Factors influencing control of convulsive status epilepticus in children

Bibek Talukdar[1], Sumit Bansal[2], Rahul Jain[3]

From [1]Professor, [2]Resident, [3]Assistant Professor, Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, New Delhi, India

Correspondence to: Dr. Bibek Talukdar, Chacha Nehru Bal Chikitsalaya, New Delhi - 110 031, India. E-mail: talukdar.b@gmail.com

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ABSTRACT

Background: Convulsive status epilepticus (CSE) is an important cause of morbidity and mortality in pediatrics. **Objectives:** The objectives of the study were to examine the influence of any clinical factor on control of CSE in children. **Methods:** Cases of CSE in the age group of 1 month–12 years, admitted to the emergency ward of a tertiary care hospital, over a period of 1 year, were studied, prospectively. Only those cases that were actively convulsing at arrival were enrolled. Difficult cases were shifted pediatric intensive care unit and were put on mechanical ventilator as needed. After initial stabilization, detailed case-work up and appropriate investigations to find the etiology were done. The data were analyzed statistically and $p<0.05$ was considered as statistically significant. **Results:** The data of 50 cases that fulfilled the enrolment criteria were analyzed. Convulsions in the majority of the cases could be controlled within 30 min. Out of the study patients, 39 cases (78%) needed >1 drug for controlling the convulsive episodes. Control was extremely difficult in 10 (20%) of the cases while 3 (6%) cases died. The time needed to control the episodes showed significant correlation with several clinical factors, namely focal seizure with impaired consciousness, multiple episodes of convulsion (discrete type), focal deficit, Glasgow Coma Scale score <9, abnormal neuroimaging finding, central nervous system infections (meningitis and encephalitis together), and prolonged duration of convulsions before arrival at the emergency ward. However, on multivariate analysis prolonged duration of convulsion before arrival at emergency was found to be the most significant predictor of time needed to control the episodes. **Conclusion:** Prolonged duration of convulsion before arriving at the hospital can be considered to be a predictor of difficult control of CSE in children.

Key words: *Convulsive disorders, Epilepsy, seizures, Convulsive status epilepticus, Status epilepticus*

Convulsive status epilepticus (CSE) is an important cause of morbidity and mortality in pediatrics [1]. Controlling an episode of CSE is not always easy and is an area of continuing research. Studies reported that the affected patients had seizers which lasted for 5 or >5 min continuously. There was an incomplete recovery of consciousness of such patients or those who were having one or more discrete seizure [2-4]. 5 min is an important time point in controlling an episode of seizure as a delay in initiation of treatment is associated with diminished response to anticonvulsant (ACT) drug therapy [5,6]. It is possible that certain clinical factor/factors might have an important influence on controlling the episodes. Knowledge of these might be of help in quicker control of such episodes; studies in this direction, i.e., looking for any clinical factor that can influence control of convulsion in pediatric CSE, are however lacking. This study was planned to examine if any clinical factor has any influence on the control of episodes of CSE in children, through a prospective design.

METHODS

This prospective control study was conducted for a period of 1 year in a tertiary care hospital. After obtaining the Ethical Committee Approval and written consent from the respective parents, we enrolled the eligible subjects in the study. Consecutive cases of CSE, irrespective of cause, between 1 month and 12 years of age arriving at the emergency ward of the hospital were enrolled. Cases were diagnosed to be in status epilepticus if they were having 5 or >5 min of continuous seizures or were having one or more discrete seizure between which there was the incomplete recovery of consciousness [2-4]. The inclusion criteria were the cases that were actively convulsing at arrival in the emergency ward.

A clearly defined uniform protocol was used for managing the cases. As soon as, the patient arrived in the emergency ward, a quick clinical assessment was done that included pulse, blood pressure, temperature, respiration, and oxygen saturation. Oxygen was administered to all the cases. Insertion of the oral airway, oropharyngeal suctioning, and artificial ventilation was resorted depending on the need. An intravenous catheter was inserted and blood samples were drawn for complete blood counts, blood sugar, serum electrolytes, serum calcium, blood urea, serum creatinine, and antiepileptic drug level (in cases of known epileptics). Dextrostix was also used to check the blood sugar immediately. Intravenous ACTs, used in sequence depending on control, were intravenous diazepam, phenytoin, phenobarbitone, and finally midazolam infusion in usual pediatric doses. An ACT was repeated only once before going to the next drug. If

convulsions persisted even after midazolam infusion, other drugs/pharmacologic agents such as valproate, levetiracetam, and pyridoxine were tried; however, not uniformly. Vital signs and oxygen saturation were monitored throughout until control of convulsions was achieved. The response was recorded after the administration of each drug. Control of convulsion was defined as the complete and lasting cessation of all motor activity.

The patients were also monitored closely for side effects of antiepileptic drugs such as respiratory depression, hypotension, and arrhythmia. State of consciousness was assessed using the Glasgow Coma Scale (GCS) after the child was relatively stabilized. All the cases were kept on intravenous fluid initially; further, any child in shock was managed according to the cause. Treatable cause and biochemical derangement, if found, were treated immediately. In infants and children with suspected hypocalcemic seizure (in the presence of signs of rickets, malnutrition, or inadequate feeding history), intravenous calcium was administered first and if convulsion was controlled, no other ACT drug, i.e., diazepam, phenytoin, phenobarbitone, and midazolam, was used. Patients were initially managed in the general ward. Difficult cases were shifted to the pediatric intensive care unit and were put on mechanical ventilator as needed. After initial stabilization, detailed case-work up and appropriate investigations to find the etiology were done.

Computer analysis of the data was done using the program SPSS version 16. Chi-square test and Fisher's exact test were done for proportions. Mann–Whitney U-test was used for comparing a parameter with variables having two groups. Kruskal–Wallis and Bonferroni tests were used for comparing a parameter with variables having more than two groups. Multivariate analysis with stepwise regression was performed with total time to control convulsions as the dependent variable and important clinical factors as independent variables. The significance level was set at $p<0.05$.

RESULTS

A total of 50 cases were included in the present study of which 30 were males and 20 were females. Mean age of the cases was 3.93 and median 2 years. There were 15 (30%) cases in the age group of 1 month–1 year, 12 (24%) in the age group of 1–3 years, 5 (10%) in the age group of 3–5 years, and 18 (36%) in the age group of 5–12 years. Thirty two (64%) cases were seen in the age group of < 5 years ($p=0.002$) and there was a significant male preponderance ($p=0.022$).

Common and important clinical findings at initial assessment were a fever in 33 (66%), hypotension in 6 (12%), shock in 6 (12%), papilledema in 6 (12%), and Todd's palsy in one. Focal deficits, namely 3rd, 6th, and 7th nerve palsies, hemiparesis, and quadriparesis were seen in 15 (30%) cases. These focal deficits were seen in association with tuberculous meningitis, viral meningoencephalitis, and pre-existing cerebral palsy and post-encephalitic sequelae. Twenty seven (54%) cases had markedly altered sensorium at initial assessment, of whom 4 (8%) continued to be in altered sensorium even at 24 h after admission with GCS score < 9. Mechanical ventilation was needed in 7 cases (14%), 1 soon after admission, and 6 later during management.

Laboratory investigations done at the time of admission showed several interesting findings such as leukocytosis in 23 (46%), thrombocytosis in 20 (40%), hypoglycemia in 2 (4%), hyperglycemia in 3 (6%), hyponatremia in 10 (20%), hypernatremia in 4 (8%), hypokalemia in 4 (8%), hyperkalemia in 4 (8%), and hypocalcemia in 9 (18%), 20 (40%) cases were malnourished and also anemic. Imaging studies (CT) in 6 and magnetic resonance imaging [MRI] in 44 showed abnormality in 26 (52%) cases. Electroencephalography, done in 47 (94%) cases after they were well stabilized, showed abnormality in 13 cases (27.6%), in the form of epileptiform discharges in 7 (focal in 6 and generalized in 1) and slowing of background activity in 6 (generalized in 5, focal in 1).

The etiologic diagnosis in the cases arrived at after-clinical work up and investigation and classified as per the current International League Against Epilepsy guideline [7,8] were acute disorders in 43 (86%), remote disorders in 5 (10%), and progressive disorders in 2 (4%). The acute disorders were a febrile seizure in 7, meningitis in 5 (3 tuberculous and 2 pyogenic), viral encephalitis in 5, cerebral malaria in 2, neurocysticercosis in 6, hypocalcemic seizures in 5, hypertensive encephalopathy in 1, and epilepsies (generalized tonic-clonic seizure and focal) in 8. The remote disorders were congenital malformation (Lissencephaly) in 1, cerebral palsy with developmental delay in 3, and post-encephalitic sequelae in 1. The progressive disorder seen was a neurodegenerative disorder (metachromatic leukodystrophy) in 2.

Characteristics of seizures and features related to control of the episodes of convulsions were as follows: Generalized tonic-clonic was the predominant type of convulsion. Duration of convulsions till arrival at emergency ranged from 5 to 240 min (mean 62 min) (Table 1).

Nearly 25% of the cases were convulsing for >30 min, while 48% were convulsing for <30 min. Convulsive episodes were continuous

Table 1: Convulsion related features at initial assessment (n=50)

Features	Number (%)
Duration of convulsions before arrival in an emergency (in min)	
5–10	9 (18)
11–30	17 (34)
31–60	10 (20)
61–120	9 (18)
121–240	5 (10)
Seizure type	
Generalized tonic-clonic	30 (58)
Focal motor	10 (20)
Focal motor evolving into bilateral convulsive seizure	6 (12)
Tonic	1 (2)
Clonic	3 (6)
Number of convulsions	
Single episode, continuous	24 (48)
Multiple episodes, discrete	26 (52)

(the same type continuing often in series) in 24 (48%) and discrete (multiple episodes) in 26 (52%). Some important findings associated with the convulsive episodes were up-rolling of eyeballs in 43 (86%), frothing from mouth in 36 (72%), vomiting in 16 (32%), conjugate deviation of eyes in 7 (14%), involuntary passage of urine in 24 (48%), and involuntary passage of stool in 3 (6%).

Six cases (12%) could be controlled with diazepam alone. The rest needed two or more drugs. Five cases responded to a single dose of intravenous calcium alone given on strong suspicion of nutritional hypocalcemic convulsion. These cases were in the age group of 3–4.9 months and had clinical features suggestive of rickets that were subsequently confirmed radiologically and biochemically.

The total time needed to control the convulsive episodes, henceforth called "time to control" was calculated from the time of administration of the first dose of an ACT drug to the time of administration of the last drug after which the patient had lasting control of the episode of convulsion. This "time to control" in the cases is shown in Table 2. About 34% of the cases needed > 1 h for control.

Three (6%) patients died; they were aged 11 months, 18 months, and 4 years. They all had seizures lasting for >30 min before arriving at the hospital, needing multiple ACT for control of convulsions and also ventilatory support.

An effort was made to find if any clinical factor had any influence on the control of convulsions. Pertinent data in the areas of clinical finding, investigation, etiology, treatment, and immediate outcome in the cases were found out, and these were correlated to "time to control" the convulsive episodes. It is a common experience that cases of difficult status epilepticus need multiple drugs and ultimately more time for control. We considered the "time to control" as an important parameter for measuring the ease/difficulty in controlling an episode of CSE.

Univariate analysis of discrete variables (Tables 3) showed several factors to be significantly associated with "time to control," namely, focal seizure with impaired consciousness, characteristic of convulsions (discrete), focal deficit, GCS score < 9, abnormal neuroimaging finding, acute central nervous system (CNS) infection (meningitis and encephalitis), and suggesting that more time is likely to be needed to control an episode in the presence of these factors.

Analysis continuous variables showed the duration of convulsion before arrival at the hospital to be positively correlated with "time to control" the convulsions (Pearson's r=0.521, p≤0.000). Multivariate analysis using stepwise regression was done taking "time to control" as the dependent variable and other factors mentioned above as independent variables. It was found that significant predictors for "time to control" were the duration of convulsion before arrival at the hospital (p=0.000) and GCS at/around admission (p=0.04).

Table 2. Time to control the convulsions after starting ACT drugs (n=50)

Time to control convlusion (in min)	Number (%)
<5	4 (8.8)
5–30	19 (42.2)
31–60	5 (11.1)
61–120	7 (15.5)
>120	10 (22.2)

ACT: Anticonvulsant

Table 3: Correlation of discrete variables with "time to control" the convulsive episodes

Variables	Time to control (min)	p value
Seizure type		
Focal	987.96	0.031
GTCS	254.76	
Number of convulsions		
Continuous	40.56	
Discrete	707.88	0.002
GCS		
GCS<9	1179.96	0.001
GCS>9	236.64	
Focal neurological deficit		
No	286.2	0.044
Yes	849.24	
Imaging findings		
Normal	139.98	
Abnormal	616.08	0.033
Etiology		
Acute CNS infections (meningitis and encephalitis)	2607	
Others (febrile seizure, hypocalcemic seizure, and epilepsy (genetic/idiopathic)	256.21	0.023

GTCS: Generalized tonic-clonic seizure, CNS: Central nervous system, GCS: Glasgow coma scale

DISCUSSION

CSE is a problem of young children as shown by our observation of the mean age of 3.9 years and the preponderance of cases in children <5 years of age. This can be seen in one prospective [9] and several retrospective studies [10-13]. The clinical characteristics and investigational findings, we found are known to occur in pediatric CSE, as can be seen in some earlier reports [9-13]. Although the findings are not strictly comparable due to methodological differences, i.e., we took 5 min as the time to define status epilepticus as per the most recent guideline while all the earlier reports had taken 30 min to define it. Furthermore, the current study included only those cases who were actively convulsing at the time of arrival in the emergency ward. This particular fact remained unclear in earlier reports leaving a possibility that some cases that had stopped convulsing at arrival were also included in the study. Some of the current studies showed marked differences from earlier reports.

We found abnormalities in blood glucose, serum sodium, serum potassium, and serum calcium in 72% of cases that are much more than 6% (all biochemical abnormalities inclusive) reported earlier by Riviello *et al*. [14] This may be partly due to the relatively high incidence of malnutrition in our cases. In the current study, approximately 50% of the cases of CSE also had

abnormal neuroimaging findings (CT and MRI taken together). It was higher than the earlier report of 30% by Singh *et al*. in their prospective study on status epilepticus in children [9]. This higher incidence of imaging abnormality in our study could be due to the presence of more infective conditions. It was interesting to find that hypocalcemia and neurocysticercosis precipitating CSE in some of our cases, such report in pediatric CSE is scarce.

Quick control of the episode in a case of CSE is of utmost importance. Our observations show that if the duration of convulsion before arrival in hospital is prolonged, control becomes difficult as they need more drugs and also more time to control. The outcome is also likely to be adversely affected as shown by prolonged and protracted convulsions in the cases who died. Prolonged duration of convulsion before arrival in the hospital thus may be considered an important predictor of difficult control of CSE. We feel it is extremely important to take a very accurate history of how long the child was convulsing before arriving at the hospital. It is also important that the time needed for controlling an episode of convulsion should be counted from the point of starting the ACT drug.

GCS at or around the time of arrival at the hospital is also an important factor that can influence the control of status epilepticus. Cases who continue to be in altered sensorium for a longer time are likely to be difficult to control. However, GCS in a child who is convulsing and is being given an ACT drug that has psychotropic effects, may not be accurate, is likely to be subjected to observer variation and may be fallacious at times. Few other factors, namely focal seizures with altered consciousness, multiple convulsions, focal neurological deficit, and abnormal neuroimaging findings, might also have some influence on the control of the episodes; these factors might be considered as risk factors for difficult control of CSE.

CONCLUSION

CSE, thus, commonly afflicts children younger than 5 years of age and is still an important cause of mortality and morbidity. CNS infection was the most common etiology. Control is difficult in a good proportion of cases. Prolonged duration of convulsion before arriving at the hospital is a predictor of "difficult control" of CSE in children.

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