Clinical profile and outcomes in adults with status epilepticus - A prospective observational study

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Abstract

***Objectives*: Status epilepticus (SE) is a common life-threatening medical emergency, and its neurological outcome requires prompt recognition and management. The present study aimed to determine the clinical profile and outcome of patients with status epilepticus.**

***Design*: Prospective observational study.**

***Setting*: The study was conducted in intensive care units under Emergency Medicine, General Medicine, Neuro Medicine, and Neurosurgery Departments of a tertiary care centre from March 2018 to September 2019.**

***Patients and participants*: Forty-six status epilepticus patients attending intensive care units under Emergency Medicine, General Medicine, Neuro Medicine, and Neurosurgery Departments of a tertiary care centre were included and followed for 45 days.**

***Measurements and results*: Baseline data on demographics, comorbidities, duration of each episode, number of episodes, treatment, brain imaging findings (computed tomography [CT] and magnetic resonance imaging [MRI]) and other comorbidities. The collected data was analyzed by analysis of variance (Anova) and independent t-test. P-value <0.05 was considered statistically significant. Out of 45 subjects included in the final analysis, 34 (75.6%) survived, and 11 (24.4%) had died during hospitalization. Mean±standard deviation of age was 43.1±1.02. Thirteen (71.1%) had diabetes mellitus as comorbidity. Twenty-four (53.3%) of them had >15 mins of seizure, 22 (48.9%) were in between 5 to 12 of Glasgow coma scale score. Among the study population, the probable etiology was head trauma 5 patients (11%), viral meningoencephalitis 7 patients (15.6%), acute cardiovascular system 9 patients (24.4%), and alcohol withdraw 14 patients (8.9%). Majority of them (18 patients [40%]) required third-line treatment, 33 patients (73.3%) required in hospital ventilator assistance, and 19 patients (42.2%) developed refractory status epilepticus (RSE). The duration of hospital stay was found to be significant for third-line treatment (21.9 days), mechanical ventilation (21.30 days), and RSE (23.8 days) with a p-value of 0.001.**

***Conclusion*: The duration of hospital stay was significantly associated with the findings on brain MRI, the requirement of in-hospital ventilatory support, the treatment given, and the presence of RSE.**

Key words: Status epilepticus, etiology, neurodegenerative diseases, ventilation.

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Introduction

Status epilepticus (SE) is a common life-threatening medical emergency, and its neurological outcome requires prompt recognition and management. The estimated convulsive status epilepticus (CSE) prevalence is 14.5 per 100,000 per year in developed countries, but population-based studies are not available from developing countries. (1) There is a significant morbidity (28-34%) and mortality (7-22%) with SE despite advancement in treatment protocols in the last decade. (2,3)

The classical definition of SE requires that seizures

(continuous or intermittent without return to baseline mental status) last for a minimum of 30 minutes. However, seizures which last longer than 5 minutes are unlikely to stop spontaneously. As part of operational definition put forth within the past few years, status epilepticus is defined as continuous seizure activity or recurrent seizure activity without regaining consciousness, lasting for more than 5 minutes. The use of operational definition allows early treatment before the seizure becomes refractory to antiepileptic drugs. (4)

Seizure disorder affects about 50 million people worldwide. (5) Although various factors influence the incidence and prevalence of seizures, 5-10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood. (6)

The etiology of seizures is different in India as compared to the developed world. (5) Causes of acute symptomatic seizures can be a head injury, neurocysticercosis (NCC), tuberculoma, brain abscess, encephalitis, cerebrovascular accident (CVA), hepatic or renal failure, drug toxicity, alcohol withdrawal, and metabolic derangements. Causes of remote symptomatic seizures can be old CVA, post-traumatic gliosis, calcified lesion, operated brain tumour, treated encephalitis, and birth asphyxia. (3)

The triggering factors for seizures can be sleep deprivation, alcohol (particularly withdrawal), recreation drug misuse, physical and mental exhaustion, flickering lights, television and computer screens (for primary generalized epilepsies), infection, metabolic disturbances, and, uncommonly, loud noises, music, reading, hot baths. (7)

Etiology and clinical profile of seizures in adults necessitate decisions about the initiation and discontinuation of pharmacotherapy that are different for adults and younger patients. (8) The electroencephalogram (EEG) along with neuroimaging techniques (computed tomography [CT]/magnetic resonance imaging [MRI]) is the most important investigation in the diagnosis and management of epilepsies (5) in adult patients. For evaluation of adults with new-onset seizures, MRI has been shown to be superior to CT scan for the detection of cerebral lesions causing seizures; but, CT scan is an appropriate choice in emergency settings. (9)

Many previous studies in India by Chaudhri et al. (5) and Joshi et al. (10) have described clinical manifestations and outcomes of partial seizures and new-onset seizures. In a previous study by De la Morena Vicente et al., (11) ten patients (11.9%) died when treatment failed to control SE and percentage of success achieved was 8.3% with the first treatment, 27.3% for the second, and 48.7% for the third line. Most of the studies available for SE are from retrospective data, and there is a dearth of data about generalized status epilepticus in India. Hence, there is a need for a clinical study of SE to establish the proper etiology and clinical profile in adults visiting tertiary care hospital in India.

Aims and objectives

To study the clinical profile and outcome of adult patients diagnosed with generalized convulsive status epilepticus in a tertiary care setting.

Materials and methods

Study design

It is a prospective observational study.

Study setting

Wards and intensive care units under Emergency Medicine, General Medicine, Neuro Medicine, and Neurosurgery Departments of a tertiary care centre.

Study population

Status epileptics patients attending intensive care units under Emergency Medicine, General Medicine, Neuro Medicine, and Neurosurgery Departments of a tertiary care centre.

Study period

For one and a half year from March 2018 to September 2019.

Sample and sampling technique

All 46 patients with SE attending our hospital during the mentioned study period were included and followed for 45 days. Universal sampling was done since the sample size was not calculated.

Inclusion criteria

- Age more than 18 years
- Patients diagnosed to have generalized convulsive status epilepticus (defined as continuous seizure activity or recurrent seizure activity without regaining consciousness lasting for >5 min)

Exclusion criteria

- Patients with partial or pseudoseizures
- Patient with psychogenic cause for abnormal movements
- Patients below 18 years
- Patients in whom the information regarding seizure duration was incomplete or unclear

Ethics Committee approval and informed consent

The Ethics Committee duly approved the study pro-

tocol of the concerned tertiary care centre. Written informed consent was obtained from the attendant of patient, and confidentiality of the participants was maintained.

Data collection

Data collection was done by obtaining history using a designed questionnaire, clinical examination, and by accessing the patient's inpatient file for required data. All the adult patients admitted and diagnosed as generalized convulsive status epilepticus in setting from admission to discharge were studied.

Demographics, comorbidities, duration of each episode, number of episodes compliance with the treatment, and other comorbidities were noted, and history of other presenting complaints was taken from the patient's family or attenders. Detailed physical examination was done with importance to the level of consciousness as per Glasgow coma scale (GCS) score. Development of in-hospital refractory status epilepticus (RSE) as a first episode or in addition to SE at admission was also noted. Investigations were collected from the inpatient files, emphasizing blood sugars, serum electrolytes, and brain imaging findings (CT and MRI). Drugs were given as per the treating physician's advice, in-hospital ventilator support requirements were noted. The data thus collected, and was analyzed in association with the outcomes.

Statistical methods

Mortality, duration of hospitalization, discharge parameter etc., were considered as primary outcome variables. Age, gender was considered as explanatory variables. Descriptive analysis was carried out by mean and standard deviation (SD) for quantitative variables, frequency and proportion for categorical variables. All quantitative variables were checked for normal distribution within each explanatory variable category by using visual inspection of histograms and normality Q-Q plots. Shapiro-Wilk test was also conducted to assess normal distribution. Shapiro-Wilk test p-value of >0.05 was considered as a normal distribution. The distribution of baseline risk factors and clinical presentation with outcomes and hospital stay were compared using analysis of variance (Anova) test. P-value <0.05 was considered statistically significant. coGuide version 1.0 was used for statistical analysis. (12)

Results

Of total 46 patients enrolled in this study, only 45 were considered. One patient had been excluded from the analysis due to prolonged stay of 250 days, which would have caused bias in the analysis of hospital stay and other outcomes. Out of 45 patients, 34 (75.6%) survived, and 11 (24.4%) had died during hospitalization.

Table 1 shows that among the study population, mean±SD of age was 43.1±1.02 (the age range of the patients was 18 to 82 years), 28 (62.2%) were male, and 17 (37.8%) were female. Participants comorbidities: 7 (15.6%) of them had a seizure with regular medication, 13 (71.1%) had diabetes mellitus, 4 (8.9%) had chronic kidney disease, 2 (4.4%) had chronic artery disease. Twenty-four patients (53.3%) had >15 mins of seizure, 41 (91.1%) had two or more episodes of seizures, 22 (48.9%) were in between 5 to 12 of Glasgow coma scale score. The majority of them required second-line treatment (23 [51.1%]) and third-line one (18 [40%]).

Table 2 shows that among the study population the probable etiology was head trauma (5 [11%]), viral meningoencephalitis (7 [15.6%]), acute cardiovascular system (9 [24.4%]), and alcohol withdrawal (14 [8.9%]) was more. Twenty-one patients (26.5%) and 24 (33.4%) had abnormal CT and MRI scan, respectively. Thirty-three patients (73.3%) required in hospital ventilator assistance, while 19 (42.2%) developed refractory SE. Ten patients (29.4%) had altered sensorium, 9 (26.5%) required mechanical ventilation at discharge, 8 (23.5%) had paresis at discharge, 3 (8.8%) had persisting seizures at discharge, and 18 (52.9%) had no deficit during discharge during 45 days follow up.

Table 3 shows us that only 13 subjects, who required general anesthesia or the anesthetic dose of midazolam, in addition, stayed for 21.9 days in hospital, which was statistically significant. Fourteen subjects who developed refractory SE stayed for 23.8 days, and nine subjects who required mechanical ventilation or tracheostomy stayed for 21.3 days, which were statistically significant (p=0.001). Other variables did not show any association with duration of hospital stay.

Discussion

The present study was intended to investigate the clinical profile and outcomes in patients with SE, and also the underlying etiologies associated with SE. Out of 46 patients enrolled, only 45 were considered and one patient had been excluded from the analysis due to prolonged stay of 250 days**,** which would have caused bias in the analysis of hospital stay and other outcomes. Out of 45 patients, 34 (75.6%) survived, and 11 (24.4%) had died during hospitalization. Mean age was 43.1±1.02, 28 (62.2%) were male, and 17 (37.8%) were female. Seven (15.6%) of them had a seizure with regular medication, 13 (71.1%) of them had diabetes melli-

tus as comorbidity. Twenty-four (53.3%) of them had >15 mins of seizure, 41 (91.1%) had two or more episodes of seizures, 22 (48.9%) were in between 5 to 12 of Glasgow coma scale, and majority of them required second-line (23 [51.1%]) and third-line treatment (18 [40%]). Thirty-three (73.3%) required in hospital ventilator assistance and 19 (42.2%) developed refractory SE. The duration of hospital stay was found to be significant for third-line treatment (21.9 days), mechanical ventilation (21.3 days), and refractory SE (23.8 days), with a p-value of 0.001. Ten patients (29.4%) had altered sensorium, 9 (26.5%) required mechanical ventilation at discharge, 8 (23.5%) had paresis at discharge, 3 (8.8%) had persisting seizures at discharge, and 18 (52.9%) had no deficit during discharge during 45 days follow up.

Majority of the subjects (33 [73.3%]) required in hospital ventilatory support. Various studies have identified acute or potentially fatal etiologies, advanced age, de novo presentation, and severe consciousness impairment before treatment as some clinical prognostic predictors in SE patients. (13) Out of 45 patients, 34 (75.6%) survived, and 11 (24.4%) had died during hospitalization. This finding of our study was in comparison to a recent study by Hay Aet al., that in-hospital mortality was reported to be 5%, and the mean ICU and hospital stay was 38.5 hours and 6.3 days, respectively. (14) The mean age of patients who survived (34 patients) was 45.1 years, and those who died (12 patients) was 36.6 years. Age was not found to be associated with in-hospital mortality. The literature proposes that older age is generally linked with poor outcomes. (15) However, in a cohort study, Rudin D. et al. had reported that older age was associated with the more favourable course, which was in contrast to the present study. (16)

The patient population was predominated by male, i.e. 62.2%. However, the male had to stay for shorter duration when compared to female and had a slight lower rate of mortality when compared to female (21.4% vs 29.4%). Previous studies have reported that evidence for a link between sex and SE outcome has been inconsistent. (17)

In the present study, the mean GCS score was 6.7. The GCS score 3-4, 5-12, and 13-15 was observed in 16, 22, and 7 patients, respectively. The patients with GCS score 3-4 had to stay for longer duration in hospital (mean 18.5 days), patients with 5 to 12 score had to stay for 11.8 days, and patients with 13 to 15 score had to wait for least duration, i.e. for 6.9 days. Moon J et al. in a study have observed the in-hospital outcomes and delayed neurologic sequelae of seizure-related endosulfan poisoning with GCS score. (18) Whereas, Hay A et al. had previously observed mean GCS score of 10.3, which was found to be statistically associated with in-hospital outcomes ($p<0.001$) and mechanical ventilation ($p<0.001$). (14)

The drugs and combinations were given as per the advice of the treating physician. Four (8.9%) patients required 1st and 2nd line drugs to manage SE, 23 (51.1%) patients required 1st line, 2nd line, and add on drugs to manage SE, and 18 (40%) patients required general anesthesia or an anesthetic dose of midazolam in addition. The type of treatment was found to be strongly associated with the duration of hospital stay ($p=0.001$), such that patients who required general anesthesia or an anesthetic dose of midazolam, in addition, had to stay for the longest duration (21.9 days). The cases which required this type of treatment were significantly associated with the requirement of mechanical ventilation at discharge i.e. most patients who required general anesthesia (61.5%) required mechanical ventilation/tracheostomy at discharge ($p=0.01$). In a previous study, Sutter R et al. had reported that the patients who were given anesthetics had to stay for longer duration in hospital than those who were not given anesthetics ($p=0.005$). (19)

There were various etiologies for the occurrence of SE. Of those, and the most common cause, was acute CVA, followed by viral meningoencephalitis. The etiologies were not allied with the duration of hospital stay, however, acute CVA, alcohol withdrawal, and viral meningoencephalitis had a higher impact on prolongation of hospital stay. Tuppuraneni et al. have stated some of the common etiologies in a recent study. (15)

RSE was observed in 19 (42.2%) patients out of the total study population (45) and 14 patients with RSE survived. Among 45 patients, 20 patients (58.82%) did not have RSE and the duration of hospital stay was 6.8±2.2 days, meanwhile 14 patients (41.17%) had RSE and the duration of hospital stay increased to 21.2±1.2 days, and the association was significant ($p=0.01$). This finding was in comparison to Kantanen AM et al., which reported in-hospital mortality of 6% and 10% for refractory and super refractory SE, respectively. (20)

Literature suggests a significant relationship between the need for mechanical ventilation and death, and in between brain lesions and longer hospital stay. (21) Any type of paresis and persisting seizures at discharge were also associated with a longer hospital stay, but the increase was not significant.

Limitations of the study

A small sample size limited the study. Evaluation of the predictors by the treating physicians was not recorded. Another study limitation was the lack of a long-term evaluation, which warranted prospective time-extended studies, which could have differentiated the consequences. Another limitation could be only single hospital setting was considered, which could mislead the information regarding the generalizability of the study findings. Further research should be conducted with a large sample including many hospital settings in a geographical area considering multicentric trials.

Conclusion

In light of these results, it can be concluded that in status epilepticus patients, the duration of hospital stay was significantly associated with MRI brain findings, the requirement of in-hospital ventilatory support, the treatment given, and the presence of RSE. Acute symptomatic etiology is a major cause of SE among adults in a developing country, which increased the progression to RSE. Despite aggressive management, the risk of death or severe disability associated with SE in adults is significant (nearly one-third).

Conflict of interests

The authors declare no conflicts of interest.

Source of funding

The project was self-funded. No external agency had funded the project.

Table 1. Descriptive analysis of baseline variables in the study population (n=45)

Parameters	Summary statistics
Age in years, mean±SD (range)	43.1±1.02 (18 to 82)
Gender, n (%)	
- Male	28 (62.2%)
- Female	17 (37.8%)
Comorbidities, n (%)	
- Diabetes mellitus	13 (71.1%)
- Chronic artery disease	2 (4.4%)
- Chronic kidney disease	4 (8.9%)
- Respiratory system	2 (4.4%)
- Seizure with regular medication	7 (15.6%)
Duration of seizure, n (%)	
- 1-5 mins	16 (35.6%)
- 6-10 mins	2 (4.4%)
- 11-15 mins	3 (6.7%)
- >15 mins	24 (53.3%)
Number of seizure episodes without recovery in between, n (%)	
- Single	4 (8.9%)
- Multiple (2 or >2)	41 (91.1%)
Glasgow coma scale score, n (%)	
- 3 to 4	16 (35.6%)
- 5 to 12	22 (48.9%)
- 13 to 15	7 (15.6%0
Treatment given, n (%)	
- Required 1st and 2nd line drugs	4 (8.9%)
- Required 1st, 2nd, and add on drugs	23 (51.1%)
- Required general anesthesia or anesthetic dose of midazolam in addition	18 (40%)

Legend: SD=standard deviation.

Table 2. Descriptive analysis of clinical parameter in the study population (n=45)

Clinical parameter	Summary statistics, n (%)
Probable etiology	
- Head trauma	5 (11%)
- Hypertensive encephalopathy	3 (6.7%)
- Hypoglycemia	1 (2.2%)
- TB meningoencephalitis	1 (2.2%)
- Gliotic changes	2 (4.4%)
- Idiopathic new onset status epilepticus	2 (4.4%)
- Post-partum eclampsia	2 (4.4%)
- Anti-epileptic drug withdrawal status epilepticus	3 (6.7%)
- Idiopathic breakthrough status epilepticus	3 (6.7%)
- Sepsis	3 (6.7%)
- Alcohol withdrawal	4 (8.9%)
- Viral meningoencephalitis	7 (15.6%)
- Acute cerebrovascular accident	9 (24.4%)
Brain CT scan	
- Abnormal	21 (26.5%)
Brain MRI	
- Abnormal	24 (33.4%)
In-hospital ventilatory assistance	33 (73.3%)
Refractory status epilepticus	19 (42.2%)
At discharge after 45 days (n=34)	
- Altered sensorium	10 (29.4%)
- Mechanical ventilation/tracheostomy	9 (26.5%)
- Paresis	8 (23.5%)
- Persisting seizures	3 (8.8%)
- Discharged with no deficits	18 (52.9%)

Legend: TB=tuberculosis; CT=computed tomography;MRI=magnetic resonance imaging.

Table 3. Comparison of duration of hospital stay with different variables using Anova and independent t-test (n=34)

Variables	n (%)	No. of days of hospitalization (mean±SD)	P-value
Gender			
- Male	12 (35.29%)	13.4±0.5days	0.803†
- Female	22 (65.7%)	12.4±1.5days	
Glasgow coma scale			
- 3 to 4	10 (29.4%)	11.4±0.6 days	0.106*
- 5 to 12	17 (50%)	18.5±1.2 days	
- 13 to 15	7 (20.58%)	6.9±1.4 days	
Brain CT scan			
- Abnormal	13 (38.3%)	25±1.0 days	0.628*
- Normal	11 (32.35%)	14±1.2 days	
- Not done	10 (29.41%)	15.5±1.6 days	
Brain MRI			
- Abnormal	19 (55.8%)	30±0.5 days	0.001*
- Normal	6 (17.64%)	8.0±1.4 days	
- Not done	9 (26.47%)	6.2±.7 days	
Treatment			
- 1st and 2nd line	1 (2.94%)	3.0±0.5 days	0.001*
- 1st, 2nd line, and add on	20 (38.23%)	7.3±1.7 days	
- 1st, 2nd line, and general anesthesia/ anesthetic dose of midazolam in addition	13 (38.3%)	21.9±1.2 days	
Altered sensorium			
- No	24 (70.58%)	10.6±1.4 days	0.092†
- Yes	10 (29.45%)	17.9±0.8 days	
Mechanical ventilation			
- No	25 (73.53%)	8.8±1.1 days	0.001†
- Yes	9 (26.47%)	23.8±1.2 days	
Parasesis			
- No	31 (91.17%)	12.5±1.5 days	0.566†
- Yes	8 (23.52%)	14.9±1.1 days	
Persistent seizures			
- No	31 (91.17%)	12.5±1.3 days	0.689†
- Yes	3 (8.82%)	15.3±2.2 days	
Deficit			
- No	16 (47.05%)	17.6±1.1 days	0.019†
- Yes	18 (52.9%)	8.4±1.4 days	
Refractory status epilepticus			
- No	20 (58.82%)	6.8±2.2 days	0.001†
- Yes	14 (41.17%)	21.3±1.2 days	
Probable etiology			
- Acute cerebrovascular accident	8 (23.52%)	13.6±1.1 days	0.032*
- Alcohol withdrawal	4 (11.76%)	17.0±1.2 days	
- Viral meningoencephalitis	4 (11.76%)	38.0±2.2 days	
- Anti-epileptic drug withdrawal	3 (8.82%)	8.0±0.5 days	

Legend: Anova=analysis of variance; CT=computed tomography;MRI=magnetic resonance imaging; SD=standard deviation.
*One-way Anova; †independent t-test.

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