RESEARCH PAPER

Clinical Profile and Short-term Outcome of Pediatric Status Epilepticus at a Tertiary-care Center in Northern India

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Objective: To assess clinical profile and short term treatment outcomes of pediatric status epilepticus (SE) at a tertiary-care center in northern India.

Methods: Prospective cohort study enrolled children aged 1 month to 18 years presenting with SE to the emergency department. Enrolled children (109) were treated as per hospital protocols. Clinical features during hospitalization were noted. Pediatric overall performance category (POPC) scale was used for classification of outcome at the time of discharge.

Results: Acute symptomatic etiology was identified in 66 (60.6%) cases (CNS infections were predominant). Previous diagnosis of epilepsy was found in 32 (29.4%) children; and benzodiazepine responsive SE were seen in 65 (59.6%) children. Predictors of unfavorable outcome were acute symptomatic etiology (adjusted OR 4.50; 95% CI 1.49, 13.62) and no treatment administered prior to hospital (adjusted OR 3.97; 95% CI 1.06, 14.81).

Conclusions: Acute symptomatic etiology, mainly acute CNS infections, is the leading cause of SE in this region. Early and pre-hospital management with benzodiazepines may improve SE outcome.

Keywords: *Epilepsy, Etiology, Seizures, Treatment.*

Status epilepticus (SE) can present with varied clinical manifestations, and have different etiologies, which vary with age and geographical areas. It is well known that the duration of SE positively correlates with the refractoriness to treatment, and the prognosis is poor in children who have prolonged uncontrolled seizures [1-3]. Due to poor access to healthcare facilities in developing countries, there is higher likelihood of prolongation of seizures and delay in initiation of treatment. There is paucity of data regarding the etiology and treatment outcomes of SE in Indian children [4]. Therefore, the objective of the present study was to understand the clinical profile and short term treatment outcome in children with SE.

METHODS

This prospective cohort study was undertaken at a teaching government hospital in New Delhi, India from January 2017 to April 2018. Institutional ethics committee approval was obtained. Consecutive children aged 1 month to 18 years presenting in convulsive SE were enrolled. SE was defined as active seizures of ≥5 minutes duration or recurrent episodes of seizures without gaining consciousness in between [5]. Psychogenic non-epileptic seizures were excluded. Written informed consent was taken from the caregivers after initial stabilization of the child.

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The enrolled children were treated as per the hospital SE protocol in accordance with the current guidelines in India [4]. The anti-epileptic drug (AED) was considered effective if there was clinical cessation of seizures within 10 minutes of the initial dose of medication and if there was no recurrence of seizures for 30 minutes [6]. A patient was classified to have benzodiazepine - responsive SE if the SE responded with first or second dose of benzodiazepine (BZD). Established SE was defined as SE which persisted despite two BZD doses and required 2nd line AED. Refractory SE was defined as SE persisting despite the administration of two appropriate anticonvulsants at acceptable doses and responding only to 3rd line AED or midazolam infusion [7]. Super-refractory SE was defined as SE that continued 24 hours or more even after the onset of anesthesia, including those cases in which the SE recurred on the reduction or withdrawal of anesthesia [8].

Detailed history, examination and investigations were documented in a predesigned form. Neuroimaging was done in all children with SE, except in hypocalcemic seizures, typical febrile seizures, and known cases of epilepsy without any new neurological deficits. The etiology of SE was determined according to the history, examination and the investigations done. The patients were followed till discharge or death during the hospital admission. The patients with pre-morbid developmental delay were evaluated for return to their baseline functional status. Neurologically normal patients were classified using the pediatric overall performance category (POPC) scale at the time of discharge [9]. POPC scale scores of 1-2 were considered as a favorable outcome and scores of ≥3 were considered as an unfavorable outcome.

Statistical analysis: This was performed using IBM SPSS software version 21. Continuous data was represented as mean with standard deviation or median with interquartile range. Qualitative data was represented as proportions or percentages. Multivariate logistic regression model was used to predict unfavorable outcome at discharge. A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 115 children presenting as SE were assessed for eligibility during the study period and 109 were enrolled (3 declined to participate, and 3 children had psychogenic non-epileptic seizures) The median age at presentation was 2 (IQR 1-6) years. Generalized tonic clonic seizures were seen in 70 (64.2%) children. The clinico-etiological characteristics of the study population are presented in ***Table* I**.

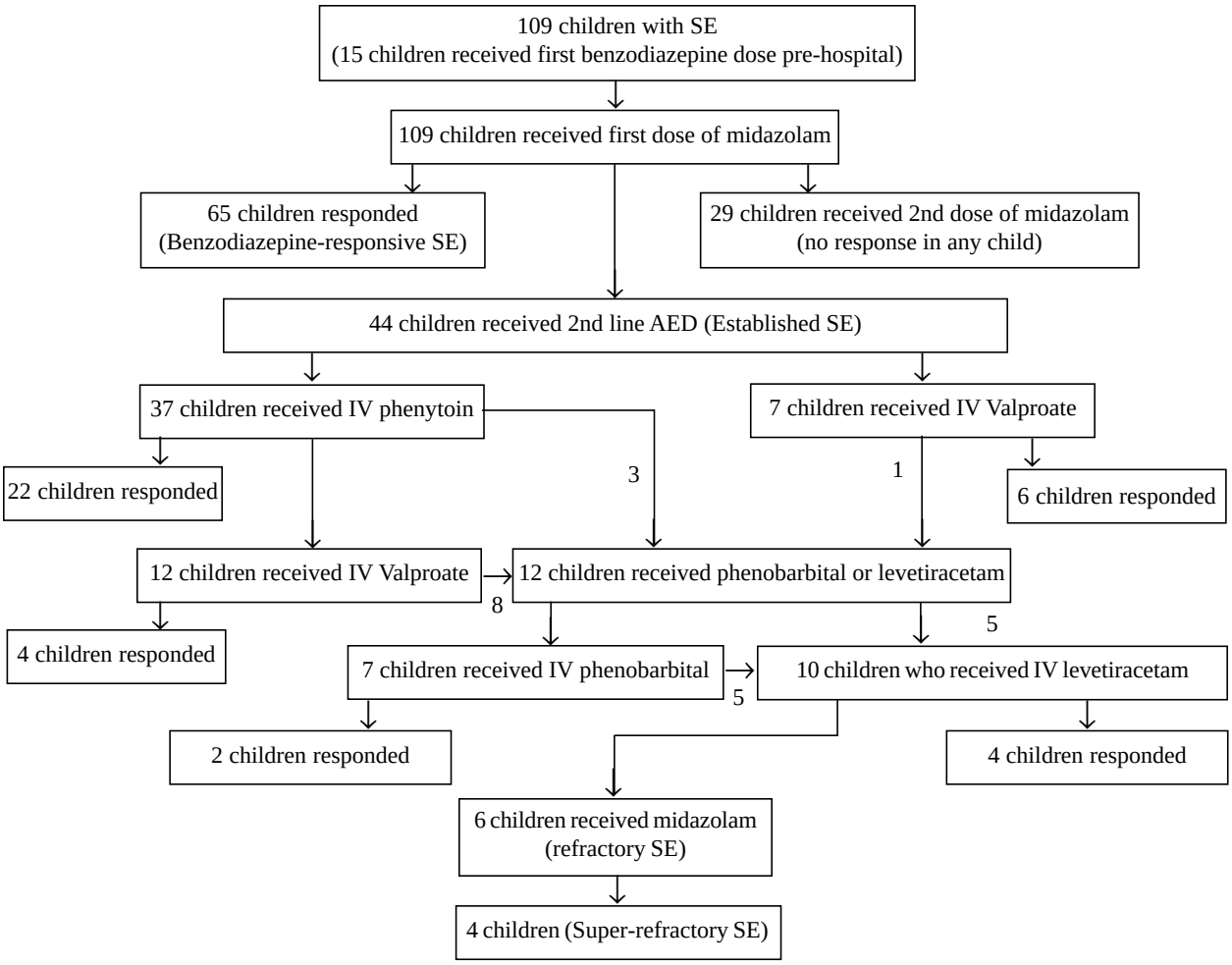
Sixty five (59.6%) children responded to first line AED (midazolam). Second dose midazolam was given in 29 patients (15 patients received one pre-hospital dose) but with no added benefit as seizures persisted in all. Out of the 44 cases who did not respond to midazolam (established SE), 28 responded to 2nd line AEDs. In the remaining 16 patients (refractory SE), 12 responded to 3rd line AEDs or midazolam infusion and 4 were classified into super-refractory SE. The response to medications in the study population is summarized in ***Fig*. 1**. In 44 children who did not respond to midazolam, 37 were given phenytoin and 7 were given valproate as second line AED. Valproate was used based on history of compliant maintenance therapy with high normal dose phenytoin or past history of adverse reaction to phenytoin. Twenty two (59.5%) responded after phenytoin and 6 (85.7%) responded after valproate. Out of the 15 who did not respond to phenytoin, valproate was used in 12 children, out of which 4 (33.3%) responded. In 12 children, where valproate was either ineffective or was not used as third line AED, phenobarbitone or levetiracetam was used. Levetiracetam was effective in 4 out of 10 children (40%), whereas phenobarbitone was effective in 2 out of 7 children (28.6%).

Six children were initiated on midazolam infusion. The seizures subsided within 24 hours of midazolam infusion in one child and did not recur on stopping the infusion (refractory SE). One child died within 24 hours of midazolam infusion. Four children had super-refractory SE; of these three received phenobarbitone infusion and one received thiopentone infusion.

TABLE I Clinico-etiological Characteristics of Children with Status Epilepticus (*N*=109)

Characteristics	*No. (%)*
#Age , y	2 (1 - 6)
Males	64 (58.7)
‡Pre-existing epilepsy	32 (29.4)
Seizure duration, min	17.5 (7 – 60)
Type of seizures	
Generalized tonic-clonic	70 (64.2)
Focal, impaired awareness	20 (18.3)
Focal evolving to bilateral tonic-clonic	10 (9.2)
Generalized tonic	9 (8.3)
Etiology of status epilepticus	
Acute symptomatic	66 (60.6)
Acute CNS infections	27 (24.8)
Febrile status epilepticus	16 (14.7)
Neurocysticercosis	14 (12.8)
Hypocalcemic seizures	7 (6.4)
ADEM	1 (0.9)
CSVT	1 (0.9)
Remote symptomatic seizures	27 (24.8)
Perinatal insult	18 (16.5)
Mesial temporal sclerosis	2 (1.8)
Focal cortical dysplasia	1 (0.9)
Congenital intrauterine infections	1 (0.9)
Hippocampal atrophy*	1 (0.9)
Miscellaneous	4 (3.7)
Unknown etiology	16 (14.7)

*All values in n (%) except #median (IQR); *One case each of late infantile neuronal ceroid lipofuscinosis type 2, Dravet syndrome, suspected case of IEM, and Wolcott Rallison syndrome; ‡Only 15 of these were receiving antiepileptic drugs; CNS: Central nervous system ADEM: Acute disseminated encephalomyelitis, CSVT: Cerebral sinus venous thrombosis.*



SE: Status epilepticus, IV: Intravenous

Fig. 1 *Response to anti-epileptic drugs in the study population presenting with status epilepticus.*

Viral meningoencephalitis was present in 14 children (12.8%), bacterial meningitis in 9 (8.3%), tubercular meningitis in 3 (2.8%), and encephalitis (non-specific) in 1 (0.9%) child. Thirty two (29.4%) children in the study were known cases of epilepsy. They were already on maintenance AEDs. Only 2 (0.1%) patients had missed AED doses, leading to precipitation of SE.

All 26 children with pre-morbid disability returned to their pre-illness state at discharge. The remaining 83 were classified according to the POPC scale. Favorable outcome was seen in 67 (80.7%) children whereas 16 (19.3%) had unfavorable outcome. Eight children (7.3%) died during the hospital stay. Out of these, 6 were diagnosed with meningoencephalitis, 1 with tubercular meningitis and 1 with late infantile neuronal ceroid lipofuscinosis type 2. Out of the 8 children who died, 3 had super-refractory SE and 3 had refractory SE.

Multivariate logistic regression showed that presence of an acute symptomatic etiology (adjusted OR 4.50, 95% CI 1.5,13.6) and no AED administered prior to hospitalization (adjusted OR 3.97, 95% CI 1.1,14.8) predicted unfavorable outcome at discharge. The age, sex, presence of pre-existing epilepsy, duration of seizures prior to reaching the hospital, and response to the first line BZD were not found to be significant.

DISCUSSION

This prospective cohort study explored the clinical profile and treatment outcomes of pediatric SE, in the setting of a developing country. Acute symptomatic etiology was identified in a majority of the cases. BZD-responsive SE was seen in more than half of the children. Predictors of unfavorable outcome were found to be acute symptomatic etiology, and absence of an AED administered prior to reaching the hospital.

TABLE II Multivariate Logistic Regression Model to Predict Unfavorable Outcome at Discharge

Independent variable	*Adjusted Odds ratio (95% CI)*	*P value*
Age	1.07 (0.94, 1.21)	0.29
Male sex	1.19 (0.47, 3.07)	0.71
Pre-existing epilepsy	0.39 (0.12, 1.22)	0.10
Acute symptomatic etiology	4.50 (1.49, 13.62)	0.008
Seizures duration	1.01 (0.99, 1.0)	0.52
No anti-convulsant drug administered pre-hospital	3.97 (1.06, 14.81)	0.04
Response to first anti-line benzodiazepine	0.72 (0.25, 2.05)	0.54

Unfavorable outcome: *Pediatric overall performance category* ≥ 3.

We used the second dose of midazolam in children who continued to have seizures after 10 minutes of the first dose. However, none of these children responded. The reason for this may be the inherent pharmacokinetics of BZDs; with higher doses of these drugs, proportionate increase in clinical effect may not be seen. We could not find any literature providing data on the use of second dose of intravenous (IV) midazolam. The response to IV midazolam noted in more than half of the patients in our study is similar to another study which observed an efficacy of around 70% in children given lorazepam or diazepam [6]. In another study, midazolam was reported to be effective in 90.3% children [10]. The 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 of studies including patients of all age groups, IV lorazepam was found to be more efficacious than diazepam; however, no difference was seen between IV midazolam, diazepam or lorazepam [11]. A few studies done in the pediatric age group have not shown superiority of any particular BZD over the others [6,12]. In a retrospective analysis of patients with SE [13], 31% of the patients required midazolam infusion [13], as compared to 5% in this study. This difference could be attributed to possible delays in reaching the centre/initiation of treatment as the study center is a busy referral centre in Northern India. Further, the retrospective collection of data might also have influenced the results.

The causes for SE differ greatly in developed and developing countries. In contrast to developing countries where CNS infections are the predominant cause of SE in children, febrile SE and idiopathic (unknown etiology) cause form the majority in developed countries [10,14]. Due to the wider age range of children in our study, we probably had a large spectrum of causes of SE. In the studies from developed countries, though the acute symptomatic cause is less common, but still CNS infections constitute the majority in the acute symptomatic group [10,14,15].

In our study, children with acute symptomatic etiology and non-administration of AED prior to the hospital were found to predict unfavorable outcome. Children with refractory SE and super refractory SE, had a significantly unfavorable outcome. In previous studies, younger age group, longer duration of SE, poor response to initial anticonvulsants, acute symptomatic group and refractoriness to the overall treatment have been shown to be associated with higher mortality [1-3,16,17].

In conclusion, CNS infections are the single leading cause of SE in children in this region. Absence of pre-hospital AED treatment predicts an unfavorable outcome for the children. However, more than half of the children have BZD responsive SE. Increasing the awareness of parents and primary health care providers about the appropriate use of BZDs may decrease the morbidity and poor outcome of SE.

Contributors: SS, SA: conceived the study; CC,SS,SBM,SA: provided clinical care to the patients; CC,SS,PJ: did the data analysis and interpretation; CC, SBM: wrote the first draft which was the read, revised and approved by all the authors. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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