CLINICAL CORRELATES OF INTRAVENOUS ANESTHETIC DRUG USE IN NONCONVULSIVE STATUS EPILEPTICUS

By

Utku Uysal

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Chairperson Theresa I. Shireman, Ph.D., RPh

_____
Edward Ellerbeck, MD, MPH

_____
Gary Gronseth, MD

Date Defended: 04/27/2015

The Thesis Committee for UTKU UYSAL
certifies that this is the approved version of the following thesis:

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Chairperson Theresa I. Shireman, Ph.D., RPh

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ABSTRACT

Objective: To determine factors associated with continuous IV anesthetic drug (IVAD) use in nonconvulsive status epilepticus (NCSE).

Methods: For this retrospective descriptive cohort study, we included all patients who met clinical and EEG criteria of NCSE from 2009 to 2014 at a tertiary academic medical center. Patients were categorized according to IVAD use. Primary outcome variables were response to treatment and in-hospital death. We used descriptive analyses for baseline characteristics, and primary and secondary outcome variables differences among patients who received IVAD and who did not receive IVAD.

Results: Forty-three patients had a total of 45 NCSE episodes. IVAD was used in 69% of the episodes. Patients treated with IVAD were younger (53.1±14.1 vs 64.1±13.3, p=0.0187). The episodes treated with IVAD were associated with more acute neurologic pathology (58% vs 21%, p=0.0236) and more commonly presenteded in comatose patients (39% vs 7%, p=0.0299). Underlying epilepsy was common in both groups (36% in IVAD vs 42% in no-IVAD group). NCSE resolved in 74% of the patients who received IVAD. There were total 13 in-hospital deaths (ten in IVAD users vs three in the no-IVAD group). Only one in-hospital death appeared to be a direct consequence of IVAD.

Conclusion: Our findings showed factors such as younger age, acute neurologic pathology and coma at presentation were associated with IVAD use in patients with NCSE. More patients died in IVAD group although this was not statistically significant. There is a need of further studies to determine the effect of IVAD use in NCSE on outcome, and these factors should be controlled in the future outcome and effectiveness studies.

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INTRODUCTION

Status epilepticus (SE), the continuous clinical and/or electrographic seizure activity lasting more than 5 minutes or recurrent seizures without recovery between the seizures [1], is a life threatening neurological emergency that requires immediate treatment. The incidence of SE varies between 9.9-41.0 per 100,000 population[2–4] with a mortality rate of as high as 22% [3,5]. There are two main subtypes of SE, convulsive SE (CSE) and nonconvulsive SE (NCSE), depending on the presence or absence of major motor signs. NCSE, in particular, is a heterogeneous medical condition with varying etiology and clinical presentation, including subtypes such as absence SE (ASE), simple partial SE, complex partial status epilepticus (CPSE), subtle SE (SSE), and NCSE in coma. NCSE has been reported in up to 27% of ICU patients with altered mental status, 8% of those in coma, and 34% of status epilepticus (SE). In these patients, NCSE is associated with excess risk for morbidity and mortality [6–8]. Its mortality risk is associated with the underlying etiology, with higher rates noted in patients with an acute medical condition and acute brain injury, and lower rates in patients with a previous known history of epilepsy, CPSE and ASE [9–11] .

First line treatment of SE generally starts with lorazepam as recommended by the Veteran's Administration trial [12] or with other benzodiazepines such as midazolam, or diazepam and continues with an anticonvulsant such as phenytoin or fosphenytoin, valproate sodium, or phenorbarbital. If SE continues, the Neurocritical Care Society and European Federation of Neurological Societies guidelines recommend continuous infusion of an IV anesthetic drug (IVAD) such as midazolam, propofol, pentobarbital, or thiopental, to achieve burst-suppression [13,14]. The guidelines note, however, that little data is available to direct continuing therapy for refractory SE

The dearth of evidence is even more apparent for refractory NCSE. Guidelines cautiously recommend use of IVAD and recommendcommend tailoring the treatment to the individual patient and using further non anesthetic anticonvulsants before IVAD due to the potential for favorable outcomes with CPSE and the other known risks of IVAD [14–16].

There is a dearth of data in the literature detailing how IVAD is used in NCSE management. This limits our understanding of the association between IVAD use and patient outcomes. Although recent reports suggest an increased risk of poor outcomes with use of IVAD in SE, more research specific to NCSE is needed [17–19]. In addition, identification of potential confounders, such as underlying etiology or co-morbidities in relation to IVAD use, is needed. Therefore, we characterized our center's management of a cohort of NCSE patients to identify the clinical context, outcomes and factors associated with IVAD use in order to support further outcome and effectiveness studies and to determine if IVAD use is associated with higher mortality rate.

MATERIAL AND METHODS

Setting and Design. We performed a retrospective cohort study of patients with NCSE at the University of Kansas Medical Center, Kansas City, KS, a tertiary academic medical care center. The study was approved by the Institutional Review Board.

Case Identification. To provide the initial sample, we reviewed electronic medical records of patients admitted and treated between January 1st, 2009 through June 30th, 2014 who had undergone an EEG (with at least daily follow-up EEG) and/or continuous-video EEG (cvEEG), and had one or more of the following ICD-9 diagnosis codes for SE (345.2, 345.3) or epilepsia

partialis continua (345.70, 345.71). Inclusion criteria were those patient who met both the clinical definition of NCSE and who met EEG criteria. The clinical definition of NCSE was ”a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms.”[20]. The onset of NCSE was determined as the onset of clear clinical change in the neurologic condition even before the first EEG. EEG criteria are shown in Table 1[21]. Exclusion criteria were: 1) lack of or insufficient EEG or cvEEG to confirm the diagnosis, 2) simple partial status epilepticus, 3) poor clinical documentation on findings at presentation, 4) diagnosis of Creutzfeldt-Jacob disease, and 5) anoxic brain injury at presentation. We excluded patients with anoxic brain injury because of the uncertainty about the epileptic nature of status myoclonus and its independent association with poor outcomes [22–25]. Treatment of NCSE was left to the discretion of the attending epileptologists and neurointensivists.

Table 1. Working clinical criteria for nonconvulsive status epilepticus. ***Adapted from Beniczky et al*[21]**.

Working criteria for nonconvulsive status epilepticus
Patients without known epileptic encephalopathy
Epileptiform discharges with a frequency > 2.5 Hz, or
Epileptiform discharges with a frequency ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) and one of the following:
EEG and clinical improvement after iv anticonvulsant, or
Subtle clinical ictal phenomena during the EEG patterns mentioned above, or
Typical spatiotemporal evolution (change in voltage and frequency or location)
Patients with known epileptic encephalopathy
Increase in prominence or frequency of the features mentioned above, when compared to

baseline with observable change in clinical state
Improvement of clinical and EEG features with iv anticonvulsant

Data Collection and Variables. We extracted data from electronic medical records.Variables included demographics and clinical symptoms at the time of admission: level of consciousness at the onset of NCSE, presence of subtle motor findings (gaze or head deviation, rhythmic twitching of facial, ocular or extremity muscles), presence of GTC at the onset, co-morbidities, history of epilepsy, underlying etiology (individual diagnosis and acute medical pathology or acute neurologic pathology), sepsis at the time of diagnosis, presence of coma or intubation status. Acute neurologic pathology was defined as presence of meningoencephalitis, brain tumor, white matter changes, hypoxic-ischemic, metabolic or pharmacologic encephalopathy and stroke. Acute medical pathology was defined as presence of underlying infection, trauma other than traumatic brain injury, recent surgery before NCSE, or organ or system problem other than CNS were classified as having an acute medical condition.

We used the Status Epilepticus Severity Score (STESS) to grade the severity of NCSE. This score was calculated based on consciousness (alert or somnolent=0, stuporous/comatose=1), worst seizure type (simple partial, complex partial, absence or absence seizures=0, generalized convulsive seizures=1, NCSE in coma=2), age (<65 years=0, ≥65 years=1), and history of previous seizures (yes=0, no or unknown=1) and is dichotomized asas favorable (0-2) and unfavorable (3-6) to predict death as proposed by Rosetti et al [26].

We classified the antiepileptic treatment as a benzodiazepine (BZD) for the initial dose of IV lorazepam, IV/IM/rectal diazepam, or IV/intranasal midazolam; as intravenous non-anesthetic AED for IV phenytoin/fosphenytoin, valproate sodium, phenobarbital, levetiracetam or

lacosamide; as IVAD for continuous IV infusion of midazolam, propofol, pentobarbital, thiopental, or ketamine to achieve burst-suppression. If the patient was already on IVAD for other reasons, we did not count this as antiepileptic treatment unless IVAD dose was modified to treat NCSE to achieve burst-suppression.

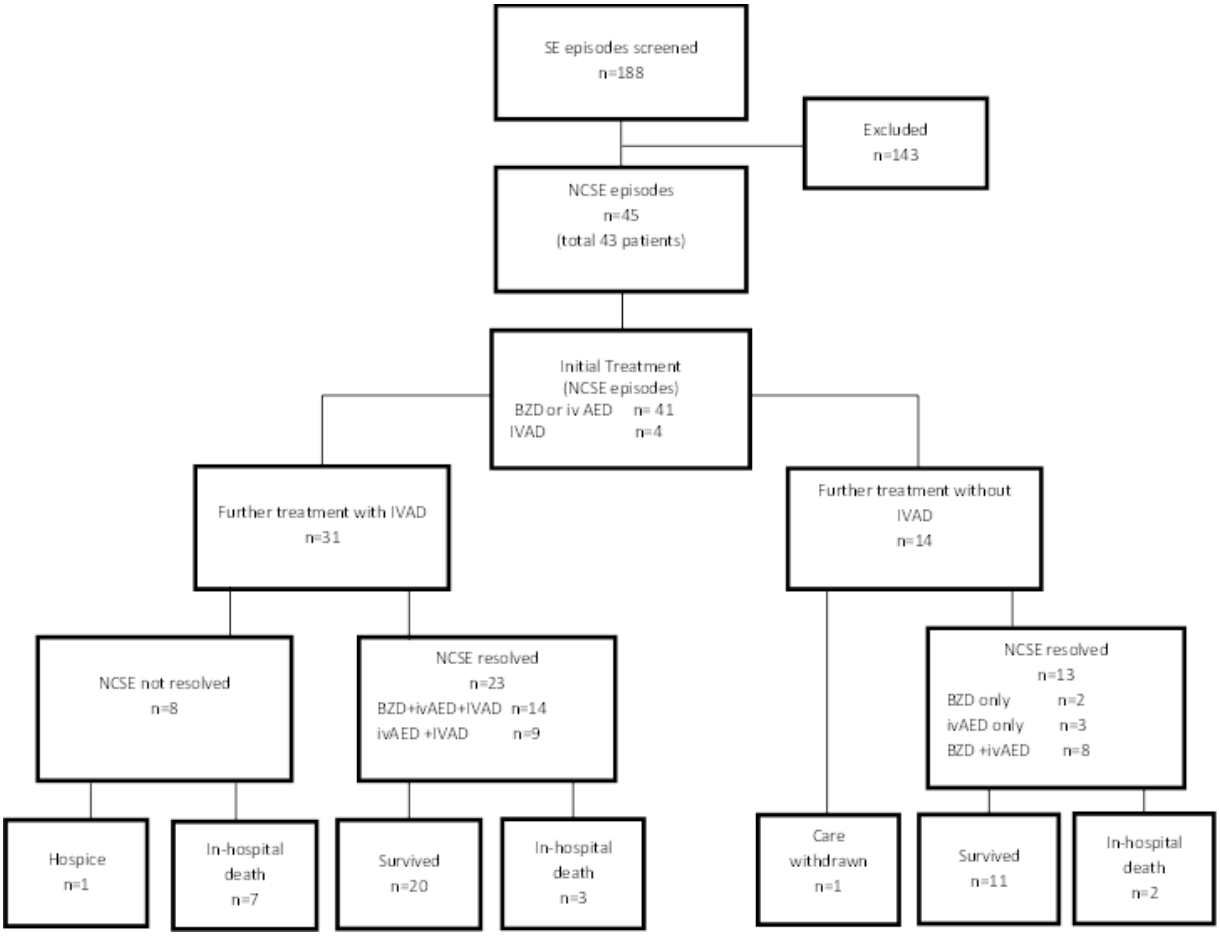
Primary and secondary outcomes. Our primary outcome variables were response to treatment and in-hospital death. Our secondary outcomes were used for exploratory analysis and included first choice treatment and use of more than one AED. Response to treatment was categorized as no response or resolution of NCSE with resolution ascertained by clinical improvement and/or EEG findings. We defined time to resolution as the number of days between the clinical and electroencephalographic diagnosis of NCSE and their clinical and/or electroencephalographic resolution of NCSE. We reported days as more exact time parameters were not consistently available. Temporary improvement was defined as either transient stopping of subtle motor movements or improvement in mental status without complete resolution of clinical findings, or temporary decrease in number or duration of electrographic seizures, fragmentation of rhythmic activity or decreased duration of rhythmic discharges with emergence of background in between.

Statistical analysis. All results were limited to descriptive analyses due to the small sample size. We compared primary and secondary variables among patients who received IVAD and who did not receive IVAD. We applied the Shapiro-Wilk test for continuous variables to assess normal distribution. Categorical variables were compared by Fisher exact test and continuous variables by t-tests if the data were distributed normally and Mann-Whitney U test if data were non-normal.

RESULTS

Using the electronic medical record, we identified 188 episodes treated between January 1st, 2009 and June 30th, 2014. Forty-three patients met study criteria. Two patients had two episodes of NCSE for total of 45 NCSE episodes (Figure 1).

Figure 1. Sample identification and treatment responses of the NCSE episodes



NCSE= Noncounvulsive status epilepticus, ivAED= iv non-anesthetic antiepileptic drug, BZD= benzodiazepine, IVAD=iv anesthetic drug.

Demographics and baseline clinical characteristics. Of the 45 NCSE episodes, 69% were treated with IVAD (Table 2). Patients treated with IVAD were younger. The episodes treated

with IVAD were associated with more acute neurologic pathology, higher STESS score, and more common in patients who were comatose. IVAD was used more commonly to treat NCSE when the patient was already intubated.

In seventeen episodes (38%) patients had history of epilepsy. The most common presenting symptom was AMS with subtle motor symptoms without preceding GTCS. Only 29% of the NCSE episodes had preceding GTCS with no recovery in mental status afterwards. About 18% of the NCSE episodes were associated with coma, and 47% had an underlying acute neurologic pathology.

Table 2. Demographics and clinical characteristics.

	Whole Group	No IVAD	IVAD	p-value
Number of patients	43	14	29	
Age	56.7±14.7	64.1±13.3	53.1±14.1	0.0187*
Sex-Male	20 (46.5%)	6 (42.9%)	14 (48.3%)	NS
Number of NCSE episodes	45	14	31	
Symptom at onset				
AMS only	12 (26.7%)	5 (35.7%)	7 (22.6%)	NS
AMS/subtle motor findings	20 (44.4%)	5 (35.7%)	15 (48.4%)	NS
AMS following GTCS	9 (20.0%)	3 (21.4%)	6 (19.3%)	NS
AMS/subtle motor finding following GTCS	4 (8.9%)	1 (7.1%)	3 (9.7%)	NS
Epilepsy	17 (37.8%)	6 (42.9%)	11 (35.5%)	NS
Acute Medical Pathology	26 (57.8%)	8 (57.1%)	18 (58.1%)	NS
Acute Neurologic Pathology	21(46.7%)	3 (21.4%)	18 (58.1%)	0.0236*
STESS ≥3 (Status severity score)	23 (51.1%)	6 (42.9%)	17 (54.8%)	NS
Coma	8 (17.8%)	0 (0%)	8 (25.8%)	0.0366*
Already intubated before NCSE	13 (28.9%)	1 (7.1%)	12 (38.7%)	0.0299*

IVAD=iv anesthetic drug, AMS= Altered mental status, GTCS= Generalized tonic-clonic seizure, STESS= Status Epilepticus Severity Score.

Etiology. Out of 17 NCSE episodes in patients with a history of epilepsy, five were due to medication non-compliance, two were due to sepsis, and two were due to other infections (Table 3). In the remaining episodes, infection caused seven and intracranial hemorrhage caused five episodes. Medication-induced NCSE occurred in four episodes (three from tacrolimus and one from cefepime), meningoencephalitis in four episodes, autoimmune encephalitis in two episodes, and ischemic stroke in two episodes. Trauma, meningioma, metabolic abnormality, and Non Hodgkin Lymphoma with leptomeningeal involvement caused NCSE in one episode. Sepsis with or without history of epilepsy, ICH, and meningoencephalitis were more common etiologies in episodes treated with IVAD.

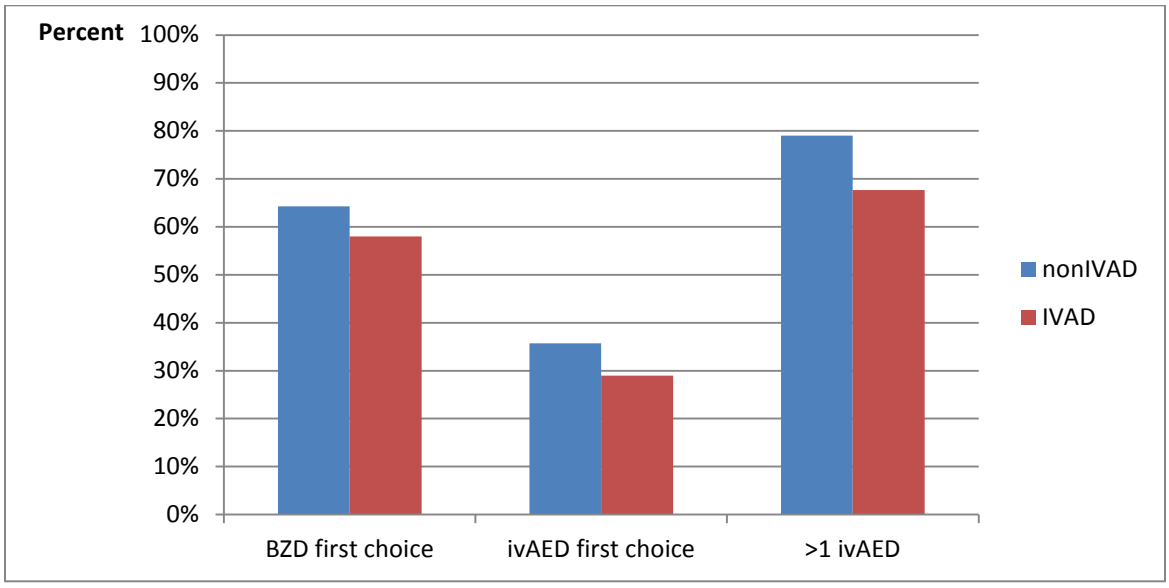
Table 3. Etiology of nonconvulsive status epilepticus

Etiology	Whole Group	No IVAD	IVAD
Epilepsy (total)	17 (37.8%)	6 (42.8%)	11 (35.5%)
Epilepsy-medication noncompliance	5 (11.1%)	2 (14.3%)	3 (9.7%)
Epilepsy-sepsis	2 (4.4%)	0 (0.0%)	2 (6.45%)
Epilepsy-infection	2 (4.4%)	0 (0.0%)	2 (6.45%)
Infection (excluding cases with epilepsy)	7 (15.5%)	2 (14.3%)	5 (16.1%)
Sepsis	5 (11.1%)	1 (7.1%)	4 (12.9%)
Infection-no sepsis	2 (4.4%)	1 (7.1%)	1 (3.2%)
Intracranial hemorrhage	5 (11.1%)	1 (7.1%)	4 (12.9%)
Medication	4 (8.9%)	2 (14.3%)	2 (6.4%)
Meningoencephalitis	4 (8.9%)	0 (0.0%)	4 (12.9%)
Autoimmune encephalitis	2 (4.4%)	1 (7.1%)	1 (3.2%)
Stroke	2 (4.4%)	0 (0.0%)	2 (6.4%)
Trauma	1 (2.2%)	0 (0.0%)	1 (3.2%)
Non Hodgkin Lymphoma	1 (2.2%)	1 (7.1%)	0 (0.0%)
Meningioma	1 (2.2%)	0 (0.0%)	1 (3.2%)
Metabolic	1 (2.2%)	1 (7.1%)	0 (0.0%)

IVAD=iv anesthetic drug, CNS= Central nervous system., IVAD=iv anesthetic drug.

Treatment. BZDs were used in 27 (60%) episodes as first choice (Figure 22). In 11 episodes it was given before the EEG – three in outside hospital before transfer- and in 16 episodes during the EEG. In both groups majority of the episodes were treated with BZD as first-line treatment; nine episodes (64%) in no IVAD and 18 episodes (58%) in IVAD group. A non-sedating intravenous AED was first choice in nine (29%) episodes in IVAD group and in five episodes (36%) in no IVAD group. In all episodes when IVAD was used patients were intubated, whereas patients were intubated in only two episodes (14%) for airway protection when IVAD was not used. Only in four episodes with already intubated patients was IVAD started to treat NCSE before use of BZD or intravenous AED. Intravenous AED was used in all of the NCSE episodes. In 68% of episodes treated with IVAD and in 79% of episodes treated with no IVAD, patients had additional non-anesthetic intravenous AED.

Figure 2. Distribution of medications administered to stop NCSE stratified by use of IVAD



IV AED= iv non-anesthetic antiepileptic drug, BZD= benzodiazepine, IVAD=iv anesthetic drug.

Out of 31 episodes treated with IVAD, 11 episodes (36%) required more than one IVAD. Propofol was used in total 24 episodes; in 19 episodes as first choice, in 12 episodes as only IVAD and in five episodes as the second choice. Midazolam was used in 21 episodes; in 11 episodes as first choice, in six episodes as only IVAD and in eight episodes as second or third choice. Pentobarbital is used in four episodes but only in one episode as first choice. Ketamine was used in three episodes as second and third choice.

Outcomes. Of 45 NCSE episodes, 9 (20%) did not respond to treatment. Among those who did not respond to treatment, one patient's family denied further care after the diagnosis of NCSE; in eight episodes burst-suppression pattern was achieved, but seven patients expired; and one patient was sent to hospice. Of 27 episodes treated with BZD as first choice, two episodes (4%) showed resolution and nine episodes (20%) showed temporary clinical or EEG improvement. BZD and intravenous AED together appeared to lead to resolution of NCSE in 18% of the episodes. About 50% of NCSE appeared to respond to IVAD. Among patients who were treated with IVAD, 74% of the NCSE episodes resolved after initiation of IVAD (Table 4).

Table 4. Outcome variables

	Whole Group	**No IVAD**	**IVAD**	**p-value**
Resolution of NCSE				
No resolution	9 (20.0%)	1 (7.14%)	8 (25.8%)	NS
With BZD only	2 (4.4%)	2 (14.3%)	NA	
With ivAED only	3 (6.7%)	3 (21.4%)	NA	
With BZD+ivAED	8 (17.8%)	8 (57.1%)	NA	
With ivAED+IVAD	9 (20.0%)	NA	9 (29.3%)	

BZD+ivAED+IVAD	14 (31.1%)	NA	14 (45.2%)	
Time to resolution sincefrom NCSE diagnosis				
Median (Days)	1	1	1	NS
Mean (Days)	2.0±2.1	1.5±1.1	2.4±2.5	NS
In-hospital death	13 (28.9%)	3 (21.4%)	10 (32.3%)	NS

ivAED= iv non-anesthetic antiepileptic drug, BZD= benzodiazepine, IVAD=iv anesthetic drug.

There were total 13 in-hospital deaths, ten in the IVAD group and three in patientspatient without IVAD group (Table 5). All patients but two had potentially fatal medical conditions. Among patients on IVAD, one patient who had epilepsy died from propofol infusion syndrome. This patient also met the sepsis criteria after starting IVAD. Four patients died from sepsis, three of whom had either sepsis or infection at the admission. The rest of the patients died due to worsening of their underlying medical conditions or complications. All three patients who died in no IVAD group were also very sick with multiple medical problems. In one of them, the family denied further care. The second had pneumonia, pancytopenia, progressive multifocal leukoencephalopathy and graft versus host disease. The third had Non-Hodgkin lymphoma with leptomeningeal involvement.

Table 5. Etiology and EEG findings of the patients who died in the hospital

Patient	**Reason for death**	**Etiology of NCSE**	**EEG finding at the time of death**
IVAD			
1	Multi organ dysfunction	Meningoencephalitis	NCSE-BS-NCSE
2	Meningoencephalitis	Meningoencephalitis	Diffuse slowing
3	NCSE	Meningoencephalitis	NCSE-BS-NCSE
4	Sepsis	Stroke	BS
5	Sepsis	Sepsis	BS
6	Stroke	Ruptured thoracic aortic aneurysm	Diffuse slowing
7	Sepsis	Epilepsy/ Urinary tract infection	BS

8	Sepsis	Sepsis	NCSE
9	Intracranial hemorrhage/ischemic stroke	Intracranial hemorrhage	Diffuse slow
10	Propofol infusion syndrome/sepsis	Epilepsy	BS
No IVAD			
11	Sepsis, NCSE (family denied further care)	Sepsis	NCSE
12	Non Hodgkin Lymphoma/ Leptomeningeal involvement	Non Hodgkin Lymphoma/ Leptomeningeal involvement	Diffuse slowing
13	Progressive multifocal leukoencephalopathy, graft versus host disease	Infection	Diffuse slowing/GPD

Death= In-hospital death, NCSE= Noncounvulsive status epilepticus, BS= burst-suppression, GPD=generalized periodic discharges.

DISCUSSION

In this retrospective single center cohort study, we analyzed 45 rigorously defined NCSE episodes from 43 patients to evaluate the clinical contexts and outcomes of IVAD use. The majority of the NCSE episodes (69%) at our institution were treated with IVAD. Those who were treated with IVAD were younger in age, had an acute neurologic pathology, and had been in a coma or intubated. The majority of the patients, regardless of ongoing IVAD use, received BZD as first choice treatment, and 100% in the no IVAD group and 87% of IVAD group received either BZD or an intravenous non-sedating AED as first choice of treatment showing compliance with published guidelines in general. NCSE resolved in 74% of the patients who received IVAD, though in-hospital death, and sepsis was more common among the IVAD group.

One of our most striking findings was the high rate of IVAD use. We found that 69% of the NCSE episodes treated in our center received IVAD. While this rate appears higher than previous reports of 11% to 37%, we restricted our cohort to persons with NCSE while others included NCSE as a subtype among other SE types[17,27] . The higher rate in our cohort may also reflect the selection of more refractory cases as we required ongoing EEG evidence of seizure. Higher rates of IVAD use have been reported in patients with refractory SE. For instance, Hocker et al showed that 87.3% of their refractory SE of any type received IVAD[28]. However, Novy et al reported only 30% their refractory NCSE received IVAD[29]. They attributed their low rate to their practice of escalating the use of non-sedating AEDs and monitoring response before considering IVAD use. In our cohort we noted that the majority of episodes were treated with additional intravenous non-sedating AED whether IVAD was used or not. Given the dearth of research on practice patterns in NCSE management, further examination of treatment implementation across other academic medical centers would better establish the state of the art for refractory NCSE.

One of our aims was to describe factors associated with IVAD use in NCSE. We found that IVAD use was more frequent in episodes when the patients were younger, had an acute neurological pathology as etiology, and were in a coma or already intubated before the NCSE diagnosis. In our cohort, the proportion of those treated with IVAD who had severe status (STESS $\geq$3) was higher than those who did not get IVAD, though the difference was not statistically significant. Whether these factors are associated with refractoriness in NCSE cannot be answered by our study. However, a recent study identified acute etiology, coma/stupor, and decreased serum albumin as early predictors of refractory status epilepticus [30]. We appreciate

that a direct comparison between their study and ours cannot be made due to methodological differences, but about 70% of their cohort had NCSE indicating important similarities.

Our findings showed in general that patients treated with IVAD were sicker and had more acute CNS insult, both of which can be confounders for the higher mortality rate in these patients. Whether patients treated with IVAD had better or worse outcome than patients with same etiology of epileptic injury or same severity of brain injury is not known. We believe that the establishment of multicenter consortiums may enable the accruement of larger cohorts to control for severity and etiology. From previous reports we know that acute neurologic pathology is associated with both refractoriness, high mortality and poor outcome in both in SE and NCSE [10,18,30]. Severe consciousness impairment was also independently associated with refractoriness[29]. Patients who are in a coma or intubated are expected to have higher risk of dying from their underlying medical condition. Similarly, how much age would account for poor outcomes is not very well established. For example, in previous reports patients treated with IVAD were younger than the others, but older age was associated with poor outcomes in patients treated with IVAD[17,18,31]. Whether younger patients are more appropriate for aggressive treatment by the treating physician needs to be addressed in this patient population. We did not find any difference between two groups regarding the duration of symptoms from onset till diagnosis or duration of NCSE from the diagnosis till resolution in patients who responded to the treatment. This may imply by the time the EEG is obtained, NCSE may have resolved. Although in patients with prolonged SE, the outcome is reported to be worse, neither total duration of SE nor SE >10 hours is shown to bea reliable predictor of poor outcomes[32,33].

In our study we found about 74% of the NCSE resolved in IVAD group. In all but four episodes where IVAD was first choice of treatment, IVAD was used when NCSE did not resolve

with BZD or non-sedating intravenous AED. However, thirty-five percent of the patients required more than one IVAD with an initial response of 63% to propofol and 54% to midazolam. Similar findings were reported previously in refractory SE patients. In their review Claassen et al. reported acute treatment failure rates for IVADs: midazolam (23%), propofol (32%), and pentobarbital (20%)[33]. Breakthrough seizures were more common with midazolam. Including other types of SE, they found lower failure and breakthrough seizures with pentobarbital but hypotension requiring vasopressors was more common with pentobarbital. In a randomized study comparing barbiturates to propofol, however, initial response rate to treatment was higher with propofol. Nevertheless, overall response with subsequent treatment in both groups was high[34].

Recent retrospective studies have shown that use of IVAD is associated with poor outcome[17,18,27], though their methods had inadequate control for confounders and their findings cannot be generalized to NCSE due to involvement of other types of SE in their patient population. Ten patients died in our IVAD group whereas only three patients died in the group where patients did not receive IVAD, though this difference was not statistically significant. When we look at these 10 patients, only one in-hospital death could be attributed to propofol infusion syndrome as a direct consequence of IVAD. Four of the other nine patients had sepsis, in two of whom NCSE was due to sepsis making the IVAD less likely the cause of in-hospital death. This comment should be interpreted very cautiously because worsening of the ongoing sepsis or additional problems due to IVAD could not be excluded. It is debatable whether NCSE is directly associated with higher mortality rates or poor cognitive and neurologic outcomes, although it is known that NCSE is associated with refractoriness[35,36]. Nevertheless, there is a need to address this ongoing debate with further studies that isolate the effectiveness of IVAD in

refractory NCSE[37,38]. While a randomized controlled trial including only NCSE would be the best method to assess the effect of IVAD on the outcome, this would undoubtedly be difficult given feasibility concerns, with respect to low recruitment rates and subtleties of the clinical course of NCSE[34]. A large, multi-center, prospective observational study that adjusts for confounding across multiple factors such as age, acute neurologic pathology, and presence of coma or intubation at baseline may well provide the best option to study NCSEN management.

Our study has certain limitations. First, we used a retrospective cohort design with data collected from chart review within a single academic medical setting. This poses important selection issues mainly regarding the onset and duration of NCSE. Second, we were only able to determine the duration of in-house NCSE in EEG as days as opposed to hours, partly due to inadequate archiving of EEG traces and insufficient documentation in the chart. Choice of treatment was based on discretion of treating physician leading to significant issues of treatment selection bias. Nevertheless we consider that this variability reflects real world practice and actually may be one of the strengths of the study. Third, our small sample size precluded statistical adjustments to examine the associations between several variables and IVAD use and subsequent outcomes. Fourth, by using strict EEG criteria we might underestimate the denominator of NCSE by potentially excluding NCSE cases that met clinical criteria but resolved before EEG was obtained. However, this way we have confirmed NCSE patients which would be potential catchment population for future studies.

In summary, our study contributes to sparse literature about the IVAD use in SE by evaluating patients only with NCSE. We have shown that factors such as age, acute neurologic pathology, and baseline coma and intubation status are more common in NCSE episodes treated

with IVAD. More patients died in IVAD group although this was not statistically significant. Further studies are needed to determine the effect of IVAD use in NCSE on outcome.

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