

# Treatment outcome of status epilepticus in Thammasat University Hospital, Thailand

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## Abstract

**Background and Objective:** Status epilepticus (SE) is an emergency condition with high mortality rate, particularly in patients whose treatment is delayed. This is to describe clinical characteristics, treatment process, and outcome and to determine clinical parameters which impact the SE outcome. **Methods:** This was a descriptive study in 60 SE patients admitted between 2004-2011 to the Thammasat University Hospital, Pathumthani, Thailand. The correlation between the outcome and clinical parameters was analyzed. **Results:** Sixty SE patients were included (38 men; 22 women), mean age 55 years. Generalized convulsive status epilepticus was the most common (55 events, 91.6%). Forty-three patients (71.7%) had previous diagnosis of neurological disorders. AED withdrawal and old ischemic stroke were the common causes of SE. The mean time from onset to treatment was 163.4 minutes and door to needle time was 19.8 minutes. Diazepam and phenytoin were most commonly used as first and second line AED. Eight patients (13%) developed refractory SE. The mortality rate was 25%, with 28.3% in total dependent state, 20% had incomplete recovery, and 26.7% had complete recovery. The risk factors which correlated with death were old age, long duration of seizure and coma.

**Conclusion:** In this cohort from north Bangkok and central Thailand, the mortality and morbidity rates were high. More efforts should be taken to address the long delay to treatment, and other correctable factors.

## INTRODUCTION

Status epilepticus (SE) is an emergency neurological condition with very high morbidity and mortality rates. The duration of seizures to diagnose SE has become shorter and is now suggested to be 5 minutes for earlier diagnosis and management.<sup>1</sup> Hopefully this practice will improve treatment outcome. Aggressive management, especially effective and timely antiepileptic drug (AED) treatment, is the key for seizure control. Despite advancement in medical care and new AEDs, the outcome has been poor. Recent reports from many countries showed mortality rates between 14% to 35%<sup>2-5</sup> and much higher in refractory cases, up to 65%.<sup>6</sup> However, the outcome is varied among institutions, medical care settings and countries.

The most consistent predictors for poor outcome are age of patients, duration of seizures, and underlying causes of SE. Current guideline of SE management still recommends older AEDs as first line and second line therapy, ie. diazepam or lorazepam and phenytoin.<sup>1</sup> The selection of initial AED plays important role in rapid seizure

cessation. Hence, it is directly correlated with the outcome. Therefore, in this study, we assessed the treatment process of SE, clinical parameters, outcome and predictive factors for death.

## METHODS

This was a descriptive study in patients with status epilepticus in Thammasat University Hospital regarding their clinical characteristics, treatment process, type of AEDs and their outcome, and the correlation between clinical parameters and the outcome. Thammasat University Hospital is a tertiary care hospital which situates in Pathumthani province, the Northern suburban area of Bangkok and serves the population of Northern Bangkok and lower Central region of Thailand.

After study approval from the Ethical Committee of Faculty of Medicine, Thammasat University (protocol MTU-EC-IM-1-032/54), the present study enrolled patients with SE, who were at least 15 years old and was admitted to Thammasat University Hospital between January 2004 and October 2011. SE was classified as generalized convulsive SE (GCSE) which

was characterized by clinically overt seizures with impairment of consciousness, and non convulsive SE (NCSE) which was defined as changes in behavior and/or mental state from baseline associated with continuous epileptiform activity in electroencephalogram with subtle motor phenomena.<sup>7</sup> Refractory SE was defined as inability to terminate the seizure after treatment with second line anticonvulsants such as benzodiazepines and phenytoin.<sup>1</sup>

#### Statistical analysis

Data were analyzed by SPSS version 13 (SPSS Inc, Chicago). Results were expressed as the mean and standard deviation (SD). The prevalence of medication use, complications and outcome was expressed as percent. The correlation between clinical parameters such as age, time from onset to treatment, door to needle time, length of stay, white blood cell count, etc. and death outcome was determined by using Spearman's rank correlation coefficient. Statistical significance was defined as a *p* value < 0.05.

## RESULTS

Sixty SE patients were included (38 men; 22 women), between 15-90 years of age, mean age 55 years. Elderly group (age between 60-90 years old) was 27 cases (45%). Their demographic information and investigations were shown in Table 1. Generalized convulsive status epilepticus (GCSE) was most common (55 events, 91.6%). Forty-three patients (71.7%)

had previous diagnosis of neurological disorders. AED withdrawal and old ischemic stroke were the common causes of SE. The SE etiologies were shown in Table 2.

All patients underwent basic laboratory assessment which included complete blood count, blood sugar, serum electrolytes, blood urea nitrogen, creatinine, calcium and magnesium. CT or MRI brain were performed in 50 (83.3%) and 5 (8.3%) patients respectively. Electroencephalogram was performed in 15 patients (25%). Diazepam and phenytoin were most commonly used as first and second line AED. The pattern of AED usage is listed in Figure 1. Phenobarbital was not used due to its shortage in the study period. The mean time from onset to treatment was 163.4 minutes and door to needle time was 19.8 minutes. Eight patients (13%) developed refractory SE.

Sixty six patient of patients developed major complications which included electrolyte imbalance, pneumonia and urinary tract infection (Table 3). Outcomes of SE included death (15 patients, 25%), complete recovery (16 patients, 26.7%), incomplete recovery (12 patients, 20%) and total dependent state (17 patients, 28.3%). The main causes of death were severe sepsis (8 patients, 53.3%), cerebral anoxia (5 patients, 33.3%), hyperkalemia and acute respiratory failure (1 patient each, 6.7%). Based on Spearman's rank correlation coefficient test, the risk factors which correlated with death were age more than 60 years, long duration of seizure prior to treatment and coma.

**Table 1: Demographic information**

Variables	Number of patients (total = 60)
Age (yrs) , mean (SD)	55.1 (18.5)
Male, n (%)	38 (63.3)
Underlying neurological diseases (n, %)	43 (71.7%)
Epilepsy	18 (30)
Cerebral infarction	16 (26.7)
Alcoholism	9 (15)
Head injury	8 (13.3)
Intracerebral hemorrhage	5 (8.3)
Others	7 (11.7)
Underlying systemic disease (n, %)	37 (61.7%)
Hypertension	28 (46.7)
Diabetes mellitus	16 (28.3)
Hyperlipidemia	15 (25)
Chronic obstructive pulmonary disease	6 (10)
Others	9 (15)

**Table 2: Causes and/or precipitating factors of status epilepticus**

Causes/Precipitating causes	Number (%)
Acute Symptomatic	16 (26.7)
Encephalitis	2 (3.3)
Uremia	1 (1.7)
Post cardiac arrest	2 (3.3)
Head injury	2 (3.3)
Septic encephalopathy	3 (5.0)
Brain metastasis	2 (3.3)
Intracerebral hemorrhage	1 (1.7)
Hypoglycemia	1 (1.7)
Hyponatremia	1 (1.7)
Hypocalcemia	1 (1.7)
Remote Symptomatic	24 (40.0)
Post cerebral-infarction	15 (25.0)
Post- head injury	4 (6.7)
Post-intracerebral hemorrhage	5 (8.3)
AEDs withdrawal	14 (23.3)
Alcohol related	6 (10.0)

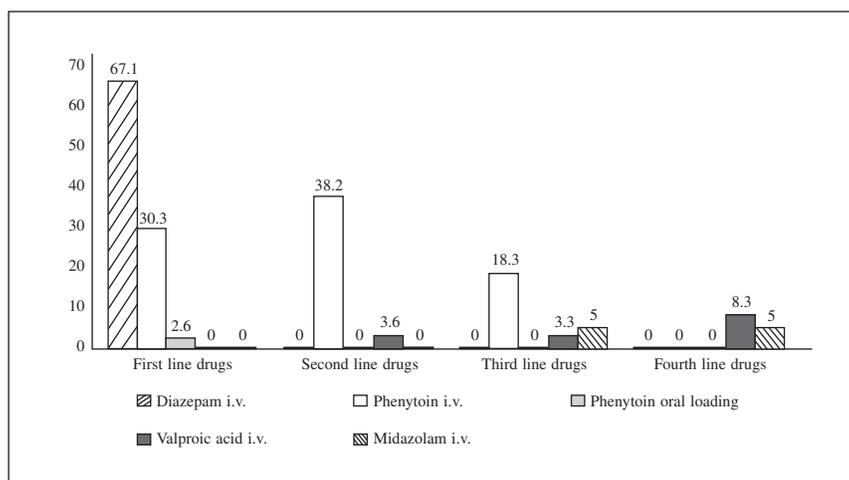


Figure 1. Pattern of antiepileptic drug usage in status epilepticus

**Table 3: Complications of SE**

Complications of SE	Number (%)
<b>With Complications</b>	33 (55.0)*
Electrolyte imbalance	29 (87.9)
Pneumonia	17 (51.5)
UTI	15 (45.5)
Rhabdomyolysis	7 (21.2)
UGI-Bleeding	6 (18.2)
Sepsis	5 (15.2)
Acute renal failure	3 (9.1)
Pressure sore	2 (6.1)
<b>Without Complication</b>	27 (45.0)*

Each patient may have more than one complication. The percent of each complication is calculated based on total number of 33 patients.

\*Based on total of 60 patients

## DISCUSSION

From the present study, the outcome of SE was not favorable in our institution, when compared to other developed countries (Table 4). One fourth of patients died and half were disabled. In Thailand, the national database of SE revealed an incidence of 5.10 cases per 100,000 population. Mortality rate in general was 0.6 case per 100,000 population or 11.96% of total patients. The important factors associated with high mortality rate are universal health care insurance, residence in the Northern region and treatment in tertiary care hospital.<sup>8</sup> Due to the referral pattern and severity of patients, the rates of unfavorable outcome in Thai University Hospital are consistently higher than the national average.<sup>9,10</sup>

The patient demographics and underlying causes of SE vary among hospital level and geographic which may influence on the mortality. Almost half of our patients were older than 60 years old with many pre-morbid conditions. Because our center is a large stroke referral center, the major cause of SE was post-stroke seizure which often occurs within two weeks after stroke.<sup>11</sup> This was significantly different from Songklanagarind hospital in the Southern region and Srinagarind hospital in the Northeastern region of Thailand which reported the mortality rate of 24.7% and 35% respectively.<sup>9,10</sup> The outcome and aetiology of status epilepticus in university hospitals in Thailand were summarized in Table 5. Remote symptomatic aetiology, predominantly post-cerebral infarction, head injury and intracerebral hemorrhage, played an important role in our centre; while CNS infection was the major cause in other parts of the country. AED withdrawal or alcohol abuse are often associated with good prognosis while the poor outcome occurs in stroke and cerebral anoxia.<sup>12</sup> This may in part explain the different outcome among hospitals in Thailand.

Regarding the treatment pattern, most patients received appropriate treatment with diazepam and phenytoin as the first and second line therapy.

However, thirteen percent of patients were refractory to treatment and need additional AEDs. The third and fourth line agents in general were valproic acid and midazolam which were in line with current clinical practice guideline.<sup>1</sup> The usage of valproic acid as the first or second line agent is becoming more common. Intravenous sodium valproate was found to be non-inferior to intravenous phenytoin as the first-line treatment in SE with no significant cardiovascular compromises.<sup>13</sup> The off-label use of newer intravenous or oral AEDs including levetiracetam, high dose enteral or parenteral phenobarbital and topiramate were seldom used in our institution.

Nevertheless, the mean time from onset to treatment or the duration of seizure in this study was over two and a half hours, which indicate poor recognition and delayed diagnosis. Despite comparable public awareness of epilepsy among Asian countries, the knowledge of this emergency condition is still lacking.<sup>14</sup> From Thai nationwide survey, most bystanders were willing to assist a person having an epileptic seizure, but almost half would avoid helping, mainly because of a lack of proper first-aid knowledge, and not because of negative feelings toward the person.<sup>15</sup> Although our hospital location is convenient for referral, the treatment is still delayed. Therefore, paramedics should be more equipped or able to give benzodiazepine en route to improve the outcome.<sup>16</sup> Moreover, the door to needle time was around 20 minutes which should also be shortened to less than 10 minutes to prevent the refractoriness. Non convulsive SE, especially in the elderly, may be overlooked and undertreated by medical professionals.<sup>17</sup> For these reasons, the education for both public and health care professionals is urgently needed to improve this timing.

Complications of SE were common and played important role in final outcome. Superimposed infection, especially from aspiration pneumonia, urinary tract infection and sepsis caused significant

**Table 4: Comparative outcome of status epilepticus from previous studies**

Reference	Country	Number of case	Mortality (%)
Scholtes <i>et al.</i> (1994) <sup>19</sup>	Netherlands	346	11
Coytaux A, <i>et al.</i> (2000) <sup>20</sup>	Switzerland	172	7.6
Koubeissi, <i>et al.</i> (2007) <sup>21</sup>	USA	11580	3.45
Tiamkao <i>et al.</i> (2010) <sup>9</sup>	Thailand	40	35
Tiamkao, <i>et al.</i> (2013) <sup>8</sup>	Thailand	2190	11.96
Phabphal, <i>et al.</i> (2013) <sup>10</sup>	Thailand	180	26.7
This study	Thailand	60	25

**Table 5: The outcome and aetiology of status epilepticus in university hospitals in Thailand**

	Tiamkao (2010) <sup>9</sup>	Phabphal (2013) <sup>10</sup>	This study
Region in Thailand	Northeast	South	Central
Mortality rate (%)	35	26.7	25
<b>Important etiologies (%)</b>			
Low AED/AED withdrawal	25	5.6	23.3
Remote symptomatic (post cerebral infarction, head injury, intracerebral hemorrhage, etc) (%)	7.5	15	40
Encephalitis / meningitis / CNS infection	22.5	39.6	3.3
Cerebral infarction / intracerebral hemorrhage	12.5	6.1	1.7
Alcohol related	15	1.6	10
Hypertensive or metabolic encephalopathy	7.5	8.3	11.8
Hypoxic ischemic encephalopathy	2.5	6.1	3.3

deterioration in general medical condition of the patients and final death outcome. The predictors of death in this study were old age, long duration of seizure and coma, in agreement with the latest meta-analysis findings, which is independent of the etiology and EEG finding.<sup>18</sup>

Due to the nature of retrospective design, the information in some cases was incomplete. The number of patient was less than expected due to the limitation of medical records search as far as 2004 and some records were lost during the severe flood period in our hospital.

In conclusion, most SE patients are old and have underlying neurological disorders. The mortality and morbidity rate in our institution were higher than the developed countries, but in line with other tertiary care hospitals in Thailand. Death is associated with old age, long duration of seizure and coma. More efforts should be taken to address the long delay to treatment, and other correctable factors identified in this study.

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## DISCLOSURE

Conflict of interest: None

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