ORIGINAL RESEARCH

Clinico-aetiological profile and short-term outcome of children presenting with convulsive status epilepticus- Experience of a tertiary care center

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Received: 19April, 2023 Accepted: 29May, 2023

ABSTRACT

Background and Objectives: Paediatric status epilepticus (SE) is a common major medical and neurological emergency of utmost importance due to the associated mortality and morbidity. It can present with variable clinical features and may have different aetiologies which vary with age and community. Despite some progress made over the last decade due to protocolised treatment, the mortality (10-20%) and morbidity (25-35%) related to paediatric SE remains high. This study was undertaken to study demography, clinical features, aetiology, response to treatment with AEDs and short-term outcome of children with SE.**Methods:**The present study was conducted at Paediatrics department of a tertiary care level teaching institute over two years from August 2020 to July 2022 on children >6 months to <15 years of age presenting to I.P.D or E.R of our deptartment with status epilepticus OR children admitted for other illnesses but developing status epilepticus during the course of their illness.**Result:** Over the study period, 82 children were enrolled in this study out of which 48 were males and 34 were females with male: female ratio of 1.4:1. Mean age of the study participants was 5.08 ± 2.46 years and mean weight of the children was 16.84 ± 4.58 kg. Majority of the children (n=49, 59.8%) were less than five years of age. Onset of SE occurred before hospitalization to our institute in the majority of children (n= 75, 91.5%). A total of 37 (45.1%) patients had received pre-hospital treatment with one or more AED. The most common etiological group for SE was found to be acute symptomatic group (57.3%) followed remote symptomatic group (23.1%). Overall, the seizure episode terminated after administration of BZD in 38 (46.3%) children and the rest required administration of second- and/or third-line drugs. Mean duration of midazolam infusion at which convulsions were controlled was 8.43± 5.76 hours and mean dose of midazolam infusion required for controlling convulsions was 4.49± 2.65 mcg/kg/min. Mean duration of PICU stay was 4.23 ± 3.14 days and mean duration of hospitalization was 6.4 ± 4.07 days. 12 children (14.6%) died during the hospital stay.**Conclusion:**Acute symptomatic aetiology (predominantly infectious causes) was the commonest cause of SE in our region. BZD is effective in controlling seizures in nearly half of such children. So, community physicians and the paramedics should be trained about early initiation of intravenous or nasal/buccal BZD in developing countries.**Abbreviations:** AED: antiepileptic drug; BZD: benzodiazepine; S.D: standard deviation; SE: status epilepticus; ESE: established status epilepticus; RSE: refractory status epilepticus

Key words:aetiology, antiepileptic drug, outcome, Seizure, status epilepticus

INTRODUCTION

Paediatric status epilepticus (SE) is a common major medical and neurological emergency of utmost importance due to the associated mortality and morbidity. It can present with variable clinical features and may have different aetiologies which vary with age and community.[1] Annual prevalence of childhood convulsive SE in developed countries has been reported to be in the range of 15- 20/100,000 children.[2] Population based studies on status epilepticus is lacking in India, but the rates are estimated to be considerably higher (80-100/100,000

children). Age is a major determinant of the epidemiology of SE and even within the paediatric age group substantial variations exists between older and younger children in terms of incidence, aetiology, frequency and outcome of SE.

Previously, the cut off time for labelling a seizure activity as status epilepticus was taken as 30 minutes.[3] But it was soon realised that if a seizure event persisted beyond 10 minutes, the risk of neural injury as well as difficulty in seizure control increases significantly.[4] SE is now defined by the International League Against Epilepsy (ILAE) as any active seizure of ≥5 minutes' duration or recurrent episodes of seizures without gaining consciousness in between the seizure episodes.[5] It can present as convulsive (tonic clonic, clonic, tonic or myoclonic) or non-convulsive (absence, simple partial, complex partial) seizures.

Despite some progress made over the last decade due to protocolised treatment, the mortality (10-20%) and morbidity (25-35%) related to paediatric SE remains high.[6,7]It has been documented that many survivors of SE suffer from neurological impairment in the form of developmental delay, cognitive impairment, intellectual disability and recurrent seizures. Therefore, clinicians must emphasise on controlling the seizure activity within 5-10 in order to achieve a favourable neurological outcome. However, this may not always be possible due to poor access to healthcare facilities in developing countries or undue delay in reporting to the hospital. Benzodiazepines (diazepam, midazolam, lorazepametc) are used as first-line drugs to control seizure within 5-10 minutes of convulsion. If the seizure persists, second line AED is given within next 10 minutes. If seizure still persists, child should be shifted to ICU and administration of second or third line drugs or anaesthetic medications should be started within 30-60 minutes of hospitalisation. Most of the Indian studies are retrospective in nature and there is paucity of data regarding the clinical profile, aetiology and treatment outcomes of SE in children from eastern India. Based on this background the present study was conducted at our tertiary care level institute.

Aim and Objectives

To study demography, clinical features, aetiology, response to treatment with AEDs and short-term outcome of children with status epilepticus.

MATERIALS AND METHODS

Study Duration: 2 years fromOctober 2020 to September 2022.

Study Setting: I.P.D and E.R of deptt of Paediatrics of Nalanda Medical College and Hospital. Patna, Bihar, India.

Study Design: hospital-based cohort study.

Inclusion Criteria: Children >6 months to <15 years of age presenting to I.P.D or E.R of our department with status epilepticus OR children admitted for other illnesses but developing status epilepticus during the course of their illness. SE was defined as active seizures of ≥5 minutes duration or recurrent episodes of seizures without gaining consciousness in between as per ILAE criteria.

Exclusion Criteria

Children with psychogenic non-epileptic seizures and with incomplete history about the seizure event were excluded from the study**.**

Data Collection

After obtaining written informed consents from the parents, potential children were enrolled in this study. Detailed history and focussed clinical examination were done on all such patients. A structured proforma was used to obtain information about demographic factors (such as age, sex, weight, socioeconomy), duration and the type of seizures, known cases of epilepsy or developmental delay, previous AED dose duration and adherence, precipitating events if known (such as a recent illness, infection, missed AED dose, trauma etc) and immediate previous treatments received elsewhere, if documented (AED type and dose). Laboratory investigations included RBS at admission & serum electrolytes in all cases plus other relevant investigations as deemed appropriate from history and clinical examination. Neuroimaging was done in all children with SE, except in hypocalcaemic or hypoglycaemic seizures, febrile seizures and known cases of epilepsy without any new neurological deficits. Aetiology of SE was derived at on the basis of information obtained from history, examination and the investigations done. Enrolled children were treated as per standard treatment guidelines. Anti-epileptic drug (AED) was considered effective if the seizure was controlled clinically within 10 minutes of administration of the drug with no recurrence of the seizure for another 30 minutes. The child was labelled to have benzodiazepine responsive SE if the seizure abated with first or second dose of benzodiazepine (BZD). SE was labelled as established SE if the seizure persisted despite two BZD doses and required 2nd line AED. SE was labelled as refractory SE if the seizure persisted despite the administration of two appropriate anticonvulsants at acceptable doses and required administration of 3rd line AED or midazolam infusion. SE was labelled as super refractory SE if the seizure continued for 24 hours or more even after administration of anaesthesia, including those cases in which the SE recurred on reduction or withdrawal of anaesthesia. All cases with SE were followed up till discharge or death during their period of hospitalisation. Children with pre-existing developmental delay were evaluated for return to their baseline functional status. Neurologically normal patients were classified using the paediatric overall performance category (POPC) scale[8] at the time of discharge. POPC scale scores of 1-2 was considered as a favourable outcome and scores of ≥3 was considered as an unfavourable outcome.

Statistical Analysis

Information so collected was tabulated and entered in Microsoft excel sheet and further analysed by SPSS ver.20® software for Windows. parameters were expressed as mean, standard deviation, percentages, proportions or percentiles as applicable. We used Pearson's chi-square test for categorical parameters and independent samples' t test for continuous parameters. P-value <0.05 was taken as significant.

RESULTS

Over the study period, 82 children were enrolled in this study out of which 48 were males and 34 were females with male: female ratio of 1.4:1. This sex difference was not statistically significant (p=0.07). Mean age of the study participants was 5.08 ± 2.46 years and mean weight of the children was 16.84 ± 4.58 kg. Table 1 shows important demographic and clinical parameters of study group. Majority of the children (n=49, 59.8%) were less than five years of age. Onset of SE occurred before hospitalization to our institute in the majority of children (n= 75, 91.5%). A total of 37 (45.1%) patients had received pre-hospital treatment with one or more AED. Fever was an accompanying feature in 54 (65.9%) children at the time of hospitalization. Prior history of seizure was found in 27 (32.9%) cases, whereas the rest presented as SE during their first episode of seizure event. Duration of the SE event was less than 30 minutes in majority of children (n=45, 54.9%).

Table1: Demography and clinical parameters of children with SE

Parameters	Value
Age in years (Mean ± SD)	5.08 ± 2.46
Weight in kg (Mean ± SD)	16.84 ± 4.58
Duration of SE in minutes (Mean ± SD)	23.29 ± 8.57
Male gender (number, percentage)	48, 58.5%
Inhabitant of rural area (number, percentage)	55, 67.1%
Lower socioeconomic strata (number, percentage)	58, 70.7%
Previous history of seizures (number, percentage)	27, 32.9%
Children with pre-existing developmental delay (number, percentage)	22, 26.8%
Poor compliance to previous AED therapy (number, percentage)	5, 6.1%
SE event started before admission to our hospital (number, percentage)	75, 91.5%
SE event started post hospitalisation at our hospital (number, percentage)	7, 8.5%
Received ≥1 AED before admission to our hospital (number, percentage)	37, 45.1%
Fever during or immediately after the SE event (number, percentage)	54, 65.9%
Duration of SE <30 minutes (number, percentage)	45, 54.9%
Type of seizure: Primary generalized tonic-clonic(number, percentage) Focal with impaired consciousness (number, percentage) Focal evolving to generalised tonic-clonic (number, percentage) Generalised tonic (number, percentage)	 59, 71.9% 8, 9.8% 9, 11.0% 6, 7.3%

(AED: antiepileptic drug; BZD: benzodiazepine; S.D: standard deviation; SE: status epilepticus)

Aetiology: The most common etiological group for SE was found to be acute symptomatic group (57.3%) followed remote symptomatic group (23.1%) as shown in detail in table 2 below. Unfortunately, the aetiology could not be determined in 15.8% children. Neuroinfectious accounted for 35.3% of cases which was the single most leading cause of SE (viral meningoencephalitis in 13, acute bacterial meningitis in 8, tubercular meningitis in 5, non-specific encephalitis in 2 and neurocysticercosis in 1). Interestingly, acute symptomatic etiologies were the major causes of SE in children less than five years of age, whereas remote symptomatic causes were more in children aged 5-10. Twenty-seven (32.9%) children in the study were known case of epilepsy and were already on 1 or more maintenance AEDs. Only 5 (6.1%) children had missed AED doses, leading to precipitation of SE whereas the rest 22 children suffered from SE despite adhering to their prescribed AED dosage.

Table 2: Aetiology of the status epilepticus event

Parameter	Value	Percentage
Acute symptomatic group	**47**	**57.3%**
Acute CNS infections	28	34.1%
Febrile status epilepticus	11	13.4%
Neurocysticercosis	1	1.2%
Hypocalcaemic seizures	3	3.6%
ADEM	2	2.4%
CSVT	1	1.2%
Head Injury	1	1.2%

Remote symptomatic seizures	**19**	**23.1%**
Perinatal insult	11	13.4%
Mesial temporal sclerosis	1	1.2%
Focal cortical dysplasia	2	2.4%
Congenital intrauterine infections	4	4.9%
Hippocampal atrophy	1	1.2%
Progressive encephalopathy	**3**	**3.6%**
Unknown aetiology	**13**	**15.8%**

(CNS: Central nervous system; ADEM: Acute disseminated encephalomyelitis; CSVT: Cerebral sinus venous thrombosis;)

Treatment and response: A total of 37 (45.1%) patients had received pre-hospital treatment with one or more AED. Among them, 30 had received only one dose of BZD, 7 had received 2 dose of BZD and 3 had even received loading dose of second line AED. Among these 30 children who had received only single dose of BZD prior to hospitalization, only 9 (30%) had their seizure controlled with second dose of BZD at our hospital and the rest needed 2nd and/or 3rd line AEDs as shown in table 2 below. Overall, the seizure episode terminated after administration of BZD in 38 (46.3%) children and the rest required administration of second- and/or third-line drugs. 11 (13.4%) children responded to the first dose of BZD and 27 (32.9%) responded to the second dose of BZD. Out of the 44 children who did not respond to BZD (established SE), 30 (36.6%) responded to 2nd line AEDs. Among these 44 children, 32 were given phenytoin and 12 were given valproate as second line AED. Valproate was used in >2-year age children if history was suggestive of good compliance to high normal maintenance dose of phenytoin (6-8 mg/kg/day) or past history of adverse reaction to phenytoin. Phenytoin was effective in 22 (68.7%) of such children whereas valproate was effective in 8 (66.7%) cases. In the remaining 14 patients (refractory SE), 12 (14.6%) responded to 3rd line AEDs or midazolam infusion and 2 (2.4%) were classified into super-refractory SE. Among refractory SE cases, 6 children were given midazolam infusion. The seizures subsided within 24 hours of midazolam infusion in 5 such children and did not recur on stopping the infusion. Mean duration of midazolam infusion at which convulsions were controlled was 8.43± 5.76 hours and mean dose of midazolam infusion required for controlling convulsions was 4.49± 2.65 mcg/kg/min. 2 children had super-refractory SE, of these one responded to phenobarbitone and the other required propofol infusion in addition.

Table 3: Response to the antiepileptic drugs used

Drug given (i.v route only)	Number	Percentage
Benzodiazepine responsive S.E: (All 82 children received BZD)	**38**	**46.3%**
Responded to single dose of BZD	11	13.4%
Responded to second dose of BZD	27	32.9%
Response to AED in Established S.E (n=44): (32 received Phenytoin and 12 received Valproate)	**30**	**36.6%**
Responded to Phenytoin	22	26.8%
Responded to Valproate	8	9.8%
Response to AED in Refractory SE (n=14): (3 received levetiracetam, 6 received Midazolam infusion, 3 received Valproate and 2 received Phenobarbitone)	**12**	**14.6%**
Responded to Levetiracetam	3	3.7%
Responded to Valproate	3	3.7%
Responded to Phenobarbitone	1	1.2%
Responded to Midazolam infusion	**5**	6.1%
Response to AED in super refractory SE (n=2): (Both received Phenobarbitone infusion and 1 needed Propofol infusion in addition)	2	2.4%
Responded to Phenobarbitone	1	1.2%
Responded to Propofol	1	1.2%

Outcome: Mean duration of PICU stay was 4.23 ± 3.14 days and mean duration of hospitalization was 6.4 ± 4.07 days. 12 children (14.6%) died during the hospital stay. Out of these, 5 were diagnosed with acute meningoencephalitis, 2 with tubercular meningitis, 1 each with cerebral sinus venous thrombosis, focal cortical dysplasia, congenital intrauterine infection and 2 with unknown aetiology. Among these unfortunate children, 2 had super-refractory SE, 6 had refractory SE and 4 had established SE. Of 22 children with preexisting developmental delay, 1 died but 20 (90.9%) returned to their pre-illness state at discharge. The rest

neurologically normal children were classified according to the POPC scale. Favorable outcome was seen in 38 (73.1%) children whereas 14 (26.9%) had unfavorable outcome. Children with refractory or super refractory status epilepticus and seizure events lasting more than 1 hour were more likely to have a poor outcome.

DISCUSSION

The present study was conducted at our tertiary care level institute to study the clinico-aetiological profile and treatment outcomes of paediatric SE, in the setting of a developing country. Access to specialised care is a major problem in developing countries because of poor infrastructure, connectivity or delay in transportation. A period of latency between the onset of SE and initiation of appropriate treatment has been highlighted in the series reported from developing countries.[9]

Similar to other studies, we also found a male preponderance in this study with male:female ratio of 1.4:1, but this was not statistically significant. No definite causal relationship was found in literature for male preponderance. Many researchers have reported SE to be commoner in young children <5 years of age. Involvement of younger age group has been reported previously in many studies. In the present study, majority of the children (n=49, 59.8%) were less than five years of age which is comparable to the findings of Gulati et al.[10] Probably, mechanisms for control of seizure activity are immature in younger children and may get disrupted with minimal abnormalities in neurofunction. Aetiology of SE in developing countries is quite different when compared to developed countries. In the present study, acute symptomatic aetiology accounted for 57.3% of the cases. Similar high occurrence of acute symptomatic aetiology has been reported in the hospital-based series in developing countries.[11,12] Of the acute symptomatic group, cerebrovascular disease is the predominant cause in developed countries,[13] whereas in developing countries CNS infections accounted for 28–67% of etiological spectrum.[14]In the present study, viral meningoencephalitis was the leading cause of SE, especially in 2-5 years age group. This was probably due to high incidence of neuroinfection by Japanese encephalitis and other neurotropic viruses in our part of country. This was followed by other CNS infection including acute bacterial meningitis and tubercular meningitis. In older children idiopathic aetiology and history of previous epilepsy was more commonly associated.

The critical duration of SE resulting in irreversible long term neurological sequelae in humans remains unknown but experimental studies have shown that the shortest duration of SE that is likely to produce significant neuronal damage is only 30 minutes. Purpose of aggressive treatment of SE is to shorten the duration of this condition and thus minimize neuronal damage caused by noxious systemic and electrical features of SE. In this study, duration of the SE event was less than 30 minutes in majority of children (n=45, 54.9%). Most of the seizures lasted between 10-180 minutes and responded to standard AEDs. SE lasting more than 3 hours and not responding to the usual AEDs were associated with poor final outcome. Intravenous Midazolam and phenytoin were the common antiepileptic drugs used for control of SE in our study. Nearly half (46.3%) of SE cases responded to one or two dose of BZD which makes BZD the drug of choice for initial control of SE like any other case of seizure. Kravljanac et al reported midazolam to be effective in 90.3% children.[15] Reason for such a high response rate was that they considered it effective even if it failed as initial injection, but was effective as infusion. In a Cochrane review, no difference was seen between IV midazolam, diazepam or lorazepam. Mortality rate in our study was 14% which is comparable to the range of 10.5 to 28% as reported by earlier studies.[16] In the present study, there was trend towards a poor outcome in children with acute symptomatic aetiology. As duration of SE is the only potentially modifiable determinant of mortality, improvisation of peripheral institutes in critical care, need for high-end ambulances to transport children with SE should be the futuristic goal of the government.

CONCLUSION

Acute symptomatic aetiology (predominantly infectious causes) is the commonest cause of SE in our region. BZD is effective in controlling seizures in nearly half of such children. So, community physicians and the paramedics should be trained about early initiation of intravenous or nasal/buccal BZD in developing countries as shortening the duration of the seizure event by early treatment can minimize or prevent the systemic and neurological complications of SE.

Limitations

The present study has few limitations. First, it is a single centre tertiary care level hospital-based study and so the majority of patients we treated were generally quite sick. Second limitation is related to the relatively smaller number of cases with SE due to which a multivariate analysis was not performed for assessing factors related to mortality. Third, long term follow-up of children with SE was not done. Fourth, EEG monitoring of the children was not done. Fifth, aetiology could not be determined in nearly 15% children.

Conflict of interest: None to declare.

Financial disclosure: The authors hereby declare that this study has not been conducted under any financial assistance.

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