ORIGINAL CLINICAL REPORT

OPEN

Effectiveness of Ketamine As a Rescue Drug for Patients Experiencing Benzodiazepine-Resistant Status Epilepticus in the Prehospital Setting

Kenneth A. Scheppke, MD[1,2]
Paul E. Pepe, MD, MPH[1,3,4]
Sebastian A. Garay, BS, EMT-P[1]
Charles W. Coyle, BS, EMT-P[1]
Peter M. Antevy, MD[1,4]
Michael C. Perlmutter, MD[5]
Eric K. Scheppke, DO[6]
Remle P. Crowe, PhD[7]

OBJECTIVES: Accumulating basic science data, early clinical findings and various feasibility considerations have provided rationales for administering ketamine as a proposed rescue medication for midazolam-resistant status epilepticus (SE) in the logistically challenging prehospital environment. This report details the multiyear experience of paramedics managing midazolam-resistant SE following the introduction of a ketamine-rescue protocol.

DESIGN: A 7-year, population-based, observational study was conducted to evaluate outcomes of patients treated with IV, intraosseous, intramuscular, or intranasal ketamine for SE despite sufficient midazolam dosings. Tracked outcomes included: 1) rapid/sustained termination of clinical seizures in adults while under paramedics' care; 2) corresponding evaluations in children/adolescents; 3) any concerning observations regarding need for assisted ventilation, intubation, or other active interventions post-ketamine; and 4) any identifiable associations between outcomes and circumstances, demographics, or medical history.

SETTING: Emergency response 9-1-1 system serving a large, diverse U.S. county (jurisdictional population, 961,000/1,769 sq miles).

PATIENTS: Those receiving ketamine from paramedics for persistent seizures.

INTERVENTIONS: Adults and adolescents: 100 mg ketamine IV/intraosseous/intramuscular/intranasal; children: 1 mg/kg intramuscular/intranasal.

MEASUREMENTS AND MAIN RESULTS: Among 81 total cases, 57 involved adults (18–86 yr old) receiving the SE-midazolam + ketamine protocol. Ketamine rapidly terminated convulsions in 56 (98.2%) without recurrence during prehospital and hospital arrival phases. For approved reasons, paramedics administered ketamine directly (no midazolam) in eight adults and one child, terminating convulsions in every case. Among 15 childhood/adolescent cases treated per protocol, ketamine rapidly terminated SE activity in 11, but only mitigated it in four, including two retrospectively judged to involve nonseizure activity and two involving intranasal administration. Among all 81 ketamine-treated cases, there were no identifiable clinically significant complications attributable to ketamine, particularly the need for any additional active interventions.

CONCLUSIONS: Ketamine appeared to be consistently effective in treating adults with ongoing out-of-hospital seizures that were resistant to sufficient dosings of midazolam. Similar results were observed in children/adolescents.

KEYWORDS: status epilepticus; seizures; benzodiazepine-resistant convulsions; ketamine; prehospital critical care

Status epilepticus (SE) can result in substantial mortality and persistent functional impairment in over a third of patients (1–5). Midazolam, a fast-acting benzodiazepine, has become the first-line treatment in most

DOI: 10.1097/CCE.0000000000001186

KEY POINTS

Question: What options are available to responding 9-1-1 system paramedics when sufficient doses of midazolam fail to terminate ongoing seizures?

Findings: Consistent with basic science findings of gamma-aminobutyric acid-A receptor down-regulation and N-methyl-D-aspartate receptor up-regulation during prolonged seizures, ketamine rapidly terminated convulsions resistant to midazolam treatment in greater than 98% of adults' cases, without recurrence throughout the entire prehospital phase of care. No clinically significant complications were identified. Most children and adolescents experienced similar results.

Meaning: For paramedics contending with ongoing out-of-hospital seizures resistant to sufficient dosings of midazolam, ketamine appears to be a very effective option for terminating seizures.

emergency care settings. However, more than 25% of patients treated out of hospital by paramedics will experience persistent clinical seizures with convulsive motor activity despite sufficient benzodiazepine dosings (6, 7). Although a relatively infrequent event, when benzodiazepine-resistant SE does occur, it is a time dependent critical care challenge for emergency medical services (EMS) responders. Rapid hospital transport becomes the default option but that can be a relatively hazardous circumstance carrying significant risk for progressive neurologic insults and physical harm for both the patient and responders. Therefore, a readily available second-line intervention to control persistent seizures immediately would be of great benefit (5).

METHODS

Based on evolving laboratory studies and clinical experience, ketamine has been proposed as a second-line rescue medication for midazolam-resistant SE in the out-of-hospital setting (6, 8–37). Ketamine is carried by many EMS agencies and can be given intramuscularly with rapid onset, or even intranasally, when IV or intraosseous access cannot be obtained in these convulsing patients, particularly children.

In 2016, an EMS agency serving a large, diverse U.S. county ([38]; jurisdictional population 961,000/1,769 sq miles) introduced a protocol to administer ketamine for midazolam-resistant SE (**Appendix A**, http://links.lww.com/CCX/B439). An investigation was planned to observe how often clinical seizures were terminated using this modified approach in both adults (age ≥ 18 yr) and children/adolescents. Patients also were observed for ketamine attributable complications.

Considered a test of change in real-world EMS environments, this population-based study, conducted from September 01, 2016, to April 30, 2023, was designed as a descriptive observational investigation. **Appendix B** (http://links.lww.com/CCX/B439) provides additional setting, demographics and design information.

The protocol specified 100 mg IV/intraosseous/intramuscular or intranasal ketamine for adults and adolescents when seizures persisted despite sufficient midazolam dosings (7). Adolescents were defined as those 17 years young or younger who manifested signs of puberty (Appendix A, http://links.lww.com/CCX/B439). Younger children received 1 mg/kg intramuscular/intranasal when corresponding midazolam dosings failed. SE was defined as seizures persisting greater than 5 minutes or multiple ongoing seizures with incomplete recovery of consciousness (1, 2).

Tracked outcomes included: 1) rapid and sustained prehospital termination of clinical seizures while under paramedics' care including the emergency department (ED) arrival phase (before ED staff assumed management); 2) any observed seizure recurrence; and 3) frequency of assisted-ventilation/intubation or other active interventions (e.g., IV fluid boluses) initiated post-ketamine. When measurable in convulsing patients, systolic blood pressure (SBP), oxygen saturation (Spo_2), and end-tidal co_2 ($ETco_2$) were recorded to demonstrate seizure-related aberrations (pre-ketamine) and observe for post-ketamine changes. While recognizing accuracy limitations in the prehospital setting, any SBP less than 100 mm Hg, Spo_2 less than or equal to 90%, and/or $ETco_2$ greater than or equal to 45 mm Hg was reported and analyzed.

Patients were evaluated for evidence of trauma, pregnancy/recent pregnancy, fever, or hypoglycemia and later analyzed for identifiable demographic, historical, clinical, or circumstantial associations with ketamine effectiveness.

Comprehensive datasets were collected through electronic health records (CodeStat; Stryker, Portage, MI) including automated capture and manual-entry components. The software contained validation rules that ensured complete dataset entry. Per protocol, supervisors were notified about midazolam-resistant SE cases to ensure follow-up and identify problems. County government regulations allowed for abstracted follow-up information from receiving facilities when EMS requested it or when hospital liaisons provided alerts.

Summary descriptive statistics for pertinent patient characteristics were reported as numbers and percentages for categorical variables, and means (with SDs) and medians (with interquartile ranges) where appropriate for continuous variables. To evaluate associations between patient characteristics and convulsion termination, multivariable logistic regression models were performed to estimate odds ratios and 95% CI. Statistical analyses used Stata/SE-Version 16.0 (Stata Corporation, College Station, TX).

Procedures remained in accordance with ethical standards of responsible committees on human experimentation and the 1975 Helsinki Declaration. The Pearl Institutional Review Board approved the study with waiver of informed consent (No. 2023-0153). Strengthening the Reporting of Observational Studies in Epidemiology guidelines (https://www.strobe-statement.org/checklists/) were followed (**Appendix C**, http://links.lww.com/CCX/B439).

RESULTS

During the multiyear study, paramedics managed 2098 seizure cases overall. Among these, 81 incidents involved ketamine administration for SE, including 57 adult and 15 adolescent/childhood cases (n = 72) applying the SE-midazolam + ketamine protocol. In nine other incidents (eight adult/one child), paramedics administered ketamine directly for preapproved off-protocol circumstances (e.g., family administered sufficient benzodiazepine doses immediately before paramedics arrived). Patient characteristics are provided in **Table 1**; and Appendix B (http://links.lww.com/CCX/B439). None had hypoglycemia and only three (one child/two adults) had significant fever. All patients were transported to hospitals.

At least one dose of midazolam was administered by paramedics in all 72 protocol cases before administration of ketamine (**Supplemental Table 1**, http://links.lww.com/CCX/B439). A second dose was not provided by paramedics in 18% (11 adult and two childhood/adolescent cases), most often because patients had received adequate dose equivalents of benzodiazepines before paramedic arrival on-scene. Except for two cases, all adult administrations (first and second doses) involved 5 mg of midazolam. First and second doses for nonadults ranged from 0.5 to 5 mg, with the latter dose given in ten of 15 cases (Supplemental Table 1, http://links.lww.com/CCX/B439).

For those 57 on-protocol adult cases, ketamine administration usually involved IV infusion (75%); 11% intramuscular, 9% intraosseous, and 5% intranasal. Among off-protocol incidents (n = 9), eight involved the IV route (seven adult cases and one child) while one adult received intranasal administration. For the 15 on-protocol childhood/adolescent administrations, eight were IV, four intramuscular, and three intranasal.

Thirty-one adult women received ketamine per protocol; five had two separate incidents, one had three, and one experienced four events. Among 15 adult men, one had two incidents. This case predominance of women (n = 41 vs. 16 men) contrasted with 9-1-1 seizure cases overall (55% women; Appendix B, http://links.lww.com/CCX/B439). Seizure or anti-seizure medication histories were documented (Table 1) in 45 (79%).

For these 57 on-protocol adult events, ketamine rapidly terminated the clinical seizures in 56 without recurrence throughout prehospital and ED arrival phases (98.2%). The lone exception involved a chronically unresponsive, institutionalized 64-year-old woman with in-dwelling tracheostomy. Her midazolam-resistant seizures ceased immediately after ketamine infusion without recurrence prehospital (> 20 min), but a convulsion was observed just after paramedics transferred care. It was later reported that she had sepsis and was later placed into hospice care.

In follow-up interviews, paramedics consistently reported seizure termination within 1–2 minutes of initiating treatment, well before the entire IV or intraosseous dose (100 mg in a 50 mL drip) was delivered (typically taking 2–3 min to fully infuse). While intramuscular-related cessations occasionally took 1–2 minutes longer, injections generally were delivered earlier.

TABLE 1.

Characteristics of Adults and Children Treated by Paramedics in the Prehospital Setting With Ketamine for Benzodiazepine-Resistant Status Epilepticus (*n* = 72 Encounters) As Well As Nine Other Patient Encounters in Which Paramedics Administered Ketamine Directly (No Midazolam)

	Midazolam First		Ketamine First
	Adults (≥ 18 yr Old) (*n* = 57 Encounters)	Children/Adolescents (*n* = 15 Encounters)	Eight Adults, One Child (*n* = 9 Encounters)
Age, yr			
Median (IQR)	35 (30–59)	14 (3.5–15.5)	30 (27–43) plus one 9-yr-old boy
Sex, % (*n*)			
Female	71.9 (41)	66.7 (10)	55.6 (5)
Male	28.1 (16)	33.3 (5)	44.4 (4)
Race/ethnicity, % (*n*)			
White/Caucasian	68.4 (39)	26.7 (4)	89.9 (8)
African-American	10.5 (6)	13.3 (2)	11.1 (1)
Hispanic/Latino	10.5 (6)	46.7 (7)	0
Pacific Islander/Asian	1.8 (1)	0	0
Unknown	8.8 (5)	13.3 (2)	0
Documented history of seizures or seizure medications % (*n*)			
Yes	79.0 (45)	86.7 (13)	100 (9)
No	21.0 (12)	1.3 (2)	0
Fever (≥ 99.5°F), % (*n*)			
Yes	3.5 (2)	6.7 (1)	0
No	98.2 (56)	93.3 (14)	100 (9)
Hypoglycemia, % (*n*)			
Yes	0	0	0
No	100 (57)	100 (15)	100 (9)
Scene time, min			
Median (IQR)	19.2 (14.6–22.7)	15.4 (11.3–20.6)	17.8 (14.4–21.8)
Transport time, min			
Median (IQR)	10.6 (7.3–13.6)	16.0 (10.3–18.9)	10.2 (9.0–11.1)

IQR = interquartile range.

With limited variability in the primary outcome of interest (56/57 with sustained convulsion cessation), comparative statistical testing by either patient or encounter characteristics was precluded.

In the nine off-protocol incidents, family/medical professionals already provided considerable (or repeated) benzodiazepine doses (e.g., rectal diazepam/IV lorazepam) before paramedic arrival ($n = 4$) or benzodiazepine "allergies" were reported ($n = 4$). Another patient was considered "benzodiazepine-resistant" based on prior experience. Ketamine rapidly terminated seizures in all nine incidents (100%) including an adult with protracted recurrent events before EMS arrival. All nine had known seizure disorders.

Among the 15 childhood/adolescent on-protocol cases, ketamine rapidly terminated clinical seizures in 11 but only mitigated abnormal motor activity in four. Two were young children who received ketamine intranasal. Both experienced relative improvements, but complete cessation was either delayed or remained

unresolved. However, the unresolved case was assessed subsequently to be acute post-asphyxial anoxic posturing and the other received relatively low (0.5 mg) midazolam doses.

One adolescent receiving full IV-midazolam + ketamine protocol treatments had relative improvements but did not have complete prehospital resolution. Reportedly, she experienced a head injury the day before. She also had rapid/sustained seizure termination post-ketamine during a prior incident. The fourth patient, an adolescent with a known seizure syndrome, had immediate termination of convulsions, but some abnormal motor activity appeared to persist. Later, those movements were identified as his typical postictal movements.

In the 11 child/adolescent cases with rapid/sustained SE termination, paramedics administered only one midazolam dose in two cases because family members had already provided comparably equivalent benzodiazepines doses (Supplemental Table 1, http://links.lww.com/CCX/B439).

Clinically, there were no apparent complications attributable to ketamine and no active post-ketamine interventions among all 81 cases. However, pre-ketamine Spo_2 and $ETco_2$ aberrations were identified in 15 of the 47 on-protocol adult patients with recorded data (**Supplemental Table 2**, http://links.lww.com/CCX/B439).

Post-ketamine, vital signs, and respiratory metrics were documented in 90%, all within normal limits. The nine off-protocol (ketamine only) cases had complete datasets with no post-ketamine abnormalities identified (Supplemental Table 2, http://links.lww.com/CCX/B439). For the six on-protocol adult cases with incomplete post-ketamine datasets, all were clinically stable upon hospital arrival. Again, no concerning post-ketamine problems or active interventions were reported by paramedics or responding supervisors.

Among on-protocol childhood/adolescent cases (n = 15), post-ketamine SBP and Spo_2 were undocumented in six and two cases, respectively, but all patients were reported as clinically stable upon hospital arrival. Among cases with complete datasets, abnormalities were absent. Only one adult and one child received ventilatory support for significant pre-ketamine desaturations and both improved post-ketamine. That child was the one later identified as having a post-anoxic posturing condition.

DISCUSSION

These data provide promising evidence that ketamine should be considered as a potential rescue drug for EMS systems encountering midazolam-resistant seizures in the challenging prehospital environment.

No claim is made that ketamine is the "best" or "preferred" second-line agent for settings where expanded pharmacies of anti-seizure medications are stocked and immediately available. Rather, the clinical experiences reported here indicate that ketamine is a feasible option for paramedics contending with these actively seizing patients. Ketamine consistently terminated prehospital convulsions in adults, generally mitigated related respiratory aberrations (Appendix B, http://links.lww.com/CCX/B439) and facilitated less-risky extrication and transport without clinically significant complications.

Among limitations and caveats to consider, midazolam-resistant SE is a high impact event but is also relatively infrequent. Only 81 cases were reported and the study involved a single EMS system in one U.S. region. Most in-hospital follow-up data were not included such as in-hospital outcomes, seizure recurrence, other potential diagnoses (e.g., psychogenic nonepileptic seizures), or electrographic findings. Several studies indicate that patients may stop convulsing but still have ongoing electrographic seizures (39–41). While ketamine consistently terminated convulsions (motor activity), it may not have always controlled electrographic seizures in every case. Future studies should address these considerations.

Despite such limitations, the study findings remained consistently positive over many years and the sample size was relatively large for this infrequent but high impact event ([6, 7]; Appendix B, http://links.lww.com/CCX/B439). This particular 9-1-1 system also provided several advantages for a pilot investigation, namely a nonexclusionary population-based study cohort with patient care being provided within a matured EMS system possessing relatively robust clinical and operational oversight. In addition, the medical record software required prospective capture of all study data and the reported findings reflected real-world experiences by providing descriptions of off-protocol cases as well as treated patients who, in retrospect, were not having seizure activity.

This study also had its roots in basic science investigations indicating that benzodiazepine-targeted gamma-aminobutyric acid-A receptors down-regulate with ongoing seizures, whereas ketamine-targeted N-methyl-D-aspartate receptors reciprocally up-regulate (8–16). Damage to brain cells is common, severe and progressive when seizures persist (3–5). Therefore, this preliminary translational investigation provides additional hope that such progressive damage may be mitigated in these challenging prehospital scenarios.

As reported, two children receiving ketamine intranasally did not experience rapid termination of convulsions, suggesting a potential therapeutic limitation of intranasal administration. One study involving out-of-hospital midazolam-resistant pediatric SE cases (n = 6) reported that ketamine uniformly suppressed convulsions, but only IV (n = 5) and intramuscular (n = 1) routes were used (27). Larger scale retrospective studies also indicate superiority of intramuscular benzodiazepines over intranasal in seizing children (42, 43). Accordingly, future research evaluating intranasal ketamine is encouraged.

In summary, these results suggest that when SE is resistant to sufficient dosings of midazolam, ketamine appears to be effective and logistically feasible as a rescue drug in the challenging prehospital environment. Larger investigations/trials should now be conducted to corroborate these findings.

ACKNOWLEDGMENTS

We extend our deepest gratitude to the many emergency medical services (EMS) responders, EMS trainers, and administrative staff who, quite supportively, participated in investigating and applying these clinical care techniques to help those endangered patients who experience status epilepticus and its many detrimental consequences. We also thank the dedicated hospital liaisons who ensured conscientious and accurate follow-up information that both assured the integrity and the quality of the data reported here, as well as the detailed information reported in this article and its Appendices (http://links.lww.com/CCX/B439).

1 *Palm Beach County Fire Rescue, Palm Beach County, West Palm Beach, FL.*

2 *Florida Department of Health, Tallahassee, FL.*

3 *Department of Management, Policy and Community Health, University of Texas Health Sciences Center, School of Public Health, Houston, TX.*

4 *Coral Springs/Parkland Fire Department, City of Coral Springs, FL.*

5 *Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN.*

6 *Edward Via College of Osteopathic Medicine, Auburn, AL.*

7 *Department of Clinical and Operational Research, ESO, Austin, TX.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Every author meets and agrees with all of the International Committee of Medical Journal Editors (ICMJE) criteria for authorship: 1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; 2) drafting the work or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. K. A. Scheppke, Dr. Pepe, Chief Coyle, Dr. Antevy, and Dr. Perlmutter were involved in conceptualization. Lt. Garay and Dr. Pepe were involved in data curation. Dr. Pepe, Dr. K. A. Scheppke, Dr. Crowe, and Lt. Garay were involved in formal analysis. Dr. K. A. Scheppke, Dr. Pepe, Dr. Crowe, Dr. E. K. Scheppke, Chief Coyle, and Dr. Antevy were involved in resources (and literature review). Dr. K. A. Scheppke, Dr. E. K. Scheppke, Dr. Antevy, Dr. Perlmutter, Dr. Pepe, and Lt. Garay were involved in investigation. Dr. K. A. Scheppke, Dr. Pepe, Lt. Garay, Dr. Antevy, Dr. Crowe, and Dr. Perlmutter were involved in methodology. Chief Coyle, Dr. K. A. Scheppke, Lt. Garay, and Dr. Pepe were involved in project administration. Lt. Garay was involved in software. Dr. K. A. Scheppke, Dr. Pepe, Lt. Garay, and Chief Coyle were involved in supervision, validation, and visualization. Dr. Pepe was involved in writing—original draft. Dr. Pepe, Dr. K. A. Scheppke, Dr. Crowe, Dr. E. K. Scheppke, Dr. Antevy, and Dr. Perlmutter were involved in writing—review & editing.

The study was conducted as an extension of the routine quality assurance processes of a public safety agency in the State of Florida.

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: Dr.PaulPepe@GMail.com

Procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation and the Helsinki Declaration of 1975. The study was designed as a formal investigation stemming from routine quality assurance functions of emergency medical services agencies to follow outcomes after introducing a new protocol. Before study implementation, a prospective plan was made to formally investigate and publish the outcomes of the newly introduced protocol reported here. The study was submitted to the Pearl Institutional Review Board (IRB), which approved the investigation with a waiver regarding the need for full review (IRB No. 2023-0153).

The seizure management training, data collection, and related quality assurance activities are routine functions for public safety agencies providing medical care to the public.

The study was performed in the 9-1-1 emergency medical care system of Palm Beach County, Florida, where emergency medical responses are provided by Palm Beach County Fire Rescue (PBCFR) responders under the supervision of the PBCFR Fire Administrator (Fire Chief), Emergency Medical Services Chief, and Chief Medical Officer.

REFERENCES

1. Lowenstein DH, Bleck T, Macdonald RL: It's time to revise the definition of status epilepticus. *Epilepsia* 1999; 40:120–122
2. Trinka E, Cock H, Hesdorffer D, et al: A definition and classification of status epilepticus—report of the ILAE task force on classification of status epilepticus. *Epilepsia* 2015; 56:1515–1523
3. Rodin E, Krogstad MH, Aukland P, et al: High long-term mortality after incident status epilepticus in adults: Results from a population-based study. *Epilepsia* 2019; 60:33–41
4. Legriel S, Azoulay E, Resche-Rigon M, et al: Functional outcome after convulsive status epilepticus. *Crit Care Med* 2010; 38:2295–2303
5. Dingledine R, Varvek NH, Dudek FE: When and how do seizures kill neurons, and is cell death relevant to epileptogenesis? *Adv Exp Med Biol* 2014; 813:109–122
6. Glauser T, Shinnar S, Gloss D, et al: Evidence-based guideline: Treatment of convulsive status epilepticus in children and adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr* 2016; 16:48–61
7. Silbergleit R, Durkalski V, Lowenstein D, et al; NETT Investigators: Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012; 366:591–600
8. Deeb TZ, Maguire J, Moss SJ: Possible alterations in GABA-A receptor signaling that underlie benzodiazepine-resistant seizures. *Epilepsia* 2012; 53:79–88
9. Feng HJ, Matthews GC, Kao C, et al: Alterations of GABA-A-receptor function and allosteric modulation during development of status epilepticus. *J Neurophysiol* 2008; 99:1285–1293
10. Fang Y, Wang X: Ketamine for the treatment of refractory status epilepticus. *Seizure* 2015; 30:14–20
11. Zeiler FA, Teitelbaum J, Gillman LM, et al: NMDA antagonists for refractory seizures. *Neurocrit Care* 2014; 20:502–513
12. Dingledine R, Borges K, Bowie D, et al: The glutamate receptor ion channels. *Pharmacol Rev* 1999; 51:7–61
13. Mazarati AM, Wasterlain CG: N-methyl-D-aspartate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. *Neurosci Lett* 1999; 265:187–190
14. Rosati A, De Masi S, Guerrini R: Ketamine for refractory status epilepticus: A systematic review. *CNS Drugs* 2018; 32:997–1009
15. Rai S, Drislane FW: Treatment of refractory and super-refractory status epilepticus. *Neurotherapeutics* 2018; 15:697–712
16. Niquet J, Lumley L, Baldwin R, et al: Early polytherapy for benzodiazepine-refractory status epilepticus. *Epilepsy Behav* 2019; 101:106367
17. Zaccara G, Giannasi G, Oggioni R, et al; convulsive status epilepticus study group of the uslcentro Toscana, Italy: Challenges in the treatment of convulsive status epilepticus. *Seizure* 2017; 47:17–24
18. Borsato GS, Siegel JL, Rose MQ, et al: Ketamine in seizure management and future pharmacogenomic considerations. *Pharmacogenomics J* 2020; 20:351–354
19. Hsieh CY, Sung PS, Tsai JJ, et al: Terminating prolonged refractory status epilepticus using ketamine. *Clin Neuropharmacol* 2010; 33:165–167
20. Tarocco A, Ballardini E, Garani G: Use of ketamine in a newborn with refractory status epilepticus: A case report. *Pediatr Neurol* 2014; 51:154–156
21. Pin JN, Leonardi L, Nosadini M, et al: Efficacy and safety of ketamine for neonatal refractory status epilepticus: Case report and systematic review. *Front Pediatr* 2023; 11:1189478
22. Synowiec AS, Singh DS, Yenugadhati V, et al: Ketamine use in the treatment of refractory status epilepticus. *Epilepsy Res* 2013; 105:183–188
23. Alkhachroum A, Der-Nigoghossian CA, Mathews E, et al: Ketamine to treat super-refractory status epilepticus. *Neurology* 2020; 95:e2286–e2294
24. Jacobwitz M, Mulvihill C, Kaufman MC, et al: Ketamine for management of neonatal and pediatric refractory status epilepticus. *Neurology* 2022; 99:e1227–e1238
25. Höfler J, Rohracher A, Kalss G, et al: (S)-Ketamine in refractory and super-refractory status epilepticus: A retrospective study. *CNS Drugs* 2016; 30:869–876
26. Srinivas M, Parker D, Millis S, et al: Factors associated with refractory status epilepticus termination following ketamine initiation: A multivariable analysis model. *Neurocrit Care* 2023; 38:235–241
27. Perlmutter M, Price M, Kothari K, et al: Prehospital treatment of benzodiazepine-resistant pediatric status epilepticus with parenteral ketamine: A case series. *Prehosp Emerg Care* 2023; 27:920–926
28. Fernandez AR, Bourn SS, Crowe RP, et al: Out-of-hospital ketamine: Indications for use, patient outcomes, and associated mortality. *Ann Emerg Med* 2021; 78:123–131
29. Scheppke KA, Braghiroli J, Shalaby M, et al: Prehospital use of IM ketamine for sedation of violent and agitated patients. *West J Emerg Med* 2014; 15:736–741
30. Höfler J, Trinka E: Intravenous ketamine in status epilepticus. *Epilepsia* 2018; 59:198–206
31. Sathe AG, Underwood E, Coles LD, et al: Patterns of benzodiazepine underdosing in the established status epilepticus treatment trial. *Epilepsia* 2021; 62:795–806
32. Chamberlain JM, Kapur J, Shinnar S, et al; Neurological Emergencies Treatment Trials: Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): A double-blind, responsive-adaptive, randomised controlled trial. *Lancet* 2020; 395:1217–1224
33. Anupama S, Poovazhagi V, Nisha R, et al: Comparison of levetiracetam as second-line drug with fosphenytoin in convulsive status epilepticus among children: A single center, open-label randomized controlled trial. *J Pediatr Crit Care* 2023; 10:18–23

34. Fujikawa DG: Neuroprotective effect of ketamine administered after status epilepticus onset. *Epilepsia* 1995; 36:186–195
35. McKinley K, Panakos P, Yousef D: Characterization of ketamine usage in a large tertiary-care emergency department. *Am J Emerg Med* 2021; 47:149–153
36. Mo H, Campbell MJ, Fertel BS, et al: Ketamine safety and use in the emergency department for pain and agitation/delirium: A health system experience. *West J Emerg Med* 2020; 21:272–281
37. Williams NC, Morgan LA, Friedman J, et al: Ketamine efficacy for management of status epilepticus: Considerations for prehospital clinicians. *Air Med J* 2024; 43:84–89
38. United States Census Bureau: Palm Beach County Florida Population Estimates. 2022. Available at: https://www.census.gov/quickfacts/palmbeachcountyflorida. Accessed July1, 2022
39. Bleck TP: Status epilepticus and the use of continuous EEG monitoring in the intensive care unit. *Continuum (Minneap Minn)* 2012; 18:560–578
40. Migdady I, Rosenthal ES, Cock HR: Management of status epilepticus: A narrative review. *Anaesthesia* 2022; 77:78–91
41. Rodriguez-Quintana JH, Bueno SJ, Zuleta-Motta JL, et al: Utility of routine EEG in emergency department and in-patient service. *Neurol Clin Pract* 2021; 11:e677–e681
42. Ramgopal S, Martin-Gill C: Prehospital seizure management in children: An evaluation of a nationally representative sample. *J Pediatr* 2023; 257:113379
43. Ramgopal S, Owusu-Ansah S, Crowe RP, et al: Association of midazolam route of administration and need for recurrent dosing among children with seizures cared for by emergency medical services. *Epilepsia* 2024; 65:1294–1303