Midazolam and Ketamine for Convulsive Status Epilepticus in the Out-of-Hospital Setting

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Study objective: To determine if ketamine, when added to midazolam for the treatment of out-of-hospital seizures, is associated with an increase in the rate of cessation of convulsions prior to hospital arrival.

Methods: We performed a retrospective cohort study of out-of-hospital patients with an active convulsive seizure being transported to a hospital by a large emergency medical services system in Florida, using data from August 1, 2015 and August 5, 2024. Per protocol, patients received midazolam first for their seizure. Starting in June 2017, a new protocol was developed in which patients who continued to convulse after midazolam received ketamine. We used propensity score matching and multivariable logistic regression to determine if patients who received ketamine were more likely to stop convulsing prior to hospital arrival than those who received midazolam alone.

Results: Overall, 479 (80.1%) of 598 actively convulsing patients who received 2 doses of midazolam (without subsequent ketamine) had resolution of their convulsions prior to hospital arrival compared with 85 (94.4%) of 90 who received ketamine after midazolam, an absolute difference between groups of 14.3% (95% CI 8.6% to 20.1%). After propensity matching, 82.0% of those in the midazolam only group had resolution of convulsions compared to 94.4% in the ketamine group, a difference of 12.4% (95% CI 3.1% to 21.7%).

Conclusion: In this retrospective study of out-of-hospital patients with active convulsive seizures, patients who received ketamine were more likely to have stopped convulsing prior to hospital arrival than those who received midazolam alone. [Ann Emerg Med. 2025;85:305-312.]

Please see page 306 for the Editor's Capsule Summary of this article.

Keywords: Midazolam, Ketamine, Status epilepticus.

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INTRODUCTION

Background

Status epilepticus is defined as a seizure lasting more than 5 minutes or multiple seizures with incomplete recovery of consciousness.[1,2] Status epilepticus has a substantial inhospital mortality rate, and after 90 days, more than one third of patients may have functional impairment.[3,4] To help avoid neuronal damage and the long-term sequelae that may develop after status epilepticus, it is important to stop it as soon as possible. Benzodiazepines are generally considered the first-line medications, but in one prior study, 27% to 37% of status epilepticus patients who received properly dosed benzodiazepines in the out-of-hospital setting continued to seize.[5-7]

Importance

Biochemical and animal data suggest that status epilepticus persistence is related to increased expression of *N*-methyl-D-aspartate receptors to the synapse, so *N*-methyl-D-aspartate receptor antagonists (such as ketamine) can break it.[8] Therefore, some experts have suggested that ketamine should be considered for status epilepticus.[9-12] However, there are currently no data from prospective studies evaluating the efficacy of ketamine in status epilepticus. Data supporting the use of ketamine for status epilepticus come from case reports, case series, and one small retrospective cohort study of pediatric patients with refractory status epilepticus.[13-24] Moreover, although the use of ketamine for seizures in the out-of-hospital setting has increased since 2018, there have been no comparative studies

Editor's Capsule Summary

What is already known on this topic

Benzodiazepines are the mainstay of emergency medical services seizure management but are not always effective.

What question this study addressed

When a first dose of midazolam fails to terminate seizures prior to hospital arrival, which next step is more likely to work: additional midazolam or ketamine 100 mg?

What this study adds to our knowledge

In this before-and-after study, the authors propensity-matched 89 patients receiving 2 sequential doses of midazolam (before) with 89 for whom ketamine followed first midazolam (after). There was more frequent seizure resolution in those receiving ketamine (94.4% versus 82.0%, Δ=12.4% [95% CI 3.1% to 21.7%]).

How this is relevant to clinical practice

These nonrandomized data suggest a role for ketamine in emergency medical services treatment of sustained seizures after an initial midazolam dose.

published about ketamine use for seizures in the out-of-hospital setting.[25] Thus, there is a need for higher quality data about the use of ketamine for status epilepticus.

Goals of This Investigation

Our emergency medical services (EMS) system enacted a protocol to use ketamine to treat seizures starting in June 2017. We therefore have a unique data set and sought to use it to determine if ketamine, when added to midazolam for the treatment of out-of-hospital seizures, is associated with an increase in the rate of cessation of convulsions prior to hospital arrival.

METHODS

Study Design and Setting

We conducted a retrospective cohort study to compare the outcomes of patients treated by a single EMS system who received midazolam followed by ketamine for active convulsive seizures with those who received midazolam alone. We followed the Strengthening the Reporting of Observational Studies guidelines. This study was approved by the Pearl Institutional Review Board.

Our EMS system is located in Florida, United States. It services a population of approximately 1.5 million people. They transport an average of 230 patients by ground per day and respond to approximately 400 emergency scene aeromedical transports per year.

Selection of Participants

We included patients of all ages who were transported by ground between August 1, 2015 and August 5, 2024 and who received 2 doses of midazolam or at least 1 dose of midazolam followed by ketamine for convulsive status epilepticus. We defined patients to have convulsive status epilepticus if they received a second dose of medication for convulsive seizures during transport to the hospital. Our EMS system enacted an official protocol for the use of ketamine for seizures starting June 2017. As per that protocol, pregnant patients were not given ketamine. Additionally, we excluded repeat patient encounters, those transported by air, those who received dextrose for hypoglycemia, those for whom the documentation did not specify if their convulsions stopped, and those for whom other data points were not documented. Patients who received midazolam followed by ketamine before the official protocol started were allowed to be included.

Interventions

Starting in January 2016, ketamine was available to be used for seizures, but it was not part of a protocol, so it was used only in rare situations as directed by medical control.

Before June 2017, the protocol for treating adults with active seizures was midazolam 2.5 mg intravenous (IV) or intraosseous (IO) route, or 5 mg intranasal (IN) or intramuscular (IM) route. The protocol allowed for the midazolam dose to be repeated once if seizures persisted after 5 minutes. For children with active seizures, the dose of midazolam was 0.1 mg/kg IV or IO route (maximum 2.5 mg) or 0.2 mg/kg IN or IM route (maximum 5 mg). Again, the protocol allowed for the dose to be repeated once.

Starting June 2017, ketamine was officially added to the seizure treatment protocol. The protocol also changed as follows: adult patients with active seizures began to receive midazolam 5 mg IV, IO, IM, or IN route (a higher dose for the IV and IO routes). After 5 minutes, this dose of midazolam could be repeated once if seizures persisted. If the seizures persisted despite 2 doses of midazolam, the updated protocol recommended 100 mg of ketamine in 50 mL of 0.9% saline solution administered intravenously or intraosseously (with approval from the EMS captain). If unable to establish vascular access, ketamine 100 mg could

be administered through the IN or IM route. For children, the maximum dose of midazolam was increased to 5 mg for IV or IO routes and remained the same for the IN and IM routes. The ketamine dose for pediatric patients was 1 mg/kg IN or IM. Starting in January 2021, approval from the EMS captain was no longer required to use ketamine in this protocol.

Our EMS system did not use any other type of medications for seizures during the study period (except for dextrose, receipt of which excluded the patient).

For weight-based dosing in pediatric patients, our EMS system used the Handtevy method, which is an accurate method for estimating weight in children.[26]

Measurements

We searched our EMS system's electronic medical record systems (SafetyPAD and MetroPCR) for patients who received midazolam or ketamine and whose reason for transport mentioned the word "seizure." Data in SafetyPAD were available from August 2015 until June 2023, and subsequent data came from MetroPCR. The means by which data elements were recorded and abstracted were the same for these 2 medical record systems, except that in MetroPCR, EMS clinicians were forced to document a reason for usage any time they documented the administration of ketamine (whereas in Safety PAD, they were not).

The following data were collected for each patient: age, gender, race, ethnicity, medications (route and dose) administered by EMS, cessation of convulsions after medication (yes or no), time of EMS arrival at the patient, time of EMS arrival to the hospital, endotracheally intubated during transport after medications (yes or no), and cardiac arrest during transport (yes or no). The difference between the time of EMS arrival at the patient and the time of arrival at the hospital was used to calculate the variable "duration of out-of-hospital care."

In our system, the cessation (or not) of active convulsions is consistently documented by the treating EMS clinician in a discrete field in the medical record system template. It is assessed 5 minutes after the medication is administered or on arrival to the hospital (if <5 minutes since the last medication administered). Medical history (such as a history of epilepsy), home medications (including use of antiepileptics), and duration of the seizure prior to EMS arrival are inconsistently documented, so these variables were not collected.

We were able to automate the abstraction of the data points listed above from the medical records into a spreadsheet. This data abstraction was performed by a paramedic with experience in this technique. The principal investigator developed a data dictionary and trained the paramedic abstractor on the definitions of the variables. Meetings were held to clarify questions and confirm the accuracy of the data. The abstractor was aware of the study related to the treatment of seizures, but they were blinded from the specific study hypothesis. A sample of 10% of the charts were manually abstracted to confirm the automated data abstraction provided accurate data; no errors were identified. For all included cases in which the dose of midazolam or ketamine strayed from the protocolized dose, the chart was manually reviewed to confirm that the patient received the medications for a seizure. (This was not an issue for the cases from MetroPCR as EMS clinicians had to consistently specify the reason for ketamine usage.) In unclear cases, the principal investigator adjudicated. Otherwise, there was no manual chart review.

Missing Data

Based on an internal review of data prior to formal analysis, we determined that missing data points (among the collected variables) would be very rare (<1%), so patients with missing data points were simply excluded.

Outcomes

The primary outcome, determined a priori, was the cessation of convulsions prior to hospital arrival. Secondarily, we assessed the frequency of cardiac arrest and endotracheal intubation during transport after receiving seizure medication.

Primary Analysis

We used all eligible patients in our database, so our sample size was not driven by a power calculation. However, we performed an a priori power calculation to ensure our sample size would be sufficient. In particular, we knew that patients in our system who receive 2 doses of midazolam for seizures stop convulsing approximately 75% of the time before hospital arrival. We hypothesized ketamine administration after midazolam would increase the rate to 90%. We estimated there would be approximately 6 times as many patients in the midazolam (only) group compared with the ketamine group. Therefore, with an alpha of 0.05 and a power of 0.8, we calculated that we would need 357 patients (306 in the midazolam group and 51 in the ketamine group) to show a 15% absolute difference in the unadjusted rate. Our quality assurance data suggested that approximately 100 patients had received ketamine for seizures, so we deemed our sample size sufficiently large.

For our primary analysis, we compared patients who received ketamine (following at least 1 dose of midazolam) with those who received 2 doses of midazolam (without subsequent ketamine). We compared the outcomes of the 2 groups in an unadjusted fashion. We also used propensity score matching as described in the next section, and we compared the percent difference of the propensity-matched groups.

We aggregated our data in Excel (version 16.89 [Microsoft]) and analyzed it in R Studio (version 2023.09.0+463). Categoric variables are reported as counts (percentages), and continuous data as mean (SD).

Propensity Matching and Logistic Regression

First, we used absolute standardized differences to assess the baseline balance of covariates between groups. Covariates with absolute standardized differences of more than 0.1 were considered unbalanced.[27] Then, using the *MatchIt* function in R Studio, we performed multivariable logistic regression to estimate the probability of receiving ketamine for each covariate. The propensity score model included the following variables which were chosen a priori based on previous literature and investigator judgment: age (continuous), sex (man or woman), race/ethnicity (non-Hispanic White or not), duration of out-of-hospital care (continuous), IV administration of first dose of midazolam (yes or no), IV administration of second dose of midazolam (yes or no), and total dose of midazolam given by EMS (continuous).[6]

The modeled probabilities were then used to perform a nearest neighbor one-to-one matching without replacement between patients who received ketamine and those who did not with caliper of 0.2SD of the logit of the propensity score. Groups were well balanced with this strategy except with regard to race (Table). We subsequently attempted full matching to see if this resulted in better-matched groups; the balance between groups with full matching was similar, so we used the groups from the nearest neighbor match for further analysis.

Table. Baseline characteristics and characteristics after propensity score matching of out-of-hospital patients with active convulsions treated with midazolam (only) versus midazolam plus ketamine.

	Unadjusted			Propensity-Matched		
Characteristic	**Two Doses Midazolam Only (n=598)**	**Midazolam Plus Ketamine (n=90)**	**Absolute Standard Difference***	**Two Doses Midazolam Only (n=89)**	**Midazolam Plus Ketamine (n=89)**	**Absolute Standard Difference***
Age, mean (SD), y	36.7 (21.2)	34.6 (20.8)	0.10	33.0 (20.5)	34.6 (21.0)	0.08
sex, men, n (%)	275 (46.0%)	28 (31.1%)	0.32	24 (27.0%)	28 (31.5%)	0.09
Race and ethnicity						
Non-Hispanic White, n (%)	322 (53.9%)	53 (58.9%)	0.10	45 (50.6%)	53 (59.6%)	0.18
Black, n (%)	131 (21.9%)	15 (16.7%)				
Hispanic White, n (%)	105 (17.6%)	14 (15.6%)				
Duration of out-of-hospital care, mean (SD), min	27.5 (7.7)	28.9 (8.0)	0.18	29.2 (9.7)	28.6 (7.3)	0.07
Route first dose midazolam						
IV, n (%)	199 (33.3%)	18 (20.0%)	0.33	15 (16.9%)	17 (19.1%)	0.06
IN, n (%)	301 (50.3%)	51 (56.7%)				
IM, n (%)	90 (15.1%)	21 (23.3%)				
IO, n (%)	8 (1.3%)	0				
Route second dose midazolam						
IV, n (%)	402 (67.2%)	25 (27.8%)	0.88	26 (29.2%)	25 (28.1%)	0.03
IN, n (%)	115 (19.2%)	22 (24.4%)				
IM, n (%)	61 (10.2%)	16 (17.8%)				
IO, n (%)	20 (3.3%)	6 (6.7%)				
No second dose, n (%)	0 (0.0%)	21 (23.3%)				
Total dose midazolam, mean (SD), mg	7.6 (2.6)	8.3 (2.6)	0.23	8.3 (2.6)	8.3 (2.6)	0.002

*The absolute standard difference reported is the mean difference for all continuous variables and the risk difference for all proportions.

Subgroup Analysis

Given that the efficacy of anti-seizure therapies may differ in children versus adults, we decided to calculate the unadjusted outcomes for adults and pediatric patients (defined as age <18 years) separately.[6] We also calculated the unadjusted outcomes for patients who received ketamine alone for seizures (without preceding midazolam). Finally, we assessed outcomes of patients who received ketamine, stratified by route of ketamine administration.

RESULTS

Characteristics of Study Subjects

From August 1, 2015 until August 5, 2024, our EMS system administered midazolam to 2,610 unique patients for an active seizure (Figure). Among those, 690 (26.4%) received a second dose of midazolam or ketamine for persistent convulsions. We included 688 of these patients in our analysis, excluding two for whom it was not documented as to whether or not convulsions ceased. There were no other missing data points. None of these 688 patients received dextrose.

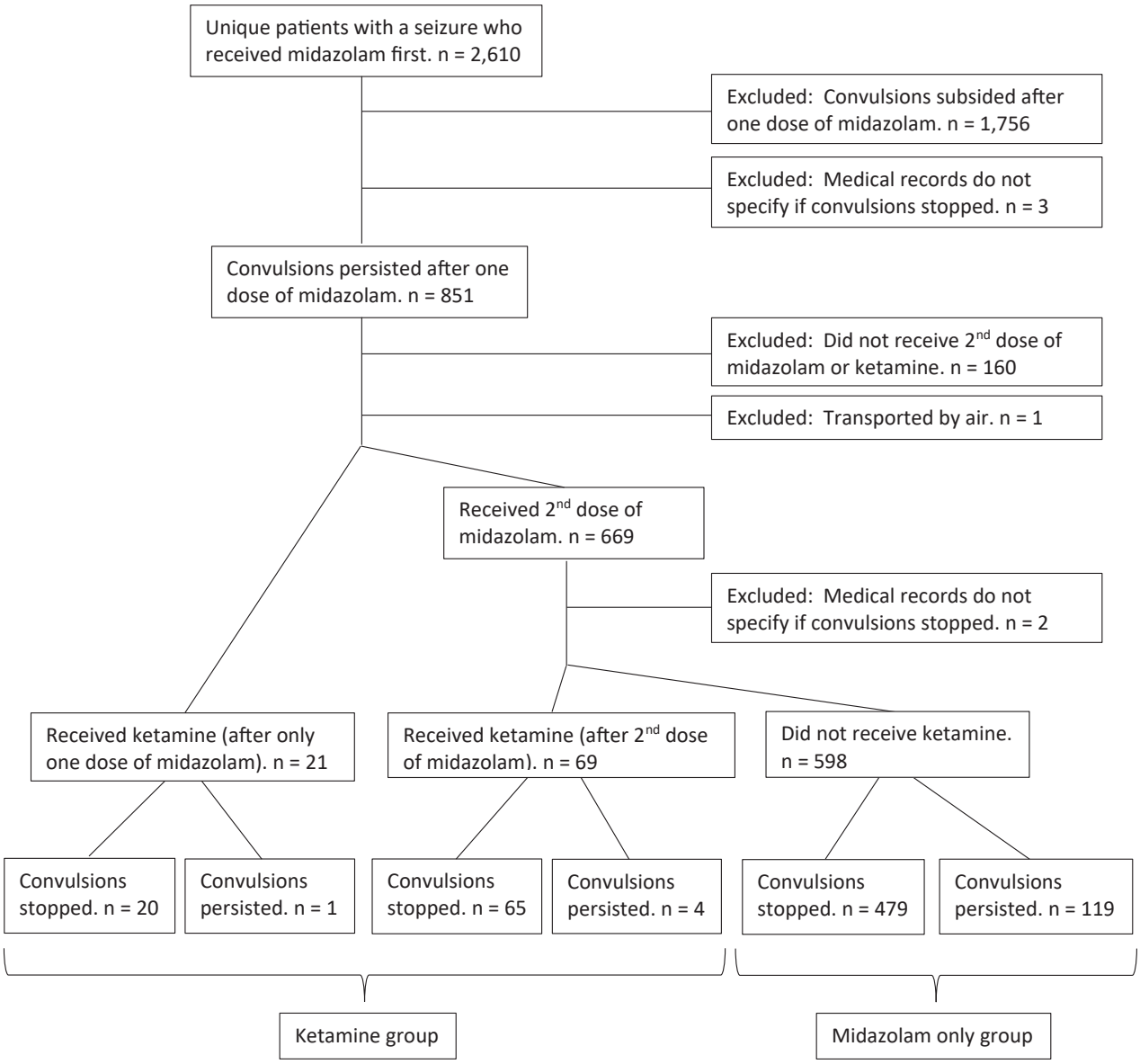

Figure. Flow of out-of-hospital patients who received midazolam (sometimes followed by ketamine) for a seizure between August 2015 and August 2024.

There were 100 total patients who received ketamine for an active seizure, but 10 of them did not receive midazolam before ketamine, so were excluded. Additionally, 21 of the patients in the ketamine group received ketamine after receiving only 1 dose of midazolam (instead of 2 as dictated by the protocol). These patients were still included.

Among the 90 patients who received ketamine after midazolam, the routes of administration were as follows: 60 (66.7%) IV, 15 (16.7%) IM, 9 (10.0%) IN, and 6 (6.7%) IO. In total, 85 (94.4%) received the ketamine dose specified in the protocol (100 mg or 1 mg/kg for children). Among the 5 who received ketamine but did not receive the protocolized dose, there was 1 patient who received ketamine 400 mg intramuscularly before the protocol was initiated. This patient's chart was manually reviewed, and they were adjudicated to be included in the analysis.

As shown in the Table, there were some differences in the baseline characteristics of the patients who received only midazolam versus those who received ketamine after midazolam. In particular, patients who received ketamine were less likely to be men, had longer durations of out-of-hospital care, received less of their doses of midazolam intravenously, and received higher total doses of midazolam.

Main Results

Overall, 479 (80.1%) of 598 patients with convulsive status epilepticus who received 2 doses of midazolam (without subsequent ketamine) had resolution of their convulsions prior to hospital arrival compared to 85 (94.4%) of 90 who received ketamine after midazolam, a difference of 14.3% (95% CI 8.6 to 20.1%).

After propensity score matching, 89 patients remained in each group (Table). In the propensity-matched groups, the percentage of patients whose convulsions had ceased prior to hospital arrival were 82.0% for the midazolam only group and 94.4% for the ketamine group, a difference of 12.4% (95% CI 3.1% to 21.7%).

No patients went into cardiac arrest during transport in either group. In the unadjusted groups, 7 (1.2%) of 598 patients in the midazolam only group were endotracheally intubated by EMS after medication administration compared with 1 (1.1%) of 90 in the ketamine group. The one patient in the ketamine group who was intubated was the one who received ketamine 400 mg intramuscularly. After propensity matching, the rates of intubation were 1.1% for both groups.

Subgroup Analyses

Of the 688 analyzed patients, 132 (19.1%) were pediatric and 556 (80.8%) were adults. In the pediatric group, 18 were treated with ketamine after midazolam, and convulsions resolved in 14 (77.8%). In contrast, convulsions resolved in 86 (75.4%) of the 114 pediatric patients treated with midazolam alone. The difference between groups was 2.3% (95% CI –18.4% to 23.1%).

Among the 556 adults, 393 (81.2%) of the 484 treated with midazolam alone had resolution of convulsions prior to hospital arrival as compared to 71 (98.6%) of the 72 in the ketamine group, a difference of 17.4% (95% CI 13.0% to 21.8%).

There were 10 patients who received ketamine for active convulsions without receiving preceding midazolam. In all 10 (100%), the convulsions ceased before the patient arrived at the hospital.

The rates of cessation of convulsions prior to hospital arrival by route of ketamine administration were as follows: 58 (96.7%) of 60 IV, 14 (93.3%) of 15 IM, 7 (77.8%) of 9 IN, and 6 (100%) of 6 IO.

LIMITATIONS

First, our data came from a single EMS system and may not be generalizable to other settings. Additionally, as a retrospective study using EMS records, our findings were likely influenced by confounding variables that were incompletely accounted for or not assessed at all. In particular, we did not have access to patients' medical history and anti-epileptic medications, which are important to consider in treating seizures. Indeed, having a history of epilepsy has been found to be associated with an increased chance of cessation of status epilepticus with ketamine.[21] Also, as discussed in the Methods section, the dose of midazolam increased when the ketamine protocol was initiated, which may have contributed to the higher rate of seizure cessation in the ketamine group (although we attempted to account for this with our propensity matching). Lastly, the patients in the ketamine group may have benefited from selection bias in that patients after June 2017 with persistent convulsions should have received ketamine but may not have because they arrived in the hospital before administration. We attempted to account for this by using propensity scores to balance the duration of out-of-hospital care between groups, but this may have been insufficient.

DISCUSSION

In this retrospective cohort study, we found that out-of-hospital patients who received ketamine were more likely to have cessation of convulsive status epilepticus before arrival to the hospital than those who received only midazolam. Except for one small study of pediatric patients with

refractory status epilepticus,[24] prior publications about ketamine for seizure treatment have lacked a comparison group.[13-21,23,28] Moreover, nearly all the previous data regarding the use of ketamine for seizures have related to the use of ketamine for refractory status epilepticus in which patients were already in the ICU, had already received multiple medications for status epilepticus, and received widely variable doses of ketamine.[14-21] Two strengths of our study were that patients only received one medication (midazolam) other than ketamine for seizures, reducing the potential for confounding, and 94.4% of patients in the ketamine group received the protocolized dose of ketamine.

Traditionally, second-line medications for status epilepticus (after benzodiazepines) have included fosphenytoin (or phenytoin), levetiracetam, valproate, and phenobarbital.[6] The Established Status Epilepticus Treatment Trial published in 2020 found that patients with status epilepticus respond similarly to fosphenytoin, levetiracetam, and valproate, but treatment success occurred in only about 50% of patients.[29] Although our primary outcome (the cessation of convulsions) does not equate to successful treatment of status epilepticus, the promising results of this study should prompt a randomized trial to determine if ketamine should replace traditional second-line status epilepticus medications.

In addition to our positive findings, ketamine has several other potential benefits with regard to its use in status epilepticus. Ketamine is quicker and easier to administer than traditional second-line medications, which are often administered by infusion over 10 to 20 minutes.[29,30] Additionally, data from animal studies suggest a neuroprotective effect of ketamine when administered after the onset of status epilepticus, an effect not yet demonstrated in humans but that could be important.[31,32] Finally, ketamine is also already widely used in out-of-hospital settings and emergency departments for other indications, which would likely make an uptick in its use for seizure treatment straightforward.[33-35]

Lastly, our study included pediatric patients, but the number of pediatric patients who received ketamine was too small to draw conclusions.[18] It has been suggested that pediatric and adult patients may have different responses to anti-seizure therapies, which could be the case for ketamine.[6]

In conclusion, in this single system retrospective cohort study of out-of-hospital patients, those who received ketamine after midazolam for convulsive status epilepticus had higher rates of cessation of convulsions than those who received 2 doses of midazolam. The results suggest that ketamine may be a useful agent to use in early status epilepticus, but data from randomized trials are needed to confirm these findings.

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Author contributions: TZ, KAS, PA, CC, and DAF conceived the study. TZ and DAF designed the study. CC, SG, and ES collected the data. TZ, KAS, CC, and DAF supervised the conduct of the study and data collection. CC and SG managed the data, including quality control. TZ provided statistical advice on study design. TZ, KAS, CC, and SG analyzed the data. TZ, CC, and DAF drafted the manuscript, and all authors contributed substantially to its revision. TZ takes responsibility for the paper as a whole.

Data sharing statement: The entire deidentified data set and data dictionary for this investigation are available on request, from the date of article publication by contacting Tony Zitek, MD, at zitek10@gmail.com.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (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.

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