สาเหตุและผลลัพธ์ทางคลินิกของภาวะชักต่อเนื่องอ้างอิงตามคำนิยามใหม่

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Abstratc: Etiology and Clinical Outcomes of Status Epilepticus in Adults, Based on the New Definition

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Background: Status epilepticus (SE) is a common neurological emergency associated with a high morbidity and mortality rate. In 2015, the International League Against Epilepsy (ILAE) proposed a new status epilepticus (SE) definition. Objective: We aimed to apply the new definition of SE and analyze seizure types, clinical presentation, causes, complications, and predictors of poor outcome based on the new definition. Method: 150 adult patients aged 18-90 years old with SE in Vajira hospital between January 2016 and January 2019 were enrolled with a retrospective chart review of all. SE was defined and classified according to the ILAE 2015. Results: Out of 150 participants, 86 (57.3%) were men with the mean age of 61.35 (±20.32) years. Acute symptomatic seizures were the most common causes, with 89.9%. The mortality rate was 48.7%. The clinical factors that statistically significantly affected the outcome were age, complications during admission, and low AEDs levels. Patients tended to have poorer outcomes of 1.03 times per a year of increased age (*p*-value 0.007, 95%CI 1.01–1.05), and 16.64 times higher (*p*-value < 0.001, 95%CI 4.65–59.63) among those with complications during the admission. Whereas epilepsy patients who had low AED levels, which resulted in SE, were found to have a significantly better outcome. The common complications were respiratory failure, pneumonia, and septicemia. Conclusion: According to the new definition of SE, older age and complications during the hospital stay have potential associated with poor neurological outcomes. In contrast, an epilepsy patient who had SE due to a low AEDs level seems to have a better prognosis. The acute symptomatic etiologies were still the most common cause of status epilepticus, and infection was thought to be the most corresponding cause.

Keyword: status epilepticus, epilepsy, seizure

บทคัดย่อ

ภูมิหลัง: ภาวะชักต่อเนื่องเป็นภาวะฉุกเฉินทางระบบประสาทที่สำคัญและพบบ่อยซึ่งเป็นเหตุที่ทำให้ผู้ป่วยทุพพลภาพและเสียชีวิต ในปี ค.ศ. 2015 The International League Against Epilepsy (ILAE) ได้มีการกำหนดนิยามใหม่สำหรับภาวะชักต่อเนื่อง วัตถุประสงค์: เพื่อศึกษาลักษณะอาการชัก สาเหตุ ภาวะแทรกซ้อน รวมทั้งปัจจัยพยากรณ์โรคของภาวะชักต่อเนื่องที่อ้างอิงตามคำนิยามใหม่ วิธีการ: การวิเคราะห์ข้อมูลย้อนกลับจากการรวบรวมเวชระเบียนผู้ป่วยที่ได้รับการวินิจฉัยภาวะชักต่อเนื่องที่เข้ารับการรักษาในโรงพยาบาลวชิรพยาบาล ตั้งแต่ 1 มกราคม 2558-31 มกราคม 2561 จำนวน 150 คน ในช่วงอายุ 18-90 ปี เพื่อหาปัจจัยที่มีความสัมพันธ์ต่อภาวะชักต่อเนื่อง อ้างอิงตามคำนิยามภาวะชักต่อเนื่อง จาก ILAE ปี ค.ศ. 2015 ผล: ผู้ป่วยชักต่อเนื่องจำนวน 150 ราย อายุเฉลี่ย 61.35 (±20.32) ปี พบว่าส่วนมากมีสาเหตุกระตุ้นการเกิดชักอย่างเฉียบพลันถึงร้อยละ 89.9 อัตราการเสียชีวิตพบสูงถึงร้อยละ 48.7 ปัจจัยด้านสาเหตุและลักษณะทางคลินิกที่มีผลต่อผลการรักษาที่ไม่ดี ได้แก่ อายุของผู้ป่วยโดยอายุที่เพิ่มขึ้นทุก ๆ 1 ปี จะมีผลต่อการเกิดผลการรักษาที่ไม่ดี 1.03 เท่า (p-value 0.007, 95%CI 1.01-1.05) และผู้ป่วยที่มีภาวะแทรกซ้อนเกิดขึ้นระหว่างนอนโรงพยาบาลพบสูงถึง 16.64 เท่า (*p*-value < 0.001, 95% CI 4.65-59.63) ส่วนผู้ป่วยที่มีสาเหตุการชักจากระดับยากันชักที่

ต่ำกว่ามาตรฐาน มีการพยากรณ์โรคที่ดีกว่าอย่างมีนัยสำคัญทางสถิติ ภาวะแทรกซ้อนที่พบร่วมมากที่สุด ได้แก่ การมีภาวะระบบหายใจล้มเหลวฉับพลัน โรคปอดอักเสบ และการติดเชื้อในกระแสเลือด **สรุป:** จากภาวะชักต่อเนื่องตามนิยามใหม่ อายุที่เพิ่มขึ้นและการเกิดภาวะแทรกซ้อนระหว่างนอนโรงพยาบาลมีความสัมพันธ์กับผลการรักษาที่ไม่ดี ในขณะที่ผู้ป่วยภาวะชักต่อเนื่องที่มีสาเหตุจากระดับยากันชักต่ำกว่ามาตรฐานจะมีผลการรักษาที่ดีกว่า โดยพบว่าผู้ป่วยส่วนมากจะมีสาเหตุกระตุ้นการเกิดชักอย่างเฉียบพลัน โดยพบสาเหตุเกี่ยวข้องกับภาวะติดเชื้อมากที่สุด

คำสำคัญ: ชักต่อเนื่อง, ลมชัก, ชัก

Introduction

Status epilepticus (SE) is a common neurological emergency associated with a high morbidity and mortality rate. SE is traditionally defined as 30 minutes of ongoing epileptic activity or seizures without recovery in between. In 2015, a Task Force of the International League Against Epilepsy (ILAE) proposed SE as bilateral tonic-clonic activity lasting longer than 5 minutes, the absence of SE, and focal SE exceeding 10 minutes. The new ILAE classification of SE 2015[1] distinguishes nonconvulsive SE (NCSE) from SE with prominent motor phenomena. This classification allows the epidemiologic investigation of NCSE and its different subtypes in population-based studies.

Few studies have investigated the causes and outcomes of status epilepticus according to a traditional definition of status epilepticus and the results varied by the definition of SE used in each study[2,3]. A study informed that patients with status epilepticus in Thailand from 2004 to 2012 showed 24.8 percent of the population had poor results after the treatment of status epilepticus, which were mostly found in patients older than 60 years, and females, 36.1 and 39.6 percent, respectively[3]. The population mortality rate was 11.96 percent from 2004 to 2012, and it was associated with comorbidities such as hypertension, diabetes, and prior cerebral infarction, which differed from previous studies[4,5], as CNS infection was the leading cause. Because of the shorter diagnostic time with the new definition, we expect to identify more patients with SE and assess the etiology and impact on the clinical outcome.

Objectives

The primary objective was to provide types and causes of SE according to the 2015 ILAE definition and classification. *The secondary objective* was to provide clinical characteristics associated with the outcome of status epilepticus.

Materials and Methods

Study design: This study was a retrospective study. The ethics committee of the Faculty of Medicine Vajira Hospital Navamindradhiraj University reviewed and approved this study.

Population: The population was patients who presented with seizures and needed admission to Vajira Hospital, which meet the diagnostic criteria of a new onset of SE based on the new ILAE 2015 criteria[1].

Inclusion criteria:

1. Age 15-90 years.

2. All patients presented with seizures who were admitted to the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, from Jan 2016- Jan 2019, and classified as SE based on the new ILAE diagnostic criteria. SE was diagnosed if the diagnostic time exceeded 5 minutes of ongoing seizure activity for convulsive SE or 10 minutes for absence or focal SE with or without impaired consciousness.

2.1 Convulsive SE[6]: included bilateral tonic-clonic seizures at any time, SE with prominent focal motor phenomena, tonic SE, hyperkinetic SE, and myoclonic SE that was described or diagnosed by a physician or a neurologist from the medical record.

2.2 Non-convulsive SE (or NCSE) was clinically defined as an enduring epileptic condition with reduced or altered consciousness, behavioral or vegetative abnormalities, or merely subjective symptoms like auras, but (by definition) without prominent focal or generalized convulsive movements at any time.[7] Diagnosis via electroencephalography (EEG)and the application of Salzburg consensus EEG are the criteria for confirmation of NCSE, including patients with subtle clinical phenomena such as minor jerks or conjugate gaze deviation and a very high clinical and paraclinical suspicion of NCSE based on history, clinical presentation, and neuroimaging. The diagnosis of NCSE was counted only after it was confirmed by neurologists.

2.3 We defined etiology as either symptomatic (acute, remote, progressive, and SE defined in electroclinical syndromes) or cryptogenic. Acute etiology referred to the first week after the onset of the brain insult.[8]

Exclusion criteria

1. Patients who had seizures but did not meet the new ILAE 2015 diagnostic criteria of SE[1]

2. Patients who are unable to retrieve their medical records or have incomplete medical records.

Data analysis

• Descriptive statistics used to describe the personality characteristics, history of illness, etiology, underlying disease, and history of epilepsy of the samples consisted of the percentage, mean, and standard deviation.

• The quantitative analysis consisted of a t-test and Chi-square or Fisher exact test.

The statistical significance was defined as $p < 0.05$. Then, the relationships of factors affecting poor outcomes in patients with status epilepticus were analyzed by multiple logistic regressions.

Result

Our search algorithm identified 987 patients diagnosed with seizures and admitted to Vajira hospital from January 2016 to January 2019. Based on the new criteria, 153 patients were diagnosed as status epilepticus and recruited by reviewing their medical records. 3 patients with incomplete medical records were excluded from the study. Of the 150 status epilepticus patients included in the study, 86 (57.3%) were male, and 64 (42.7%) were female. Demographic data and etiologies of our patient population are shown in Table 1. The data were categorized into two groups: convulsive status epilepticus and non-convulsive status epilepticus (Table 2).

Table 1 Demographic characteristics of 150 status epilepticus patients

Data	No.	Percentage
Age (years) (Mean±SD)	61.35 ± 20.32	
Sex		
Male	86	57.3
Female	64	42.7
Comorbid conditions		
Unknown	7	4.7
No comorbid conditions	14	9.3
With comorbid conditions	129	86.0
History of cerebral Infarction	47	36.4
History of cerebral hemorrhage	15	11.6
Myocardial infarction	16	12.4
Hypertension	77	59.7
History of traumatic brain injury	1	0.8
Dementia	15	11.6
CNS neoplasm	14	10.8
COPD	10	7.7
Cirrhosis	17	13.2
Chronic renal failure	17	13.2
Diabetes mellitus	43	33.3
HIV disease	4	3.1
Other	75	58.1

We found that more than half of the population presented with focal onset evolving into bilateral convulsive SE (54.7%). The onset time-to-diagnose duration within 30 minutes, 30-60 minutes, and 1-24 hours were 86%, 11.3%, and 2%, respectively.

Table 2 The clinical characteristic of 150 status epilepticus patients

Data	No.	percentage
Type of status epilepticus		
Convulsive status epilepticus	146	97.4
Generalized convulsive status epilepticus	64	43.8
Focal motor SE (Epilepsia partialis continua)	21	14.4
Focal onset evolving into bilateral convulsive SE	61	41.8
Nonconvulsive status epilepticus	4	2.6
NCSE with coma	2	50.0
Focal NCSE with impaired awareness	2	50.0
EEG monitoring Performed	38/150	25.3
Positive	9/38	23.7
Duration of status epilepticus		
<30 mins	129	86.0
30-60 mins	17	11.3
1h-24h	3	2.0
>24h	1	0.7
Complications during the hospital stay		
No	40	26.7
Yes	110	73.3
Respiratory failure	77	70.0
Pneumonia	53	48.2
Septicemia	65	59.1
Pressure sore	6	5.4
Urinary tract infection	11	10.0
Shock	5	4.5
Cardiac arrest	1	0.9
Heart failure	1	0.9
Hepatitis	2	1.8
Rhabdomyolysis	3	2.7
Upper gastrointestinal hemorrhage	3	2.7

Table 2 The clinical characteristic of 150 status epilepticus patients (continue)

Data	No.	percentage
Brain imaging		
Normal	26	17.3
Abnormal	124	82.7
Mass	8	6.4
Generalized brain edema	10	8.1
Infraction	45	36.3
Hemorrhage	32	25.8
Encephalomalacia	15	12.1
Others	14	11.3
Laboratory findings (Mean ± SD)		
Na (mmol/L)	137.8 ± 7.99	
Mg (mg/dL)	2.0 ± 0.48	
Corrected calcium (mg/dL)	9.3 ± 1.05	
Capillary blood glucose (mg/dL)	186.28 ± 124.96	
History of epilepsy		
Yes	46	30.7
Duration of hospital stay, days (Mean ± SD)	30.64 ± 37.49	
Type of discharge status		
Improved	77	51.3
Dead	73	48.7

For the acute cerebrovascular diseases, acute cerebral hemorrhage was related to the SE more than the infarction, as shown in Table 3. Most identifiable causes of status epilepticus in this study based on ILAE classification (Table 4) were acute symptomatic etiologies caused by infection (40%), followed by electrolyte imbalance, toxic and low AED levels (27.5%), as well as acute cerebrovascular disease (21.2%).

Table 3 Etiologies* of 150 status epilepticus patients

Etiology	No.	Percentage
Acute cerebrovascular disease		
Cerebral infarction	10	6.7
Cardioembolism	4	40.0
Large vessel atherosclerosis	5	50.0
Other determine cause	1	10.0

Table 3 Etiologies* of 150 status epilepticus patients (continue)

Etiology	No.	Percentage
Cerebral hemorrhage	23	15.3
Extracerebral location	18	78.3
Intracerebral location	16	69.6
Cerebral venous sinus thrombosis	1	0.7
Infection	64	42.7
Sepsis	55	85.9
CNS infection	9	14.1
Toxic	11	7.4
Alcohol related	10	90.9
Dilantin overdose	1	9.1
CNS neoplasm	11	7.3
Trauma	4	2.7
Genetics	1	0.7
Hypoxic	18	12.0
Low AED levels	24	16.0
Electrolyte imbalance	9	6.0
Neurodegenerative	1	0.7
Anemia	1	0.7

***** Twenty-eight patients have more than one presumed etiologies of SE

Table 4 Classification of etiology as ILAE Task Force on Classification of Status Epilepticus, 2010 [18]

Etiology	No. of etiology	Percentage*
Acute	160	89.9
Cerebrovascular disease	34	21.2
Infection	64	40.0
Electrolyte imbalance, Toxic, and low AED levels	44	27.5
Hypoxic	18	11.2
Other	5	3.1
Remote	4	2.2
Progressive (CNS neoplasm)	8	4.5
Cryptogenic	1	0.6

* Calculated from 178 presumed etiologies of SE found in this study

Factors significantly associated with the poor outcome of status epilepticus were age and the presence of complications during the hospital stay. Patients tended to have 1.03 times poorer outcomes per a year of increased in age (95% CI of adjusted OR: 1.01-1.05, *p*-value = 0.007) and 16.64 times higher (95% CI of adjusted OR: 4.65-59.63, p-value < 0.001) among those with complications during the admission. Whereas epilepsy patients who had low AED levels, which resulted int SE, were found to have a significantly better outcome (Table 5).

There were no significant differences among outcomes for the following clinical factors: gender, underlying diseases, duration of the hospital stay, seizure type, and etiologies of status epilepticus.

Table 5 Predictive factors for poor clinical outcomes

Clinical characteristic	Crude OR	p-value	Adjusted OR (95% CI)	p-value
Age (Mean ± SD)	1.03	0.001	1.03 (1.01-1.05)	0.007
Complication during admission				
Yes	11.33	< 0.001	16.64 (4.65-59.63)	< 0.001
Etiology				
Low AED levels	0.17	0.001	0.19 (0.06-0.67)	0.01

* Selection technique: Forward stepwise method

Discussion

Based on the new ILAE 2015 definition and classification of SE.[1,6] Reducing the diagnostic time from 30 to 5 minutes in CSE or 10 minutes in focal SE or absence SE, the presuming causes of status epilepticus were infectious causes, metabolic disturbances (electrolyte imbalance, toxic and low AED levels), and acute cerebrovascular disease, respectively which differ from the prior studies. The focal convulsive SE is the most common SE in this study (82 patients, 56.2%). This high number can be explained by the fact that we included adults, which are more likely to have focal brain pathology.[11]

Complications during admission were also the significant independent factors for non-favorable outcomes. The complication was found to be high at 73.3%, and respiratory failure was the most common (70%), followed by septicemia (59.1 %) and pneumonia (48.2%), corresponding with the previous study[10,12]. Having these complications during hospital stays was significantly associated with non-favorable discharge status. We also found that the patients with epilepsy who had low AEDs levels and become SE had a more favorable outcome than the other etiologies, which differed from the previous study that showed inconsistency[13].

As a result, patients' age of more than 60 years old and the complications during the hospital stay have potential been associated with poor outcomes correlated with the previous studies.[10,14] While the etiologies, history of epilepsy, type of SE, gender, comorbid conditions, duration of hospital stay, and number of AEDs used had no significant correlation with the outcome.

Even though the type of seizures did not correlate with an outcome, we found that the occurrence of NCSE was very low in this study, and the evolution of seizure semiology was not described in sufficient detail to conclude. Increasing awareness and a learning curve might also be responsible for the increase in incidence over time. The previous study found that poor outcome is not correlated with prominent motor phenomena but with of nonconvulsive phases in the semiologic sequence[15]. Therefore, it seems crucial to search for nonconvulsive phases in the semiologic sequence to estimate the risk for poor outcomes.

In this study, we reported the higher mortality rates in our center at 48.7 % compared to the previous study[16] with mortality rates of 25%. This result might be because of the high occurrence of in-hospital medical complications, and we included patients who

developed SE after cardiac arrest, which usually had poor outcomes. Moreover, it is possible to over-diagnose SE in post-cardiac arrest patients based on clinical (post-hypoxic myoclonus) and the use of Salzburg's criteria to apply for EEG interpretation.

There were several limitations to this study. The study's retrospective nature might have introduced bias; errors in diagnosis and the incomplete detail of the underlying disease may have led to the under-ascertainment of cases. There was no immunological screening for immune-mediated SE in this study, which can explain the cause of SE, especially for refractory and super-refractory SE groups, and may affect the outcome.

We highlighted the study's practical advantage, which we should focus on patients over 60 years and patients with medical complications, as well as prevention strategies. The researchers hope that this study's benefits will help reduce the mortality rate from status epilepticus in the future.

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