



Status Epilepticus in Children: A Study of 54 Cases

Fu-Yong Jiao^{1*}, Lei Ma¹, Robert Ouvrier² and Patrick Ho²

¹Department of Pediatrics, Children's Hospital of Shaanxi Provincial People's Hospital, China

²Department of Pediatrics, Royal Alexandra Hospital for Children, Australia

Abstract

Objectives: To review the clinical character, the management and outcome of status epilepticus in childhood.

Methodology: We conducted a retrospective review of 54 cases treated between 1996 and 1997 at the Royal Alexandra Hospital for Children, Sydney, Australia.

Results: Of the status epilepticus, 61% were in male and 39% in female, with age range of 3 months to 15 years (average 5.3 years). Etiology of status epilepticus is age related, with acute causes common in the 1 to 3 years and 4 to 7 years, both totals together were 44 (81.5%) cases. The etiology of status epilepticus included febrile (35.18%), acute symptomatic (27.58%) and idiopathic (16.6%), total was 44 (81.4%) cases. Median length of PICU stay and days of mechanical ventilation were 3.02 ± 1.6 days and 1.24 ± 0.5 days respectively. Mortality was 5.3%. Most patients had used diazepam and phenytoin. The total number of the patients with good outcome or effect was 41 (75.89%).

Conclusion: One of the most common neurologic emergencies in children-status epilepticus remains a major problem in morbidity and mortality. The commonest cause of status epilepticus is still idiopathic. Intravenously administered phenytoin and diazepam remains the first-line therapy for status epilepticus. Most of the patients will respond to the treatment.

Keywords: Status epilepticus; Children, Management

Introduction

Status Epilepticus (SE) is one of the most common emergencies in paediatric neurology and is associated with a high mortality and morbidity, with an incidence of 20 per 100,000 children per year [1,2]. SE is more frequent in children than in adults. SE occurs in a variety of settings especially in children with infections and patients with previously established epilepsy, cerebral malformations, hypoxia, hypoglycemia and head trauma, but in many cases SE can be the first unprovoked manifestation of a seizure disorder. Mortality rates associated with SE in children of between 3 and 20 percent have been reported, with higher rates if a significant metabolic disturbance is present or there is a delay in termination [3,4]. Although many studies have been devoted to the clinical, EEG, neuro pathological features of SE, little information is available concerning etiological and prognostic features of SE. This paper presents the etiological and clinical characteristics, effect of treatment and prognosis in a large group of children with status epilepticus. Special attention was paid to their intensive care course and the presence of anticonvulsant toxicity.

Materials and Methods

The study was approved by the ethics committee of the Royal Alexandra Hospital for Children, West mead, Sydney, Australia. Using the International Classification of Disease (ICD-9-CM) codes for seizures (780.3), SE (345.3) and convulsions (345.9) for ascertainment. 62 patients presenting with SE hospitalized from 01 January, 1996 to 31 December, 1997 (with 88 admissions) were identified, only 56 patients (with 61 admissions) had records available during the time of research. SE has been defined as any continuous seizure lasting longer than 30 minutes or a series of seizures without return of consciousness for at least 30 minutes. Seizures were classified as generalized (absence, myoclonic, clonic, tonic, tonic-clonic, atonic) or partial (simple, complex, secondarily generalized) according to the classification of International League against Epilepsy [5]. The etiology of SE was definite using the modification of the classification of Hasue et al., [4,6] as follows:

Idiopathic: No acute CNS or metabolic dysfunction.

Febrile: Status epilepticus provoked only by fever ($>38.4^{\circ}\text{C}$).

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*Correspondence:

Fu-Yong Jiao, Department of Pediatrics, Jiaotong University, Children's Hospital of Shaanxi Provincial People's Hospital, Xian, 710068, China, Tel: (86) 029 -85368194; 85521331 ext 2361; E-mail: jiaofy@yeah.net

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Table 1: Age and Sex Distribution of Status Epilepticus.

Number of Cases			
Age	Male	Female	Total
1-3M	2	1	3
4M-1Y	5	5	10
1Y-3Y	5	6	11
4Y-7Y	12	8	20
8Y-15Y	7	3	10

Acute Symptomatic: SE occurring during an acute illness with known CNS (eg: meningitis).

Remote Symptomatic: SE without acute causes occurring in patients with a prior history of CNS insult known to be associated with increased risk of convulsion.

Progressive Neurological: SE occurring during progressive neuropathy (eg: neuro cutaneous diseases).

Utilizing the advice definitions, 54 patients were selected, 47 patients had generalized convulsive status (grand mal), 2 patients had partial SE, 3 patients had non-convulsive SE and 2 patients had tonic status. All patients' diagnosis had been confirmed by Computed Tomography (CT), MRI, EEG, cerebrospinal fluid finding and (or) culture except 2 patients who suffered neurofibromatosis and neuro cutaneous disease (Sturge-Weber syndrome) were documented by biopsy. The 2 patients who died underwent autopsy. All patients received standard initial evaluation and therapy including physical examination, CPK, SGOT, CBC, phenytoin and phenobarbital serum levels, other anticonvulsant levels as indicated.

Standards of the hospital's clinical laboratory were used as the criteria for therapeutic and sub therapeutic range. The therapeutic range for phenytoin was 40 $\mu\text{mol/L}$ to 89 $\mu\text{mol/L}$, phenobarbital 60 $\mu\text{mol/L}$ to 120 $\mu\text{mol/L}$ and carbamazepine 15 $\mu\text{mol/L}$ to 40 $\mu\text{mol/L}$.

SE is a medical emergency requiring prompt therapy. In the hospital the treatment protocol we often use for SE has consisted of three steps as most protocols recommend:

(a) Benzodiazepine (BZD) and phenytoin (PHT): Benzodiazepine (BZD) and Phenytoin (PHT) to terminate and prevent seizure recurrence. Main BZD used was Diazepam (DZP) and Clonazepam (CZP). Diazepam's initial dose was 0.25 mg/kg to 0.4 mg/kg (max 10 mg), rate of <2 mg/min, often need repeated within 10 minutes to 15 minutes (Max 40 mg over 24 hours). Some patients received rectal administration at an initial dose of 0.5 mg/kg (max 20 mg). The way is the most useful in prehospital settings. Phenytoin IV (Intravenous) loading dose of 15 mg/kg to 20 mg/kg, rate <0.5 mg/kg to 1.0 mg/kg.min (<4 years old) or 25 mg/min (>4 years old). The combination of DZP and PHT stopped seizures in almost all the patients.

If this fails,

(b) Phenobarbitone (PB): Phenobarbitone (PB) as the third drug will be needed, loading dose of 20 mg/kg (max 100 mg), rate <100 mg/min.

(c) General anaesthesia (GA): General Anaesthesia (GA) will be needed once SE continues >60 minutes or the first and second line drugs fail. Short barbiturate anaesthesia: this is induced by a short-act in barbiturate thiopentone sodium, used by at 30 mg/kg over 1

Table 2: The Etiology of Status Epilepticus.

The Etiology of Status Epilepticus	Number (%)
Idiopathic	9
Febrile	19
Acute Symptomatic	16
CNS infection	9
Brain Trauma	3
Sepsis	2
Hydrocephalus (shunt obstruction)	2
Remote Symptomatic	
Congenital CNS malformation	3
Prior CNS insult	3
Progressive Neurological	
Neurocutaneous	2
Metabolic	2

hour, then 5 mg/hr as maintenance infusion, increased to 10 to 20 mg/kg/h. The patients were admitted to the PICU intubated and adapted to a respirator, mechanical ventilated, continuous EEG and cardio respiratory monitoring. An arterial line, vascular access and intravenous access were placed in all patients. Anaesthesia was usually maintained at this rate for approximately 24 hours and if electrical status returns as the general anaesthesia slowly withdraws, EEG should be re-converted to burst suppression or isoelectric tracing with GA during the following 24 hours. After oral trachea cannula and administering oxygen, cardio respiratory and BP monitoring was carried out, then were hypoxia, acidosis, hypotension, cerebral edema and causes and triggers of SE.

Results

Age and sex

The 54 cases with SE were identified, of which were 33 males and 21 females with a ratio of 1.57:1.24 (44.4%) cases were under 3 years old and 20 (37.1%) cases between 4 to 7 years old. Both totals together were 44 (81.5%). So SE in children is more common among the 1 to 3 and 4 to 7 years. The average age was 5.3 years, with an age range of 3 months to 15 years old (Table 1).

Etiology of status epilepticus

Etiology of SE was idiopathic in 9 cases, febrile in 19 cases and acute symptomatic in 16 cases. The most common etiologies of SE were febrile, idiopathic and acute symptomatic. Total was 44 (81.5%) cases (Table 2).

Type of seizure

The seizure type grand mal was the commonest type involved in 47 (87.3%) cases, remain were partial SE 2 cases, tonic status 2 cases, non convulsant SE 3 cases, previously diagnosed and treated epilepsy was present in 12 (22.22%) cases.

Serum anticonvulsant level (use of phenytoin)

Within the 61 admissions, intravenous phenytoin was employed in 29 (47.5%) cases (maximum serum levels were known, ranging from 65 to 270 $\mu\text{mol/L}$, therapeutic range of 40 to 80 $\mu\text{mol/L}$). Phenytoin was helpful in preventing PICU admission in 5 admissions, 3 of which belonged to the febrile category, 1 idiopathic and 1 progressive. One child was admitted to ICU without mechanical ventilation

Table 3: Afflicts of the Patients and Subsequent Patient Managements.

Afflicts of the Patients	Median Length of the PICU
Recurrent Seizure in PICU	28 (51.8%)
PICU Admission	45 (83.1%)
Intubation required	41 (75%)
Length of PICU (day)	3.02 ± 1.6 (Range 0.5-9days)
Length of Mechanical ventilation (day)	1.24 ± 0.5 days (Range 9h-10d)
Total days of PICU of the patients	136
Total days of ventilation of the patients	58
Number of deaths	3
General anaesthesia-Thiopentone	6

after phenytoin. In one case the child was experiencing respiratory depression while on phenobarbitone. Phenytoin substituted for phenobarbitone because of its good seizure control and no respiratory complication. In 4 admissions, there were progressive ataxia, nystagmus or intention tremors associated with phenytoin use. No cardiac complication was reported. These were the children with acute bacterial meningitis and ALL. The deaths were not considered as a consequence of phenytoin use. None of the children suffering from the side effects of phenytoin had been on prior treatment with phenytoin. Three levels were available: 85, 113 and 270 µmol/l.

Use of phenobarbitone

Intravenous phenobarbitone was used in 20 (33%) admissions suffering SE, 5 with etiology of febrile, 3 acute CNS, 7 idiopathic, 2 chronic CNS and 3 progressive. 10 maximum serum levels were obtainable, ranging from 75 µmol/l to 195 µmol/l (therapeutic 40 to 130 µmol/l). In 2 cases, PICU admission was not required for the management of SE. One child had febrile SE, the other had lissencephaly before using phenobarbitone. In all the other cases, phenobarbitone use was associated with mechanical ventilation. In 1 case, irritability developed and was attributed to phenobarbitone. The child who passed away with ALL also had phenobarbitone injection. Phenobarbitone levels were not known in either case.

Median length of PICU stay and days of mechanical ventilation

Among children admitted to the PICU between January 1996 and December 1997, 45% were patients with SE. 45 (83.3%) of 54 cases with SE were admitted to the PICU. The median length of the PICU stay for the patients was 3.02 ± 1.6 days (range of 0.5 to 9 days), total was 136 days in the 45 cases. The mean day of mechanical ventilation of the patients was 1.24 ± 0.5 days (range of 9 hm to 10d), total was 55.8 days in all the cases (Table 3).

Outcome

SE is a serious problem since it will be associated with high mortality if persists longer than 60 minutes. So this medical emergency requires prompt therapies including a proper airway ensured, oxygen administered and anticonvulsant drugs used as soon as possible to terminate the seizure. The total number of the patients with good outcome or effect was 41 cases and was invalid in 8 cases mainly because of complications and inadequate dosages. 6 cases used thiopentone came to control seizure, 36 cases had used diazepam in pre-hospital. Phenytoin combined with diazepam was the first line anticonvulsant drugs. The overall mortality was 3 (5.3% of all the patients, 4.9% of all the admissions) (Table 4). The deaths in the acute CNS group were due to acute bacterial meningitis in one and

Table 4: Mortality Rate of Status Epilepticus (SE).

Etiology	Mortality 1% Each Group
Febrile	0
Acute CNS injury	2 (22%)
Idiopathic	0
Chronic CNS injury	0
Progressive encephalopathy	1 (11%)

encephalopathy associated with hepatic failure in the other. The death in the progressive encephalopathy group was in a child with relapsed acute lymphoblastic leukemia post bone marrow transplantation.

Discussion

Despite significant advances in treatment, SE is still one of the common causes of mortality and neurologic sequelae in infants and children, particularly in those with chronic encephalopathies and pre-existing epilepsy [7-10]. A revised operational definition based on the indication to commence treatment has defined CSE as seizures of duration of five minutes or more [11]. In this study we found that the age of the patients at episode of SE was commonest in 3 months to 3 years of 24 (44.4%) cases, and 4 to 7 years of 20 (37.1%) cases, total was 44 (81.5%) cases. Our data showed that for the etiology of SE, half were idiopathic and febrile, 9 (16.6%) and 19 (35.18%) respectively. CNS infection is also one of the major causes, a total of 9 (16.66%) cases. This is different from Scholte's report that chronic non-progressive encephalopathy was the primary cause [8,9,12,13]. The literature suggests that the etiology and outcome of SE in children are different from those in adult patients. Within etiologies, such as idiopathic, febrile, or remote symptomatic, there was no difference in outcome among the two groups. There were 12 patients with pre-existing epilepsy and 7 patients had anticonvulsant drug withdrawal before the onset of status so this may have played a role in inducing SE in a minority of patients [14]. Mortality rate in our study was 5.3%. Another report said it was 6% to 7% and we think that the co-existing severe systemic illness in our patients led to such a high rate, eg: ALL, MOF and fulminant liver failure which could cause an especially bad outcome. Mortality and morbidity for SE have relations with three major factors including damages to the CNS caused by acute insult precipitation, the systemic effects of repeated convulsions and neural injuries from repetitive electrical discharges within the CNS. The first factor is clearly associated with the etiology of SE and the other two factors are related to the duration of SE. A recent study of adults by Stecker was similar to ours at the outcome and mortality of SE [15]. Two patients underwent post-mortem examination of the brain and body. Patient 1 was a 3-month girl. There were severe extensive cystic infarction of the white mater of the cerebral hemispheres with evidence of neuronal dropout on the cerebral cortices, cerebellar purkinje cells and dentate nucleus neurons. Evidence of recent hypoxic damage to neurons of thalamus belonged to patient 2-a 16-month girl and the autopsy revealed changes of bacterial meningitis. There were large numbers of neutrophils in the subarachnoid space of both cerebral hemispheres and cerebellum. The inflammatory infiltration extended to the sulcus and there was patchy inflammatory infiltration of the cerebellar folia. The most common complications of SE were pneumonia (4%) and tonsillitis (5%) and intracranial hypertension (5%). The existence of more than one medical complication was related to worse outcome. The most severe complications were respiratory and aspiration insufficiency. Besides, cardiac arrhythmia, hypotension and phlebitis also contributed

to a poor result. A study in India shows appropriate prehospital management and treatment targeting resolution of cardiovascular dysfunction during resuscitation could reduce mortality in children with SE [10,16,17]. So importance of prompt treatment of medical complications during general convulsions-SE has been stressed. The commonest cause of SE was idiopathic, and then was febrile. The acute CNS, the chronic CNS and the progressive encephalopathy groups were of equal distribution. Most of the presentations of SE required PICU admission. Most of the PICU admissions required mechanical ventilation probably reflecting good clinical judgment of the Emergency and PICU physicians in selecting admitted cases. This study confirmed the findings of Maytal et al. [4] regarding the mortality. Status epilepticus itself is associated with low mortality. It is the concurrent pathological processes (acute CNS injury or progressive encephalopathy) that mostly determine the cause of death [7,9,10,17]. There was great concern for the emergency or PICU physicians regarding the oversubscribing of phenzodiazepines or barbiturates in the acute resuscitative period, hence the necessitation of PICU admission. The use of phenytoin has been encouraged. Most emergency centers will recommend the use of intravenous phenytoin when the seizure persists after 30 minutes. According to this study, around 50% of the cases employed phenytoin for seizure control. In 21% (6/29) of children receiving intravenous phenytoin, the need for intubation was avoided and in terms of budget, 5 PICU beds were saved. However, it could not be established whether the SE stopped spontaneously because of the direct effect of phenytoin. 13.8% (4/29) of children receiving intravenous phenytoin suffered from acute cerebellar toxicity. Except for 1 child with level of 270 $\mu\text{mol/l}$, there was no correlation with the levels, nor the prior treatment with phenytoin. There were no other side effects seen in this study although we did not follow any of these children up prospectively. With this relatively small and crude study, it seems the use of phenytoin should be encouraged to prevent artificial ventilation and its possible adverse effects. Most of the phenobarbitone use was in the febrile or the idiopathic group. It prevented only 2 mechanical ventilations. This might reflect the sedative nature of the drug itself. Only 1 behavioral side effect was recorded. We have demonstrated that intravenously administered diazepam and phenytoin remain the first-line therapy for SE [18]. Phenytoin combined with diazepam is effective and safe. Besides, there has been a lot of research on whether Intravenous (IV) levetiracetam or IV phenytoin is the better second line treatment for the emergency management of CSE in children, suggesting that IV levetiracetam is safer and more effective [13,19-21]. More than a half of patients will respond to the initial treatment. The SE treatment also includes high-dose phenobarbital or inhalation of anaesthetic agents, proper airway must be ensured, oxygen administered, blood pressure supported and intracranial pressure controlled and soon. One of the most recent major advances in management of seizure disorders is availability of methods for rapid determination of anticonvulsant blood level. Dosage schedule of anticonvulsant can now be adjusted to maintain serum drug level within the therapeutic ranges, this provides a means of checking patient compliance and provides insights of drug metabolism of these compounds in normal individual, particularly in young infants who may have variable absorption when seizures are uncontrolled on therapy, drug toxicity is suspected, or changes in drug treatment are planned. Diazepam is a good agent to arrest SE, but should not be used in combination with phenobarbital because of the risk of hypotension and respiratory depression, particularly in infants [13,17,21].

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