ORIGINAL RESEARCH

Electroencephalographic Seizures in Emergency Department Patients After Treatment for Convulsive Status Epilepticus

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Purpose: It is unknown how often and how early EEG is obtained in patients presenting with status epilepticus. The Established Status Epilepticus Treatment Trial enrolled patients with benzodiazepine-refractory seizures and randomized participants to fosphenytoin, levetiracetam, or valproate. The use of early EEG, including frequency of electrographic seizures, was determined in Established Status Epilepticus Treatment Trial participants.

Methods: Secondary analysis of 475 enrollments at 58 hospitals to determine the frequency of EEG performed within 24 hours of presentation. The EEG type, the prevalence of electrographic seizures, and characteristics associated with obtaining early EEG were recorded. Chi-square and Wilcoxon rank-sum tests were calculated as appropriate for univariate and bivariate comparisons. Odds ratios are reported with 95% confidence intervals.

Results: A total of 278 of 475 patients (58%) in the Established Status Epilepticus Treatment Trial cohort underwent EEG within 24 hours (median time to EEG: 5 hours [interquartile range: 3–10]). Electrographic seizure prevalence was 14% (95% confidence interval, 10%–19%; 39/278) in the entire cohort and 13% (95% confidence interval, 7%–21%) in the subgroup of patients meeting the primary outcome of the Established Status Epilepticus Treatment Trial (clinical treatment success within 60 minutes of randomization). Among subjects diagnosed with electrographic seizures (39), 15 (38%; 95% confidence interval, 25%–54%) had no clinical correlate on the video EEG recording.

Conclusions: Electrographic seizures may occur in patients who stop seizing clinically after treatment of convulsive status epilepticus. Clinical correlates might not be present during electrographic seizures. These findings support early initiation of EEG recordings in patients suffering from convulsive status epilepticus, including those with clinical evidence of treatment success.

Key Words: Convulsive status epilepticus, Grand Mal status epilepticus, Electrographic status epilepticus, EEG, Nonconvulsive seizures.

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Status epilepticus is a medical emergency requiring emergent therapy that affects individuals of all ages. Initial treatment with benzodiazepines is effective in 55% to 65% of patients, and failure to respond is termed established status epilepticus.[1–3] Delay in terminating status epilepticus leads to a self-reinforcing cycle of disinhibition and increased excitation that makes treatment more difficult with time. Complicating the ability to definitively terminate status epilepticus is that seizures may continue in the absence of clinically apparent seizure, which confers increased risk of mortality and morbidity.[4–10]

The Established Status Epilepticus Treatment Trial (ESETT) was conducted to compare the efficacy and safety of three second-line anticonvulsant agents (fosphenytoin, levetiracetam, and valproic acid) among patients with established status epilepticus. The details of the methodology and findings of this trial are published elsewhere.[11] Although the primary endpoint of the ESETT was determined clinically (clinical cessation of status epilepticus, determined by the absence of clinically apparent seizures and improving responsiveness, at 60 minutes), clinical care often dictated an EEG to assess the EEG evidence of treatment success or failure.[11] In this secondary analysis, we sought to quantify the prevalence of electrographic seizures in patients enrolled in ESETT. The objective of this study was to test the hypothesis that patients with benzodiazepine-resistant status epilepticus have a residual occurrence of electrographic seizures in the subsequent 24 hours after treatment with a second-line agent (fosphenytoin, levetiracetam, or valproic acid) independent of clinical success according to the ESETT primary outcome.

MATERIALS AND METHODS

Study Design and Setting

Established Status Epilepticus Treatment Trial sites were emergency departments (EDs) participating in the Neurological Emergency Treatment Trials network and the Pediatric Emergency Care Applied Research Network. The trial was conducted

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under Exception from Informed Consent. However, written informed consent to continue participation was sought from the subjects or their legally authorized representative as early after enrollment as possible. The U.S. Food and Drug Administration and the institutional review boards of the enrolling institutions approved the trial before the start of enrollment.

Participants

Established Status Epilepticus Treatment Trial enrolled adults and children 2 years of age or older, who had been treated for generalized convulsive seizures lasting more than 5 minutes with adequate doses of benzodiazepines and who continued to have persistent or recurrent convulsions in the ED for 5 to 30 minutes after the last dose of benzodiazepine. The inclusion criteria were intended to describe the population of patients for whom progression to second-line anticonvulsants is indicated. Patients were randomized to one of the three treatment arms, and the treatment success was determined clinically (cessation of convulsions and improvement in mental status) 60 minutes after randomization.[11]

This secondary analysis was performed on the subgroup of ESETT patients with an EEG recording within 24 hours of enrollment.

Interventions

The duration and type of EEG was at the discretion of physicians caring for the patient and followed local institutions' protocols and guidelines. If a seizure was detected on EEG, the epileptologists and the enrolling physicians were asked to document the presence or absence of a clinical correlate to EEG findings. EEG recordings were interpreted by local site epileptologists or clinical neurophysiologists who rated the binary presence or absence of electrographic seizure.

Outcomes

The primary outcome of the study was the overall prevalence of electrographic seizures in the 24-hour period after enrollment. The secondary outcomes were (1) the rate of electrographic seizure among those with resolution of clinical convulsions and improving mental status, meeting criteria for the primary ESETT outcome; (2) the proportion of electrographic seizure with and without a clinical correlate; and (3) the rate of electrographic seizures among intubated patients.

Analysis

Independent variables included age, gender, history of epilepsy, endotracheal intubation, time from randomization to EEG recording, clinical cessation of seizure within 60 minutes, and the anticonvulsant drug allocation.

Categorical variables are reported as percentages with 95% confidence intervals (CIs) and interval data as medians and interquartile ranges.

Bivariate comparisons were performed by χ^2 test and Wilcoxon rank-sum test as appropriate. Odds ratios with 95% CI are reported to demonstrate the association of variables of interest and possibility of undergoing an EEG or being diagnosed with electrographic seizures.

The prevalence of electrographic seizures in the study subjects was calculated by the number of EEGs showing electrographic seizures divided by the total number of subjects. The prevalence of clinically unrecognizable seizure was calculated by dividing the number of subjects with evidence of electrographic seizure by the number of subjects who were not convulsing clinically at the time of EEG recording. We measured the concordance of clinical with EEG findings by reporting the proportion of patients with electrographic seizures without clinical evidence of seizure (no motor phenomena in limbs). The prevalence of seizure in intubated patients was calculated by dividing the number of intubated patients with electrographic seizures on EEG by the total number of intubated patients who underwent EEG.

RESULTS

The characteristics of the study cohort are presented in Table 1. Of the 478 subjects, 278 (58%) had an EEG obtained within the first 24 hours after the estimated seizure onset. The median time to EEG recording was approximately 5 hours (interquartile range: 3–10 hours) from study enrollment. Type and duration of EEG recordings are shown in Table 2. Patients who were older (odds ratio for adults vs. children: 1.75; 95% CI, 1.21–2.53) and intubated (odds ratio for intubation: 3.57; 95% CI, 2.10–6.07) were more likely to undergo EEG recording. Those who were deemed treatment success clinically by ESETT criteria were less likely to undergo EEG recording (odds ratio: 0.39; 95% CI, 0.27–0.57). No difference was noted between the groups for gender, history of epilepsy, or anticonvulsant group assignment.

Electrographic seizures occurred in 14% of study subjects in whom an EEG was obtained within 24 hours of initial seizure onset (95% CI, 10%–19%; 39/278). This represented 8% of the total ESETT population when including those who did not undergo subsequent EEG. The majority (34/39; 87%) of seizures were detected on continuous EEG. The rates of endotracheal intubation, clinical treatment success, and anticonvulsant group assignments were similar between patients with and without seizure (Table 3).

The prevalence of seizure in the subgroups of patients who met the primary outcome of the ESETT (treatment success clinically within 60 minutes of randomization) was 13% (95% CI, 7%–21%; 13/102), and in the subgroup of intubated patients was 15% (95% CI, 7%–30%; 6/39).

Fifteen of the 39 subjects with documented electrographic seizures (38%; 95% CI, 25%–54%) had no clinical finding indicative of seizure at the time of EEG recording. In the small subgroup of seven subjects in whom an EEG was obtained within 60 minutes of enrollment, one (14%) had evidence of electrographic seizure. This subject met the criteria for the primary outcome of ESETT (clinical treatment success) and did not have a clinical correlate of seizure during the EEG recording.

DISCUSSION

In this secondary analysis of a large clinical trial of status epilepticus, we found that a clinically important percentage of

TABLE 1. Baseline and Clinical Characteristics by Subjects With and Without an EEG Obtained Within 24 Hours

Characteristics	**EEG Not Obtained, $N = 200$**	**EEG Obtained, $N = 278$**	**Mean Difference (95% CI)**
Age, median (IQR)	12.5 (4–39)	27.5 (6–57)	9.8 (5.3–14.3)
Characteristics	**EEG Not Obtained, $N = 200$**	**EEG Obtained, $N = 278$**	**OR (95% CI)**
Children (<18 years), *n* (%)	112 (56.0)	117 (42)	0.57 (0.40–0.82)
Adults, *n* (%)	88 (44)	161 (58)	1.75 (1.21–2.53)
Male gender, *n* (%)	115 (58)	156 (56)	0.95 (0.65–1.36)
History of epilepsy, *n* (%)	135 (68)	184 (66)	0.94 (0.64–1.39)
Endotracheal intubation within 60 minutes, *n* (%)	20 (10)	79 (28)	3.57 (2.10–6.07)
Clinical treatment success,* *n* (%)	119 (60%)	102 (37)	0.39 (0.27–0.57)
Second-line agent received per randomization,† *n* (%)			
Fosphenytoin	64 (32)	85 (31)	0.94 (0.63–1.39)
Levetiracetam	75 (38)	105 (38)	1.01 (0.69–1.48)
Valproate	61 (31)	88 (32)	1.06 (0.71–1.56)

*Defined as clinical cessation of status epilepticus, determined by the absence of clinically apparent seizures and improving responsiveness, at 60 minutes without additional antiepileptic drugs.

†The ORs for each treatment group considers the other two treatment groups, pooled, as the reference group.

CI, confidence interval; IQR, interquartile range; OR, odds ratio.

subjects had an electrographic seizure in the first 24 hours after seizure onset. Furthermore, in these subjects, a large proportion of seizures (38%) was not clinically evident and would not have been detected without EEG monitoring.

These data indicate that persistent or recurrent seizures are common in the first 24 hour after status epilepticus even in patients treated with adequate doses of first- and second-line agents, and even among patients with apparent treatment success. Our findings do not distinguish between those with unremitting electrographic seizures indicative of continued status and those with transient recurring electrographic seizures. The overall pattern remains concerning, however, as continued electrographic seizures are associated with worse outcomes.[8,12] It may be especially concerning that an EEG was not obtained in nearly half of the subjects. Since 38% of electrographic seizures did correlate with clinical findings, the rate of missed events in those who were not monitored may also be clinically important. Among subjects in whom EEGs were obtained, persistent or recurrent seizures were similarly likely (about 14%) whether the subject met the trial's primary outcome for initial clinical treatment success.

It is common practice to order EEG in patients who require endotracheal intubation because these patients may commonly be heavily sedated or paralyzed for airway management. Our study revealed that 15% (6/39) of patients who had electrographic seizures on EEG were those who were intubated, further confirming that EEG is necessary in these intubated patients after status epilepticus. However, the occurrence of electrographic seizures in intubated status epilepticus patients might be deferred beyond the 24-hour window assessed here, as some third-line treatment agents such as propofol or midazolam infusions might briefly mask electrographic seizures during the period of EEG recording.

Another important finding of this study is the relatively low concordance between EEG and clinical findings at the time of electrographic seizures detection on EEG. Approximately two thirds of patients who had evidence of EEG seizures did not show clinical manifestations of seizure at the time of EEG recording. This finding is in line with some other studies indicating the high prevalence of electrographic seizures after convulsive status epilepticus.[4–6,8–10] Delorenzo et al.[4] performed continuous EEG monitoring on 164 subjects after cessation of convulsive status epilepticus. This prospective study found that 48% of the patients still had evidence of seizure on EEG despite a lack of clinical findings consistent with seizure. More than a third of the detected seizures were status epilepticus. Abend et al.[5] reported the results of EEG monitoring in a pediatric intensive care unit. In this study, 36% of patients who had evidence of seizure on EEG had no evidence of obvious seizure clinically. The Consensus Statement on Continuous EEG in Critically Ill Adults and Children published by the American Clinical Neurophysiology Society recommends continuous EEG monitoring for all patients after convulsive status epliepticus.[13]

TABLE 2. EEG Recording Characteristics in the Study Cohort

EEG Characteristic	
Subjects in whom an EEG was obtained, *n*/*N* (%)	278/478 (58)
Time from study enrollment to EEG initiation	
Initiation within 60 minutes, *n*/*N* (%)	7/278 (2.5)
Minutes to initiation, median (IQR)	322 (182–619)
Type and duration of EEG	
Routine EEG, total, *n*/*N* (%)	90/278 (32)
Duration <1 hour, *n*/*N* (%)	65/90 (72)
Duration 1–2 hours, *n*/*N* (%)	8/90 (9)
Duration >2 hours, *n*/*N* (%)	15/90 (17)
Duration unknown, *n*/*N* (%)	2/90 (2)
Prolonged/continuous EEG, total, *n*/*N* (%)	188/278 (68)
Duration <24 hours, *n*/*N* (%)	110/188 (59)
Duration >24 hours, *n*/*N* (%)	76/188 (40)
Duration unknown, *n*/*N* (%)	2/188 (1)

IQR, interquartile range.

TABLE 3. Characteristics of Subjects With or Without Seizure on EEG*

Subject Characteristics	No Seizure, $N = 238$	Seizure, $N = 39$	Mean Difference (95% CI)
Age, median (IQR)	29 (5–57)	16 (6–55)	2.2 (−6.9 to 11.4)
Subject Characteristics	**No Seizure, $N = 238$**	**Seizure, $N = 39$**	**OR (95% CI)**
Children (<18 years), *n* (%)	143 (60)	18 (46)	0.57 (0.29–1.13)
Adults, *n* (%)	95 (40)	21 (54)	1.75 (0.89–3.47)
Male gender, *n* (%)	132 (55)	24 (62)	1.28 (0.64–2.57)
History of epilepsy, *n* (%)	152 (64)	31 (80)	2.19 (0.96–4.98)
Endotracheal intubation within 60 minutes, *n* (%)	72 (30)	6 (15)	0.42 (0.17–1.04)
Clinical treatment success,† *n* (%)	89 (37)	13 (33)	0.84 (0.41–1.71)
Second-line agent received per randomization,‡ *n* (%)			
Fosphenytoin group	73 (31)	11 (28)	0.88 (0.42–1.90)
Levetiracetam group	92 (39)	13 (33)	0.79 (0.39–1.62)
Valproate group	73 (31)	15 (39)	1.4 (0.70–2.89)

*One subject, with EEG recorded, withdrew consent before interpretation is excluded from this table.
†Defined as clinical cessation of status epilepticus, determined by the absence of clinically apparent seizures and improving responsiveness, at 60 minutes without additional antiepileptic drugs.
‡The ORs for each treatment group considers the other two treatment groups, pooled, as the reference group.
CI, confidence interval; IQR, interquartile range; OR, odds ratio.

The unique nature of the ESETT cohort provides evidence to justify EEG early in the ED phase of care, separate from prior evidence supporting its use during critical care. The median time to EEG initiation in our study was approximately 5 hours. This indicates that most of the patients with evidence of electrographic seizures on EEG had their seizures early after presentation to the ED and most likely when they were still in the ED. Most studies assessing the risk of clinically unrecognized seizures after convulsive status epilepticus were conducted in the intensive care units. In fact, the study by Kaplan[14] revealed that more than 50% of cases of clinically unrecognized status epilepticus are diagnosed more than 24 hours after presentation. The need for early EEG in the ED is also supported by the two trials targeting ED patients with undifferentiated altered mental status including those with prolonged postictal state. These trials revealed a prevalence of 5% for clinically unrecognized seizures in the study cohort.[15,16] These findings justify the early initiation of EEG monitoring in the ED. As the treatment of status epilepticus is time sensitive, early identification and treatment benefit the subjects.[17–19]

Our study has clear limitations. First, only 58% of all patients enrolled in the ESETT underwent an EEG recording, resulting in some referral bias when determining the prevalence of electrographic seizures. The decision to order the EEG was at the discretion of site investigators; patients undergoing EEG may have shown unmeasured clinical characteristics that prompted EEG, such as late deterioration, initial but incomplete recovery, or seizure precipitant. However, there is no current standard for determining the degree and timing of clinical improvement that affords a clinical decision rule to triage patients to early EEG, and these data clarify that the proportion of patients may be substantial, even early after clinically documented treatment success. Additionally, the prevalence of electrographic seizures in our cohort was consistent with other studies. A second limitation is the potential for electrographic seizures before initiation of EEG recording, such that we cannot determine if electrographic seizures identified on EEG were present at the time of determining ESETT primary endpoint (60 minutes from randomization). However, the short timing to EEG initiation (median 5 hours) supports that these electrographic seizures may have started close to the determination of the clinical trial endpoint, regardless of whether they represent treatment failure at 60 minutes or electrographic seizure recurrence after initially successful therapy. A third limitation is that EEGs were interpreted locally at each site. Therefore, we could not review the video recording to verify the clinical finings at the time of seizure. Additionally, since the EEGs were not interpreted centrally, we were not able to measure interrater reliability; however, this has been reported as relatively high for the binary determination of seizure in the hospital setting.[20,21] Fourth limitation is that the use of paralytic agents in some of the study subjects might have masked the clinical manifestation of seizure and affected the assessment of clinical correlates at the time of electrographic seizures. Finally, the CIs for the reported point estimates in small subgroups would benefit from be replication in larger cohorts.

CONCLUSION

Electrographic seizures may occur in patients who stop seizing clinically after treatment of convulsive status epilepticus. Clinical correlates might not be present during electrographic seizures. These findings support early initiation of EEG recordings in patients suffering from convulsive status epilepticus, including those with clinical evidence of treatment success.

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