

# Evaluation of Short-term Mortality of Status Epilepticus and Its Risk Factors

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## Original Article

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**Background and Purpose:** Status epilepticus (SE) is defined as epileptic seizures of greater than five minutes or more than one seizure within a five minute period without returning to normal consciousness between them. It is a life-threatening condition particularly if treatment is delayed. Previous studies reported age, duration and etiology of SE as primary determinants of mortality.

**Methods:** This prospective cross-sectional study performed on the patients with status epilepticus admitted in Rasoul-e-Akram hospital in Tehran. Patients followed at 30th day after SE to assess their living status.

**Results:** Sixty-five patients, (56.9% was male) with 15 to 88 years of age entered the study. Mean duration of SE was 40 minutes and for hospital stay was 7 days. 84.6% of patients responded to treatment and 11 patients (16.9%) died within 30 days after SE. Mortality rate in patients with refractory SE was 70%. Mean interval between SE and death was  $11.9 \pm 11.7$  days. Age, duration of SE and hospital stay, history of head trauma and neurosurgery were not predictors of mortality. Negative history for epilepsy had significantly higher mortality rate. Anoxic encephalopathy increased the mortality rate and response to treatment decreased it.

**Conclusions:** Short-term mortality rate of SE was comparable with most of the previous reports. Since our hospital has equipped emergency department, resuscitation and primary treatment of SE is usually start soon, percentage of anoxic encephalopathy is decreased and lower mortality rate is expected. We conclude that early treatment by decrease chance of anoxic encephalopathy, has significant role in outcome of SE. (2015;5:13-16)

**Key words:** Status epilepticus, Mortality rate, Refractory seizure

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## Introduction

Status epilepticus (SE) is defined by the International Classification of Epileptic Seizures and by the Epilepsy Foundation of America's Working Group as an epileptic seizure of greater than five minutes or more than one seizure within a five minute period without the person returning to normal consciousness between them.<sup>1</sup> The seizures can tonic-clonic, absence or complex partial seizures. Status epilepticus is a life-threatening condition particularly if treatment is delayed.<sup>2</sup>

According to a large prospective database compiled through the Greater Richmond Metropolitan Area Status Epilepticus Project (GRMASE), by using the 30-minute definition, 30-day mortality rates for subjects with seizures lasting 10 to 29 minutes was only 2.6% compared with a 19% rate in patients diagnosed with SE but who

otherwise had comparable clinical features.<sup>3</sup>

As it is uncommon for patients to die during SE, studies generally define SE-related mortality in terms of days lived after resolution of SE. Typically, death rates peak within 30 days after SE<sup>4</sup>

Status epilepticus may occur in those with a history of epilepsy as well as those with an underlying problem of the brain such as trauma, infections, or strokes.<sup>5</sup>

Status epilepticus is the second common neurologic emergency (after acute stroke) with annual incidence of 10 to 40 cases per 100,000 persons and 10 to 20% of these patients experience their first seizure.<sup>5</sup> Apart from duration, an episode that continuous after sufficient dose of Benzodiazepines and at least one other anti-epileptic drug (AED) is called refractory status epilepticus, which is seen in 23 to 43% of the patients.<sup>6</sup>

Previous studies showed 32% mortality rate in SE episodes lasting for more than one hour versus 2.7% mortality rate in episodes less than an hour.<sup>7</sup>

Short term mortality rate of refractory SE has been estimated as 16 to 39%. Mortality after refractory SE is three times greater than non-refractory episodes. In the majority of cases, death occurs after SE episode and is related to underlying medical conditions.<sup>8</sup>

After duration and etiology age is the third determinant factor: Age at time of SE predicts a bimodal mortality, with peak rates for the very young and the very old.<sup>9</sup>

Usual mortality rates in adult studies range from 16% to 25%, although risk steadily increases with advancing age. In the GRMASE study, overall adult mortality was 26%, but 38% for patients older than 60 years and greater than 50% in patients older than 80 years.<sup>10</sup>

The overall mortality rates of partial and generalized convulsive SE (GCSE) EEG patterns have not been found to be significantly different.<sup>10</sup> However, the disassociation of EEG from clinical seizures appears to have a striking effect on mortality. In the Veterans Affairs cooperative study of the treatment of GCSE, patients who have generalized convulsive movements coincident with EEG discharges (overt GCSE) were found to have a 30-day mortality of 26.8%, compared with 64.9% in those who had no obvious convulsive movements (subtle GCSE).<sup>11</sup>

Mortality rate after SE episode varies in different areas, which can be due to different treatment modalities and geographic conditions.<sup>7</sup> In the study by Logroscino et al<sup>12</sup> in 2005, mortality after first SE episode evaluated in the United States and Europe. Incidence and mortality rate of SE was significantly higher in the USA (22% vs. 10% mortality rate after exclusion of anoxic encephalopathy cases.)

In the study by Hocker et al<sup>13</sup> in 2013, 63 non-anoxic refractory SE episodes in 54 adults evaluated. 55 episodes (87.8%) controlled by anesthetic drugs. Mean duration of admission in hospital was 27.7 days and 31.7% of patients expired in the hospital. Duration of drug induced coma, cardiac dysrhythmia and pneumonia were predictors of poor prognosis. Patients underwent mechanical ventilation had higher mortality rate.

In the Classen et al<sup>14</sup> study on 74 patients and 85 episode of SE, 21% of episodes were fatal and 23% of non-fatal episodes, led to decrease functioning of the patient. Old age and acute symptomatic seizure were predictors of mortality.

In a descriptive study by Kulkantrakorn et al<sup>15</sup>, on 60 patients with SE, most common causes include AED withdrawal and ischemic stroke.

13% of patient had refractory SE and 25% expired. Factors associated with higher mortality rate included advanced age, longer duration of seizure and coma.

Although some clinical series have suggested a decrease in mortality in SE patients in the recent years, the Rochester Epidemiologic Study,<sup>4</sup> which calculated incidence and case-fatality rates (CFR) over 30 years (1955 to 1984), found that the 30-day CFR remained stable. However, incidence rates increased as a result of greater numbers of elderly patients and survivors of cardiac arrest with anoxic etiology for SE. Thus, despite the better treatment options and trends toward recommending more aggressive ICU management for SE, it appears that these improvements in patient care are merely matching the increased proportion of high-mortality SE cases.

The aim of the present study is to evaluate 30-day mortality rate and prognostic factors in patients with SE, who are admitted in Rasoul-e-Akram hospital, Tehran, Iran.

## Methods

This study has been designed as a prospective cross-sectional study. Study population is all the patients with status epilepticus *that visited emergency department and admitted in* Rasoul-e-Akram hospital in Tehran, Iran, from October 2013 to December 2014.

Inclusion criteria are: consent of patient or his/her family to enter the study, more than 15 years of age. Patients with other forms of SE (other than tonic-clonic SE) did not enter the study.

SE is confirmed by clinical judgment and EEG findings; *as well as witness report. Patients with suspicious history regarding status seizures or whom we couldn't judge about the exact duration of seizure were excluded.* A check list is made for each patient and data such as age, gender, history of epilepsy or SE, history of surgery, presence of anoxic encephalopathy, duration of SE and duration of admission are recorded.

### Treatment protocol

*Initial assessment:* ensuring adequate ventilation, oxygenation, blood pressure, intubation if low oxygen saturation and labored breathing; inserting intravenous line, administration of glucose in appropriate circumstances and for rare cases in Iran thiamine if history of alcoholism is obtained. Send blood samples for toxicology and AED level assessment.

*Immediate suppression of convulsions:* diazepam 2-4 mg/min IV to a total dose of 10-15 mg with monitoring of Vital signs

*Initiation or reloading with anticonvulsants:* slow infusion of phenytoin 15-20 mg/kg (25-50 mg/min, diluted in normal saline)

*General anesthetic doses of medication for SE:* if convulsions continued, the patient is considered to have refractory SE (ten patients); then Midazolam 0.2 mg/kg loading dose followed by infusion at 0.1-0.4 mg/kg/h or Propofol 2 mg/kg/h were administered; and if convulsions persist after several hours, Valproate or Phenobarbital 10 mg/min to total dose of 20 mg/kg were administered intravenously. Alternatively, Carbamazepine or Levetiracetam were administered by nasogastric tube if bowel activity present, and if convulsions persist, neuromuscular paralysis was done with...

All the patients admitted to intensive care unit after suppression of convulsion in emergency department.

Hypoxic encephalopathy was suspected if patient had prolonged loss of consciousness for more than time we expect as post ictal phase, without any other cause. The diagnosis was confirmed if parkinsonism signs with cognitive impairment or abnormal movements (myoclonus or choreoathetosis) which didn't exist before SE, develop; laboratory reveal acidosis in blood gas analysis, neuroimaging show loss of distinction between cerebral gray and white matter and diffuse signal changes specially in striatal regions, and generalized slow waves seen in electroencephalogram.

All the patients received a phone – call at 30th day after SE to assess their living status.

Data analysis is done by SPSS version 18 and descriptive analysis such as mean, standard deviation and range are calculated. Student-t-test is used for quantitative analysis and Chi-2 test is used for analysis of qualitative variants.

## Results

Sixty-five patients, who referred to emergency department of Rasoul-e-Akram hospital with SE, treated and admitted in neurology ward, entered the study with informed consent. 37 patients (56.9%) were male. Patients had 15 to 88 years of age with mean of 44.6 years.

Mean duration of SE in the cases was 40 minutes and mean duration of hospital stay was 7 days. 21.5% and 6.2% of patients had history of head trauma and neurosurgery, respectively. About half of them (47.7%) were previously diagnosed with epilepsy and 12.3% had experienced previous episode of SE. Anoxic encephalopathy was seen in 13.8% of the cases (Table 1).

Fifty-five patients (84.6%) responded to treatment (ten other pa-

tients had refractory SE) and 11 patients (16.9%) died within 30 years after SE. Mortality rate in patients with refractory SE was 70%. Mean interval between SE and death was  $11.9 \pm 11.7$  days. Mortality rate did not differ between the two genders ( $p = 0.18$ ).

Age, duration of SE and duration of hospital stay were not significant predictors of mortality in our patients ( $p = 0.08$ , 0.65 and 0.41, respectively).

Mortality in patients with history of head trauma and neurosurgery was equal with those with negative history ( $p = 0.1$  and 0.99, respectively).

Patients with negative history for epilepsy had significantly higher mortality rate. ( $p < 0.0001$ , Odds Ratio = 7.7) But mortality rate in those with positive and negative history for previous SE episode was not different. ( $p = 0.99$ )

Anoxic encephalopathy significantly increased the mortality rate. ( $p < 0.0001$ , OR = 20.4) and desirable response to treatment sig-

**Table 1.** Basic characteristics of the patients

Value	
Male/female	37 (56.9%)/ 28 (43.1%)
Age (year)	44.69 $\pm$ 20.7
Underline disease	DM 3 (4.6%) HTN 4 (6.2%) CKD 3 (4.6%)
Head trauma history	14 (21.5%)
Brain surgery history	4 (6.2%)
Epilepsy history	31 (47.7%)
Status Epilepticus (SE) history	8 (12.3%)
Anoxic Encephalopathy history	9 (13.8%)

Values are expressed as frequency (percent) or Mean  $\pm$  SD

**Table 2.** Factors influencing mortality rate of SE

Variable	$p$ value
Sex (f/m)	0.054
Age	0.064
History of head trauma (+/-)	0.1
History of neurosurgery (+/-)	0.99
History of previous SE (+/-)	0.99
Epilepsy history (+/-)	0.997
Response to treatment (+/-)	0.018*
Anoxic encephalopathy (+/-)	$P < 0.0001$
Duration of SE	0.65
Duration of hospital stay	0.41

\*expresses significant influence of response to treatment on the mortality rate of SE.

nificantly decreased it ( $p < 0.0001$ , OR = 29.7) (Table 2).

## Discussion

Status epilepticus, as the second most common neurologic emergency, has high risk of mortality and morbidity. Previous studies estimated 16 to 39% mortality rate for refractory SE, which is three times greater than non-refractory SE.<sup>8</sup>

In this study, total mortality rate was 16.9% and slightly higher in females; however, the difference was not statistically significant. In the study by Koubeissi et al, female patients had significantly greater mortality rate.<sup>16</sup>

Mortality rate in first month after SE reported 31.7% by Hocker et al<sup>13</sup> and 21% by Classen.<sup>14</sup> Another study performed in 2005, reported 10% mortality rate for SE<sup>12</sup> In pediatric age group, 14.6% mortality rate was reported<sup>11</sup> and in study by Koubeissi in the USA, in-hospital mortality rate was 3.45%.<sup>16</sup>

In this study short-term mortality rate of SE was comparable with most of the previous reports and even lower than some others.<sup>13,14</sup> Since Rasoul-e-Akram is a referral hospital, it has well-equipped emergency department, resuscitation and primary treatment of SE is usually started very soon and metabolic causes for SE and electrolyte imbalances are corrected rapidly. Thus, percentage of patients with anoxic encephalopathy is decreased and less mortality rate, compared to some other hospitals, is expected.

Previous studies reported long-term mechanical ventilation,<sup>13</sup> advanced age;<sup>16,17</sup> longer duration of SE;<sup>4,17</sup> coma at presentation;<sup>17</sup> female sex, hypoxic-ischemic brain injury, higher rate of comorbidities;<sup>14</sup> generalized myoclonic seizure, acute symptomatic etiology for seizure<sup>4,12</sup> and refractory SE, as predictors of higher mortality. However, in our study, age, sex, duration of SE, duration of hospital stay, history of head trauma or neurosurgery and previous episode of SE were not associated with mortality; but mortality rate was significantly less in patients who responded to treatment; which is comparable with Saenz's study.<sup>11</sup> Moreover, patients with anoxic encephalopathy and those with negative history for epilepsy had higher mortality rate.

Furthermore, from another aspect we found that patients with negative history for epilepsy had significant higher mortality rate that a hypothesis is refractory SE and its sequels are maybe because of an underlying cause as drug poisoning or other causes that our source of history is not aware of that and can't be demonstrated in routine toxicity lab tests.

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