MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 649-658
DOI: 10.12659/MSM.900826

Received: 2016.07.29
Accepted: 2016.09.27
Published: 2017.02.04

Continuous Electroencephalography (cEEG) Monitoring and Outcomes of Critically Ill Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1,2 Ayaz M. Khawaja
CD 3 Guoqiao Wang
CD 3 Gary R. Cutter
ADEG 1,4 Jerzy P. Szaflarski

1 Department of Neurology, University of Alabama at Birmingham (UAB) Hospital, Birmingham, AL, U.S.A.
2 Department of Neurology, Birmingham Veterans Affairs Medical Center, Birmingham, AL, U.S.A.
3 Department of Biostatistics, University of Alabama at Birmingham (UAB), Birmingham, AL, U.S.A.
4 University of Alabama at Birmingham (UAB) Epilepsy Center, Birmingham, AL, U.S.A.

Corresponding Author: Ayaz M. Khawaja, e-mail: dr.ayazmk@gmail.com
Source of support: This study was supported in part by funds from the UAB Epilepsy Center

Background: It is not clear whether performing continuous EEG (cEEG) in critically ill patients during intensive care unit (ICU) treatment affects outcomes at discharge.

Material/Methods: We prospectively matched 234 patients who received cEEG (cases) by admission diagnosis and sex to 234 patients who did not receive cEEG (controls) and followed them until discharge. Patients admitted due to seizures were excluded. The primary measures of outcome were Glasgow Coma Scale at Discharge (GCSD) and disposition at discharge, and the secondary measures of outcome were AED modifications, Glasgow Outcomes Scale, and Modified-Rankin Scale. These outcomes were compared between the cases and controls.

Results: Some differences in primary outcome measures between the groups emerged on univariate analyses, but these differences were small and not significant after controlling for covariates. Cases had longer ICU stays (p=0.002) and lower admission GCS (p=0.01) but similar GCSD (p=0.10). Of the secondary outcome measures, the mean (SD) number of AED modifications for cases was 2.2±3.1 compared to 0.4±0.8 for controls (p<0.0001); 170 (72.6%) cases had at least 1 AED modification compared to only 56 (24.1%) of the controls (p<0.0001).

Conclusions: Performing cEEG did not improve discharge outcome but it significantly influenced AED prescription patterns. Further studies assessing long-term outcomes are needed to better define the role of cEEG in this patient population.

MeSH Keywords: Anticonvulsants • Electroencephalography • Intensive Care Units • Patient Outcome Assessment • Seizures

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/900826

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Background

The use of continuous EEG (cEEG) in Intensive Care Units (ICU) is rapidly expanding [1,2]. Current indications include monitoring and diagnosis of convulsive and non-convulsive status epilepticus [3], characterization of spells and sudden or unusual movements, monitoring sedation, providing prognostic information, and detection of cerebral ischemia [2]. CEEG is also recommended for diagnosis, management, and prognosis of seizures in traumatic brain injury, hypoxic-ischemic encephalopathy [4], acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, infectious and non-infectious encephalitis [5], and severe sepsis [6]. Delay in the diagnosis and management of seizures associated with these conditions may lead to increased morbidity and mortality [5]. One retrospective study indicated that cEEG monitoring resulted in significant changes in antiepileptic medications (AED) in more than half of all patients, but a comparison to patients who did not receive cEEG was not performed [7]. In another study, information obtained from cEEG also affected AED dosage adjustments and AED discontinuations, avoiding unnecessary AED prescriptions by proving the non-epileptic nature of spells, and obtaining urgent neuroimaging due to detection of focal epileptiform abnormalities or changes in cEEG rhythms [8]. A retrospective study conducted in Medicare beneficiaries suggested improved outcome in patients receiving cEEG as part of ICU neuro-monitoring when compared to patients who received routine EEG [9]. However, prospective studies on how cEEG monitoring affects AED modifications and clinical outcomes have not been conducted. We hypothesized that ICU cEEG monitoring leads to more AED modifications and better clinical outcomes in critically ill patients than no cEEG and investigated these hypotheses through a prospective case-control study.

Material and Methods

Study design

In this prospective, case-control, observational study performed in consecutive ICU patients, we compared those receiving (cases) with those not receiving (controls) cEEG monitoring as part of their standard care.

Recruitment

Patients aged >18 years admitted to any ICU from 2013 to 2015 were prospectively identified, enrolled, and followed until discharge from the hospital. Due to matching and logistic reasons, a maximum of 3–5 patients who received cEEG per week were enrolled, and then matched by sex and admission diagnosis to those enrolled within the same week but not receiving cEEG. Based on the first 20 subjects per group, we estimated that a sample size of 200 per group would provide at least 80% power to detect a 2-point difference in mean GCSD between the 2 groups, given the estimated standard deviation of 7. To account for anticipated attrition of up to 20% due to events such as death or lack of/missing data, we planned to include a total of up to 500 patients. The reasons for admission included traumatic brain injury, any intracranial hemorrhage (extra-axial, subarachnoid, intraparenchymal, or any combination), stroke, brain tumor, hypoxic-ischemic encephalopathy, cardiopulmonary arrest, central nervous system (CNS) infection, sepsis, and non-specific mental status changes. Inclusion criteria were: 1) age >18 years; 2) admission to any ICU and request for cEEG (cases), with exception of admission for seizures/epilepsy; 3) cEEG duration >6 h (cases). Exclusion criteria were: 1) patients admitted with known seizures or status epilepticus prior to or at the time of admission; 2) patients monitored only with routine EEG; 3) patients admitted to non-ICU units (both groups); 4) cross-overs - patients originally enrolled as controls, but excluded if primary management team later obtained cEEG. In this scenario, the matched-patient (case) was also excluded. The reasons for acquiring cEEG during hospitalization were divided into 3 categories: 1) encephalopathy (defined as a rapid change in, or persistently altered, mental status); 2) seizure suspicion (defined as paroxysmal events observed by staff, such as changes in intracranial pressure, tremors, or spells); and 3) seizure witnessed (defined as a generalized or focal convulsion identified either by medical staff or family members). This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. The requirement for obtaining informed consent was waived by the Board.

Continuous EEG protocol

In all cases, cEEG monitoring was initiated within 1 h of request (hospital standard) using a digital bedside monitoring system (XLTEK, Natus Medical Inc., San Carlos, CA). Standard location of EEG electrodes was utilized (10–20 system). All cEEGs were reviewed and reported at least once daily by board-certified or eligible clinical neurophysiologist. More frequent review was performed when warranted by clinical situation, such as request from primary management team, suspicion of seizures, and unusual EEG activity noted by providers at bedside or an EEG technologist who monitored the cEEG 24/7. Where significant abnormalities were identified (e.g., seizures, periodic discharges, and non-epileptic physiologic events), the neurophysiology staff immediately contacted the primary management team to convey the results. Neither the primary management team nor the electrophysiologist reading the cEEG study were contacted by the study team for any reason during the study. Collection of study variables was based on the official reports. Decisions regarding continuation or discontinuation

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of the cEEG monitoring were at the discretion of the treating physician and the reading electrophysiologist, as the study investigators did not participate in either the decision to start or discontinue cEEG monitoring.

Data collection

Demographics and disease characteristics

Age, sex, admission diagnosis, GCS at the time of the hospital admission (GCSA), reason for cEEG, number of comorbidities, duration and results of cEEG (any epileptiform activity such as focal or multi-focal epileptiform discharges, periodic-lateralized epileptiform discharge, generalized periodic epileptiform discharges, and seizures) were collected via chart and record review.

Outcome measures

The primary measures of outcome were disposition at discharge and Glasgow Coma Scale at Discharge (GCSD), whereas the secondary measures of outcome were Glasgow Outcomes Scale (GOS) and Modified-Rankin Scale (mRS) at discharge from hospital, and the number of AED modifications. An AED modification was defined as an initiation or discontinuation of AED, or an increase or decrease in AED dose throughout the course of hospitalization. Bolus AED administrations were not recorded. Disposition was designated as: favorable (home or inpatient rehabilitation), and unfavorable (nursing home or death). GCSD was used to quantitatively determine the change in clinical status based on the Glasgow Coma Scale (GCS) calculated at the time of the hospital admission. GCSD was calculated based on the last physical exam documented in the medical chart prior to, or at the time of the discharge from hospital. GCS at the time of the ICU admission and discharge were not calculated. mRS and GOS were used to assess the overall disability and functional independence, as patients with favorable discharge disposition and GCSD could still be functionally dependent (e.g., mRS of 5). mRS was dichotomized as favorable (score 0–2) or unfavorable (3–6). Similarly, GOS was dichotomized as favorable (score 4–5) and unfavorable (1–3).

Data collection method

A standardized case report form for each subject was filled out by 1 investigator (AK) using a data dictionary with explicit and pre-specified data definitions [10].

Analysis

Descriptive statistics were used to characterize the study cohort. Pearson chi-square tests were used to compare the proportions of categorical variables. Normally distributed continuous variables were tested using analysis of variance (ANOVA). The number of AED modifications was considered count data and assumed to follow a negative binomial distribution to account for the over-dispersion after verifying that the data did not fit a Poisson distribution. The impact of cEEG monitoring on AED modifications was tested using log-linear regression incorporating an offset to account for the variation in the duration of hospital stay, in addition to adjustment for GCS and comorbidities at admission. The number of AED modifications during cEEG was compared to the combined AED modifications both before and after cEEG using log-linear regression incorporating the offset to account for the variation in the duration of hospital stay. The number of comorbidities was analyzed as count data using a log-linear regression model incorporating an offset to account for the variation in age. The association between the results of the cEEG monitoring and disposition was investigated using logistic regression with adjustment for age and GCSA. The association between the results of the cEEG monitoring and dichotomized GOS or mRS was tested using logistic regression with adjustment for GCSA, and duration of hospital stay. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). All p values were based on 2-sided tests. Because 5 outcomes were explored in this study, using the Bonferroni correction, $p<0.01$ (=0.05/5) were considered significant to control for Type I error.

Results

Patient characteristics

Data collection was initiated on 269 cases and 269 controls, but during data collection 35 control patients were found to have cEEG requested by primary provider at some point of their admission; these patients and their matched cases were therefore excluded from analyses. At the time of final analysis, a total of 234 patients receiving cEEG were enrolled (cEEG group; cases) and matched to 234 patients who did not receive cEEG (non-cEEG group; controls). Enrollment of new subjects was halted when the first 200 subjects in each group were completed. Because of the lag between enrollment and completion of data collection, additional subjects were entered into the database and complete datasets on these subjects were also collected. Patients who received cEEG had a significantly longer duration of hospital and ICU stay ($p=0.02$; Table 1), and patients who had any epileptiform activity discovered on monitoring (cEEG-EA) had the longest duration of hospital and ICU stay ($p=0.004$ and $p=0.002$, respectively; Table 1). GCS at admission (GCSA) in cases was lower than in controls ($p=0.01$) and this difference remained significant after adjusting for age ($p=0.009$), as higher age was also associated with a lower GCSA ($p<0.0001$). Although patients in the cEEG-EA group had a higher number of comorbidities compared to other groups,

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Table 1. Patient characteristics in the cEEG and the non-cEEG groups is shown in the first part of the table, and patient characteristics in the cEEG patients who had any epileptiform activity (cEEG-EA) in comparison to cEEG patients who had negative monitoring (cEEG-non-EA) and non-cEEG group is shown in the second part of the table.

Variable	Non-cEEG group (N=234)	cEEG group (N=234)	p-value	Non-cEEG group (N=234)	cEEG-non-EA (N=141)	cEEG-EA (N=93)	p-value
Female, N (%)	111 (47.4%)	111 (47.4%)	1.0	111 (47.4%)	58 (41.1)	53 (57.0)	0.06
Age, year, mean (SD)	56.9 (17.6)	57.3 (15.7)	0.8	56.9 (17.6)	55.5 (16.4)	59.9 (14.2)	0.13
Number of comorbidities, mean (SD)	3.6 (2.5)	3.9 (2.5)	0.19	3.6 (2.5)	3.6 (2.6)	4.5 (2.3)	0.02
Admission GCS, mean (SD)	11.1 (3.8)	10.1 (4.0)	0.01	11.1 (3.8)	10.2 (4.0)	10.2 (4.0)	0.04
Duration of hospital stay, days, mean (SD)	18.4 (19.8)	22.7 (20.9)	0.02	18.4 (19.8)	20.2 (18.8)	26.6 (23.3)	0.004
Duration of ICU stay, days, mean (SD)	13.1 (15.4)	18.0 (17.3)	0.002	13.1 (15.4)	16.3 (16.1)	20.5 (22.5)	0.002

the number of comorbidities in the cases as a whole was similar that of the controls (Table 1). The mean (SD) duration of cEEG monitoring was 4.2±4.9 days. There were 73 patients admitted with traumatic brain injury (TBI) only, 99 patients with stroke only, 2 patients were admitted with stroke and TBI (1 case and 1 control), and 294 patients were admitted with diagnosis other than TBI or stroke. One patient with TBI and 1 with stroke could not be matched to their controls; therefore, these patients were instead matched to patients with a diagnosis of intracranial hemorrhage. For the cases, the most common reason for monitoring during hospitalization was encephalopathy (Table 2). In 1 patient, the reason for obtaining cEEG could not be ascertained (Table 2). There were no significant differences in sex, age, GCSA, the number of comorbidities, and durations of hospital and ICU stay by reason for acquiring cEEG (Table 2).

AED modifications

A total of 170 (72.6%) of cases had at least 1 AED modification compared to only 56 (24.1%) of the controls. Prior to admission, 54 (23.1%) cases were already prescribed an AED compared to 30 (12.8%) controls. The median number of AEDs used among those already prescribed an AED prior to admission was 1 and it was similar between the groups (p=0.73). The mean (SD) number of AED modifications (mean-nAED) for cases was 2.2±3.1 compared to 0.4±0.8 for controls, which was significantly different even after adjusting for GCSA and comorbidities (p<0.0001; Table 3). Among cases, 65% of patients had AEDs initiated, 18.8% had AEDs discontinued, 34.6% had doses increased, and 13.3% had dose decreased, whereas among controls, 20.9% had AEDs initiated, 6.4% discontinued, 5.6% increased, and 2.1% decreased (p<0.0001). Among cases, the mean-nAED during cEEG was 3.5 times the mean-nAED in the interval both before and after cEEG (p<0.0001; Table 3). There were 123 (52.6%) patients who had AED modifications made before, 102 (43.6%) during, and 48 (20.5%) after cEEG monitoring. Only 20 (8.5%) patients had AED modifications made in all 3 intervals: before, during, and after cEEG monitoring. Patients with witnessed seizures had the highest mean-nAED (3.3±4.1) compared to seizure suspicion (2.4±2.7), and encephalopathy (1.6±2.4) during the ICU stay, after adjusting for age, GCSA, and number of comorbidities (p<0.0001). For patients with encephalopathy, any epileptiform activity was discovered in 48/140 (34.3%), and non-convulsive seizures in 18/140 (12.9%) patients. These findings led to a significantly higher mean-nAED during ICU stay of 1.6±2.4 in all patients with encephalopathy compared to 0.4±0.8 (p<0.0001) for controls during their hospital stay. Age, GCSA, and comorbidities were not significantly associated with AED modifications.

Clinical outcomes

The study did not achieve significance in its primary outcome measure. GCSD was lower in cases when compared to controls but this difference was not significant (11.1 *vs.* 12.1; p=0.10) (Table 4). Disposition was similar between the groups with the exception of a higher number of controls discharged home (86/234 *vs.* 65/234; p=0.04). This was not significant after adjusting for age and GCSA, both of which predicted discharge to home (p=0.001). A favorable mRS score of 0–2 was observed in 19 (8.1%) cases compared to 40 (17.1%) controls (p=0.0034). This difference was no longer significant after adjusting for age, GCSA, and duration of hospital stay (p=0.21) (Table 4). Similarly, although fewer cases had a favorable GOS score of 4-5 (82; [35.0%]) compared to controls (114 [48.7%])

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Table 2. Patient characteristics categorized by reason for acquiring cEEG monitoring.

Variables	Encephalopathy (N=140)	Seizure witnessed (N=40)	Seizure suspicion (N=53)	p-value
Age, year, mean (SD)	57.1 (16.0)	61.3 (15.8)	54.7 (14.5)	0.14
Admission GCS, mean (SD)	10.4 (3.9)	9.7 (3.5)	9.8 (4.4)	0.46
Duration of cEEG, days, mean (SD)	3.8 (3.3)	5.0 (6.6)	3.9 (4.4)	0.28
AED modifications during cEEG, mean (SD)	0.8 (1.8)	2.0 (3.2)	1.3 (2.0)	0.004
AED modifications during the hospital stay, mean (SD)	1.6 (2.4)	2.4 (2.7)	3.3 (4.1)	<0.0001
Duration of hospital stay, days, mean (SD)	23.4 (21.4)	22.0 (21.8)	20.4 (16.8)	0.71
Duration of ICU stay, days, mean (SD)	18.8 (18.8)	18.3 (22.3)	13.4 (12.3)	0.26

Table 3. AED modifications according to cEEG and non-cEEG groups.

Variables	Non-cEEG group	cEEG group	p-value
Number of AED modifications for all patients, mean(SD)/median	0.4(0.8)/0.0	2.2(3.1)/1.0	<0.0001
Percent of patients with AEDs started	20.9%	65.0%	<0.0001
Percent of patients with AEDs stopped	6.4%	18.8%	<0.0001
Percent of patients with AED dose increased	5.6%	34.6%	<0.0001
Percent of patients with AED dose decreased	2.1%	13.3%	<0.0001
Number of AED modifications (Mean (SD)/Median) for patients in cEEG group before, during and after monitoring*			
Before cEEG	**During cEEG**	**After cEEG**	**p-value***
0.7(0.7)/1.0	1.2(2.4)/0.0	0.3(0.8)/0.0	<0.0001

* p-Value was obtained by comparing the during-cEEG group to the before-and-after cEEG group.

Table 4. Disposition and other clinical outcomes by cEEG and non-cEEG groups.

Variables	non-cEEG (n=234)	cEEG (n=234)	p-Value
Home, n (%)	86 (36.8)	65 (27.8)	0.04
Inpatient rehab, n (%)	54 (23.1)	56 (23.9)	0.08
Nursing home, n (%)	55 (23.5)	61 (26.1)	0.52
Death, n (%)	39 (16.7)	52 (22.2)	0.13
GCS at admission, mean (SD)*	11.1 (3.8)	10.2 (4.0)	0.009
GCS at discharge, mean (SD)**	12.1 (4.4)	11.1 (4.7)	0.10
No. (%) of patients with discharge mRS of 0–2	40 (17.1)	19 (8.1)	0.0034#
No. (%) of patients with discharge mRS of 3–6	194 (82.9)	215 (91.9)	
No. (%) of patients with discharge GOS of 4–5	114 (48.7)	82 (35.0)	0.0027#
No. (%) of patients with discharge GOS of 1–3	120 (51.3)	152 (65.0)	

* p-Value was adjusted for age, and age was associated with admission GCS (0.001); ** p-Value was adjusted for age (0.02), admission GCS (<0.0001), and duration of hospital stay (0.02); # No longer significant after adjusting for age, GCSA and duration of hospital stay.

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Table 5. Disposition and other clinical outcomes for patients with cEEG by reasons for acquiring cEEG.

Variables	Encephalopathy (N=140)		Seizure witnessed (N=40)		Seizure suspicion (N=53)		p-value
Home, n (%)	30	(21.4)	17	(42.5)	18	(34.0)	0.017
Inpatient rehab, n (%)	33	(23.6)	11	(27.5)	12	(22.6)	0.85
Nursing home, n (%)	43	(30.7)	6	(15.0)	11	(20.8)	0.09
Death, n (%)	34	(24.3)	6	(15.0)	12	(22.6)	0.46
GCS at admission, mean (SD)	10.4	(3.9)	9.7	(3.5)	9.8	(4.4)	0.46
GCS at discharge, mean (SD)	10.7	(4.7)	12.3	(4.2)	11.1	(4.9)	0.15
No. (%) of patients with discharge mRS of 0–2	8	(5.7)	4	(10.0)	7	(13.2)	0.21
No. (%) of patients with discharge mRS of 3–6	132	(94.3)	36	(90.0)	46	(86.8)	
No. (%) of patients with discharge GOS of 4–5	38	(27.1)	23	(57.5)	21	(39.6)	0.0014#
No. (%) of patients with discharge GOS of 1–3	102	(72.9)	17	(42.5)	32	(60.4)	

P-value is 0.001 after adjusting for age, GCS at admission and duration of hospital stay.

(p=0.0027), this was not significant after adjusting for age, GCSA, and duration of hospital stay (p=0.08).

Among cases, those who were monitored due to a witnessed seizure had the highest rate of discharge home (42.5%) and favorable outcome as measured by GOS of 4–5 (57.5%), although the proportion of patients with favorable outcome as determined by mRS of 0–2 was similar to that in other patients (Table 5). Patients with encephalopathy had the highest rate of unfavorable GOS score of 1–3 (72.9%) (Table 5). In comparison to controls, the cEEG patients who had any epileptiform activity (cEEG-EA) had a higher proportion of deaths (29.0% *vs.* 16.7%; p=0.01), a lower GCSD (10.2 *vs.* 12.1; p=0.001), and unfavorable outcomes as determined by mRS and GOS on univariate analysis (Table 6). After adjusting for age, GCSA, and duration of hospital stay, the higher proportion of patients with unfavorable scores of mRS and GOS was no longer significant. Although patients who were monitored but did not have any epileptiform activity (cEEG-non-EA) had a lower admission GCS than controls, the outcome variables were similar (Table 6). A total of 93/234 cases had any epileptiform activity (cEEG-EA). In comparison to cEEG patients without any epileptiform activity (cEEG-non-EA), fewer patients (16.1% *vs.* 29.1%; p=0.02) were discharged to inpatient rehabilitation, and more patients died (29.0% *vs.* 17.7%; p=0.04) (Table 7). CEEG-EA patients had a worse GCSD compared to cEEG-non-EA patients (Table 7) but this difference was not significant. Other outcomes measures were similar between groups.

Discussion

This is a first prospective, case-control, observational study in adults that investigated how the information obtained from cEEG monitoring enables clinicians to manage AEDs in critically ill patients and how AED modifications differ between those with and without cEEG monitoring. Our findings have implications for better understanding of the importance of cEEG monitoring in the critically ill patients and for deciding what outcomes of such monitoring should be expected. We found that the mean number of AED modifications in the cEEG group was much higher than in controls – performing cEEG has resulted in more AED adjustments and, presumably, more individualized care. Contrary to our original hypothesis, cEEG monitoring has not resulted in better short-term outcomes when compared to controls. After controlling for clinical variables, the GCSD and dispositions were similar between the 2 groups and both groups of patients had a high level of disability and functional dependence at the time of discharge.

Of the patients monitored with cEEG, 72.6% had at least 1 AED change, which is higher than reported in previous studies [7,8]. While 52.6% of patients had an AED change before the start of cEEG, most changes occurred during monitoring. The decision to change therapy prior to cEEG initiation was due to the standard practice of initiating seizure prophylaxis in patients with acute brain injury [11], witnessed spells suspicious for seizures, or an increasing awareness of non-convulsive seizures as a cause of encephalopathy [12]. However, cEEG yielded important information that resulted in additional fine-tuning of the existing therapy, as evidenced by nearly a 3.5 times higher number of AED modifications during cEEG when compared to total changes both before and after cEEG. Although patients undergoing cEEG due to a witnessed seizure are expected and have been shown to have more AED modifications [7], those monitored due to encephalopathy of variable etiology also had more AED modifications than controls. Therefore, the observed increase in treatment changes

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Table 6. Disposition and other clinical outcomes comparing patients in non-cEEG group with those in cEEG group with any epileptiform activity (cEEG-EA), and those in cEEG group without epileptiform activity (cEEG-non-EA).

Variables	non-cEEG (N=234)	cEEG-EA (N=93)	p-value	non-cEEG (N=234)	cEEG-non-EA (N=141)	p-value
Home, n (%)	86 (36.8)	25 (26.9)	0.09	86 (36.8)	40 (28.4)	0.10
Inpatient rehab, n (%)	54 (23.1)	15 (16.1)	0.16	54 (23.1)	41 (29.1)	0.20
Nursing home, n (%)	55 (23.5)	26 (28.0)	0.40	55 (23.5)	35 (24.8)	0.77
Death, n (%)	39 (16.7)	27 (29.0)	0.01	39 (16.7)	25 (17.7)	0.79
GCS at admission, mean (SD)	11.1 (3.8)	10.2 (4.0)	0.051	11.1 (3.8)	10.2 (4.0)	0.03
GCS at discharge, mean (SD)	12.1 (4.4)	10.2 (5.1)	0.001	12.1 (4.4)	11.6 (4.4)	0.287
Change in GCS from admission to discharge	1.0 (5.1)	0.1 (5.6)	0.14	1.0 (5.1)	1.4 (5.2)	0.45
No. (%) of patients with discharge mRS of 0–2	40 (17.1)	6 (6.5)	0.0012#	40 (17.1)	13 (9.2)	0.25^
No. (%) of patients with discharge mRS of 3–6	194 (82.9)	87 (93.6)		194 (82.9)	128 (90.8)	
No. (%) of patients with discharge GOS of 4–5	114 (48.7)	27 (29.0)	0.013#	114 (48.7)	55 (39.0)	0.35##
No. (%) of patients with discharge GOS of 1–3	120 (51.3)	66 (71.0)		120 (51.3)	86 (61.0)	

No longer significant after adjusting for age, GCS at admission and duration of hospital stay with p values increased to 0.09 and 0.45 respectively; ## Not significant before and after adjusting for age, GCS at admission, and duration of hospital stay.

Table 7. Disposition and other clinical outcomes comparing cEEG patients with any epileptiform activity (cEEG-EA) with those without any epileptiform activity (cEEG-non-EA).

Variables	cEEG-non-EA (N=141)	cEEG-EA (N=93)	p-Value
Home, n (%)	40 (28.4)	25 (26.9)	0.80
Inpatient rehab, n (%)	41 (29.1)	15 (16.1)	0.02
Nursing home, n (%)	35 (24.8)	26 (28.0)	0.59
Death, n (%)	25 (17.7)	27 (29.0)	0.04
GCS at admission, mean (SD)	10.2 (4.0)	10.2 (4.0)	0.9851
GCS at discharge, mean (SD)	11.6 (5.1)	10.2 (4.4)	0.035
Change in GCS from admission to discharge	0.1 (5.6)	1.4 (5.2)	0.06
No. (%) of patients with discharge mRS of 0–2	13 (9.2)	6 (6.5)	0.45#
No. (%) of patients with discharge mRS of 3–6	128 (90.8)	87 (93.6)	
No. (%) of patients with discharge GOS of 4–5	55 (39.0)	27 (29.0)	0.12#
No. (%) of patients with discharge GOS of 1–3	86 (61.0)	66 (71.0)	

Not significant before and after adjusting for age, duration of hospital stay and GCS at admission.

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is unlikely to be related to seizures only. While AEDs were initiated in a substantial proportion of controls, this was based largely on prophylactic antiepileptic therapy for seizure prevention in patients with intracerebral hemorrhage [13], and traumatic brain injury [14].

In a retrospective study, Kilbride et al. have shown that performing cEEG leads to AED modifications in 52% of patients, including therapy initiation in 14%, modification in 33%, and discontinuation in 5% [7]. A total of 101 studies showed no AED modifications at the initiation of cEEG monitoring, but seizures were eventually detected in 20 studies, all of which led to AED initiation. In another study, Abend et al. reported that AEDs were started in 28%, modified in 15%, and discontinued in 4% as a result cEEG monitoring [8]. Their AED modification rates are lower compared to our study. This discrepancy is due to different study designs. First, our study did not include patients admitted with seizures because we could not find a control group for comparison, whereas other studies did include such patients but no control groups were included. This exclusion was based on our hospital guideline that indicates all patients admitted with seizures should receive cEEG unless they recover to baseline or the admitting provider documents another reason for not obtaining cEEG. Second, in contrast to Kilbride et al., our study only included adult patients admitted to ICU rather than to any hospital unit [7]. Therefore, it was likely that our patients, as a group, had higher morbidity and a higher likelihood of identifying conditions such as super-refractory status epilepticus, which may be linked to prolonged durations of hospital stay and cEEG monitoring, and an increase in the overall AED modifications [15].

In addition to AED prescription patterns, we also investigated outcomes at discharge using previously validated scales: the Glasgow Outcomes Scale (GOS) and modified-Rankin Scale (mRS) [16,17]. These scales are categorized according to the degree of disability, whereby 4 or 5 on GOS, and 0–2 on mRS indicates mild or no disability [18,19]. Although the mRS scores are influenced by the ability to ambulate, the scores of 0–2 closely replicate the scores of 4–5 on GOS [19]. Overall there was high disability and unfavorable outcome profile in both cases and controls. Patients who received cEEG were less likely to have favorable outcome at discharge than controls, but this difference was not significant after adjusting for covariates. This difference was potentially driven by cases who had any epileptiform activity discovered on cEEG (39.7% of all cEEG patients), as they had less favorable outcomes and lower discharge GCS on univariate analysis compared to cases whose monitoring did not reveal such abnormalities and whose outcomes were similar to controls. The reason for obtaining cEEG monitoring also affected outcomes because patients who were monitored due to encephalopathy had significantly less favorable outcomes compared to those who were monitored due to seizure-witnessed or seizure-suspicion. However, this was apparent only on discharge GOS and not discharge mRS, possibly due to a disproportionate distribution of patients across the mRS scores of 0–2 and 3–6. The effect on outcomes of the group of patients with seizures or status epilepticus at admission is unknown because these patients were excluded from the study. Duration of hospital stay, along with other factors such as GCSA, may explain a lack of differences in outcomes between the groups. In fact, longer ICU stay has been associated with the development of severe disability or death [20], and cEEG patients had longer stays both in the ICU and hospital (Table 1). It is also possible that a longer ICU stay in patients receiving cEEG is, in part, an artefact related to artificially prolonging the evaluation by the primary management team in order to increase the yield of the cEEG, but our study was not designed to test this hypothesis. In addition, patients who had any epileptiform activity discovered on cEEG had even longer duration of hospital and ICU stay, and a greater number of comorbidities compared to cEEG patients with negative-for-epileptiform activity monitoring results, and it is the former group that was likely driving the less favorable outcomes in the cEEG group, in comparison to the non-cEEG group (Table 1).

A high level of disability is likely associated with, rather than caused by, the use of cEEG, as causation cannot be established based on an observational study. Furthermore, cEEG as a diagnostic test cannot directly influence outcomes, but rather influence direct treatment choices that may then influence the outcome. Seizures are an epiphenomenon frequently occurring in the setting of acute brain injury (stroke, TBI, and intracranial hemorrhage) and may reflect the severity of the injury, thus directly contributing to worse outcomes [21]. Further, their treatment may not necessarily improve the eventual outcome. While both non-convulsive and convulsive status epilepticus have been associated with increased morbidity and mortality [22], and it may be assumed that their detection by cEEG and subsequent treatment improves morbidity and mortality, this assumption is difficult to prove in practice since obtaining a control population group would be both challenging and potentially unethical [23]. Furthermore, the overall outcomes are likely to be influenced by disease-specific factors, such as the intracerebral hemorrhage (ICH) score upon initial presentation for ICH, rather than seizures, in addition to age, admission GCS, and duration of hospital stay [24].

Our findings are not necessarily at odds with the study by Ney et al., which demonstrated lower in-hospital mortality in almost 6000 patients monitored with cEEG compared to almost 35000 patients monitored with routine EEG [9]. Comparisons between the studies are difficult since patients in the Ney et al. study received routine EEG, whereas in our study controls did not receive any EEG. The capture rate of seizures increases with the duration of the cEEG with the routine, 20-min EEG

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known to miss >50% of patients who eventually have seizures when monitored for more than 24–72 h [25]. Further, the data collection methods were different (retrospective database mining *vs.* prospective single-center collection), with the pitfalls of retrospective database mining studies already recognized [26]. Additionally, in the study by Ney et al. [9], there was no difference in duration of hospital stay between the 2 groups, whereas our study found longer durations of hospital and ICU stay for the cEEG group.

There are limitations to this study. First, outcomes were only studied at discharge; therefore, long-term outcomes were not ascertained. There may be a potential benefit in improving both long-term seizure and cognitive outcomes with early detection and treatment of non-convulsive seizures [27,28], and these are unlikely to be reflected at the time of discharge. Further, the outcome measures used in this study are specific for certain diagnoses; for example, GOS was designed to study outcome after TBI [17], while mRS was designed to study outcomes after stroke [16]. These scales may be not optimal for measuring outcomes in the present setting in patients with variable diagnoses presenting for treatment. As such, development of a specific scale that allows for monitoring outcomes in patients with variable diagnoses at presentation may be of importance for the field. Second, variability in reporting and interpretation of certain EEG characteristics, such as background rhythm, epileptiform discharges, and diagnosis of non-convulsive seizures, may have contributed to the results of our study. This has been demonstrated in prior studies [29] and another study recently documented that how the EEG is interpreted affects the treatment choices [30]. Development and cross-sectional validation of EEG measures is of importance [31,32]. Third, there were inherent differences between the groups, with cEEG patients being sicker overall (lower admission GCS and longer duration of hospital and ICU stay). Although the outcome comparisons between the groups were controlled for these factors, it is possible that other factors that were not directly investigated influenced outcomes in patients who received cEEG. While groups were matched in a way that minimized potential practice pattern and selection biases, it is possible that other factors played additional roles in clinical decisions regarding ordering or not ordering cEEG. The "intent to monitor" may itself be an indicator of the overall severity of illness of patients and may be a marker for poor outcomes. Certainly, the patients who had epileptiform abnormalities identified were also the sickest, as evidenced by more comorbidities and longer ICU stays. Thus, the overall morbidity may be driving the outcomes. Because of the observational nature of the study, we were unable to examine the influence of human factors on the decision-making process for obtaining or not obtaining cEEG monitoring. Therefore, we were unable to assess this possibility. Furthermore, the presence of multiple etiologies makes it challenging to control for overall severity of disease burden in either group, although correlative markers such as number of comorbidities and admission GCS were used for this purpose. Additionally, the diagnosis at admission may not necessarily be the diagnosis at discharge; for example, in a patient admitted with encephalopathy, the diagnosis may later be changed to other conditions such as CNS infection and stroke. Such information was not collected as part of this study. Finally, a major proportion of patients that would otherwise be monitored with cEEG (seizures and status epilepticus at admission) were excluded from data collection due to inability to find controls. Had our study incorporated these patients, the outcomes may have been different.

Conclusions

The use of cEEG in the critical care setting influences how AEDs are prescribed. Although information acquired from cEEG influences the clinical decision-making, this does not translate, at least in this study, into improved outcomes at discharge, which may have been more strongly influenced by other factors, such as admission Glasgow Coma Scale score and duration of hospital and ICU stays. While numerous and variable admission diagnoses were incorporated, the outcomes analyses did not address patients who were admitted with seizures and status epilepticus, thereby excluding a major proportion of patients that would otherwise be monitored. Further research can incorporate longer-term follow-up and other outcome measures more suitable for the studied population to determine the clinical utility of cEEG as part of neuromonitoring in patients with diagnoses other than epilepsy/seizures.

Disclosures

Dr. Khawaja reports no disclosures.

Dr. Wang reports no disclosures.

Dr. Cutter is the President of Pythagoras, Inc., a private consulting company located in Birmingham, AL. He participates in various data and safety monitoring committees including Apotek, Biogen-Idec, Cleveland Clinic (Vivus), Glaxo-Smith Klein Pharmaceuticals, Gilead Pharmaceuticals, Modigenetech/Prolor, Merck/Ono Pharmaceuticals, Merck, Merck/Pfizer, Neuren, Sanofi-Aventis, Teva, NHLBI (Protocol review committee), NINDS, and NICHD (OPRU oversight committee). He serves as a consultant for or is on the advisory board for Consortium of MS Centers (grant), D3 (Drug Discovery and Development), Genzyme, Jannsen Pharmaceuticals, Klein-Buendel Incorporated, Medimmune, Novartis, Opexa Therapeutics, Receptos, Roche, EMD Serono, Spiniflex Pharmaceuticals, Teva pharmaceuticals, and Transparency Life Sciences.

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Dr. Szaflarski received funding from NIH, Shor Foundation for Epilepsy Research, Epilepsy Foundation of America, Department of Defense, UCB Biosciences, Epilepsy Study Consortium, University of Alabama at Birmingham, Neuroscan Compumedics Inc., Food and Drug Administration, American Epilepsy Society, SAGE Therapeutics Inc., GW Pharmaceuticals, and Eisai, Inc. He serves or has served as a consultant or on advisory boards for SAGE Therapeutics Inc., Biomedical Systems Inc., GW Pharmaceuticals Inc., Upsher-Smith Laboratories, Inc., and Elite Medical Experts LLC. He serves as an editorial board member for Epilepsy & Behavior, Journal of Epileptology, Restorative Neurology and Neuroscience, Journal of Medical Science, and Folia Medica Copernicana.

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