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What You Don't Look for, You Won't Find: Value of EEG After Clinical Resolution of Convulsive Status Epilepticus

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

Zehtabchi S, Silbergleit R, Chamberlain JM, et al. *J Clin Neurophysiol*. 2020. Publish Ahead of Print. doi:10.1097/WNP.0000000000000800

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.

When patients presenting with convulsive seizures or convulsive status epilepticus (CSE) do not promptly improve after control of the motor activity, ongoing nonconvulsive seizures (NCS, also called electrographic seizures) or nonconvulsive status epilepticus (NCSE, also called electrographic SE) is a concern. A 1998 study from the Virginia Commonwealth University Status Epilepticus program demonstrated that after control of CSE, 14% of patients showed persistent NCSE with continuous electroencephalographic monitoring (cEEG).[1] The VA Cooperative CSE study showed that 11% of patients in whom overt SE was successfully treated had recurrence of NCSE.[2]

The recently reported Established Status Epilepticus Treatment Trial (ESETT) comparing levetiracetam (LEV), fosphenytoin (fPHT), and valproate (VPA) reported similar effectiveness for all 3 antiseizure medications (ASM); CSE was controlled in 47% of patients receiving LEV, 45% receiving fPHT, and 46% receiving VPA.[3] Patients were enrolled in this trial if they continued to have CSE after initial treatment with benzodiazepines, and the primary endpoint of treatment success was cessation of convulsions and improvement in level of consciousness. Use of cEEG was left to the discretion of the treating providers and was not used in primary endpoint determination.

In a secondary analysis of the ESETT data, Zehtabchi and colleagues[4] report the results of the EEGs performed on 278 of the 475 (58%) patients enrolled in ESETT. The median time to start of EEG recording was 5 hours (IQR = 310 hours). Electrographic seizures occurred in 14% of study patients (95% CI, 10%19%), and 38% of these did not have obvious clinical features. Importantly, there was no difference in the prevalence of seizures in patients considered a treatment success (13%, 95% CI, 7%21%) and those that were not (15% (95% CI, 7% 30%). In 7 patients, EEG was obtained within 60 minutes of enrollment, and one of these (14%) had electrographic seizures. Interestingly, this patient had been deemed a treatment success before the EEG was started.

In this study, EEG was more likely to be performed in adults than children (OR = 1.75; 95% CI, 1.212.53) and in patients who were intubated than those who were not (OR = 3.57 (95% CI, 2.106.07). As might be expected, patients who were thought to be treatment successes by the investigator were less likely to undergo cEEG than those in whom SE was thought to be ongoing (OR = .39, 95% CI, 0.27.57).

Many studies over the last few decades have shown that about 20% of critically ill adult patients undergoing continuous

electroencephalographic monitoring (cEEG) have electrographic seizures or SE; in pediatrics, the number may be even higher.[5-7] While one of the foremost indications for cEEG is diagnosis of nonconvulsive seizures and NCSE in patients with impaired consciousness, another common indication is to determine the effectiveness of treatment.[8] The latter includes cEEG for patients with CSE after convulsions have stopped but impaired mentation persists. Indeed, the presence of convulsions prior to starting cEEG increases the likelihood of detecting electrographic seizures.[5,9,10]

Importantly, the 14% rate of electrographic seizure occurrence after cessations of convulsions in CSE in the Zehtabchi et al study is remarkably consistent with earlier observational studies and randomized clinical trials, which showed a rate of persistent electrographic seizures of approximately 1114%.[1,2] Despite a separation of about 20 years between publication dates, these studies show comparable results.

Persistence of seizures after CSE is not limited to adult patients. Pediatric CSE studies suggest a comparably high rate of continued electrographic seizures following cessation of the convulsions. In one study of 98 children who presented in CSE, 32 (32.7%) had ongoing seizures after the convulsions; 46.9% of these patients had NCSE.[11] A previous diagnosis of epilepsy and interictal abnormalities on EEG were more often associated with persistence of electrographic seizures. Neonates frequently have dissociation between motor activity and electrographic seizures after treatment with ASM. Studies suggest that between 4258% of neonates presenting with convulsions had continued electrographic seizures after the cessation of the motor manifestations of seizures.[12,13]

Zehtabchi et al noted that 38% of patients in the current study did not have an obvious clinical correlate to the ongoing seizures. Other studies have noted that a clinical correlate is frequently absent when electrographic seizures are seen in comatose patients.[5,6,14] Lack of obvious clinical features makes diagnosis of SE more challenging; the resolution of motor activity is tempting to interpret as resolution of the electrographic seizure activity as well. cEEG is the most viable method of confirming the presence of electrographic seizures in such patients.

A recent review on the value of cEEG after CSE noted several factors that increase the risk of electrographic seizures after CSE.[15]

- Younger patients are at higher risk of continued electrographic seizures after CSE compared to adults. Neonates and infants are at the highest risk.
- Presence of structural abnormalities (such as prior stroke, brain tumor, and traumatic brain injury) increases the risk of having electrographic seizures.
- Patients with a severely depressed mental status are at higher risk of having electrographic seizures than those who are awake.

There are features of the initial EEG obtained after convulsions stop that are suggestive of the occurrence of electrographic seizures. Of course, these risks factors can only be assessed after an EEG has been obtained. These abnormalities include epileptiform and periodic discharges and background abnormalities.[15]

In the cohort of patients reported by Zehtabchi et al, adults were more likely than children to get cEEG. Given the higher frequency of electrographic seizures in children than adults reported in literature, the opposite would have been expected. However, they also note that comatose patients were more likely to get cEEG; this is consistent with other studies. Interestingly, while the lower frequency of cEEG in patients that were clinically thought to be successfully treated is understandable, the frequency of seizure was comparable in the group considered to be a treatment success and the group that was not. This suggests that relying on clinical improvement may result in overlooking some patients with electrographic seizures.

Diagnosing and treating ongoing electrographic seizures is important in improving long-term outcomes. In one study, children with electrographic seizures for more than 12 minutes per hour were more likely to have worse neurological outcomes compared to those with a lower seizure burden.[16] Another pediatric study showed that electrographic SE, but not brief electrographic seizures, resulted in worse neurodevelopmental outcomes.[17]

With their recent study, Zehtabchi et al have reestablished the frequency of ongoing electrographic seizures after the control of convulsions in patients presenting in CSE. They have also reaffirmed the need for cEEG in these patients. These investigators, as well as the investigators of ESETT, must be congratulated and commended for designing and conducting a challenging clinical trial that has provided excellent data that informs of us of how effective various ASM are for the treatment of established SE.

Randomized trials for SE are difficult and complicated. Future clinical trials in SE will need to consider how to confirm the termination of CSE. A recent review discusses the issues that need to be addressed in clinical trials in various stages of SE (early, established, refractory and super refractory).[18] While the emergent deployment of EEG in the diagnosis and treatment of SE remains challenging, technological advances have made "quick look" EEGs possible. Confirmation of true termination of SE will not only allow better differentiation between ASM in clinical trials but also allow more effective treatment of critically ill patients.

By Aatif M. Husain

ORCID iD

Aatif M. Husain https://orcid.org/0000-0001-7954-1755

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