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Intravenous Anesthesia in Treatment of Nonconvulsive Status Epilepticus: Characteristics and Outcomes

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Abstract

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

Methods—Retrospective cohort study of 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. Outcome variables were response to treatment and in-hospital death. We used descriptive analyses for baseline characteristics and outcome variable differences among patients who did and 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 , $p=0.019$). The episodes treated with IVAD occurred more frequently in patients with an acute neurologic pathology (58% vs 21%, $p=0.024$) and those presenting in a coma (39% vs 7%, $p=0.030$). NCSE resolved in 74% of the patients who received IVAD. Duration of NCSE did not differ significantly by treatment group. There were total 13 in-hospital deaths: ten in IVAD users vs three in the no-IVAD group ($p > 0.05$). Only one in-hospital death appeared to be a direct consequence of IVAD

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use. Mortality was more common among episodes that were not treated according to the published status epilepticus treatment guidelines compared to the episodes where guidelines were followed.

Conclusion—Our findings showed that factors such as younger age, acute neurologic pathology and coma at presentation were associated with IVAD use in patients with NCSE. These factors should be controlled in the future outcome and effectiveness studies to determine the effect of IVAD use on outcome of NCSE.

Keywords

Nonconvulsive status epilepticus; Refractory status epilepticus; antiepileptic drugs; anesthetic drugs; benzodiazepines

Introduction

Status epilepticus (SE), the continuous clinical and/or electrographic seizure activity lasting more than five minutes or recurrent seizures without recovery between seizures (Lowenstein and Alldredge, 1998), is a life threatening emergency that requires immediate treatment. The incidence of SE varies between 9.9-41.0 per 100,000 population (Coeytaux et al., 2000; DeLorenzo et al., 1996; Hesdorffer et al., 1998) with a mortality rate of as high as 22% (DeLorenzo et al., 1996; Rossetti et al., 2006). Nonconvulsive status epilepticus (NCSE) lacks major motor signs of continued seizures (as opposed to convulsive SE) and comprises heterogeneous conditions with varying etiologies and clinical presentations. NCSE has been reported in up to 37% of ICU patients with altered mental status, 8% of those in coma, and majority of patient with SE (Privitera et al., 1994; Rudin et al., 2011; Towne et al., 2000). Although particular subtypes – complex partial (CPSE) and absence SE (ASE) – may carry less risk of mortality. Most studies demonstrate that mortality is associated with the underlying etiology: higher rates noted in patients with acute medical conditions and acute brain injuries, and lower rates in patients with previous known history of epilepsy (Scholtes et al., 1996; Shneker and Fountain, 2003; Young et al., 1996).

First line treatment of SE generally starts with lorazepam as recommended by the Veteran's Administration trial (Treiman et al., 1998) or with other benzodiazepines (BZD) such as midazolam or diazepam followed by intravenous non-anesthetic antiepileptic medications (AED) such as phenytoin, fosphenytoin, valproate sodium, or phenobarbital. If SE continues, Neurocritical Care Society (NCS) and European Federation of Neurological Society (EFNS) guidelines recommend continuous infusion of an intravenous anesthetic drug (IVAD) such as midazolam, propofol, pentobarbital, or thiopental, to achieve burst-suppression (Brophy et al., 2012; Meierkord et al., 2010). The guidelines note, however, that little data is available to direct subsequent therapy for refractory SE.

There is even less evidence to guide treatment decisions in the setting of NCSE. Previous studies have shown that 11%-37% of patients with NCSE have received IVADs, though these reports included a mix of SE subtypes (Marchi et al., 2015; Sutter et al., 2014). Tailoring the treatment to the individual patient and using further non-anesthetic antiepileptics before IVAD is generally recommended (Meierkord et al., 2010; Pang and Drislane, 2012; Walker, 2001) though recent retrospective studies have shown that use of

IVAD is associated with poor outcome (Kowalski et al., 2012; Marchi et al., 2015; Sutter et al., 2014). These studies, however, 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. In order to call out the major confounders in the treatment selection of IVAD therapy, we characterized our center's management of a cohort of NCSE patients to identify the clinical context, outcomes and factors associated with IVAD use. We also captured their outcomes, in-hospital death and resolution of NCSE, in order to support the design of more definitive effectiveness studies in the future.

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 medical records of patients admitted between 1/1/2009 - 6/30/2014 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 epilepsy partialis continua (345.70, 345.71). Inclusion criteria were those patients 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.” (Walker et al., 2005). The onset of NCSE was determined as the onset of clear clinical change in the neurologic condition even before the first EEG. We followed established EEG criteria for NCSE presented as in Table 1 (Beniczky et al., 2013). We accepted 30 minutes as minimum duration of ongoing epileptic activity necessary to diagnose NCSE. We also diagnosed the cases as NCSE if the clinical findings were at least 30 minutes but EEG findings resolved with treatment before 30 minutes of recording. Exclusion criteria were: 1) insufficient EEG or cvEEG to confirm the diagnosis, 2) simple partial SE, 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 outcome (Bauer and Trinka, 2010; Meierkord and Holtkamp, 2008; Rossetti et al., 2007; Treiman, 1993). Treatment of NCSE was left to the discretion of the attending epileptologists and neurointensivists.

Data Collection and Variables

Data pulled from the electronic medical record 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 generalized tonic-clonic seizure (GTCS) at the onset, comorbidities, history of epilepsy, underlying etiology (individual diagnosis and acute medical pathology or acute neurologic pathology), sepsis at the time of diagnosis or later in the

course, presence of coma or intubation status. Acute neurologic pathology was defined as presence of meningoencephalitis, autoimmune encephalitis, brain tumor, white matter changes, hypoxic-ischemic, metabolic or pharmacologic encephalopathy and stroke. Acute medical pathology was defined as presence of underlying non-CNS infection, trauma other than traumatic brain injury, recent surgery before NCSE, or organ or system problem other than CNS.

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 as favorable (0-2) and unfavorable (3-6) to predict death as proposed by Rossetti et al (Rossetti et al., 2008).

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 non-anesthetic intravenous 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.

Outcome

Our outcome variables were response to treatment of NCSE episodes and in-hospital death. Response to treatment was categorized as no response or resolution of NCSE (defined by clinical improvement and/or resolution of EEG findings). We defined duration of NCSE as number of days since the clinical and electroencephalographic diagnosis of NCSE till the clinical and/or electroencephalographic resolution of NCSE. We defined this period in days since more exact time parameters were inconsistently 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

Results were limited to descriptive analyses due to the small sample size. We compared outcomes among patients who received IVAD and who did not receive IVAD (nonIVAD). 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. Duration of NCSE by treatment group was evaluated with Kaplan-Meier curves censoring patients who either did not remit or died before remission.

Results

Demographics and baseline clinical characteristics

Our initial screening identified 188 NCSE episodes, but only 43 patients met study criteria (Figure 1). The 43 patients had a total of 45 episodes, 69% of which were treated with IVAD (Table 2). Patients treated with IVAD were younger. The episodes treated with IVAD were associated with younger age, more acute neurologic pathology, and more commonly in patients who were comatose. IVAD was used more commonly to treat NCSE when the patient was already intubated.

The median duration from symptom onset to diagnosis was three days. In seventeen episodes (38%), patients had history of epilepsy. The most common presenting symptom was acute mental status changes (AMS) with subtle motor symptoms without heralding 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.

Etiology

Table 3 summarizes the underlying etiologies. Out of 17 NCSE episodes in patients with a history of epilepsy, five were due to AED non-compliance. In the remaining episodes, non-CNS infection and intracranial hemorrhage were other common etiologies. Sepsis, ICH, and meningoencephalitis were more common etiologies in episodes treated with IVAD.

Treatment

Distributions of treatment courses by treatment group are summarized in Figure 2A. BZDs were used in 27 (60%) episodes as first choice. In 10 episodes it was given before the EEG – three in outside hospital before transfer – and in 17 episodes during the EEG. BZD was choice of drug as first-line treatment in majority of the episodes; 58% in the IVAD group and 64% in the non-IVAD group. A non-anesthetic intravenous AED was first choice in nine (29%) episodes in the IVAD group and in five episodes (36%) in the non-IVAD group. Intubation occurred in all episodes of IVAD use and in only two episodes in the non-IVAD group. Prior intubation may have influenced aggressiveness of treatment; four episodes of IVAD use without prior trials of BZD or AED occurred in patients already intubated and sedated for other indications. Use of IVAD did not preclude other AED use; in 68% of IVAD episodes and in 79% of non-IVAD episodes, patients had additional non-anesthetic intravenous AED (Figure 2A). Out of 31 episodes treated with IVAD, 11 episodes (36%) required more than one IVAD. Propofol was used in 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

The distribution of outcomes is summarized in Figure 1. Of 14 episodes of nonIVAD episodes, 13 resolved with treatment. In one episode of unresolved NCSE, the family denied

further care. Only two (14%) episodes resolved with BZD only, three (21%) episodes with a non-anesthetic intravenous AED, and eight (57%) episodes with BZD followed by non-anesthetic intravenous AED (Table 4). Of 31 NCSE episodes treated with IVAD, 23 (74%) resolved with treatment and eight (26%) did not respond to treatment. NCSE resolved in IVAD group in 14 (45%) episodes when IVAD followed BZD and a non-anesthetic intravenous AED, and in nine (29%) episodes when IVAD preceded or followed intravenous non-anesthetic intravenous AED without BZD use (Table 4).

The median duration of NCSE in patients who responded to treatment (clinical improvement and/or cessation of electrographic seizure activity) was 1.0 day. Duration of NCSE did not differ significantly by treatment group, although there was a trend for longer durations in NCSE in those in the IVAD group (p values for log rank =0.20, generalized Wilcoxon = 0.27, Tarone-Ware = 0.23) (Figure 2B).

Three patients died within the nonIVAD group; two after the resolution of NCSE and one without resolution because the family denied further care. Among those who did not respond to treatment, seven died in the hospital, and one was sent to hospice. Out of 23 episodes in which NCSE resolved, three ended with in-hospital death. One mortality who met sepsis criteria also experienced propofol infusion syndrome. The possible causes of in-hospital death and EEG findings at the time of in-hospital death are listed in Table 5. Finally, eight episodes of NCSE within the IVAD group did not resolve with maximum therapy; seven died and one was discharged to hospice.

We also assessed whether choice of treatment, in other words following the treatment guidelines, makes a difference in outcome. Of the 27 episodes that were treated according to the NCS and EFNS guidelines and received BZD as first choice, 25 episodes (93%) resolved with treatment. Mortality was seen in 4 episodes (15%). Of the 18 episodes that did not receive BZD as first choice treatment, 11 episodes (61%) resolved and mortality was seen in 9 episodes (50%). The difference between two groups for both resolution (Fisher Exact Test, 2-sided p-value=0.019) and mortality (Fisher Exact Test, 2-sided p-value= 0.018) were statistically significant.

In eight episodes patients were comatose and all of these episodes were treated with IVAD constituting 26% of the IVAD group. A separate analysis of the episodes with comatose patients and of the cohort without coma showed resolution of EEG in 5 of the 8 comatose episodes (62%) while 31 of the 37 episodes (84%) resolved in episodes without coma (Fisher Exact Test, 2-sided p-value=0.326). Death rate was however significantly higher in episodes with coma compared to episodes without coma; 62% in comatose vs 22% without coma (Fisher Exact Test, 2-sided p-value= 0.034).

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. Although IVAD use is thought to be a “last resort”, 69% of NCSE episodes were treated with IVAD. Those who were treated with IVAD were younger in age, more often had acute

neurologic pathologies, and were comatose or intubated more often than non-IVAD-treated episodes. Sixty percent of the patients, regardless of IVAD treatment status, were treated as per prevailing NCS and EFNS guidelines receiving first line acute BZD followed by non-anesthetic intravenous AED. Mortality rate was significantly higher while rate of resolution was significantly lower among episodes that were not treated according to the guidelines compared to the episodes where guidelines were followed. NCSE resolved in 74% of episodes treated with IVAD. Although not statistically significant, in-hospital death and sepsis were more common within those treated with IVAD, suggesting that outcomes followed the severities of underlying acute neurological or systemic illnesses.

We were surprised to find that the majority of NCSE episodes treated in our center received IVAD. While our rate of 69% is higher than previous reports of 11%-37%, we restricted our cohort to persons with NCSE while others included NCSE as a subtype among other SE types (Marchi et al., 2015; Sutter et al., 2014). Our higher rate may 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 (Hocker et al., 2013). However, Novy et al reported only 30% their refractory NCSE received IVAD (Novy et al., 2010). They attributed their low rate to their practice of escalating the use of non-anesthetic intravenous AEDs and monitoring response before considering IVAD use. In our cohort we noted that the majority of episodes were treated with additional non-anesthetic intravenous AED whether IVAD was used or not. Because the choice of treatment was at the discretion of the treating physician, we could not comment on the matter of how much IVAD use could have been avoided if more conservative approach was used. 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 3) was higher than those who did not get IVAD, though the difference was not statistically significant.

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 (Kowalski et al., 2012; Shneker and Fountain, 2003; Sutter et al., 2015). Severe consciousness impairment was also independently associated with refractoriness (Novy et al., 2010). Patients who are in a coma or intubated are expected to have higher risk of dying from underlying medical condition. The prognosis of comatose NCSE, which itself is a spectrum of varying etiologies with varying outcome, is worse than other treatable NCSE types (Bauer and Trinka, 2010). Our findings also showed higher mortality rate in comatose patients although rate of NCSE resolution was similar whether the patients were comatose or not. Similarly, how 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 outcome and death in patients treated with IVAD(Holtkamp et al., 2005; Kowalski et al., 2012; Sutter et al., 2014). Whether the patients younger age deemed to be more appropriate for aggressive treatment by the treating physician needs to be addressed in this patient population. Duration of NCSE in our cohort was not an important factor in treatment with IVAD. Although in patients with prolonged SE the outcome is reported to be worse, neither total duration of SE nor SE >10 hours has been shown to be a reliable predictor of the outcome when additional clinical factors (etiology, presentation in coma and type of SE) are controlled (Claassen et al., 2002; Drislane et al., 2009).

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. Recent retrospective studies have shown that use of IVAD is associated with poor outcome(Kowalski et al., 2012; Marchi et al., 2015; Sutter et al., 2014), 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 ten patients, only one death was 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(Agan et al., 2009; Mayer et al., 2002). Nevertheless, there is a need to address this ongoing debate with further studies that isolate the effectiveness of IVAD in refractory NCSE(Fountain and Fugate, 2014; Sutter and Kaplan, 2015). 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. 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 NCSE management. We believe that the establishment of multicenter groups – such as the Critical Care EEG Monitoring Research Consortium(American Clinical Neurophysiological Society)– may enable the accrual of larger cohorts to control for severity and etiology.

Only 60% of NCSE episodes were treated according to the guidelines. This is lower than expected and therefore we think it is important to report this finding. We found the episodes treated according to the NCS and EFNS guidelines have higher resolution and lower mortality rate suggesting that following the recommendations in published guidelines yield to improved outcomes.

Our study has certain limitations. First, we used a retrospective cohort design with data collected from chart review within 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 trace 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, and these factors should be controlled in the future outcome and effectiveness studies.

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Highlights

1. Although IVAD use is thought to be a “last resort”, 69% of NCSE episodes were treated with IVAD.
2. IVAD use was more common in episode when patients are younger, have acute neurologic pathologies, and are comatose or intubated.
3. In-hospital death and sepsis trended to be more common with IVAD use, suggesting that outcomes followed the severities of underlying medical condition.
4. These factors should be controlled in the future IVAD outcome and effectiveness studies.

Figure 1.

Sample identification and treatment responses of the NCSE episodes.

NCSE= Nonconvulsive status epilepticus, ivAED= iv non-anesthetic antiepileptic drug,

BZD= benzodiazepine, IVAD=iv anesthetic drug.

Figure 2.

A. Distribution of medications administered to treat NCSE stratified by use of anticonvulsant groups. B. Kaplan-Meier curve showing duration before remission of NCSE divided by use of intravenous anesthetic anticonvulsants (IVAD) versus no IVAD. BZD= benzodiazepine, ivAED= iv non-anesthetic antiepileptic drug, IVAD=iv anesthetic drug.

Table 1

Working clinical criteria for nonconvulsive status epilepticus. Adapted from Beniczky et al. (Beniczky et al., 2013).

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 $\geq$ 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	

Table 2

Demographics and clinical characteristics.

	Whole Group	NonIVAD	IVAD	p-value
Number of patients	43	14	29	
Age	56.7±14.7	64.1±13.3	53.1±14.1	0.019*
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 with 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 with 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%)	0.024*
STESS 3 (Status severity score)	23 (51.1%)	6 (42.9%)	17 (54.8%)	NS
Coma	8 (17.8%)	0 (0%)	8 (25.8%)	0.036*
Already intubated before NCSE	13 (28.9%)	1 (7.1%)	12 (38.7%)	0.030*

IVAD=iv anesthetic drug, AMS= Altered mental status, GTCS= Generalized tonic-clonic seizure, STESS= Status Epilepticus Severity Score, NS=Not significant.

Table 3
Etiology of Nonconvulsive Status Epilepticus

Etiology	Whole Group	NonIVAD	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- non-CNS infection without sepsis	2 (4.4%)	0 (0.0%)	2 (6.45%)
Non CNS-Infection (excluding cases with epilepsy)	7 (15.5%)	2 (14.3%)	5 (16.1%)
Sepsis	5 (11.1%)	1 (7.1%)	4 (12.9%)
Non-CNS Infectionwithout 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

Table 4
Outcome variables

	Whole Group	NonIVAD	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%)	0	
With iv AED only	3 (6.7%)	3 (21.4%)	0	
With BZD+ivAED	8 (17.8%)	8 (57.1%)	0	
With ivAED+IVAD	9 (20.0%)	NA	9(29.3%)	
BZD+ivAED+IVAD	14 (31.1%)	NA	14 (45.2%)	
Time to resolution				
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

NCSE= Nonconvulsive status epilepticus, ivAED= non-anesthetic iv antiepileptic drug, BZD= benzodiazepine, IVAD=iv anesthetic drug, NS=Not significant.

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		Pneumonia/Progressive multifocal leukoencephalopathy, graft versus host disease	Infection Diffuse slowing/GPD

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