Journal of Neurology & Neurophysiology

Al Kasab et al., J Neurol Neurophysiol 2016, 7:3
DOI: 10.4172/2155-9562.1000381

Research Article Open Access

Incidence of Electrographic Seizures in Pharmacologically Paralyzed Patients

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Received date: June 05, 2016; **Accepted date:** June 24, 2016; **Published date:** June 28, 2016

Abstract

Objective: Pharmacologically paralyzed patients frequently undergo continuous EEG monitoring (cEEG) to assess for seizures. However, cEEG is costly, consumes valuable resources and there is limited data regarding seizure frequency in this population.

Methods: Clinical and EEG data was collected from medical records for patients undergoing cEEG at Emory University between January 1, 2009 and August 31, 2011 and from an ICU EEG database between February 26, 2013 and July 2, 2014. Seizure incidence was compared between paralyzed and non-paralyzed patients. Neurological diagnosis, cEEG duration, medications and outcome were also assessed.

Results: Three of the 103 (2.9%) paralyzed patients experienced seizures compared to 335/1955 (17.1%) that were non-paralyzed ($p<0.001$). Average duration of cEEG for patients receiving paralytics was 7.45 days vs. 2.38. Most patients in the first study period had a poor outcome (60/64, 93.8%). In the second study period, there were more sedatives used in the paralytic group (median 3 vs. 0).

Conclusion: Seizures in pharmacologically paralyzed patients are uncommon and likely related to co-administered sedatives while cEEG duration is long and patient outcomes are poor.

Significance: cEEG may be unnecessary in patients undergoing pharmacological paralysis and alternative means of monitoring sedation like Bispectral index may be more cost effective.

Keywords: EEG monitoring; Electrographic seizures; Critical care; Bispectral analysis; Pharmacological paralysis

Introduction

Critically ill patients sometimes require neuromuscular blockade for facilitation of ventilation, control of intracranial pressure or muscle spasms. These patients typically undergo continuous EEG monitoring (cEEG) during neuromuscular blockade to assess for seizure activity and to monitor the depth of sedation. However, cEEG is costly and resource-intensive.

In addition, heavy sedation is used to prevent discomfort, agitation and awareness during induced paralysis. These sedative medications often have strong anticonvulsant properties which would predict low incidence of seizures in this population. However, there is limited data about the frequency of seizures in critically ill patients undergoing neuromuscular blockade.

The aim of this study was to identify the incidence of electrographic seizures in patients undergoing pharmacological paralysis and to compare seizure incidence, duration of cEEG monitoring, outcome and administration of sedative medications to non-paralyzed patients.

Methods

This study was approved by the Emory Internal Review Board. Electronic medical records were reviewed to assess paralytic use (cisatracurium), incidence of electrographic seizures, primary neurological diagnosis and average duration of monitoring for all patients undergoing cEEG at Emory University Hospital between January 1, 2009 and August 31, 2011. In addition, data was collected from an ICU EEG data base which was developed by the Critical Care EEG Monitoring Research Consortium. Utilizing the ICU EEG database, the same clinical features were identified in all patients undergoing cEEG at Emory University Hospital between February 26, 2013 and July 2, 2014 in addition to anti-epileptic drug and sedative use and individual monitoring durations. Discharge disposition was only available and assessed for patients undergoing cEEG in the first study period. Pooled data from both study periods was used to compare the incidence of seizures in paralyzed versus non-paralyzed patients using the Fisher's exact test. Number of sedatives and anti-epileptic drugs administered was compared between the paralytic and control group using the negative binomial regression.

Patients with documented electrographic seizures during the exact timing of neuromuscular blockade were identified from review of EEG

monitoring reports and medication administration records. Patients were selected to undergo cEEG by the treating neurointensivist based on an institutional protocol. Indications for monitoring included acute structural brain injury, history of clinical seizures, involuntary movements suspicious for seizure, post-cardiac arrest undergoing hypothermia protocol, and pharmacological paralysis for pulmonary reasons or for management of elevated intracranial pressure. All EEG recordings were reviewed and reported in the same standardized manner for the both the paralyzed and non-paralyzed patients groups. All raw EEG was screened by neurophysiology fellows and/or senior EEG technologists and reviewed by a board eligible attending neurophysiologist. In addition, quantitative EEG displays were utilized to assist in identification of specific portions of the raw EEG that may contain clinically significant changes and hence, require more in depth review.

Results

Pooled data from both study periods revealed that 103/2058 (5%) of patients undergoing cEEG received cisatracurium for the purpose of neuromuscular blockade. The most common primary neurological diagnosis for patients requiring neuromuscular blockade was subarachnoid hemorrhage (53.4%) followed by intraparenchymal and/or intraventricular hemorrhage (11.6%) and ischemic stroke (8.7%). In the non-paralyzed group, the most common primary neurological diagnosis was seizures (20.9%), altered mental status (19%) and subarachnoid hemorrhage (13.6%) (Table 1). Primary neurological diagnosis was not available for 38 patients in the non-paralytic group. In addition, only 2/103 (1.9%) of paralyzed patients had a primary neurological diagnosis of seizures or status epilepticus vs. 537/1917 (28%) of non-paralyzed patients. Electrographic seizures were detected in 3/103 (2.9%) of patients undergoing pharmacologic paralysis compared to 335/1955 (17.1%) of non-paralyzed patients ($p<0.001$) (Table 2). All three patients who experienced seizures during paralysis were identified from the second study period and two of these patients had recognized electrographic seizures on cEEG prior to initiation of paralytic. In addition, three of the 64 patients during the first study period experienced electrographic seizures during cEEG but not while cisatracurium was being administered. From pooled data, the average duration of cEEG for the patients undergoing neuromuscular blockade was 7.45 days while the average duration of cEEG for non-paralyzed patients monitored during a similar time period was 2.38 days. Number of cEEG monitoring days for all paralyzed patients comprised 13% of the total number of monitoring days during the aggregate of these 2 studies time periods.

	Paralyzed, n=103 (%)	**Non-Paralyzed, n=1917* (%)**
Subarachnoid Hemorrhage	55 (53.4)	261 (13.6)
Intracerebral and/or Intraventricular Hemorrhage	12 (11.6)	170 (8.9)
Ischemic Stroke	9 (8.7)	105 (5.5)
Brain Neoplasm	5 (4.9)	118 (6.2)
Subdural Hematoma	2 (1.9)	76 (4.0)
Seizures	2 (1.9)	399 (20.9)
Status Epilepticus	0	138 (7.2)
Altered Mental Status	7 (6.8)	363 (19.0)
Hypoxic Ischemic Encephalopathy	3 (8.7)	63 (3.3)
Other	8 (7.8)	224 (11.5)

Table 1: Primary neurological diagnosis of paralyzed vs. non-paralyzed patients (Pooled Data). (*Primary neurological diagnosis data not available for 38 patients and omitted from denominator).

		Paralyzed			**Non-Paralyzed**	
	Period 1	**Period 2**	**Pooled**	**Period 1#**	**Period 2**	**Pooled**
	n=64	**n=39**	**n=103**	**n=1243**	**n=712**	**n=1955**
Seizures	0	3	3 (2.9%)*	208	127	335 (17.1%)*
Avg. Duration (days)	8.8	5.17	7.45	2.62	1.85	2.38
#AEDs, median	N/A	1	N/A	N/A	1	N/A
#Sedatives, median	N/A	3**	N/A	N/A	0**	N/A
Poor Outcome at Discharge	60 (93.8%)	N/A	N/A	582 (46.9%)	N/A	N/A

Table 2: Summary of seizure incidence and other clinical features in paralyzed vs. non-paralyzed patients. (*$p<0.001$, Fisher's Exact Test, **$p<0.001$, Negative binomial regression, # Period 1, non-paralyzed group contained 1243 patient monitoring sessions in 1241 individual patients, Period 1=January 1, 2009 to August 31, 2011, Period 2=February 26, 2013 to July 2, 2014, N/A=Data not available, Poor Outcome defined as expired, hospice, skilled nursing or long term care facility).

Discharge disposition was available for the patients undergoing cEEG during the first study period (January 1, 2009 to August 31, 2011). Disposition was categorized as having favorable outcome (home, home health or rehabilitation) or unfavorable outcome (skilled nursing facility, long term care, hospice, expired or transfer to another hospital). Unfavourable outcome was higher in patients receiving neuromuscular blockade (93.8% vs. 46.9%).

Detailed information was available regarding anticonvulsant and sedative use for the patients undergoing cEEG during the second study period (February 26, 2013 to July 2, 2014) All pharmacologically

paralyzed patients were receiving at least one sedative medication, median of 3, compared to only 45% of the non-paralyzed patients, median number of 0 ($p<0.001$ negative binomial regression). In the paralyzed patients, the most commonly used sedative was fentanyl (95%) followed by midazolam (72%) and propofol (69%) compared to fentanyl (32%), propofol (25%) and midazolam (12%) in the non-paralyzed group. There was no difference in administration of anticonvulsant medications between the two groups (median of 1) with levetiracetam being the most commonly used medication in both groups (85% of paralytic patients and 75% of non-paralytic patients).

Discussion

Previous reports of the occurrence of non-convulsive seizures in critically ill patients undergoing cEEG have ranged from 8% to 48% [**1-4**]. Specifically, studies of patients with subarachnoid hemorrhage who undergo cEEG have shown the incidence of non-convulsive seizures to range from 7-15% [5-7]. However, in our series of 103 critically ill patients undergoing cEEG during pharmacological paralysis, we found only 3/103 (2.9%) with electrographic seizures, despite the majority of these patients having an underlying diagnosis of subarachnoid hemorrhage and hence, at relatively high risk for seizures. In addition, 2 of the 3 patients noted to have electrographic seizures while paralyzed were undergoing cEEG monitoring and experiencing electrographic seizures prior to initiation of paralytic. In comparison, seizures were seen in 335/1955 (17.1%) of patient undergoing cEEG at Emory University Hospital during these two study periods but not receiving neuromuscular blockade. This suggests that critically ill patients undergoing cEEG and neuromuscular blockade are at decreased risk for seizures compared to the general ICU population receiving cEEG who are not paralyzed and undergoing cEEG for other indications. We hypothesize that the marked decrease in seizure frequency is due at least in part to concurrent use of multiple sedative medications given that a much larger percentage of paralyzed patients were receiving sedatives with strong anticonvulsant properties (propofol and midazolam).

The mean duration of cEEG monitoring in patients requiring pharmacological paralysis was relatively long (7.45 days) compared to non-paralyzed patients (2.38 days). There remains some uncertainty in clinical practice regarding the duration of monitoring needed to exclude subclinical seizures in ICU patients. One recent study found that of patients with electrographic seizures during cEEG, 80% of comatose patients and 95% of noncomatose patients had the first seizure within 24 h of monitoring, and 87% of comatose patients and 98% of non-comatose patients experienced seizures within 48 h of monitoring [3]. A period of 24 h has been suggested as a reasonable duration of monitoring to screen for seizure activity in noncomatose patients with longer periods for comatose patients or patients with periodic discharges [3,4]. A recent survey of practicing neurologists found that most clinicians would continue monitoring for 24 h if no seizure activity was detected [8]. These suggested durations are significantly shorter than the average duration of monitoring in our subset of patients with neuromuscular blockade who were undergoing cEEG monitoring for the primary purpose of monitoring depth of sedation. In addition, although paralyzed patients comprised only 5% of the pooled cohort, number of cEEG monitoring days represented 13% of total monitoring days during these 2 study periods, indicating that paralyzed patients utilize a disproportionate quantity of cEEG resources. In addition to increased utilization of cEEG resources, poor outcomes seen in the majority of patients undergoing neuromuscular blockade suggests that prolonged EEG monitoring in this patient population may not be cost effective.

Alternate means to objectively assess levels of sedation are available and have been used in operating room settings. Bispectral analysis (BIS) was originally developed to measure the hypnotic effect of general anesthesia, and has been FDA approved for reducing intraoperative awareness during general anesthesia [9]. Some studies have shown a good correlation between bispectral analysis and recognized clinical sedation scales [10,11]. Though the utility of BIS is still primarily in the operating room setting, several studies have examined the use of BIS for monitoring depth of sedation in intensive care unit settings. Two studies of critically ill patients undergoing barbiturate therapy for increased intracranial pressure reported good correlation between BIS and suppression ratio (SR) [12,13]. Additional studies are needed to further explore the potential value and reliability of BIS monitoring in this patient population, particularly patients undergoing neuromuscular blockade. However, in specific patient populations with very low incidence of electrographic seizures and when the sole purpose of EEG monitoring is to ensure depth of sedation, BIS might offer a practical, cost-effective option.

This study had several limitations. The main limitation is driven from its retrospective nature; also our study site was limited to a single hospital site and as such may not be generalizable to other settings. Additionally, clinical data is limited by documentation in the electronic medical record and the ICU EEG database. Finally, the finding of low seizure incidence might be confounded by the fact that fewer of the paralyzed patients had a primary diagnosis of seizures or status epilepticus compared to the patients not undergoing paralysis (1.9 vs. 27.5%). However, this finding further supports that patients undergoing paralysis rarely have a primary neurological diagnosis of seizures or status epilepticus and hence, another indication that they are at lower risk for electrographic seizures.

Conclusion

Continuous EEG monitoring is resource-intensive, requiring around the clock support from EEG technologists as well as highly trained neurophysiologists. Although cEEG is an invaluable tool for detection of subclinical seizures in high risk populations, prolonged cEEG recording may not be necessary in all critically ill patients, particularly those receiving neuromuscular blockade concurrent with high dose sedatives and no primary neurological diagnosis of seizures or status epilepticus. Furthermore, cEEG is a costly and limited resource which needs to be utilized judiciously. Therefore, clinical be nefit and ability to alter outcome are important factors to consider when selecting patients for cEEG. If the primary indication for monitoring is not detection of subclinical seizure activity but rather assessment for depth of sedation, it may not be necessary or cost-effective to utilize cEEG. Future prospective studies are needed to explore our findings, until then alternative means for monitoring such as bispectral analysis could be considered.

Acknowledgement

Suzette LaRoche declares that she has received research funding from UCB Pharma, NIH (SBIR in collaboration with Optima Neuroscience), and receives royalties from Demos Publishing.

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