

Abstract

Objective: Status epilepticus is a major medical and neurologic emergency that has to be treated immediately to avoid severe morbidity and mortality. The aim of this study was to describe mortality rate and mortality-related factors of status epilepticus in Maharat Nakhon Ratchasima Hospital.

Method: This retrospective study was conducted in a large tertiary-care hospital including 315 patients with status epilepticus. Mortality was defined as death during hospital admission.

Result: There were 315 patients in this study. The mean age was 53.9 years old and 184 patients (58.4%) were male. The overall mortality rate of status epilepticus was 39.7%. The mortality-related factors were as follows: over 60 years of age ($p < 0.01$, HR 1.96, 95% CI: [1.22-3.13]), female ($p = 0.035$, HR 1.63, 95% CI: [1.03-2.58]), duration of seizure ($p < 0.01$, HR 3.28, 95% CI: [1.81-5.96]), acute symptomatic etiology ($p = 0.047$, HR 3.5, 95% CI: [0.95-12.82]), patient who developed complications ($p < 0.01$, HR 19.16, 95% CI: [9.16-40.08]), and refractoriness of status epilepticus ($p < 0.01$, HR 19.16, 95% CI: [9.16-40.08]). The medical complications of status epilepticus were reported in 61%. The mortality rate of refractory and super-refractory status epilepticus was 90%.

Conclusion: The mortality rate of status epilepticus in Maharat Nakhon Ratchasima Hospital was 39.7%. The mortality-related factors were elderly, female, duration of seizure, acute symptomatic etiology, patient who developed complications and refractoriness of seizure. The development of better system of care and clinical practice guideline for reducing the mortality of status epilepticus patients in Maharat Nakhon Ratchasima Hospital is necessity.

Mortality and Related Factors of Status Epilepticus in Maharat Nakhon Ratchasima Hospital

อัตราการเสียชีวิตและปัจจัยที่เกี่ยวข้องของภาวะชักต่อเนื่องในโรงพยาบาลมหาสารนครราชสีมา

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บทคัดย่อ

วัตถุประสงค์: ภาวะชักต่อเนื่องเป็นภาวะฉุกเฉินทางระบบประสาทที่พบได้บ่อยในเวชปฏิบัติ การวินิจฉัยและการรักษาที่ทัน่วงที่ส่งผลดีต่อผลการรักษาอย่างมาก วัตถุประสงค์ของการศึกษานี้คือศึกษาอัตราการเสียชีวิตของภาวะชักต่อเนื่องและศึกษาปัจจัยที่เกี่ยวข้องกับการเสียชีวิตของภาวะชักต่อเนื่องในโรงพยาบาลมหาราชนครราชสีมา

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาแบบย้อนหลังโดยการทบทวนเวชระเบียน ศึกษาผู้ป่วยที่อายุมากกว่า 18 ปี ที่ได้รับการวินิจฉัยภาวะชักต่อเนื่องในโรงพยาบาลมหาราชนครราชสีมา

ผลการศึกษา: ผู้ป่วยทั้งหมด 315 ราย อายุเฉลี่ย 53.9 ปี เป็นเพศชาย ร้อยละ 58.4 อัตราการเสียชีวิตของภาวะชักต่อเนื่องเท่ากับร้อยละ 39.7 ปัจจัยที่เกี่ยวข้องกับการเสียชีวิตได้แก่ อายุมากกว่า 60 ปี ($p < 0.01$, HR 1.96, 95% CI: [1.22-3.13]) เพศหญิง ($p = 0.035$, HR 1.63, 95% CI: [1.03-2.58]) ระยะเวลาที่ชัก ($p < 0.01$, HR 3.28, 95% CI: [1.81-5.96]) สาเหตุของชักชนิด acute symptomatic ($p = 0.047$, HR 3.5, 95% CI: [0.95-12.82]) การเกิดภาวะแทรกซ้อน ($p < 0.01$, HR 19.16, 95% CI: [9.16-40.08]) ภาวะชักต่อเนื่องที่ไม่ตอบสนองต่อการรักษา ($p < 0.01$, HR 19.16, 95% CI: [9.16-40.08]) ภาวะแทรกซ้อนของภาวะชักต่อเนื่องพบสูงถึงร้อยละ 61 และอัตราการเสียชีวิตในผู้ป่วยชักต่อเนื่องที่ไม่ตอบสนองต่อการรักษาเท่ากับร้อยละ 90

สรุปผลการศึกษา: อัตราการเสียชีวิตของภาวะชักต่อเนื่องในโรงพยาบาลมหาราชนครราชสีมาเท่ากับร้อยละ 39.7 ปัจจัยที่เกี่ยวข้องกับการเสียชีวิตได้แก่ อายุ เพศหญิง ระยะเวลาที่ชัก สาเหตุของการชัก การเกิดภาวะแทรกซ้อน ภาวะชักต่อเนื่องที่ไม่ตอบสนองต่อการรักษา การพัฒนาระบบการรักษาผู้ป่วยภาวะชักต่อเนื่องจึงจำเป็นอย่างมากเพื่อลดอัตราการเสียชีวิตในผู้ป่วยกลุ่มนี้

Introduction

Status epilepticus (SE) is a major medical and neurologic emergency which has to be treated immediately to avoid severe morbidity and mortality. Annual incidence of SE ranges from 7 to 41 cases per 100,000¹, which is relatively high in children less than one year of age and starts rising again in older adults over 60 years of age (U-shape distribution).² Over a lifetime, up to 10 percent of adults with epilepsy and 20 percent of children with epilepsy will have one or more episodes of SE.^{3,4} Many episodes are from a superimposed new metabolic, infectious, or pharmacologic stressor such as a medication change.^{5,6}

The first and most common etiology of SE in adult, half of all cases, are acute symptomatic seizure. The second causes are remote symptomatic and antiepileptic drug nonadherence or discontinuation in patients with prior epilepsy. Other causes are withdrawal syndromes related to the discontinuation of alcohol, barbiturates, or benzodiazepines.^{7,8}

According to the latest systematic review and meta-analysis in mortality of SE in adult, the pool mortality rates were 15.9% (range from 12.7-19.2%).⁹ Previous study found that the most important factors related to mortality in SE were older age, long seizure duration, and acute symptomatic etiology such as CNS infection, acute stroke, metabolic disturbances, and anoxia.⁹ There was very high heterogeneity between studies in mortality rates and no evidence for improved survival over time. Another study shows that neurologist treated only 23% of SE patients and only 4.6% of patients arrived within 6 hours after onset of SE.¹⁰

Maharat Nakhon Ratchasima Hospital is the largest regional tertiary-care center in Thailand. Many difficult and complicated cases are referred for specialized care. The aim of this study was to describe in-hospital mortality rate and mortality-related factors of SE in Maharat Nakhon Ratchasima Hospital. In addition, the authors describe the causes, clinical profile, antiepileptic treatment, and clinical outcome. Only limited number of studies were carried out in Asian population and developing countries. Thus, the authors expected that the result of this study can lead to develop better system of care and clinical practice guideline for improving the outcome of SE patients in Maharat Nakhon Ratchasima Hospital.

Material and Method

A retrospective study was conducted from January 1st, 2017 to December, 31th 2018 at Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand. The medical records of adult patients, aged more than 18 years with the diagnosis of SE upon admission to the hospital, were reviewed. SE in this study comprised of convulsive SE and nonconvulsive SE. Convulsive SE was defined as occurrence of two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsive activity lasting for more than 5 minutes and nonconvulsive SE was defined when the patient had a coma with ictal discharges on electroencephalogram (EEG) with or without subtle convulsive movements.¹¹⁻¹⁴

The presented data included demographics, types of SE, duration of seizures, underlying neurological disease, causes of SE, laboratory

results, imaging results, EEG results, treatment, antiepileptic drugs, clinical course, complication and clinical outcomes. The etiologies were classified as acute symptomatic (secondary to an acute problem affecting brain excitability such as electrolyte imbalance or meningitis etc.), remote symptomatic (secondary to distant brain injury such as old stroke) and cryptogenic/ idiopathic (genetic tendency or unknown cause). The specific causes of SE were collected. The outcome of this study was short-term outcome or in-hospital outcome. The outcome was divided into 3 groups as follows: 1) good outcomes or completed recovery was defined by using Modified Rankin Scale for Neurologic Disability (mRS)¹⁵ 0-3 (recovered to baseline); 2) moderate to severe disability was defined as mRS 4-5 (residual neurological deficit with dependency or major functional deficit); and 3) death (mRS 6). The association between the outcomes and underlying diseases, etiology, the duration of SE and the treatment were analyzed.

Statistical analysis

The descriptive data were presented as frequency, percent, mean \pm standard deviation (SD) and median with interquartile range (IQR). The association between outcomes and related factors were analyzed by using Chi-square or Fisher's exact test in non-continuous data and student's t-test or Mann-Whitney U test for continuous data. Odd ratio (OR) or hazard ratio (HR) and 95% confidence intervals (95% CIs) were used to demonstrate the association between related factor and outcomes. A p-value of <0.05 was considered statistical significance.

Result

Baseline characteristics of study populations

During the study period (14 months), there were 315 SE patients were admitted in Maharat Nakhon Ratchasima Hospital. The baseline characteristics were showed in Table 1. Overall, mean age was 53.9 years old (SD \pm 17.7) and 184 patients (58.4%) were male. Only 64 patients (20.3%) had seizure which were the first episode seizure in their life time. About two third of the patients (209 patients, 66.3%) had 5-30 minutes of seizure duration, 88 patients (27.9%) had short seizure duration less than 5 minutes with more than one episode of seizure without full recovery of consciousness, and 18 patients (5.7%) had more than 30 minutes of seizure.

The causes of SE in this study were shown in Table 2. The causes were divided into 3 groups, the first and most common etiology was acute symptomatic seizure (192 patients, 61.0%). The second was remote symptomatic (87 patients, 27.6%), and the third was cryptogenic epilepsy (36 patients, 11.4%), respectively.

One hundred and ninety two patients (61.0%), which were in acute symptomatic seizure, including acute intracerebral hemorrhage (32 patients, 10.2%), acute central nervous system infection (32 patients, 10.2%), metabolic disturbance (26 patients, 8.3%), alcohol withdrawal seizure (20 patients, 6.3%), hypoxic ischemic encephalopathy (18 patients, 5.7%), acute ischemic stroke (17 patients, 5.4%), acute traumatic brain injury (17 patients, 5.4%), septic encephalopathy (11 patients, 3.5%), hypertensive encephalopathy (7 patients, 2.2%), cerebral venous sinus thrombosis (6 patients, 1.9%), and autoimmune encephalitis (6 patients, 1.9%). Eighty-seven patients (27.6%) had remote symptomatic seizure, which were previous ischemic stroke (36 patients, 11.4%), post traumatic brain injury (19 patients, 6%), previous intracerebral hemorrhage (15 patients, 4.8%), brain tumor (10 patients, 3.2%), previous central nervous system infection (4 patients, 1.3%), and vascular abnormality (3 patients, 1%). Only 36 patients (11.4%) were idiopathic or cryptogenic epilepsy.

Table 1 Baseline characteristic (315 patients)

Clinical profile	Number (%)
Sex	
- Male	184 (58.4)
Age, Mean \pm SD (year)	53.87 \pm 17.74
- \geq 60 years	114 (36.2)
Duration of seizure	
- < 5 min	88 (27.9)
- 5-30 min	209 (66.3)
- > 30 min	18 (5.7)
History of previous seizure	251 (79.7)
Etiology	
- Acute symptomatic	192 (61.0)
- Remote symptomatic	87 (27.6)
- Cryptogenic/ Low AEDs	36 (11.4)

Abbreviations: SD, standard deviation, AEDs, antiepileptic drugs.

Table 2 Causes of status epilepticus

Causes/Precipitating causes	Number (%)
Acute symptomatic	192 (61.0)
- Acute ICH	32 (10.2)
- CNS infection	32 (10.2)
- Metabolic disturbance	26 (8.3)
- Alcohol withdrawal seizure	20 (6.3)
- Hypoxic ischemic encephalopathy	18 (5.7)
- Acute ischemic stroke	17 (5.4)
- Acute traumatic brain injury	17 (5.4)
- Septic encephalopathy	11 (3.5)
- Hypertensive encephalopathy	7 (2.2)
- Cerebral venous sinus thrombosis	6 (1.9)
- Autoimmune encephalitis	6 (1.9)
Remote symptomatic	87 (27.6)
- Previous ischemic stroke	36 (11.4)
- Post traumatic brain injury	19 (6.0)
- Previous ICH	15 (4.8)
- Brain tumor	10 (3.2)
- Previous CNS infection	4 (1.3)
- Vascular abnormality	3 (1.0)
Cryptogenic epilepsy/ Low AEDs	36 (11.4)

Abbreviations: ICH, intracerebral hemorrhage; CNS, central nervous system, AEDs, antiepileptic drugs.

The outcomes of the patients were demonstrated in Table 3. The outcome were death (125 patients, 39.7%), moderate to severe disability (98 patients, 31.1%), and complete recovery (92 patients, 29.2%).

The complication of the patients of SE are revealed in Table 3. The other complications associated with prolonged or uncontrolled SE were refractory SE (48 patients, 15.2%) and super-refractory SE (12 patients, 3.8%). In subgroup analysis, the incidence of refractory and super-refractory SE was 19.0% (60 of 315 patients). The median length of stay was 4.0 days (IQR: 2.0-8.0).

After univariate analysis, the factors related to poor outcome were demonstrated in Table 4. Baseline factors which associated with mortality in SE were age of over 60 years ($p < 0.01$, HR 1.96, 95% CI: [1.22-3.13]), female ($p = 0.035$, HR 1.63, 95% CI: [1.03-2.58]), and duration of seizure (duration more than 5-30 min ($p < 0.01$, HR 3.28, 95% CI: [1.81-5.96])). Acute symptomatic seizure was the etiology which had been associated with death ($p = 0.04$, HR 3.5, 95% CI: [0.95-12.82]) more than remote symptomatic and cryptogenic etiology.

After subgroup analysis in acute symptomatic seizure, the causes related to mortality were acute

intracerebral hemorrhage ($p < 0.01$, HR 11.84, 95% CI: [3.56-39.04]), central nervous system infection ($p < 0.01$, HR 7.03, 95% CI: [2.18-22.69]), hypoxic ischemic encephalopathy ($p < 0.01$, HR 21.70, 95% CI: [5.05-93.29]), acute ischemic stroke ($p < 0.01$, HR 28.93, 95% CI: [6.05-132.28]), and septic encephalopathy ($p < 0.01$, HR 27.9, 95% CI: [4.61-168.77]). In remote symptomatic seizure, previous ischemic stroke ($p = 0.03$, HR 3.50, 95% CI: [1.09-11.22]) and previous central nervous system infection ($p = 0.05$, HR 3.5, 95% CI: [0.95-12.82]) were associated with mortality.

The presence of complications was the important factor that associated with death ($p < 0.01$, HR 19.16, 95% CI: [9.16-40.08]). In subgroup

analysis, the complications of SE that had significant effect to outcome were aspiration pneumonia ($p < 0.01$, HR 19.16, 95% CI: [2.98-7.89]), shock/hypotension ($p < 0.01$, HR 42.74, 95% CI: [10.83-92.08]), renal failure ($p < 0.01$, HR 12.97, 95% CI: [6.97-24.15]), hospital-acquired pneumonia ($p < 0.01$, HR 6.70, 95% CI: [3.83-11.73]), and rhabdomyolysis ($p < 0.01$, HR 4.33, 95% CI: [1.84-10.18]). Prolonged seizure or uncontrolled SE had clinical significantly higher mortality rate: refractory SE ($p < 0.01$, HR 25.26, 95% CI: [8.78-72.64]) and super-refractory epilepticus ($p < 0.01$, HR 8.17, 95% CI: [1.76-37.97]). The mortality rate of refractory and super-refractory SE was 90.0%.

Table 3 Short term clinical outcome and complications of status epilepticus

Short term clinical outcome	Number (%)*
Survive	190 (60.3)
- Complete recovery	92 (29.2)
- Moderate to severe disability	98 (31.1)
Death	125 (39.7)
Complications	192 (61.0)
- Aspiration pneumonia	138 (43.8)
- Shock/hypotension	94 (29.8)
- Renal failure	84 (26.7)
- Hospital-acquired pneumonia	83 (26.3)
- Urinary tract infection	38 (12.1)
- Rhabdomyolysis	28 (8.9)
- Pressure sore	24 (7.6)
- Pulmonary embolism	3 (1.0)
- Refractory status epilepticus	48 (15.2)
- Super refractory status epilepticus	12 (3.8)
Length of stay, median (days)	4.0 (IQR: 2.0-8.0)

Abbreviations: IQR, interquartile range. * Percent from all of 315 patients.

Table 4 Factor associated with mortality in status epilepticus

Factors	Mortality rate		p-value	HR (95% CI)
	Survive 190 (60.3%)	Death 125 (39.7%)		
Age				
- >60 years	57 (50.0%)	57 (50.0%)	<0.01	1.96 (1.22-3.13)
Sex				
- Female	70 (53.4%)	61 (46.6%)	0.04	1.63 (1.03-2.58)
Etiology				
- Cryptogenic	11 (78.6%)	3 (21.4%)	Reference	1.00
- Acute symptomatic	106 (51.2%)	101 (48.8%)	0.04	3.50 (0.95-12.82)
- Remote symptomatic	73 (77.7%)	21 (22.3%)	0.94	1.05 (0.27-4.13)
Duration of seizure				
- < 5 min	71 (80.7%)	17 (19.3%)	Reference	1.00
- 5-30 min	117 (56.0%)	92 (44.0%)	<0.01	3.28 (1.81-5.96)
- > 30 min	2 (11.1%)	16 (88.9%)	<0.01	33.41 (7.00-159.37)
Refractory condition				
- No refractory condition	184 (72.2%)	71 (27.8%)	Reference	1.00
- Refractory SE	4 (8.3%)	44 (91.7%)	<0.01	25.26 (8.78-72.64)
- Super refractory SE	2 (16.7%)	10 (83.3%)	<0.01	8.17 (1.76-37.97)
Develop complications	76 (39.6%)	116 (60.4%)	<0.01	19.16 (9.16-40.08)

Abbreviations: HR, hazard ratio, CI, confidence interval, SE, status epilepticus.

Discussion

SE is one of the most common neurologic emergencies and has high risk of mortality and morbidity. From the previous literatures, the mortality related to SE in different study population had high variability because of differences in methodology, study design, population, level of hospital, medication, medical facilities, follow-up period and especially the definition of SE (seizure duration of 5 or 30 minutes).²¹ The pool mortality rate in adult studies were 15.9% (range from 12.7-19.2%) for adult who present with SE.⁹ In previous study mortality rate in 12.1% in Singapore, 14.8% in Honduras, 15.9% in China, 19.8% in Brazil, 24.8% in Senegal, and 29% in India.^{21,22} The patient

demographics and etiologies of SE had influence on treatment outcome. There were previous three studies in university hospitals in Thailand which reported the mortality rate of 35%, 26.7, and 25% (Table 5).²³⁻²⁵ In this study, total short-term mortality rate was 39.7% which was a little higher than that from the previous. Our study was conducted in large tertiary care hospital that was not university hospital. It might be explained that our hospital is the large tertiary-care center which many difficult and complicated cases were referred for the specialized care. In addition, it might also be caused by the congestion of patients in our hospital, very low doctor rate per one patient, the referral delay from community hospital that prolongs the duration from the onset to the cessation of SE.

The results of previous study shows that advanced age, longer duration of SE, coma at presentation, female sex, hypoxic-ischemic brain injury, higher rate of comorbidities, acute symptomatic etiology and refractory SE were predictors or risk factors of high mortality.^{2,17-20} Concordance with the previous studies, the researchers found that the related factors associated with short term mortality in SE were age of over 60 years, female, duration of seizure, acute symptomatic seizure, causes of SE, number of antiepileptic drugs used, complications, and refractoriness of SE. Advanced age patients had higher mortality than younger due to their comorbidities. Duration of seizure and number of antiepileptic drugs used represented the refractoriness of SE that was directly associated with high mortality.

According to the etiologies, acute symptomatic seizure had higher mortality rate (48.8%) than remote symptomatic (22.3%) and cryptogenic

seizure (21.4%) which were corresponded with the previous study. Mortality rates in acute symptomatic SE range from 27 to 34%^{16,17,19,22}, however those were lower than our finding (48.8%). Causes of acute symptomatic seizure that associated with mortality were acute intracerebral hemorrhage, central nervous system infection, hypoxic ischemic encephalopathy, acute ischemic stroke, and septic encephalopathy. There finding could be explained by the etiologies of acute symptomatic seizure were severe and high mortality conditions such as large hematoma with extending to cortical area or acute large middle cerebral artery infarction or cortical infarction. In the same way, hypoxic ischemic encephalopathy and septic encephalopathy related to seizure usually happened from post cardiac arrest and severe sepsis or septic shock. In remote symptomatic seizure, previous ischemic stroke and previous central nervous system infection might had many comorbidities and functional dependency such as bed bound status.

Table 5 The mortality rate and etiologies of status epilepticus in Thailand

	Tiamkao (2010)	Phabphal (2013)	Kulkantrakorn (2014)	This study (2020)
Region in Thailand	Northeast	South	Central	Northeast
Number of cases	40	180	60	315
Mortality rate (%)	35	26.7	25	39.7
Common etiologies				
Acute symptomatic (%)				
- CNS infection	22.5	39.6	3.3	10.2
- Acute stroke	12.5	6.1	1.7	15.6
- Alcohol related	15	1.6	10	6.3
- Metabolic or HT encephalopathy	7.5	8.3	11.8	14
- HIE	2.5	6.1	3.3	5.7
Remote symptomatic (%)	7.5	15	40	27.6
Low AEDs/ AEDs withdrawal (%)	25	5.6	23.3	11.4

Abbreviations: CNS, central nervous system, HT, hypertensive, HIE, hypoxic ischemic encephalopathy, AEDs, antiepileptic drugs.

The complications from SE which had clearly significant effect to the outcome were aspiration pneumonia, shock/ hypotension, renal failure, hospital-acquired pneumonia, and rhabdomyolysis. In this study, the complications were reported in 61.0% of the patients which was higher incidence than that in the previous studies. The medical complications can be related to longer duration of seizure. Thus, the more aggressive and prompt treatment might be the most effective methods to prevent the development of complications.

In this study, the incidence of refractory or super-refractory SE was 19.0% and the mortality rate was 90.0%. The previous reports had incidence of refractory SE between 9 to 38%, and mortality rate in that group was generally higher than that in non-refractory condition (16 to 100%).¹⁹ The incidence (19.0%) and mortality rate (90.0%) of refractory or super-refractory SE in our subjects were similar to those in other studies.

There were some limitations in this study. This study was retrospective design which limited data interpretation in certain aspects. The data were retrieved from the medical record which were difficult to collect some in-dept information. There was a selective bias because almost all severe cases were referred to our hospital and many of mild cases were treated in community hospital. For the further study, the pitfalls of SE treatment, antiepileptic drugs details, and the mean time from onset to treatment should be collected and analyzed.

Conclusion

This retrospective descriptive study was conducted in Maharat Nakhon Ratchasima Hospital, Thailand. The Mortality rate of status epilepticus was

39.7%. The mortality-related factors were elderly, female, duration of seizure, acute symptomatic etiology, patient who developed complications and refractoriness of seizure. The development of better system of care and clinical practice guideline for reducing the mortality of status epilepticus patients in Maharat Nakhon Ratchasima Hospital is necessity

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