Status epilepticus alert reduces time to administration of second-line antiseizure medications

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Abstract

Background

Status epilepticus (SE) is a neurologic emergency with high morbidity and mortality. Delays in SE treatment are common in clinical practice and can be associated with poorer outcomes. Our goal was to determine whether the implementation of an SE alert protocol improves time to administration of a second-line antiseizure medication (ASM) in hospitalized adults.

Methods

We developed and implemented an inpatient SE alert system. A quasiexperimental cohort study was performed. We analyzed all patients aged 18–85 years who were managed at the University of Kentucky Medical Center using the SE alert protocol between March 2015 and June 2017 ($n = 19$). Controls were the first 20 consecutive patients treated for SE over the same time period, but who were managed with usual care (i.e., without SE alert protocol).

Results

Time to administration of a second-line ASM was shorter with the use of the SE alert system (22.21 ± 3.44 minutes) compared to usual care (58.30 ± 6.72 minutes; $p < 0.0001$).

Conclusion

Implementation of an SE alert system led to a marked improvement in time to administration of a second-line ASM.

Classification of evidence

This study provides Class III evidence that for adult inpatients treated for SE, implementation of an SE alert protocol reduces time to administration of second-line ASM.

Neurology resident	<ul style="list-style-type: none"> • Perform clinical evaluation • Enter orders for ASM • Determine need for EEG and neuroimaging studies • Communicate with other teams • Oversee patient management
Pharmacy resident	<ul style="list-style-type: none"> • Verify medication orders • Bedside admixture of ASM • Facilitation of medication delivery from central pharmacy • Therapeutic drug monitoring as appropriate
Rapid response team	<ul style="list-style-type: none"> • Evaluate need for airway management • Assist with intravenous line placement and drug administration
House officer	<ul style="list-style-type: none"> • Expedite bed assignment in the event that escalations in level of care are required

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→ Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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Status epilepticus (SE) is a neurologic emergency.¹ Prolonged seizure duration is consistently and independently associated with poorer outcomes, including increased refractoriness to treatment, higher mortality, greater disability, and increased risk of subsequent epilepsy.^{2–6} Treatment, therefore, should begin as quickly as possible. The administration of a first-line

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antiseizure medication (ASM; i.e., a benzodiazepine) is typically followed by a second-line agent such as phenytoin/fosphenytoin, sodium valproate, levetiracetam, or phenobarbital.⁴

A multicenter study found that late administration (>10 minutes) of first-line benzodiazepines in SE was independently associated with delayed administration of second- and third-line ASMs and with increased in-hospital mortality and morbidity (i.e., longer duration of convulsive seizures, increased need for continuous infusions, and more frequent hypotension).³ In retrospective studies, late administration of a second-line ASM was associated with delayed return of consciousness and with poorer functional outcomes.^{7,8} More rapid seizure control has the potential of decreasing these adverse outcomes.

Despite the importance of timely management of SE, treatment delays occur commonly in clinical practice. In part because second-line ASMs need to be obtained from a central pharmacy, a previous quality improvement project in our institution found that the mean time to administration of a second-line ASM was 71 ± 11.8 minutes.⁹ We found that these delays failed to improve after an educational program for residents, pharmacists, and nursing staff, or after the development of an electronic SE order set.¹⁰

Due to several barriers,¹¹ substantial delays in SE treatment have also been reported from other institutions in the United States and Europe.^{3,12-14} In addition to the use of protocol-driven therapies, implementation of SE intervention teams is proposed as a strategy that may improve the timeliness of SE treatment.¹¹

Initially developed as a quality improvement project, we hypothesized that implementation of an SE alert protocol could reduce delays in administration of a second-line ASM in hospitalized adults compared to usual care.

Methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the University of Kentucky Medical Center (UKMC) institutional review board (protocol #17-0555-P3K). The study met criteria for a Health Insurance Portability and Accountability Act waiver of authorization.

Study design

We developed an inpatient SE alert system, which was modeled after the stroke alert protocol used at UKMC. Whenever a patient admitted to the hospital or to the emergency department is suspected to have either convulsive or electrographic SE,¹ health care providers (including nurses, advanced practice providers, or physicians) can

activate an SE alert by calling a single operator (Central Monitoring Station) who then simultaneously sends a text page to the general neurology and pharmacy residents, a rapid response team (RRT, also known as medical emergency team), and the responsible primary house officer. The message reads “Status epilepticus alert” and gives the patient’s location. Neurology residents, pharmacy residents, and the RRT respond immediately to the patient’s location. Responders then work collaboratively to coordinate the patient’s emergent evaluation and treatment. The protocol workflow and the specific roles of each responder are described in the figure. The inpatient SE alert protocol became available at UKMC in March 2015. It is active 24 hours a day, 7 days per week.

In the present quasi-experimental cohort study, we compared the time to administration of a second-line ASM for hospitalized patients who were managed using the SE alert protocol vs a group of inpatients who were treated without the protocol (usual care). Our primary research question was “Is use of the SE alert protocol associated with shorter time to administration of a second-line ASM?” (Classification of Evidence Class III). We followed the Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0).¹⁵

Patients

We included all patients aged 18–85 years who were managed at UKMC using the SE alert protocol between March 2015 and June 2017 ($n = 19$). These were identified using Central Monitoring Station records. As controls, we identified the first 20 consecutive patients treated for SE over the same time period who were managed using existing institutional practices (i.e., without SE alert) by reviewing 350 cases recorded in neurology consult logs. Because the SE alert protocol was used variably in the initial period of adoption, this allowed us to identify patients managed both with and without the SE alert system over the same time period. As this was an observational cohort study, a sample size calculation was not performed.

Data collection

Two of 3 neurology residents (M.F.V., J.L.C., K.S.D.) retrospectively abstracted data from each identified patient’s electronic medical record using a standardized form. Any discrepancies were resolved by the third abstractor. Abstractors reviewed data for patients in the SE alert and the usual care groups; they were not masked to SE alert status. Data related to medication ordering/administration also were collected by at least 2 abstractors and were then verified by a pharmacist (A.M.C.).

Outcomes

The primary outcome was time to administration of second-line ASM (time between electronic order entry and ASM administration). The effect of the following variables on time to administration of second-line ASM was assessed: (1)

responding neurology resident's level of training (postgraduate year 2, 3, or 4); (2) primary service at the time when a concern for SE was noted (emergency medicine, neurology, medical, or surgical); (3) patient location at the time when a concern for SE was noted (out of hospital, emergency department, hospital floor, intensive care unit [ICU]). Secondary outcomes included the need for intubation, administration of IV anesthetics, number of days in the ICU, number of days on mechanical ventilation, and all-cause mortality during the index hospitalization.

Statistical analysis

Statisticians (C.K., Y.X.) not involved with patient care analyzed de-identified patient data. Two-sample comparisons of continuous variables (expressed as mean ± SEM) were analyzed using *t* tests. For categorical variables, either χ^2 or Fisher exact tests were used depending on expected cell numbers in the contingency tables. The relationship between time to administration of second-line ASM and (1) residents' postgraduate year, (2) primary service at the time when a concern for SE was noted, and (3) patient location at the time when a concern for SE was noted was analyzed using one-way between-subject analysis of variance. For the primary study hypothesis, a *p* value <0.05 (one-sided) was considered significant. All other *p* values were 2-sided. Data analyses were conducted using SAS 9.4 (Cary, NC). There were no missing data.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Our SE alert was modeled after our existing stroke alert protocol.

Results

Demographic and epilepsy-related characteristics were similar between the SE alert (*n* = 19) and the usual care (*n* = 20) groups (table 1). Time to administration of the second-line ASM was shorter for patients managed using the SE alert (22.21 ± 3.44 minutes) compared to those who were managed without activation of the SE alert system (58.30 ± 6.72 minutes; *p* < 0.0001). There was no difference in time to administration of the second-line ASM between the SE alert and the control groups based on (1) neurology residents' level of training ($F_{2, 16}$ = 0.8870, *p* = 0.4312 vs $F_{2, 17}$ = 0.9483, *p* = 0.4070); (2) primary service at the time when a concern for SE was noted ($F_{3, 15}$ = 0.25, *p* = 0.8622 vs $F_{3, 16}$ = 0.51, *p* = 0.6806); or (3) patient location at the time when a concern for SE was noted ($F_{3, 15}$ = 0.95, *p* = 0.4425 vs $F_{3, 16}$ = 0.26, *p* = 0.8517).

The proportion of patients who were ultimately diagnosed with nonepileptic psychogenic SE was similar between the 2 groups. There were no differences between groups in the need for intubation, administration of IV anesthetics, number of days in ICU, number of days on mechanical ventilation, or all-cause mortality during the index hospitalization (table 2).

Figure Status epilepticus alert protocol

(A) Protocol description. (B) Responders' roles. APP = advanced practice providers; ASM = anti-seizure medication; CMS = central monitoring station; SE = status epilepticus.

In our study population, the choice of the second-line ASM was guided by patient comorbidities and concomitant use of other ASMs.

Discussion

Our previous study conducted at UKMC in 2013, using the same definitions as in the current study, found that mean time to administration of a second-line ASM for patients in SE was 71 ± 11.8 minutes,⁹ which did not differ from the delay found in the current study for patients treated without

activation of the SE alert system ($p = 0.3866$). The SE alert protocol reduced time to administration of the second-line ASM across all groups analyzed. Therefore, the improvement in time to administration of a second-line ASM that was found in the SE alert group was likely due to the use of the SE alert protocol rather than secular changes in the rate of administration of second-line ASMs over time.

Because poor outcomes are associated with the duration of seizures,^{3,5,6} time to administration of an adequately dosed ASM may have an important effect on morbidity and mortality.^{3,7} In the present study, we hypothesized that the introduction of an SE alert system would reduce treatment delays compared to standard prior practice. Our SE alert was modeled after our existing stroke alert protocol. Given that the vast majority of academic institutions and many community hospitals in the United States and other developed

Table 1 Patient demographics and clinical characteristics

	Patients managed using SE alert, n = 19	Patients managed without SE alert, ^a n = 20	p Value
Age, y, mean (SEM)	52.11 (3.91)	51.85 (4.07)	0.9664
Women	14 (73.7)	13 (65.0)	0.5570
Caucasian ethnicity	16 (84.2)	20 (100)	0.1060
Previous diagnosis of epilepsy	9 (47.4)	11 (55.0)	0.6337
Previous history of SE	4 (21.1)	6 (30.0)	0.7164
Patients taking any antiseizure medications at the time of admission	8 (42.1)	11 (55.0)	0.4207
Patient location at the time when concern for SE was noted			0.4963
Out of hospital	9 (47.4)	9 (45.0)	
Emergency department	1 (5.3)	3 (15.0)	
Hospital floor	4 (21.0)	6 (30.0)	
Intensive care unit	5 (26.3)	2 (10.0)	
Primary service at the time when concern for SE was noted			0.3406
Emergency medicine	7 (36.8)	11 (55.0)	
Neurology	5 (26.3)	1 (5.0)	
Medical (other than neurology)	5 (26.3)	6 (30.0)	
Surgical	2 (10.6)	2 (10.0)	
Training level of neurology resident who managed each SE case			0.1490
PGY 2	7 (36.8)	10 (50.0)	
PGY 3	5 (26.3)	8 (40.0)	
PGY 4	7 (36.8)	2 (10.0)	

Abbreviations: PGY = postgraduate year; SE = status epilepticus; SEM = standard error of the mean.

Data are n (%) unless otherwise indicated.

^a Patients were managed following usual institutional practices.

Table 2 Outcomes for patients treated using the status epilepticus (SE) alert protocol vs those managed following usual institutional practices

	Patients managed using SE alert, n = 19	Patients managed without SE alert, ^a n = 20	p Value
Time to administration of second-line ASM, mean (SEM)	22.21 (3.44)	58.30 (6.72)	<0.0001
Patients ultimately diagnosed with NPSE	3 (15.8)	3 (15.0)	1.0000
Need for intubation	11 (57.9)	13 (65.0)	0.6485
Need for IV anesthetics	7 (36.8)	12 (60.0)	0.1481
Number of days in ICU, mean (SEM)	5.50 (1.64)	12.40 (3.10)	0.0649
Number of days on mechanical ventilation, mean (SEM)	5.64 (2.08)	9.79 (2.05)	0.1749
All-cause mortality	4 (21.1)	5 (25.0)	1.0000
Second-line ASM used			
Levetiracetam	11 (57.9)	16 (80.0)	
Fosphenytoin/phenytoin	5 (26.3)	2 (10.0)	
Lacosamide	3 (15.8)	0 (0.0)	
Sodium valproate	0 (0.0)	2 (10.0)	

Abbreviations: ASM = antiseizure medications; ICU = intensive care unit; NPSE = nonepileptic psychogenic status epilepticus; SE = status epilepticus; SEM = standard error of the mean.

Data are n (%) unless otherwise indicated.

^a Patients were managed following usual institutional practices.

countries currently have dedicated protocols for management of patients with suspected acute stroke, it may be feasible to adapt such protocols locally for the management of suspected SE. In our study, time to administration of a second-line ASM did not differ significantly based on neurology residents' level of training in either the intervention or the control groups, suggesting that very extensive physician training may not be essential for successful implementation of an SE alert protocol.

We modeled our SE alert protocol after our institution's stroke alert protocol, which also involves mobilization of a team including neurology and pharmacy residents and an RRT. Because delays in treatment of SE are associated with poor outcomes, early treatment is imperative. In comparison to the lack of effect of other approaches we had used to optimize treatment of SE patients (including an educational program for residents, pharmacists, and nursing staff, and the development of an electronic SE order set), we found that the SE alert protocol led to earlier ASM administration. In this context, mobilization of resources is justified.

Although the SE alert system reduced time to administration of a second-line ASM, this did not affect our secondary outcomes. The study, however, was not powered to detect these effects, and the lack of a difference might be due to the relatively small sample size. Studies with larger numbers of patients are needed to determine the effect of an SE alert

protocol on patient outcomes. Of note, however, the SE alert protocol did not lead to treating higher numbers of patients with nonepileptic psychogenic SE.

In our study population, the choice of the second-line ASM was guided by patient comorbidities and concomitant use of other ASMs. For example, certain drugs are best avoided in patients with liver or kidney disease. Nonetheless, it is difficult to determine clinical reasoning regarding drug choice based on medical record review. The focus of our initiative was to reduce the time of administration of the second-line ASM, regardless of the drug chosen.

The present study has limitations. The study was observational and we did not randomize patients to the SE alert protocol or to usual care. Although we found no systemic differences between patients who were vs were not treated under the protocol, there may have been unmeasured confounding. Based on our retrospective chart review, it was not possible to extract accurate information regarding seizure cessation times. The use of prospective data ascertainment or electronic methods for automated extraction of EEG data may be considered in future studies, as these methods may provide accurate and searchable information to address this question. Benzodiazepines, the first line treatment for SE, are readily available in our hospital's emergency department and in inpatient units. In urgent situations, they can be administered by nursing staff following a verbal order by the

treating physician and be removed from the automated dispensing cabinet via override. In such cases, the order may be entered in our electronic medical record system some time later. As we could not reliably determine the time the first line drug was ordered or administered, we could not assess the time to its administration or its association with SE duration. Similarly, because the time of SE onset could not be reliably determined, we assessed the delay between when the second-line ASM was ordered to when it was administered.

Although abstractors were not masked to group, this would not affect this study's primary outcome. The ordering and administration times of ASM (the primary outcome of our study) are stored in the electronic medical record and cannot be modified. At least 2 abstractors independently retrieved this information. The data were then verified by a pharmacist to ensure accurate documentation. We also recorded hard outcomes (such as all-cause mortality, use of ventilatory support, use of IV anesthetics, and duration of ICU stay). The risk of bias in the data extraction should be negligible.

As this was not one of our study outcomes, we did not assess the effect of second-line ASM on SE resolution. Nevertheless, we did evaluate the need for IV anesthetics in SE patients, which can be closely related.

Classification of evidence

This study provides Class III evidence that for adult inpatients treated for SE, implementation of an SE alert protocol reduces time to administration of second-line ASM.

Author contributions

M.F. Villamar: study concept and design, acquisition and interpretation of data, manuscript writing. A.M. Cook: study concept and design, acquisition and interpretation of data, critical revision of manuscript for intellectual content. C. Ke: statistical analysis and interpretation, critical revision of manuscript for intellectual content. Y. Xu: statistical analysis and interpretation, critical revision of manuscript for intellectual content. J.L. Clay: data collection and interpretation, critical revision of manuscript for intellectual content. K.S. Dolbec: data collection and interpretation, critical revision of manuscript for intellectual content. R. Ward-Mitchell: study concept and design, critical revision of manuscript for intellectual content. L.B. Goldstein: statistical interpretation, critical revision of manuscript for intellectual content. M. Bensalem-Owen: study concept and design, interpretation of data, critical revision of manuscript for intellectual content.

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References

1. 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.
2. Claassen J, Lokin JK, Fitzsimmons BF, Mendelsohn FA, Mayer SA. Predictors of functional disability and mortality after status epilepticus. *Neurology* 2002;58:139–142.
3. Gainza-Lein M, Sanchez Fernandez I, Jackson M, et al. Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. *JAMA Neurol* 2018;75:410–418.
4. 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.
5. Madzar D, Geyer A, Knappe RU, et al. Association of seizure duration and outcome in refractory status epilepticus. *J Neurol* 2016;263:485–491.
6. Santamarina E, Gonzalez M, Toledo M, et al. Prognosis of status epilepticus (SE): relationship between SE duration and subsequent development of epilepsy. *Epilepsy Behav* 2015;49:138–140.
7. Kamppi L, Mustonen H, Kotisaari K, Soinila S. The essence of the first 2.5 h in the treatment of generalized convulsive status epilepticus. *Seizure* 2018;55:9–16.
8. Kamppi L, Ritvanen J, Mustonen H, Soinila S. Delays and factors related to cessation of generalized convulsive status epilepticus. *Epilepsy Res Treat* 2015;2015:591279.
9. Boske A, Cook A, Bensalem-Owen M. Assessment of time of administration from time of order of anti-epileptic drugs in status epilepticus. *Neurology* 2013;80:S48–S007.
10. Callow M, Cook A, Mahmoud A, Boske A, Ward-Mitchell R, Bensalem-Owen M. Assessment of the timeliness of administration of second line antiepileptic drugs for status epilepticus after the implementation of a status epilepticus bundle order set: a single institution experience. *Neurology* 2015;84:P7.322.
11. Stredny CM, Abend NS, Loddenkemper T. Towards acute pediatric status epilepticus intervention teams: do we need “seizure codes”? *Seizure* 2018;58:133–140.
12. Sanchez Fernandez I, Abend NS, Agadi S, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. *Neurology* 2015;84:2304–2311.
13. Kamppi L, Mustonen H, Soinila S. Analysis of the delay components in the treatment of status epilepticus. *Neurocrit Care* 2013;19:10–18.
14. Pellock JM, Marmarou A, DeLorenzo R. Time to treatment in prolonged seizure episodes. *Epilepsy Behav* 2004;5:192–196.
15. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf* 2016;25:986–992.