Seizure: European Journal of Epilepsy 73 (2019) 14–16

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Short communication

Are seizures predictors of mortality in critically ill patients in the intensive care unit (ICU)?

Diosely C. Silveira[a,*], Anirudh Sagi[b], Raquel Romero[a]

[a] Hackensack Meridian Health and JFK Neuroscience Institute, 65 James Street, Edison NJ 08820, United States
[b] Stone Brook University, NY, United States

ARTICLE INFO

Keywords:
Seizures
Elderly
Mortality
Intensive care unit

ABSTRACT

Purpose: This study aimed to determine if seizures in critically ill patients are predictive of in-hospital mortality.
Methods: Patients above the age of 55 who underwent continuous electroencephalogram (cEEG) monitoring between 2015 and 2018 at the Hackensack Meridian Health and JFK Neuroscience Institute were included in the present study. Patients were subdivided into those with and without seizures. Age, sex, seizure types, CNS disorders, and other associated comorbidities were collected by chart review. After descriptive analysis, we used multiple logistic regression analyses to evaluate if seizures and mortality were associated. P-values less than 0.05 were considered statistically significant.
Results: One hundred and one critically ill patients (62.4% female) were included in this study. Sixty-six (65.3%) were between 55 and 75 years of age, while 35 (34.7%) were above 75 years of age. Most patients (n = 31, 83.8%) had focal-onset seizures, and 10 had nonconvulsive status epilepticus (NCSE). Twelve (11.9%) patients with seizures did not survive. However, seizures were not independently associated with mortality in either unadjusted (OR 1.13, CI 0.47–2.72, p = 0.773) or adjusted (OR 1.20, CI 0.35–4.05, p = 0.760) regression models. Secondary predictors of mortality included mechanical ventilation (OR 5.36, CI 1.69–16.96, p = 0.001) and acute ischemic stroke (OR 2.77, CI 1.08–7.09, p = 0.034).
Conclusion: Seizures did not predict in-hospital mortality in critically ill patients. Larger prospective studies are needed to confirm our current findings.

1. Introduction

Continuous electroencephalogram (cEEG) monitoring is commonly used in the intensive care unit (ICU) to detect seizures in patients with abnormal neurological function, including patients with encephalopathy [1]. Previous studies suggest that the seizure rate in critically ill patients undergoing cEEG is between 19% and 27% [2,3]. Seizures may occur for a variety of reasons, including provoked seizures due to metabolic, toxic, infectious, or hypoxic events. Further, acute symptomatic seizures may occur due to acute brain injuries, and breakthrough seizures may occur in patients with epilepsy. Seizure severity ranges from focal or generalized seizures to nonconvulsive status epilepticus (NCSE) or convulsive status epilepticus (SE).

SE and particularly refractory SE is associated with increased mortality [4,5]. Yechoor et al. found that 13 (28.3%) out of 46 patients with median age of 60 years admitted to the neurological ICU for the management of SE died in the hospital [5]. Currently, the relationship between seizures of distinct etiologies and mortality in critically ill patients remains unclear. Therefore, the main goal of the present study was to determine whether seizures in an ICU setting are predictive of in-hospital mortality in older patients.

2. Material and methods

This retrospective study was approved by the Institutional Review Board of the JFK Medical Center. Patients 55 years or older who were admitted to the ICU at Hackensack Meridian Health and JFK Neuroscience Institute and underwent cEEG monitoring from June 1 st, 2015 to June 30, 2018 were included in this study. The patients were then subdivided into two groups: those with and without seizures.

2.1. Demographics and disease characteristics

Age, sex, seizure types, central nervous system (CNS) disorders, and other associated comorbidities were collected by chart review. We reported the presence of comorbid conditions and CNS disorders that are

* Corresponding author.
E-mail addresses: diosely.silveira@hackensackmeridian.org, dsilve55@gmail.com (D.C. Silveira).

https://doi.org/10.1016/j.seizure.2019.10.009
Received 2 July 2019; Received in revised form 8 October 2019; Accepted 10 October 2019

commonly seen in the ICU. Seizures were classified clinico-electrographically as either focal- or generalized-onset seizures according to the ILAE classification guidelines [6]. cEEG was performed using either Grass or Nihon Kohden machines using the standard 10–20 system for EEG electrode placement. All cEEG results were reviewed by board-certified clinical neurophysiologists and classified as normal, with either nonspecific or specific EEG abnormalities (e.g. epileptiform discharges and/or seizures). NCSE was defined according to a study by Sutter and Kaplan [7].

2.2. Outcome measures

The primary outcome measure was to determine if seizures were predictive of hospital mortality in critically ill patients who were older. Secondary outcomes included associations between CNS disorders, common comorbidities in critically ill patients, and hospital mortality.

CNS disorders were defined as follows: 1) vascular CNS disorders, which comprise intra- and/or extra-hemorrhagic brain lesions including traumatic and nontraumatic intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), and subdural hematoma (SDH); 2) Neoplastic brain lesions consisting of malignant and benign primary brain tumors, and metastatic brain lesions; 3) Toxic, metabolic, infectious, or anoxic encephalopathy; and 4) Dementia.

Comorbidities included respiratory failure requiring mechanical ventilation, chronic kidney disease (CKD), sepsis and/or pneumonia, and active cancer. We also investigated associations between mortality and modifiable vascular risk factors such as hypertension, coronary artery disease (CAD), diabetes mellitus (DM), dyslipidemia, obstructive sleep apnea (OSA), atrial fibrillation, and remote stroke. Patients were subdivided into two groups: those that had two or less vascular risk factors, and those that had 3 or more.

2.3. Statistical analysis

After performing descriptive analyses, we used multiple logistic regression to evaluate the associations between seizures and mortality, as well as associations between comorbid conditions and mortality. Regression analyses included and adjusted for age (< 75 or > 75), sex, respiratory failure with mechanical ventilation, sepsis and/or pneumonia, CKD, vascular risk factors, active cancer, encephalopathy of any etiology, dementia, acute ischemic stroke, intra- and extra-cerebral hemorrhages, and brain neoplasms. Statistical significance was set at $p < 0.05$ and Stata (Version 14.0) was used for statistical analysis.

3. Results

3.1. Patients characteristics

One hundred and one critically ill patients who underwent cEEG were included in this study. Of those, 66 (65.3%) were between the ages of 55 and 74 years and 35 (34.7%) were older than 75 years. Patient characteristics are shown in Table 1.

3.2. Seizures and EEG findings

In total, 37 (36.7%) patients had seizures. Of them, 34 had seizures prior to starting cEEG monitoring, including clinical seizures and electrographic seizures recorded during the stat EEG, and three of them had seizures during cEEG monitoring. Additionally 25 (24.8%) of the 37 patients continued to have seizures despite treatment.

The vast majority (N = 31, 83.8%) of the patients in this study had either focal-onset seizures (electrographic seizures) without evident clinical signs ($n = 26$), or focal motor clonic seizures with clinical signs ($n = 5$). Lateralized periodic discharges (LPDs) were seen in 15 (48.4%) of the patients with focal-onset seizures. The remaining patients ($n = 6$, 16.2%) had generalized-onset seizures, including convulsive generalized tonic-clonic or myoclonic seizures ($n = 5$), and generalized electrographic seizures ($n = 1$). Some (8.1%) patients had persistent convulsive SE (generalized SE, $n = 2$; focal motor SE, $n = 1$). On the other hand, NCSE was diagnosed in 11 (29.7%) patients, 10 with focal NCSE and one with generalized NCSE.

Regarding treatment, the most common antiseizure drug was levetiracetam ($n = 29$, 78.4%), used as either a monotherapy (35.1%) or a polytherapy combined with fosphenytoin, lacosamide, sodium valproate, topiramate, or phenobarbital. The remaining patients ($n = 8$) received either mono- or polytherapy with lacosamide, brivaracetam, sodium valproate, lamotrigine, pregabalin or gabapentin.

3.3. In-hospital mortality

Twelve (11.9%) patients who experienced seizures died in-hospital. Five had NCSE, one had generalized convulsive SE, two had focal motor seizures, three had focal electrographic seizures, and one had generalized electrographic seizures. Seizures were not independently associated with mortality in either unadjusted (OR 1.13, CI 0.47–2.72, p = 0.773) or adjusted (OR 1.20, CI 0.35–4.05, p = 0.760) regression models (Table 2). Secondary predictors of mortality included mechanical ventilation (OR 5.36, CI 1.69–16.96, p = 0.001) and acute ischemic stroke (OR 2.77, CI 1.08–7.09, p = 0.034, see Table 2).

4. Discussion

In the present study, we did not find an association between seizures and in-hospital mortality in critically ill patients, however, the reasons for our negative results are not well defined. Currently, indications for cEEG in the ICU include but are not limited to the detection of subclinical seizures and NCSE in patients with unexplained disorders of consciousness, particularly if associated with potential epileptogenic brain lesions including acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, brain neoplasms, infectious or non-infectious encephalitis, or other encephalopathies of any etiology [8]. The widespread use of cEEG monitoring in ICUs provides an opportunity for the early detection of seizures and prompt medical treatment, which may reduce in-hospital mortality. A previous study found that patients who were monitored using cEEG in the ICU had better outcomes compared to those who only underwent routine EEGs [9]. In addition, a large retrospective epidemiological study involving more than 400,000 patients investigated the association between ICU admission diagnoses and mortality between 1988 and 2012 in the US. This study found a 35% reduction in hospital mortality during the last two decades [10]. Seizures were amongst the diagnoses that showed the highest reductions in hospital mortality [10]. Therefore, we speculate that the availability of cEEG allowing for the prompt diagnosis and

Table 1
Demographics and hospital mortality of patients (N) by age and sex.

	Female Survivor (N = 46)	Female Non-Survivor (N = 17)	Male Survivor (N = 24)	Male Non-Survivor (N = 14)
55-74 years old (N = 66)	N = 31 (47%)	N = 8 (12.1%)	N = 20 (30.3%)	N = 7 (10.6%)
75 years old or more (N = 35)	N = 15 (42.9%)	N = 9 (25.7%)	N = 4 (11.4%)	N = 7 (20%)

Table 2
Logistic regression results.

	Odds ratio	CI	p-value
Seizures	1.13	0.47–2.72	0.773
History of Epilepsy	0.33	0.07–1.59	0.127
Mechanical Ventilation	5.36	1.69–16.96	0.001*
Chronic Kidney Disease	3.11	0.95–10.19	0.061
Sepsis and/or Pneumonia	3.12	0.87–11.14	0.080
Active Cancer	1.73	0.50–5.95	0.391
Modifiable Vascular Risk Factors	0.99	0.42–2.31	0.98
Acute Ischemic Stroke	2.77	1.08–7.09	0.034*
Intra- and Extra-cranial Hemorrhage	0.56	0.2–1.56	0.255
Brain Neoplasms (benign or malignant or metastatic)	1.11	0.46–2.71	0.805
Encephalopathy: Toxic, Metabolic, Infectious, or Anoxic	2.13	0.85–5.31	0.106
Dementias	1.97	0.66–5.91	0.228

CI, confidence interval; an * denotes a p-value < 0.05.

management of seizures may have contributed to the reduction in hospital mortality during this time period. It should be noted that our findings, specifically the lack of association between seizures and in-hospital mortality, should be interpreted with caution since this was a retrospective review study with a small sample size. Larger prospective studies are necessary to confirm our findings.

The majority of our patients had one or more comorbid conditions that are commonly associated with increased mortality in geriatric patients in the ICU, including respiratory failure, kidney dysfunction, and sepsis (Table 2). In agreement with a previous report [11], mechanical ventilation was associated with hospital mortality in older patients (75 years or above). Additionally, a recent systematic review of 21 studies found a similar relationship. Specifically, critically ill patients who were receiving mechanical ventilation and were older than 65 years had a greater mortality rate [11].

Critically ill patients above the age of 75 years who had acute ischemic stroke had increased odds of in-hospital mortality in this study (Table 2). Similarly, Takashima et al. [12] conducted a study on a population-based stroke registry in Shiga, Japan, and found that 390 (13.2%) of 2956 patients passed away within 28 days following stroke. Although a large nationwide study in the US found that the odds of in-hospital mortality in patients with stroke (regardless of the type) was reduced from 1997 to 2006, multivariable analyses indicated that older age, being female, having non-Medicare insurance, and having multiple comorbidities were independently associated with higher odds of in-hospital mortality [13]. This is important, as the subpopulation of elderly patients with several comorbid conditions closely resembles the patients in the current study.

5. Conclusions

Overall, seizures did not predict in-hospital mortality in critically ill patients in this study. Future prospective studies with increased sample sizes are needed to confirm our findings.

Declaration of Competing Interest

None.

Funding

This research did not receive any specific grant from agencies in the public, commercial, or not-for-profit sectors.

References

[1] Oddo M, et al. Continuous electroencephalography in the medical intensive care unit. Crit Care Med 2009;37(6):2051–6.
[2] Claassen J, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004;62(10):1743–8.
[3] Westover MB, et al. The probability of seizures during EEG monitoring in critically ill adults. Clin Neurophysiol 2015;126(3):463–71.
[4] Sutter R, et al. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. Epilepsia 2013;54(3):502–11.
[5] Yechoor N, Adeli A, Hafeez S. External validation of the epidemiology-based mortality score in status epilepticus in an American intensive care population. Epilepsy Res 2018;148:32–6.
[6] Scheffer IE, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58(4):512–21.
[7] Sutter R, Kaplan PW. Electroencephalographic criteria for nonconvulsive status epilepticus: synopsis and comprehensive survey. Epilepsia 2012;53(Suppl 3):1–51.
[8] Claassen J, et al. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med 2013;39(8):1337–51.
[9] Ney JP, et al. Continuous and routine EEG in intensive care: utilization and outcomes, United States 2005-2009. Neurology 2013;81(23):2002–8.
[10] Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. Crit Care 2013;17(2):R81.
[11] Santa Cruz R, et al. Mortality in critically ill elderly individuals receiving mechanical ventilation. Respir Care 2019;64(4):473–83.
[12] Takashima N, et al. Incidence, management and short-term outcome of stroke in a general population of 1.4 million japanese. Shiga stroke registry. Circ J 2017;81:1636–46.
[13] Ovbiagele B. Nationwide trends in in-hospital mortality among patients with stroke. Stroke 2010;41(8):1748–54.