



CLINICAL PROFILE AND OUTCOME OF STATUS EPILEPTICUS PATIENTS ADMITTED IN PICU AT TERTIARY CARE CENTRE.

Paediatrics

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ABSTRACT

Background: Status Epilepticus (SE) is a common life threatening neurological disorder that is essentially an acute, prolonged epileptic crisis.

Objectives: To study the clinical profile and outcome of Status Epilepticus patients admitted in PICU.

Setting & Study design: Retrospective cross sectional study.

Materials and Methods: 45 Patients case record of SE in the age group of 1 month to 16 years were included in the study over a period of 2 years. Clinical history, general and systemic examination, relevant investigations, duration of PICU stay and immediate outcome from the case records were considered.

Results: Mean age for the study population was found to be 6.03 years. Preponderance of male (69%) over female (31%) was observed. Aetiology included Acute symptomatic (44.4%), Remote symptomatic (42.4%), Febrile, Idiopathic and progressive encephalopathy being (4.4%). Generalised tonic-clonic convulsion (GTC) was observed in 76% of SE patients while 22% had partial SE and 2% had myoclonic astatic epilepsy. 40% of patients had prior history of convulsion whereas 60% presented with SE as first episode of convulsion. Mean duration of PICU stay in all SE patients was found to be 5.1 days. In our study, mortality rate was found to be 18% and acute symptomatic cause were responsible for most of the deaths.

Conclusion: SE is a life threatening emergency with substantial morbidity and mortality. Patients with younger age and male sex are slightly more vulnerable to develop SE. Longer duration of SE and acute symptomatic aetiologies are independent predictors for poor outcome.

KEYWORDS

Status Epilepticus, Epilepsy, Acute Meningo Encephalitis.

INTRODUCTION:

Status Epilepticus (SE) is a major medical and neurological emergency. Despite advances in treatment, it is still associated with significant morbidity and mortality^(1,2). The incidence of childhood convulsive SE (CSE) in developed countries is approximately 20/100,000/year but it varies according to socioeconomic and ethnic characteristics of the population⁽³⁾. Age is a main determinant of the epidemiology of SE and even within the paediatric population there are substantial differences between older and younger children in terms of incidence, aetiology, and frequency of SE. Duration of SE is a major determinant of response to antiepileptics and final neurological outcome. The short-term mortality (all age groups) rates reported from India and other developing countries range between 10.5% and 28%⁽⁴⁾. Convulsive SE results in severe neurological or cognitive sequelae in 11–16% of patients⁽⁴⁾. It is estimated that 1.3% to 16% of all patients with epilepsy will develop SE at some point in their lives⁽⁵⁾.

Very few studies of SE have been reported from Western Maharashtra especially from the rural area. The objectives of the study was to determine the clinical profile, occurrence and immediate outcome of SE in paediatric age group admitted in PICU at tertiary care centre.

Methodology :

This Retrospective cross sectional study was conducted in PICU at Bharati Vidyapeeth Deemed University Medical College and Hospital Sangli, Maharashtra, India for duration of 2 years from May 2015 to April 2017. The case records fulfilling the criteria of SE from May 2015 to April 2017 admitted in PICU on the basis of medical record review of case files were included in the study. Discharging diagnosis of SE was given preference, however detailed record were reviewed and final decision of inclusion in study group was taken if criteria of SE was fulfilled. All the case files were reviewed after taking written permission from the medical superintendent. Medical record numbers were retrieved using coded system from ISD department and files reviewed to fill the Proforma. Demographic variables and clinical parameters were recorded in the Proforma. These include name, age, sex, types of seizures, cause and precipitating factor, number of anti-epileptic drugs required to control seizures, EEG, radio imaging findings, duration of ICU stay and immediate outcome in the terms of survival or death was recorded. SPSS Version 19 was used for data

entry and analysis. Descriptive statistical analyses was done for various demographic, clinical, lab parameters and short-term outcome. Detailed history including past medical and drug history, repeated clinical findings were noted. **This study was approved by Institutional Ethical Committee (IEC).**

Status Epilepticus was defined as continuous seizures lasting for 5 min or more or multiple episodes of seizures without return of consciousness to base line as per International league against Epilepsy Group new Definition⁽⁶⁾.

Inclusion criteria for the study were:

1. All the case records admitted with Status Epilepticus or who developed SE during the course of illness and fulfilled the following definitions on review of case records.
2. All case records of 1 month- 16 years of age whether having clinical or subclinical seizures.

Exclusion criteria included those case records who did not fulfil the criteria of convulsive or non-convulsive SE and incomplete record on file review.

Seizures were classified as per International League against Epilepsy Group Definitions⁽⁶⁾. Patient's demographic details, clinical features, investigations and treatment were noted in master sheet. The duration of SE before starting the treatment was also noted. Aetiology was determined by history, investigations and neuroimaging findings. All the patients were managed in PICU with standard treatment protocols. Patients were given mechanical ventilation support whenever necessary. Continuous EEG monitoring and therapeutic drug monitoring was not done in our patients as this facility was not available.

The patients of SE were divided into five groups depending upon the broad aetiology⁽⁷⁾.

1. **Idiopathic group:** Seizures occurring in the absence of acute precipitating central nervous system (CNS) insult or systemic metabolic dysfunction or both.
2. **Remote symptomatic:** Seizures occurring without acute provocation in a patient with a prior history of CNS insult known

to be associated with increased risk of convulsions e.g. stroke, head trauma, meningitis, presence of static encephalopathy.

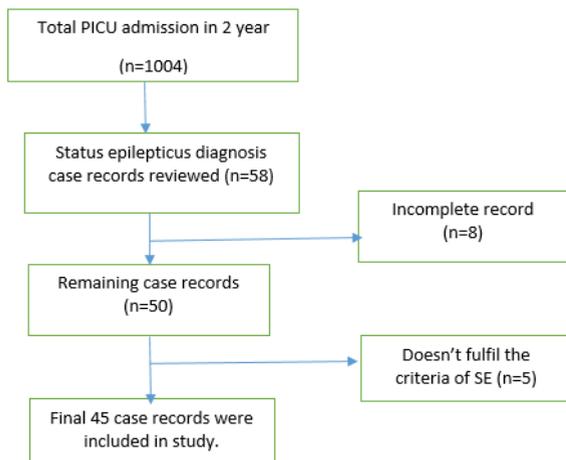
3. **Febrile group:** In this form of SE there is fever as a sole provocation of SE (fever $\geq 38.4^{\circ}\text{C}$).
4. **Acute symptomatic group:** Seizure occurring during an acute illness, in which there is a known neurologic insult or systemic metabolic dysfunction. The acute CNS insult could be caused by meningitis, encephalitis, head trauma, cerebral malaria, hypoxic encephalopathy or electrolyte imbalance.
5. **Progressive encephalopathy:** Seizures occurring at any time during progressive neurologic diseases. In this group neurodegenerative disease, malignancies not in remission, neurocutaneous syndromes were included.

In this study, benzodiazepines like Lorazepam, Midazolam were considered first-line drug where as fosphenytoin or/ and levetiracetam were considered second-line AED's. The third-line AEDs were pharmacologic coma included midazolam infusion or thiopental infusion. If an additional AED was required, it was considered a fourth-line therapy.

Clinically SE was classified as Generalised tonic-clonic, partial, absence, myoclonic and other seizures types was based on the Commission on Epidemiology and Prognosis, 1993 International League against Epilepsy. History of epilepsy was defined as two or more unprovoked seizures in the past whether on treatment or not. SE was defined as refractory, if the duration for control of seizure activity was more than one hour and use of all 1st line drugs.. Mortality was defined as death occurring in PICU during the course of treatment of SE irrespective of whether it was controlled or not.

Results:

STUDY FLOW CHART



During 2 years, 58 children were admitted in our institution with diagnosis of status epilepticus, of which 45 cases were included in study group, which were between 1 month to 16 years of age. Total PICU admission in 2 year period were 1004, the frequency (prevalence) of Status epilepticus in our hospital was found to be 4.48%.

The mean age of presentation was 6.0 years and range was 4 months to 192 months. 68.8% were males (31 patients) & females were 31.1% (14 patients), male to female ratio was found to be 2.2:1. 60% of patients (27) presented with SE without any prior history of seizures and 40% (18 patients) had one or more seizure episode in the past. Therefore it was observed that association of prior seizure episodes with occurrence of SE was not significant ($p > 0.005$).

In aetiological classification of SE, Acute symptomatic group was found to be the most common etiology & it comprised of 44.4% (20 patients) of total patients, remote symptomatic group 42.4% (19 patients), whereas progressive encephalopathy, febrile & Idiopathic group accounted for 4.4% individually. In our study it was found that age group 4 years & above were vulnerable to develop SE, which comprised of 55.5%. Acute symptomatic group had equal number of patients in < 4 years & > 4 years (50%) each.

TABLE NO 1- ETIOLOGICAL CLASSIFICATION OF STATUS EPILEPTICUS.

ETIOLOGY	NO OF PATIENTS (n=45)	PERCENTAGE
ACUTE SYMPTOMATIC	20	44.4%
REMOTE SYMPTOMATIC	19	42.4%
PROGRESSIVE ENCEPHALOPATHY	02	04.4%
FEBRILE	02	04.4%
IDIOPATHIC	02	04.4%

In clinical classification Generalised tonic clonic type was observed in 76% (34 patients), followed by partial SE in 22% (10 patients), myoclonic SE in 2% (1 patient).

In our study, duration of SE was less than 30 min in 55.5% (25) of patients. In 22.25% (10) of patients, seizure duration was 30-60 minutes & more than 60 minutes in remaining 22.25% of patients.

Fever was the most common symptoms associated with patients with SE & it was seen in 73.3% (33 patients). In most of the patients it was high grade (1030 F). Other symptoms were vomiting, unconsciousness, altered sensorium & headache.

In acute symptomatic group, acute meningo encephalitis was the commonest etiology seen in 75% of cases while familial hypomagnesaemia, hypocalcaemia seizures, hypertensive encephalopathy, hypoxic encephalopathy, toxic hepatic encephalopathy accounted for 25% of cases.

TABLE NO 2- NO OF ANTICONVULSANT DRUGS REQUIRED FOR CONTROL OF STATUS

NO OF ANTIEPILEPTICUS	TOTAL NO OF PATIENTS	PERCENTAGE
LORAZEPAM	02	4.44%
LORAZEPAM+FOSPHENYTOIN	18	40.0%
LORAZEPAM+FOSPHENYTOIN+SOD.VALPROATE/LEVETIRACETAM	17	37.7%
LORAZEPAM+FOSPHENYTOIN+MIDAZ DRIP+VENTILATOR	08	17.7%

First line of drug used to control seizure was IV lorazepam, followed by loading dose of IV fosphenytoin was required in 40% of cases in our study. IV levetiracetam or IV Sodium valproate, was used in 37.7% (17 patients) as additional antiepileptic drug. Remaining 17.7% (8 patients) who did not respond to 3 anticonvulsants were put on IV midazolam drip along with mechanical ventilation. In 55.4% of the patients required more than 2 anticonvulsant drugs to control the status because most of the patient belongs to acute symptomatic group and refractory epilepsy.

Need for mechanical ventilation was seen in 37.7% (17 patients), of which status epilepticus being 47.07% (8 patients), followed by shock 29.4% (5 patients) & respiratory failure 23.5% (4 patients).

Lumbar puncture was done in 17 patients abnormal results were seen in 7 patients. Metabolic derangements were seen in 11.1% (5 patients), common being hypoglycaemic, followed by hypocalcaemia, hypomagnesaemia.

MRI findings revealed cerebral oedema being most common finding seen in 41.3% (12 patients) followed by cortical atrophy 24.7% (7 patients), others included metachromatic leukodystrophy, massive IC bleed, high grade glioma. Normal MRI findings was seen in 13.7% (4 patients).

In our study EEG was done in 60% (27 patients). Focal symptomatic form was the commonest form & seen in 29.6% (8 patients), followed by primary generalised form 18.5% (5 patients), epileptic encephalopathy form 18.5% (5 patients), hypsarrhythmia form in 11.1% (3 patients) & burst suppression in 11.1% (3 patients). In 11.1% of children EEG was normal.

Overall mortality in our study was found to be 22.2%, of which 80%

were from acute symptomatic group and 20% were from remote symptomatic group. Mortality in acute symptomatic group when compared to other groups was found to be statistically significant ($P < 0.01$). Most of the deaths occurred because of complications which were respiratory failure, shock, hypoxic encephalopathy & VAP. Most of the observations that were seen in our study were comparable with other studies done.

DISCUSSION:

Access to specialist care is a major limiting factor in developing countries because of poor health infrastructure, connectivity, and delays in transportation. The long latency between the onset of status and initiation of appropriate treatment was noted in series reported from developing countries⁽⁸⁾.

In various studies it has been found that male were more vulnerable to develop SE as compared to females. Murthy et al, in their study found that male to female ratio was 1.3:1⁽⁹⁾. In study done by Mritunjay Kumar et al found that it was 1.5: 1. In our study it was found to be 2.2:1. However, no definite causal relationship was found in literature for this male preponderance.

Predominant involvement of younger age group has been reported previously in many studies^(10,11). Gulati et al., in their study found that 56% of patients were five years or younger⁽¹²⁾. In our study we found out that children <4 years comprised 44.4% of patients, which was similar to study done by Mritunjay Kumar⁽¹³⁾ et al, found that 43% patients were 2-4 years age group. The reason for SE in younger children is probably, mechanisms for control of seizure activity are fragile in younger children and may get disrupted with minimal abnormalities in neurofunction⁽¹³⁾.

The aetiological spectrum of SE in developing countries is distinctly different when compared to developed countries. In this study, acute symptomatic group accounted for 44.4% of the etiology, which was comparable with the study done by Mritunjay Kumar et al, where it was 47% of the etiology. Similar high frequency of acute symptomatic etiology was reported in the hospital-based series in developing countries^(14,8,15,9). Of the acute symptomatic aetiology, cerebrovascular disease is the predominant cause in developed countries^(16,17), whereas in developing countries CNS infection accounted for 28-67% of aetiological spectrum^(8,18) and this was much more so in the paediatric age group^(14,8). In the studies from developed countries, the reported frequency of CNS infections as the risk factor varied from 4% to 19%⁽¹⁰⁾. In our study acute meningoencephalitis (70%) was leading cause of SE. This was most probably due to increased incidence of Japanese encephalitis in our part of country. It was followed by acute hepatic encephalopathy, hypoxic encephalopathy. In older children history of previous epilepsy was more commonly associated.

Experimental studies have shown that the shortest duration of SE that is likely to produce neuronal damage is only 30 minutes whereas the critical duration of SE for the production of irreversible long term clinical sequelae in humans remains unknown⁽¹⁹⁾. Purpose of aggressive treatment of SE is to shorten the duration of the condition and thus to minimize the neuronal damage caused by noxious systemic and electrical features of SE. In our study most of the seizures lasted <45 minutes (73.33%), and 26.6% lasted for more than 45 min, and they responded to standard anticonvulsants. Those not responding to conventional anticonvulsants were put on midazolam infusion and ventilated, and had poor final outcome.

Intravenous lorazepam and Fosphenytoin were common antiepileptic drugs used to control of SE in our study. Combination of Fosphenytoin and levetiracetam was found to be most effective in controlling SE. The most important adverse effect of combination therapy is sedation and respiratory depression. Because of this life threatening adverse reaction of drugs used in control of SE it is always recommended to manage these patients in PICU setting. In our study first line of drug used to control seizure was IV lorazepam, followed by loading dose of IV fosphenytoin was required in 40% of cases in our study. IV levetiracetam or IV Sodium valproate, was used in 37.7% of cases as an additional antiepileptic drug. Remaining 17.7% of patients who didn't respond to 3 anticonvulsants were put on IV midazolam drip along with mechanical ventilation. In 55.4% of the patients required more than 2 anticonvulsant drugs to control the status because most of the patient belongs to acute symptomatic group and refractory epilepsy. The primary aim is to control and abort SE as the duration of seizure

activity is directly proportional to immediate mortality and later morbidity. Updated Cochrane review provides some evidence to support the use of intravenous lorazepam in the management of acute tonic clonic convulsions in childhood. It is as effective as and safer than intravenous diazepam in treating acute tonic-clonic convulsions and SE in children⁽²⁰⁾.

Mechanical ventilation was required in 37.7% of cases in our study which is relatively high incidence because most of the patients were referred to our hospital from long distance, so most of the patients were critical & in refractory status. The common indications for putting on ventilator were GCS <7 (47.07%), followed by refractory shock (29.4%) and central respiratory failure in (23.5%). Overall mortality in our study was found to be 22.2%, of which 80% were from acute symptomatic group and 20% were from remote symptomatic group. Mortality in acute symptomatic group when compared to other groups was found to be statistically significant ($P < 0.01$). In most of the studies mortality rate ranged between 10.5 to 28%^(4,21). Mortality rate in study done by Mritunjay Kumar et al, was found to be significantly higher (31.4%). However studies done by Khalid Ahmed⁽²²⁾ et al it was as low as 8%. Lowenstein DH et al in his study found the mortality rate of 30%⁽²³⁾. There are several possible explanations for this higher mortality rate in our study. As our hospital was one of the largest referral centres in our state, several cases were referred from other hospitals and therefore many patients were of refractory SE. Poor literacy rate and lack of transportation led to considerable time lapse between onset of SE and initiation of treatment. In our study with acute cause of SE, there was trend towards worse outcome. Duration of SE is the only potentially modifiable determinant of mortality⁽²⁴⁾. Unfortunately, issues that can add to critical minutes, even hours to the timing of initiation and effectiveness of treatment in developing countries are delays in transportation. In our study as well as in the study from Senegal⁽⁸⁾ the duration of SE before institution of appropriate treatment was much longer.

CONCLUSION:

SE is a life threatening emergency with substantial morbidity and mortality. Patients with younger age and male sex are slightly more vulnerable to develop SE. Longer duration of SE and acute symptomatic aetiologies are independent predictors for poor outcome. In our study, higher proportion of patients required ventilator because of the longer distance from the home setting & the tertiary care centre. Considering the large number of referrals, up gradation of intensive care facilities even in tertiary care hospital is much sought to improve the overall outcome of SE.

LIMITATION:

Small sample size and retrospective study were the limitations of our study. More prospective studies on large number of sample size are necessary for drawing good conclusion.

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