Change in Management of Status Epilepticus With the Addition of Neurointensivist-Led Neurocritical Care Team at a Rural Academic Medical Center

Hospital Pharmacy
2018, Vol. 53(5) 303–307
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DOI: 10.1177/0018578717750094
journals.sagepub.com/home/hpx

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Abstract

Learning Objective: Status epilepticus (SE) is continuous clinical and/or electrographic seizures lasting 5 minutes or more without recovery and carries a high mortality. Medication management varies by institution, as well as administration, combination of antiepileptic drugs (AEDs), and dosing. **Methods:** Single-center retrospective review of medication management of SE patients admitted to West Virginia University Hospital before and after neurointensivist implemented guidelines. Patients admitted between January 2012 and June 2014 were grouped in the prior to neurointensivist group (pre-NI) and patients admitted between July 2014 and June 2016 were grouped in the postneurointensivist group (post-NI). Baseline demographics, hospital, intensive care unit (ICU), and ventilator length of stay were recorded. Medications reviewed included number of AEDs and maximum dose of lorazepam, phenytoin, levetiracetam, and lacosamide. Outcomes included number of continuous infusions of either midazolam or propofol at seizure suppression doses as well as pentobarbital, phenobarbital, or ketamine, and need for vasopressor use. **Results:** Of the 74 patients included, the pre-NI group (n = 40) utilized more AEDs (6 vs 4) compared with the post-NI group (n = 34). The pre-NI group had less midazolam continuous infusions meeting seizure suppression doses (8 vs 9), but higher average doses (49 vs 27 mg/h) compared with the post-NI group. More patients in the pre-NI group were on propofol seizure suppression doses (15 vs 10) and phenobarbital continuous infusions (11 vs 2) than the post-NI group. Patients had less vasopressor use in the post-NI group than the pre-NI group (11 vs 23). Frequency and dosing of lorazepam, phenytoin, levetiracetam, and lacosamide were similar between the 2 groups. Ventilator use, hospital, and ICU length of stay were also similar between groups. **Discussion:** Implementation of a neurointensivist and medication guidelines resulted in fewer AEDs and less vasopressor use in the management of SE. Midazolam use was slightly higher in the post-NI group but at lower doses overall.

Keywords

anticonvulsants, clinical services, critical care, drug/medical use evaluation, neurology, disease management

Background

Status epilepticus (SE) is defined by the Neurocritical Care Society as 5 minutes or more of continuous clinical and/or electrographic seizure activity. The definition also includes recurrent seizure activity without recovery between seizures.¹ Causes of SE can include medical history of epilepsy, traumatic brain injury, consumption or drug induced, anoxia, metabolic disturbances, hypertensive encephalopathy, central nervous system infection, stroke, or tumors.¹ Morbidity can be debilitating with deterioration in functional status (21%-26%) and severe neurological or cognitive sequelae (11%-16%) in many patients.¹ Associated mortality rates

depend on age, duration of SE, and etiology but have been seen as high as 61% in nonconvulsive and refractory SE.^{1,2} However, mortality rate may be as low as 8% with adequate therapy.³

Medication management of SE as outlined in the Neurocritical Care Society guidelines include benzodiazepines

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Figure 1. Neurocritical Care Society status epilepticus guidelines.

Note. The class category (I, IIa, IIb, or III) and level of evidence (A, B, or C) represents recommendations for each medication cited in the Neurocritical Care Guidelines.

followed by loading doses of antiepileptic medications (AEDs) such as phenytoin, fosphenytoin, phenobarbital, valproic acid, or levetiracetam. Other management strategies may include a combination of other antiepileptics depending on previous response or home medications. Management is grouped in stages to reflect first, second, and third lines of therapy and are classified as emergent initial, urgent control, and refractory therapies, respectively. Emergent initial therapy includes benzodiazepines then loading doses of AEDs followed by urgent control or maintenance AED therapy. Refractory SE is defined by continued SE after receiving adequate doses of an initial benzodiazepine followed by a second AED (ILAE).^{1,4} If SE continues, continuous infusion of benzodiazepine (ie, midazolam) or barbiturates may be indicated. Current Neurocritical Care Society SE guidelines are outlined in Figure 1.

Evidence regarding management of SE is lacking with various studies showing conflicting results. It has been shown that benzodiazepines are superior to other emergency AEDs in regard to acute treatment. However, specific treatment recommendations on which AED to use next are sparse, with most prominent research completed utilizing phenytoin, levetiracetam, or valproic acid.^{1,4}

West Virginia University Medicine J.W. Ruby Memorial Hospital recently implemented a neurocritical care consult service led by a neurointensivist for recommendations in the treatment of critically ill patients with neurologic complications. This neurointensivist-led team consists of an intensivist, pharmacist, advanced practice providers, and nurses. Initiatives from this team included creating a protocol for standardized treatment of SE for the intensive care units (ICUs) of our hospital as shown in Figure 2. Lorazepam is the intravenous (IV) benzodiazepine drug of choice due to its long duration of action and quick onset. AEDs used in this sequence based on the protocol include phenytoin, levetiracetam, and lacosamide. Lacosamide has limited evidence compared with most other AEDs; however, it has promising reduction in seizure frequency as well as an IV formulation and minimal drug interactions. Evaluation of drug management related to SE management after implementation of this protocol was warranted.

Methods

This is a single-center retrospective chart review of medication management of patients with SE admitted before and after implementation of a neurointensivist-led team. This study was approved by the Institutional Review Board of West Virginia University. Patients admitted between January 2012 until June 2014 were grouped in the prior to neurointensivist group (pre-NI), and patients admitted from August 2014 until June 2016 were considered the postneurointensivist group (post-NI). Patients admitted between the time frames with the International Classification of Diseases (ICD) 9/10. codes for SE were included in the analysis. Patients were excluded from the study if they had seizures related to alcohol withdrawal, had psychogenic seizures, or were less than 18 years of age.

Data collected included baseline demographics, etiology of seizure, and the incidence of patients having a history of epilepsy. Other variables collected included hospital length of stay, ICU length of stay, days on mechanical ventilation, number of AEDs, order of administration of AEDs, average daily doses of AEDs, number of continuous infusions for sedation, seizure suppression dosage achieved by continuous infusion sedatives, ketamine use, pentobarbital use, and the incidence of vasopressor use.

The primary outcome included number of continuous infusions of either midazolam or propofol at seizure suppression doses (>0.1 mg/kg/h or 20 μ g/kg/min, respectively). Secondary outcomes included use of pentobarbital, phenobarbital, or ketamine as well as need for vasopressor support.

Figure 2. West Virginia University Medicine J.W. Ruby Memorial Hospital Status Epilepticus Protocol.

Note. IV = intravenous; q = every.

Table 1. Baseline Demographics of Patients in the Pre- and Post-NI Groups (N = 74).

	Pre-NI (n = 40)	Post-NI (n = 34)
Age, average years	57.2 ± 16.5	54.8 ± 18.0
Gender, % male	48	47
Weight, average kg	86 ± 20.7	82 ± 20.6
Height, average in	67 ± 4.4	66 ± 3.8
Race, n, (%)		
Caucasian	39 (98)	33 (97)
African American	1 (3)	1 (3)
History of epilepsy, n (%)	12 (16)	14 (19)

Note. NI = neurointensivist.

Statistical analysis of categorical variables was completed by a chi-square (χ^2) test. *P* values less than .05 were considered significant showing association between endpoint (continuous infusion) and pre- and post-NI.

Results

Baseline demographics are depicted in Table 1. There were a total of 74 patients included with 40 in the pre-NI group and 34 in the post-NI group. Patients in both groups ranged between 21 and 90 years of age (average 56 years) with about half being male (48% in pre-NI and 47% in post-NI). The majority of patients were Caucasian. The most common etiologies for SE were patients with a history of epilepsy (n = 23, 31.1%), trauma (n = 18, 24.3%), and stroke (n = 13, 17.6%). Patients with medical history of epilepsy represented 16% in the pre-NI group and 19% in the post-NI group. Other causes of SE represented less than 7% of cases which included cancer, infection, substance induced, tumor, cardiac arrest, or unknown reason.

On average, patients in the pre-NI group utilized more AEDs (6 vs 4 total agents) compared with the post-NI group during SE

event. Of the patients in the pre-NI group, 97.5% received another type of AED (other than phenytoin, levetiracetam, and lacosamide) compared with 38.2% in the post-NI group. The use of other types of AED such as fosphenytoin, valproic acid, topiramate, carbamazepine, and pentobarbital are shown in Figure 3. Other types of benzodiazepines in addition to, or in replacement of, lorazepam included midazolam, clonazepam, or diazepam. The pre-NI group utilized midazolam 91.4% (32 of 35), clonazepam 5.7% (2 of 35), or diazepam 2.8% (1 of 35) of the time, and the post-NI group utilized midazolam 95.6% (22 of 23) and diazepam 4.3% (1 of 23) of the time.

Table 2 represents the general usage and average dosing of lorazepam, phenytoin, levetiracetam, and lacosamide in both groups. Average dosing was similar among both pre-NI and post-NI groups for lorazepam, levetiracetam, and lacosamide. However, average dosing of phenytoin was lower in the pre-NI group. Phenytoin levels were not collected in this analysis.

The primary outcome of midazolam continuous infusion use was lower in the pre-NI group (8 vs 9 patients, *P* = .5096) and had higher average doses (49 ± 29.8 vs 27 ± 18.7 mg/h) compared with the post-NI group. However, another primary outcome of propofol continuous infusion use was lower in the post-NI group (15 vs 10 patients, *P* = .4635). Secondary outcomes of phenobarbital continuous infusions were higher (11 vs 2 patients, *P* = .0149) in the pre-NI group than in the post-NI group, but ketamine continuous infusions were more common in the post-NI group than in the pre-NI group (4 vs 0 patients) as seen in Figure 4. Patients had less vasopressor use in the post-NI group than in the pre-NI group (11 vs 24 patients, *P* = .0305).

There was relatively no change in either hospital (12 vs 11 days) or ICU (7 vs 7 days) length of stay in both the pre-NI or post-NI group, respectively. Ventilation days were also consistent between the groups (7 days in pre-NI and 6 days in post-NI).

Figure 3. Frequency of AED use in SE management in ICU patients: pre- and post-implementation of neurointensivist-led team.

Note. Number of occurrences of AED use between groups. Other (<2 used for either group): clonazepam, carbamazepine, and diazepam. AED = antiepileptic medication.

Table 2. Average Use and Mean Doses of Lorazepam, Phenytoin, Levetiracetam, and Lacosamide.

AED (average dose)	Pre-NI (n = 40)	Post-NI (n = 34)
Lorazepam, n (mg)	35 (2)	28 (3)
Phenytoin, n (mg)	24 (600)	25 (1000)
Levetiracetam, n (mg)	21 (1200)	27 (1300)
Lacosamide, n (mg)	18 (300)	18 (300)

Note. AED = antiepileptics medication.

Discussion

This single-center, retrospective study reviewed the implementation of a neurointensivist-led team and a protocol of SE management in the ICU. The main finding was less utilization of AEDs overall. As a result, patients in the post-NI group utilized more midazolam infusions meeting seizure suppression doses but at lower doses as compared with the pre-NI group. The post-NI group also utilized less propofol and pentobarbital infusions. Although it was not found to be statistically significant, vasopressor use in the post-NI group was lower. Lack of literature to guide treatment options for SE has made the condition difficult to manage. Treatment decisions are largely left to physician discretion in situations where time is limited. This study provides a glimpse into the changing management of SE with new techniques and expert consultation from a neurointensivist.

Other institutions reviewing SE management were similar to our hospital's SE protocol (Figure 2).

Figure 4. Number of continuous infusions used in pre- and post-neurointensivist groups.

Note. Midazolam seizure suppression dose: > 0.1 mg/kg/h. Propofol seizure suppression dose: >20 µg/kg/min.

*Statistically significant ($P < .05$).

A retrospective review of 15 hospitals' SE medication management found the average number of AEDs given was 3 medications (interquartile range [IQR]: 2-4) for the total treatment duration.⁵ This result was also found to be similar to the current study in regard to patients being managed post NI. Cook et al also found that benzodiazepines were the first agent administered in SE ~75% of the time, followed by phenytoin (33%) and levetiracetam (10%). Valproic acid and topiramate were utilized <10% of the time (8% and 6.7%, respectively). Lacosamide was actively being approved at the time of the previous study; therefore, use was about 5.3%, which did not reflect the entire duration of the study and was still found to be implemented at similar rates as valproic acid and topiramate.⁵

Specific AEDs used acutely for SE include loading doses of phenytoin, fosphenytoin, levetiracetam, and lacosamide. Due to recent manufacturer shortages of fosphenytoin, it was not seen as often in the post-NI group at our institution. Evidence regarding which AED to load first is minimal. A meta-analysis of published studies evaluating comparisons of levetiracetam and phenytoin or valproic acid was conducted. The authors included 4 studies in which there was no statistically significant difference in clinical seizure cessation (odds ratio [OR]: 1.07; 95% CI: 0.57-2.03).⁶ Lacosamide is a relatively newer AED with growing evidence in its use for refractory SE. Sutter et al retrospectively evaluated adult patients at a single center in which 45 patients received IV lacosamide. They found a trend favoring lacosamide in regard to duration of SE and seizure control but was not found to be statistically significant. However, there was a

decreasing trend of mortality which was statistically significant when adjusted for age (OR: 0.34, 95% confidence interval [CI]: 0.1-0.9).⁷

Less vasopressor use in the post-NI group could have been attributed to lower midazolam infusion doses, less overall propofol and pentobarbital use, and higher ketamine usage. Ketamine use increased in the post-NI group more frequently which has also been seen at other practices and in the literature for refractory SE.^{5,8} As mentioned, less AED use was also seen in the post-NI group which either could have been from the order of which agents were administered or utilizing evidence-based dosing strategies to achieve burst suppression. This practice of assuring correct dosing and timing of AEDs can further decrease polypharmacy as we have seen in this study by lower AED use overall.

Limitations of this study include the retrospective nature of the project and lack of documentation. The initial intent was to review timing of which agents were given prior to others. However, this was difficult to assess if patients were first seen in the emergency department (ED) or by transfer in which documentation of exact medication times was not present. Other limitations included situations if the West Virginia University SE protocol was not followed. Burst suppression rates to determine treatment success were not collected either.

Conclusion

It was found in this single-center retrospective review that the implementation of a neurointensivist and protocol for the management of SE in the ICU resulted in less AED use overall. Patients in the post-NI group also experienced more midazolam infusions at seizure suppression doses; however, further analysis found average doses were lower than in the pre-NI group. Less propofol, pentobarbital, and vasopressor use was seen in the post-NI group as well.

Acknowledgment

The authors thank Hannah Ludwick (West Virginia University) for help with statistical analysis.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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