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Treatment of electrographic seizures and status epilepticus in critically ill children: A single center experience

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ABSTRACT

Purpose: Electrographic seizures (ES) and electrographic status epilepticus (ESE) are common in encephalopathic children in the pediatric intensive care unit (PICU) and associated with worse short-term outcome. Survey data indicate most physicians treat ES and ESE with antiepileptic drugs (AEDs), but few data are available regarding AED usage patterns. We aimed to describe AED usage for ES and ESE in critically ill children.
Methods: We performed an observational study of patients who underwent continuous electroencephalographic (cEEG) monitoring in the PICU of a single quaternary care children's hospital. We collected data regarding age, clinical diagnoses, ES and ESE occurrence, and AEDs utilized.
Results: 200 subjects underwent cEEG. ES occurred in 21% (41/200) and ESE occurred in 22% (43/200). Of the 84 patients with ES or ESE, 80 received non-benzodiazepine AEDs including 48% (38 of 80) with ES and 52% (42 of 80) with ESE. The most commonly administered first AEDs were levetiracetam in 38% (30/80), phenobarbital in 31% (25/80), phenytoin–fosphenytoin in 28% (22/80), and valproate in 4% (3/80). Seizures terminated after administration of the first AED in 74% (28/38) with ES and 22% (9/41) with ESE.
Conclusions: Levetiracetam, phenobarbital, and phenytoin–fosphenytoin are commonly used to manage ES and ESE at our center. Over half of subjects received multiple AEDs.

1. Introduction

Continuous EEG monitoring (cEEG) is often utilized to identify electrographic seizures (ES) and electrographic status epilepticus (ESE) in children in the pediatric intensive care unit (PICU),[1] and recent survey data indicate cEEG use is increasing in North America.[2] ES and ESE occur in 7–47% of critically ill children who undergo cEEG[3–14] and several studies have reported an association between ES and ESE and worse short-term outcome.[13–16] When surveyed, most physicians reported that they initiated antiepileptic drugs (AEDs) in response to ES or ESE, but there was substantial variability in the specific AEDs they reported administering.[17] Further, survey responses may not reflect true practice. Data regarding AED usage patterns will help guide clinical management and develop feasible prospective AED effectiveness studies. We aimed to determine which AEDs are used to manage ES and ESE in children in our PICU.

2. Patients and methods

Children treated in the PICU of a quaternary care referral hospital who underwent clinically indicated cEEG between July 2008 and January 2011 were enrolled in a prospective observational study aimed at identifying ES-ESE risk factors[18] and the impact of ES-ESE on short-term outcome.[15] Informed written consent was obtained from the parents/guardians of patients for inclusion in the database. Neonates (<1 month) were excluded. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board.

Our institution's criteria for cEEG in the PICU were: (1) altered mental status persisting for 1–2 h after a convulsion or convulsive status epilepticus, (2) altered mental status without a preceding convulsion in a patient with an acute neurologic disorder, or (3) altered mental status and the presence of abnormal movements or vital sign fluctuations of unknown etiology. Per our clinical pathway, patients underwent cEEG for at least 24 h when screening for ES, unless they were undergoing therapeutic

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hypothermia after cardiac arrest resuscitation, in which case they were monitored for 72 h. Patients with ES or ESE identified by cEEG were monitored for approximately 24 h after their last seizure. Continuous EEG monitoring was performed using a Grass-Telefactor (Grass Technology, West Warwick, RI) video-EEG system with 21 gold-over-silver scalp surface electrodes positioned according to the international 10–20 system and affixed with collodion adhesive. EEGs were interpreted by the Neurophysiology Service. Patients were managed by the Critical Care and Neurology Consult services. There is no institutional pathway for ES or ESE management so each physician made independent management decisions. Prophylactic AEDs are not administered.

Clinical and EEG data were prospectively collected including patient age, underlying acute neurologic disorder category, EEG findings including ES or ESE occurrence, and AED usage. Patients were assigned to one acute neurologic disorder category: (1) history of epilepsy with altered mental status following a seizure or status epilepticus, (2) hypoxic ischemic encephalopathy, (3) encephalitis, (4) traumatic brain injury, (5) stroke, (6) sepsis, (7) posterior reversible leukoencephalopathy syndrome, (8) neurosurgical procedure, (9) provoked seizures (such as febrile seizures), or (10) systemic/metabolic disorders (such as electrolyte abnormalities or hepatic encephalopathy). EEG tracings were reviewed by an investigator to provide standardized categorization of ES and ESE. Seizures were classified as ES or ESE based on the seizure burden at the administration time of the initial AED. ES was defined as an abnormal paroxysmal EEG event that was different from the background lasting longer than 10 s with a temporal-spatial evolution in morphology, frequency, and amplitude, and with a plausible electrographic field. ESE was defined as either a single 30-min ES or a series of recurrent independent ES totaling more than 30 min in any 1-h period (50% seizure burden).

We performed an exploratory analysis of seizure termination following administration of an initial AED. We described the use of intravenous benzodiazepines and AEDs. Patients received benzodiazepines for both sedation and seizures, but delineation of reason was not possible from the chart review. AED's described were levetiracetam, phenobarbital, phenytoin/fosphenytoin and valproate. An AED was considered effective if within 30 min of AED administration the patient became seizure free and had no seizure recurrence for at least 12 h without administration of any new AED. During the 12 h seizure-free period AED maintenance doses and benzodiazepines could be administered.

Descriptive statistics are reported as median and interquartile ranges (IQR) for non-parametric data. The Chi-squared or Fishers Exact tests were used to determine the association between categorical variables. The Wilcoxon rank-sum and Kruskal–Wallis tests were used to test the association between continuous non-parametric data.

3. Results

During the study period 241 patients underwent cEEG. Forty-one were not enrolled due to refusal (4), legal guardianship issues (2), lack of study staff available for enrollment during their hospitalization (17), or lack of parents available at bedside for in-person consent (18). This led to 200 enrolled subjects. ES occurred in 41 of 200 (21%) and ESE occurred in 43 of 200 (22%). AEDs were administered during cEEG to 95% (80 of 84) of subjects with ES or ESE including 48% (38 of 80) with ES and 52% (42 of 80) with ESE. Four subjects with seizures (3 with ES and 1 with ESE) did not receive AEDs: three had brief ES which resolved prior to treatment including 1 with stroke, 2 with hypoxic ischemic encephalopathy, and one with ESE hypoxic ischemic encephalopathy who had withdrawal of technologic support prior to seizure treatment. Descriptive characteristics regarding the 80 subjects who received AEDs are provided in Table 1. Prior to ES or ESE onset, benzodiazepines were being administered for sedation to 59% (47 of 80) of subjects. Midazolam was the only benzodiazepine administered as an infusion while boluses included diazepam, lorazepam, and midazolam. Once ES or ESE were identified, most patients continued to receive bolus doses of benzodiazepine but the indication (seizure management versus sedation) could not be determined from chart review so efficacy analyses were not performed. The most commonly administered first AEDs were levetiracetam in 38% (30 of 80) of subjects at a median dose of 23 mg/kg intravenously (IQR 20, 30), phenobarbital in 31% (25 of 80) of subjects at a median dose of 20 mg/kg intravenously (IQR 12, 23), phenytoin–fosphenytoin in 28% (22 of 80) of subjects at a median dose of 20 mg/kg intravenously (IQR 14, 20), and valproate in 4% (3 of 80) of subjects at a median dose of 22 mg/kg intravenously (IQR 20, 30) (Fig. 1). Phenobarbital was the first AED given to younger children with a median age 0.25 years (IQR 0.17, 0.5), compared to phenytoin–fosphenytoin at 4.6 years (IQR 1.75, 10) and levetiracetam at 5.4 years (IQR 1, 10) ($p < 0.001$). There was no difference in the frequency of AED administered based on gender ($p = 0.17$) or seizure classification as ES or ESE ($p = 0.13$).

Of the 80 subjects administered AEDs, 48% (38 of 80) received one AED, 23% (18 of 80) received two AEDs, 8% (7 of 80) received three AEDs, and 21% (17 of 80) received $\geq$4 AEDs (Fig. 2). Of the 38 subjects with ES, 76% (29 of 38) received one AED, 16% (6 of 38) received two AEDs, 5% (2 of 38) received 3 AEDs, and 3% (1 of 38) received $\geq$4 AEDs. Of the 42 subjects with ESE, 21% (9 of 42) received one AED, 29% (12 of 42) received two AEDs, 12% (5 of 42) received 3 AEDs, and 38% (16 of 42) received $\geq$4 AEDs. ESE management required pentobarbital infusion, midazolam infusion, or isoflurane in 26% (11 of 42) subjects. Seizures terminated after administration of the first AED in 46% (37 of 80) of subjects including 74% (28 of 38) with ES and 21% (9 of 42) with ESE. One

Table 1
Descriptive characteristics of subjects who received AEDs.

Variable	All $N = 80$	ES (38 of 80, 48%)	ESE (42 of 80, 52%)
Age (years) median (IQR)	2.2 (0.6, 8.1)	1.4 (0.4, 3.9)	5.4 (0.6, 9.8)
Male	46 (58%)	19 (50%)	27 (64%)
AEDs prior to hospitalization	22 (28%)	12 (32%)	10 (24%)
Acute neurologic disorder			
Epilepsy	23 (29%)	13 (34%)	10 (24%)
Hypoxic ischemic encephalopathy	15 (19%)	8 (21%)	7 (17%)
Infection-autoimmune	10 (13%)	2 (5%)	8 (19%)
Stroke	7 (9%)	3 (8%)	4 (10%)
Traumatic brain injury	6 (8%)	1 (3%)	5 (12%)
Metabolic–systemic	6 (8%)	6 (16%)	0 (0%)
Neurosurgical procedure	5 (6%)	3 (8%)	2 (5%)
Posterior reversible encephalopathy syndrome	3 (4%)	1 (3%)	2 (5%)
Provoked seizures	3 (4%)	1 (3%)	2 (5%)
Sepsis	2 (3%)	0 (0%)	2 (5%)

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