed in patients with BRSE as a consequence of their seizures or because of prior treatment with benzodiazepines. Indeed,

Accepted Manuscript

Scheppke et al., observed abnormal oxygen saturation or $EtCO_2$ monitoring in 32% of BRSE patients prior to ketamine administration. Our observed rate of hypoxia is also lower than in prior reports in pediatric seizure patients receiving benzodiazepines alone. Pfeiffer et al. identified prehospital hypoxia in 25% of 156 children with seizures treated with 2 doses of benzodiazepine and 15% of 597 children treated with a single dose of benzodiazepine.(50) Shah et al., found hypoxia in 12% of 304 children with seizures and documented oxygen saturations cared for by EMS with or without benzodiazepines (12). Collectively these data suggest the hypoxia observed in our case series is consistent with that anticipated in this patient population and is not likely to be a consequence of ketamine administration.

Similarly, the rate of respiratory support provided to patients in our study is also consistent with that expected in this prehospital seizure patient population. In the Prehospital Treatment of Status Epilepticus (PHTSE) trial, 12% of participants with seizures (24/200) treated with or without benzodiazepines had a change in respiratory status requiring ventilatory assistance with a bag valve-mask or an attempt at intubation. In the Rapid Anticonvulsant Medication Prior to Arrival Trial **(**RAMPART), the rate of transient BVM support was not collected, but 1.4% of patients with seizures (14/1023) and benzodiazepines had prehospital endotracheal intubation. Respiratory support is provided more frequently in children with prehospital seizures. Pfeiffer found that 32% of children with two doses of a benzodiazepine were provided respiratory support (51), and Shah et al. found that respiratory failure occurred in 17.1% of the 533 prehospital pediatric seizure patients either prehospital or in the ED (12). The observed rates of respiratory support in our patients are, therefore, most likely attributable to their underlying pathology. However, one may speculate on ways that ketamine may contribute to the use of respiratory support. Although the pharmacology of ketamine is not typically expected to contribute to respiratory failure, it causes a dissociative sedation that EMS clinicians may interpret as airway compromise requiring assistance or airway protection, especially if they lack

Accepted Manuscript

familiarity with that response or do not allow for it in this clinical situation, as has been previously suggested with respect to emergency physicians receiving dissociated patients given prehospital ketamine for agitation (52). Additionally, EMS clinicians may have provided respiratory support partly due to an elevated EtCO2 following a prolong seizure and not due to hypoxia or medication effects. The interpretation of post-ictal irregular respirations or elevated EtCO2 as respiratory failure may have contributed to the performance of an airway procedure. In 8 of the 13 (61%) patients who received BVM support, there was a documented EtCO2 >50 mmHg. Finally, although transient laryngospasm was not reported in our case series, this known infrequent complication of ketamine may have been an unrecognized or undocumented trigger for some episodes of brief BVM respiratory support.

Regarding the dosing of medication, the high frequency of incorrect dosing has been documented in prior literature, particularly in pediatric seizure management (53-56). We observed the first benzodiazepine dose given by EMS to be underdosed in 21% (8/38) of cases suggesting this contributed little to the development of BRSE. Based on limited prior literature, we chose a cutoff range of 20% outside protocol dosing to indicate a dosing error (55, 57). Pediatric dosing was within 20% of the protocol dose in 89% of cases. Prior published research in this area which shows a roughly 30% rate of incorrect pediatric dosing (53, 57, 58). Adult dosing errors occurred in 21% of cases, however all but one of these cases involved protocol doses over 250mg IM and were underdosed by EMS clinicians. This suggests that EMS clinicians may not be comfortable administering large doses of ketamine IM. The variations in dosing observed in our study underscore the need for focused training and education to reduce dosing errors (45). Of note, the work by Zitek et al., utilized fixed dosing in adults and reported dosing errors in less than 6% of cases with similar efficacy. Finally, our study and Zitek et al., noted a 100% treatment success rate for BRSE in cases where ketamine was the only medication administered by EMS clinicians. Future prospective research is necessary to

Accepted Manuscript

evaluate dosing, particularly fixed dosing, and route of administration of ketamine for BRSE. Consideration should also be given to utilizing ketamine earlier in EMS treatment of SE.

LIMITATIONS

There are several limitations to our research. First, like any case series, these observational data are uncontrolled and lack relevant comparators to confirm causality of seizure termination after ketamine administration. However, the timing and high response rate strongly suggest a treatment effect, although with only 42 patients, the precision of estimated effect is limited. Second, this study reflects the experience in a single high performing EMS agency and may not be generalizable to other agencies with different call volumes, resources, training, or that serve different patient populations. The recent publication of concordant results in another EMS system suggest that these findings are reproducible with similarly trained personnel and resources. Third, the implementation of this protocol was limited by practice variability in dosing (or dosing errors) as previously discussed. It is unclear whether the use of lower and higher than protocol-concordant dosing may have had positive or negative effects on either the efficacy or safety of treatment. Fourth, the clinical diagnosis of seizures and seizure termination in the acute care setting is always prone to misclassification. Seizure mimics are common, and diagnosis of status epilepticus is challenging in both the prehospital and ED setting. Missed subtle, atypical, or subclinical seizures, or inclusion of psychogenic non-epileptic seizures may also affect the reliability and precision of estimates of treatment effect from chart review (59). Despite this misclassification, paramedic clinical impressions necessarily drive prehospital treatment, so the observations in this case series have the advantage of being “real-world” outcomes. Finally, lack of access to ED and subsequent clinical data precludes assessment of safety events in the hospital or longer-term outcomes after ketamine treatment. Nevertheless, termination of status epilepticus on hospital arrival has previously been shown in clinical trials to result in less hospital and intensive care unit admission, and shorter lengths of stay, so the

Accepted Manuscript

observed improved rates of seizure cessation are likely indicative of meaningful downstream outcomes (60).

CONCLUSIONS

Overall, ketamine was effective in the treatment of BRSE in our study, was more effective than other BRSE agents previously studied in the hospital setting, and was consistent with the only other large case series publication in this area (13, 48, 49). Although BVM ventilation was common, hypoxia was not, and few patients needed an advanced airway aligning with prior prehospital seizure research. Dosing variations occurred more commonly with IM administration but was effective regardless of the difference. Our findings add to growing evidence suggesting ketamine is safe and effective in the treatment of BRSE with little impact on respiratory status, at a wide range of dosing, and by multiple routes of administration.

ACKNOWLEDGEMENTS: We would like to thank the EMS clinicians of the Harris County Emergency Service District 11 Mobile Healthcare (HCESD11 MHC) for their commitment to providing excellent prehospital care to the community they serve.

FUNDING SOURCES: This project was not funded. The authors declare they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DECLARATION OF INTEREST STATEMENT: The authors report there are no competing interests to declare. The authors have no conflicts of interest to report.

Accepted Manuscript

DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING: The authors did not use a generative artificial intelligence (AI) tool or service to assist with preparation or editing of this work. The author(s) take full responsibility for the content of this publication.

DATA SHARING STATEMENT: The entire deidentified dataset, data dictionary and analytic code for this investigation are available upon request, from the date of article publication by contacting Joseph D. Finney, MD, at josephfinney@wustl.edu

AUTHORSHIP STATEMENT: JA and CP conceptualized and designed the study. JA and CP performed data collection and review. JDF performed the literature review with input from CP, JA, JS, FAA, MK, MP, RS, and BS. JW and JDF performed data analysis and interpretation of results with insight from BS, RS, FAA, JS, MP, MK, and RS. JDF, MP, and MK were directly assisted in manuscript development by FA, RS, BS, JS, MP, and CP. with additional support from JA. JDF takes responsibility for the paper.

Accepted Manuscript

REFERENCES

1. Michael GE, O'Connor RE. The diagnosis and management of seizures and status epilepticus in the prehospital setting. Emerg Med Clin North Am. 2011;29(1):29-39.
2. Ascoli M, Ferlazzo E, Gasparini S, Mastroianni G, Citraro R, Roberti R, et al. Epidemiology and Outcomes of Status Epilepticus. Int J Gen Med. 2021;14:2965-73.
3. Chegondi M, Garland MM, Sendi P, Jayakar AR, Totapally BR. Course and Outcome of Children with Convulsive Status Epilepticus Admitted to a Pediatric Intensive Care Unit. Cureus. 2019;11(4):e4471.
4. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology. 1996;46(4):1029-35.
5. Boggs JG. Mortality Associated with Status Epilepticus. Epilepsy Curr. 2004;4(1):25-7.
6. Kirmani BF, Au K, Ayari L, John M, Shetty P, Delorenzo RJ. Super-Refractory Status Epilepticus: Prognosis and Recent Advances in Management. Aging Dis. 2021;12(4):1097-119.
7. Neligan A, Noyce AJ, Gosavi TD, Shorvon SD, Kohler S, Walker MC. Change in Mortality of Generalized Convulsive Status Epilepticus in High-Income Countries Over Time: A Systematic Review and Meta-analysis. JAMA Neurol. 2019;76(8):897-905.
8. Guterman EL, Burke JF, Sporer KA. Prehospital Treatment of Status Epilepticus in the United States. JAMA. 2021;326(19):1970-1.
9. Burman RJ, Rosch RE, Wilmshurst JM, Sen A, Ramantani G, Akerman CJ, et al. Why won't it stop? The dynamics of benzodiazepine resistance in status epilepticus. Nat Rev Neurol. 2022;18(7):428-41.
10. Burman RJ, Selfe JS, Lee JH, van den Berg M, Calin A, Codadu NK, et al. Excitatory GABAergic signalling is associated with benzodiazepine resistance in status epilepticus. Brain. 2019;142(11):3482-501.
11. Ramgopal S, Martin-Gill C. Prehospital Seizure Management in Children: An Evaluation of a Nationally Representative Sample. J Pediatr. 2023;257:113379.
12. Shah MI, Ostermayer DG, Browne LR, Studnek JR, Carey JM, Stanford C, et al. Multicenter Evaluation of Prehospital Seizure Management in Children. Prehosp Emerg Care. 2021;25(4):475-86.
13. Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020;395(10231):1217-24.
14. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med. 2019;381(22):2103-13.
15. Han EJ, Chuck CC, Martin TJ, Madsen TE, Claassen J, Reznik ME. Statewide Emergency Medical Services Protocols for Status Epilepticus Management. Ann Neurol. 2021;89(3):604-9.
16. Sanchez Fernandez I, Goodkin HP, Scott RC. Pathophysiology of convulsive status epilepticus. Seizure. 2019;68:16-21.
17. Wasterlain CG, Liu H, Naylor DE, Thompson KW, Suchomelova L, Niquet J, et al. Molecular basis of self-sustaining seizures and pharmacoresistance during status epilepticus: The receptor trafficking hypothesis revisited. Epilepsia. 2009;50 Suppl 12:16-8.
18. Joshi S, Rajasekaran K, Hawk KM, Brar J, Ross BM, Tran CA, et al. Phosphatase inhibition prevents the activity-dependent trafficking of GABAA receptors during status epilepticus in the young animal. Epilepsia. 2015;56(9):1355-65.
19. Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. J Neurosci. 2005;25(34):7724-33.

Accepted Manuscript

20. Adhikari A, Yadav SK, Nepal G, Aryal R, Baral P, Neupane P, et al. Use of ketamine in Super Refractory Status Epilepticus: a systematic review. Neurol Res Pract. 2024;6(1):33.
21. Buratti S, Giacheri E, Palmieri A, Tibaldi J, Brisca G, Riva A, et al. Ketamine as advanced second-line treatment in benzodiazepine-refractory convulsive status epilepticus in children. Epilepsia. 2023;64(4):797-810.
22. Chiu WT, Campozano V, Schiefecker A, Rodriguez DR, Ferreira D, Headlee A, et al. Management of Refractory Status Epilepticus: An International Cohort Study (MORSE CODe) Analysis of Patients Managed in the ICU. Neurology. 2022;99(11):e1191-e201.
23. Fang Y, Wang X. Ketamine for the treatment of refractory status epilepticus. Seizure. 2015;30:14-20.
24. Jacobwitz M, Mulvihill C, Kaufman MC, Gonzalez AK, Resendiz K, MacDonald JM, et al. Ketamine for Management of Neonatal and Pediatric Refractory Status Epilepticus. Neurology. 2022;99(12):e1227-e38.
25. Keros S, Buraniqi E, Alex B, Antonetty A, Fialho H, Hafeez B, et al. Increasing Ketamine Use for Refractory Status Epilepticus in US Pediatric Hospitals. J Child Neurol. 2017;32(7):638-46.
26. Alkhachroum A, Der-Nigoghossian CA, Mathews E, Massad N, Letchinger R, Doyle K, et al. Ketamine to treat super-refractory status epilepticus. Neurology. 2020;95(16):e2286-e94.
27. Kitch BB. Out-of-hospital ketamine: review of a growing trend in patient care. J Am Coll Emerg Physicians Open. 2020;1(3):183-9.
28. Perlmutter M, Price M, Kothari K, Rafique Z, Rogers Keene K, De La Rosa X, et al. Prehospital Treatment of Benzodiazepine-Resistant Pediatric Status Epilepticus with Parenteral Ketamine: A Case Series. Prehosp Emerg Care. 2023;27(7):920-6.
29. Williams NC, Morgan LA, Friedman J, Siegler J. Ketamine Efficacy for Management of Status Epilepticus: Considerations for Prehospital Clinicians. Air Med J. 2024;43(2):84-9.
30. Scheppke KA, Pepe PE, Garay SA, Coyle CW, Antevy PM, Perlmutter MC, et al. Effectiveness of Ketamine As a Rescue Drug for Patients Experiencing Benzodiazepine-Resistant Status Epilepticus in the Prehospital Setting. Crit Care Explor. 2024;6(12):e1186.
31. Bredmose PP, Grier G, Davies GE, Lockey DJ. Pre-hospital use of ketamine in paediatric trauma. Acta Anaesthesiol Scand. 2009;53(4):543-5.
32. Yousefifard M, Askarian-Amiri S, Rafiei Alavi SN, Sadeghi M, Saberian P, Baratloo A, et al. The Efficacy of Ketamine Administration in Prehospital Pain Management of Trauma Patients; a Systematic Review and Meta-Analysis. Arch Acad Emerg Med. 2020;8(1):e1.
33. Frawley J, Goyal A, Gappy R, Sandoval S, Chen NW, Crowe R, et al. A Comparison of Prehospital Pediatric Analgesic Use of Ketamine and Opioids. Prehosp Emerg Care. 2023;27(7):915-9.
34. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011;57(5):449-61.
35. Howes MC. Ketamine for paediatric sedation/analgesia in the emergency department. Emerg Med J. 2004;21(3):275-80.
36. Ilvento L, Rosati A, Marini C, L'Erario M, Mirabile L, Guerrini R. Ketamine in refractory convulsive status epilepticus in children avoids endotracheal intubation. Epilepsy Behav. 2015;49:343-6.
37. Le Cong M, Gynther B, Hunter E, Schuller P. Ketamine sedation for patients with acute agitation and psychiatric illness requiring aeromedical retrieval. Emerg Med J. 2012;29(4):335-7.
38. Scheppke K, Pepe P, Antevy P, Perlmutter M, Garay S, Coyle C. 34: Termination of Benzodiazepine-Resistant Status Epilepticus with Parenteral Ketamine Administration. Critical Care Medicine. 2020;48(1):17-.
39. Ancedy D, Sebti M, Postaire M, Vidal F, Cisternino S, Schlatter J. Stability of 10-mg/mL and 50-mg/mL ketamine oral solutions. Am J Health Syst Pharm. 2021;78(9):825-31.

Accepted Manuscript

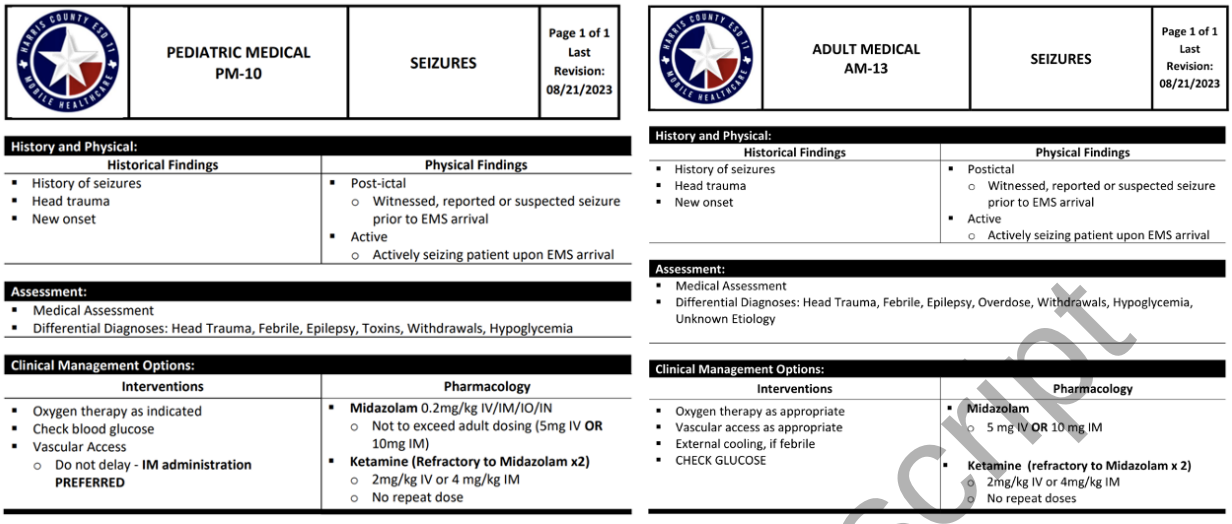
40. Foertsch MJ, McMullan JT, Harger NJ, Rodriquez D, Jr., Salvator A, Pharm DE, et al. Ketamine Stability over Six Months of Exposure to Moderate and High Temperature Environments. Prehosp Emerg Care. 2022;26(3):422-7.
41. Corwell BN, Motov SM, Davis NL, Kim HK. Novel uses of ketamine in the emergency department. Expert Opin Drug Saf. 2022;21(8):1009-25.
42. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol Rev. 2018;70(3):621-60.
43. Buckland DM, Crowe RP, Cash RE, Gondek S, Maluso P, Sirajuddin S, et al. Ketamine in the Prehospital Environment: A National Survey of Paramedics in the United States. Prehosp Disaster Med. 2018;33(1):23-8.
44. Fritz CL, Thomas SH, Schoenfeld D. The Menegazzi Scientific Sessions: Research Abstracts for the 2024 National Association of EMS Physicians Annual Meeting. Prehosp Emerg Care. 2023;28.
45. Finney JD, Schuler PD, Rudloff JR, Agostin N, Lobanov OV, Siegler J, et al. Evaluation of the Use of Ketamine in Prehospital Seizure Management: A Retrospective Review of the ESO Database. Prehosp Emerg Care. 2024:1-8.
46. Finney JD, Schuler PD, Bernardin ME, Siegler J, Ahmad FA. Evaluation of the Use of Ketamine in Prehospital Seizure Management. . American College of Emergency Physicians National Conference; September 30, 2024; Las Vegas, NV.
47. Finney JD, Kowalski M, Wang J, Perlmutter M, Siegler J, Svancarek B, et al. Prehospital Ketamine Administration in Benzodiazepine Refractory Status Epilepticus: A Retrospective Review. National Association of EMS Physicians 2025 Annual Meeting; January, 2025; San Diego, CA2025.
48. Zitek T, Scheppke KA, Antevy P, Coyle C, Garay S, Scheppke E, et al. Midazolam and Ketamine for Convulsive Status Epilepticus in the Out-of-Hospital Setting. Ann Emerg Med. 2024.
49. Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol. 2016;15(1):47-55.
50. Pfeiffer CK, Smith K, Bernard S, Dalziel SR, Hearps S, Geis T, et al. Prehospital benzodiazepine use and need for respiratory support in paediatric seizures. Emerg Med J. 2022;39(8):608-15.
51. Silbergleit R, Lowenstein D, Durkalski V, Conwit R, Neurological Emergency Treatment Trials I. RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial): a double-blind randomized clinical trial of the efficacy of intramuscular midazolam versus intravenous lorazepam in the prehospital treatment of status epilepticus by paramedics. Epilepsia. 2011;52 Suppl 8(Suppl 8):45-7.
52. Cole JB, Moore JC, Nystrom PC, Orozco BS, Stellpflug SJ, Kornas RL, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. Clin Toxicol (Phila). 2016;54(7):556-62.
53. Hoyle JD, Jr., Ekblad G, Hover T, Woodwyk A, Brandt R, Fales B, et al. Dosing Errors Made by Paramedics During Pediatric Patient Simulations After Implementation of a State-Wide Pediatric Drug Dosing Reference. Prehosp Emerg Care. 2020;24(2):204-13.
54. Lammers RL, Willoughby-Byrwa M, Fales WD. Errors and error-producing conditions during a simulated, prehospital, pediatric cardiopulmonary arrest. Simul Healthc. 2014;9(3):174-83.
55. Rappaport LD, Brou L, Givens T, Mandt M, Balakas A, Roswell K, et al. Comparison of Errors Using Two Length-Based Tape Systems for Prehospital Care in Children. Prehosp Emerg Care. 2016;20(4):508-17.

Accepted Manuscript

56. Wells M, Goldstein LN, Bentley A. The accuracy of emergency weight estimation systems in children-a systematic review and meta-analysis. Int J Emerg Med. 2017;10(1):29.
57. Kazi R, Hoyle JD, Jr., Huffman C, Ekblad G, Ruffing R, Dunwoody S, et al. An Analysis of Prehospital Pediatric Medication Dosing Errors after Implementation of a State-Wide EMS Pediatric Drug Dosing Reference. Prehosp Emerg Care. 2024;28(1):43-9.
58. Hoyle JD, Jr., Crowe RP, Bentley MA, Beltran G, Fales W. Pediatric Prehospital Medication Dosing Errors: A National Survey of Paramedics. Prehosp Emerg Care. 2017;21(2):185-91.
59. Wood AJ, Burke JF, Lowenstein DH, Guterman EL. Status Epilepticus Identification and Treatment Among Emergency Medical Services Agencies. JAMA Neurol. 2024;81(7):777-8.
60. Silbergleit R, Lowenstein D, Durkalski V, Conwit R, Investigators N. Lessons from the RAMPART study--and which is the best route of administration of benzodiazepines in status epilepticus. Epilepsia. 2013;54 Suppl 6(0 6):74-7.

Accepted Manuscript

Figure 1: Pediatric (left) and adult (right) protocols for ketamine use in BRSE



PEDIATRIC MEDICAL PM-10 | **SEIZURES** | Page 1 of 1 Last Revision: 08/21/2023

History and Physical:

Historical Findings	Physical Findings
▪ History of seizures ▪ Head trauma ▪ New onset	▪ Post-ictal ○ Witnessed, reported or suspected seizure prior to EMS arrival ▪ Active ○ Actively seizing patient upon EMS arrival

Assessment:

- Medical Assessment
- Differential Diagnoses: Head Trauma, Febrile, Epilepsy, Toxins, Withdrawals, Hypoglycemia

Clinical Management Options:

Interventions	Pharmacology
▪ Oxygen therapy as indicated ▪ Check blood glucose ▪ Vascular Access ○ Do not delay - **IM administration PREFERRED**	▪ **Midazolam** 0.2mg/kg IV/IM/IO/IN ○ Not to exceed adult dosing (5mg IV **OR** 10mg IM) ▪ **Ketamine (Refractory to Midazolam x2)** ○ 2mg/kg IV or 4 mg/kg IM ○ No repeat dose

ADULT MEDICAL AM-13 | **SEIZURES** | Page 1 of 1 Last Revision: 08/21/2023

History and Physical:

Historical Findings	Physical Findings
▪ History of seizures ▪ Head trauma ▪ New onset	▪ Postictal ○ Witnessed, reported or suspected seizure prior to EMS arrival ▪ Active ○ Actively seizing patient upon EMS arrival

Assessment:

- Medical Assessment
- Differential Diagnoses: Head Trauma, Febrile, Epilepsy, Overdose, Withdrawals, Hypoglycemia, Unknown Etiology

Clinical Management Options:

Interventions	Pharmacology
▪ Oxygen therapy as appropriate ▪ Vascular access as appropriate ▪ External cooling, if febrile ▪ CHECK GLUCOSE	▪ **Midazolam** ○ 5 mg IV **OR** 10 mg IM ▪ **Ketamine (refractory to Midazolam x 2)** ○ 2mg/kg IV or 4mg/kg IM ○ No repeat doses

Figure 1. Pediatric (left) and adult (right) protocols for ketamine use in BRSE

Patient Inclusion and Exclusion Criteria

Accepted Manuscript

Figure 2: Patient inclusion/exclusion flowchart

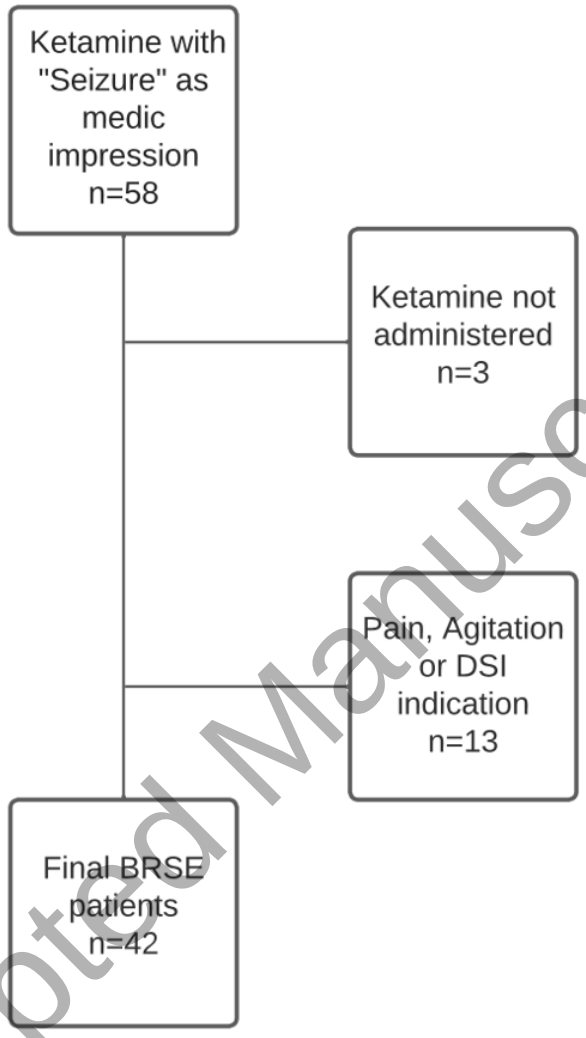


Figure 2. Patient inclusion/exclusion flowchart

Accepted Manuscript

Pediatric (left) and adult (right) protocols for ketamine use in BRSE

Table 1 Title: Description of Participants (n=42)

Description of Participants (n=42)				
Criteria	**Total**	**Hypoxia (n=9)**	**Airway Intervention (n=18)**	**Seizure Cessation (n=38)**
All Ages (years)	Mean 28 (Range 0-79)	9/42 (22%)	18 (42.9%)	38/42 (90.5%)
Pediatric <18	18 (42.8%)	6/18 (33.3%)	11/18 (61.1%)	16/18 (89%)
Adult >18	24 (57.2%)	3/24 (12.5%)	7/24 (29.2%)	22/24 (91.7%)
Gender (%)				
Male	11 (27%)	2/9 (22%)	6/18 (33.3%)	10/11 (90.1%)
Female	31 (73%)	7/9 (78%)	12/18 (66.7%)	28/31 (90.3%)
Prior Diagnosis of Seizure				
Yes (n=33)	33/42 (78.5%)	8/33 (24.2%)	15/33 (45.5%)	29/33 (87.9%)
No (n=6)	6/42 (14.2%)	0/6 (0%)	2/6 (33.3%)	6/6 (100%)
Unknown (n=3)	3/42 (7.1%)	1/3 (33.3%)	1/3 (33.3%)	3/3 (100%)
Prior Seizure Diagnosis and Home Antiseizure Medication				
Yes (n=28)	28 (66.7%)	7/28 (25%)	12/28 (42.9%)	25/28 (89.3%)
No (n=10)	10 (23.8%)	0/10 (0%)	5/10 (50%)	9/10 (90%)

Accepted Manuscript

Other (VNS) (n=1)	1 (2%)	1/1 (100%)	0/1 (0%)	1/1 (100%)
Unknown (n=3)	3 (7.1%)	1/3 (33.3%)	1/3 (33.3%)	3/3 (100%)
Patients who received at least 1 dose of Benzodiazepine prior to Ketamine (n=38)				
Pediatric	16/18 (89%)	4/16 (25%)*	10/11 (91%)	16/18 (88.9%)
Adult	26/28 (93%)	2/26 (7.7%)	5/7 (71.4%)	22/24 (91.7%)
Route of Administration of First Ketamine Dose				
IV (n=18)	18/42 (42.8%)	5/9 (55.6%)	10/18(55.6%)	17/18 (94.4%)
IO (n=2)	2/42 (4.8%)	0/9 (0%)	2/2 (100%)	1/2 (50%)
IM (n=22)	22/42 (52.4%)	4/9 (44.4%)	6/22 (27.3%)	20/22 (91%)

Summary of patient encounters in the BRSE case series, detailing demographic information, seizure history, airway support post-ketamine administration, and initial ketamine route of administration. The table categorizes patients by unique identifiers and provides a concise overview of each patient's clinical course, including termination status and any hypoxia episodes following ketamine use.

*One pediatric patient did not have oxygen saturation reported.

Accepted Manuscript