Treatment of status epilepticus in children

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ABSTRACT

Status epilepticus is a medical emergency that requires prompt recognition and urgent treatment. Successful management of status epilepticus in children depends upon implementation of a treatment protocol modified according to current practices as well as availability of antiepileptic medications, out of hospital emergency services and intensive-care facilities. We propose a treatment protocol for status epilepticus in children in the Kingdom of Saudi Arabia.

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Status epilepticus (SE) has been defined as an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition.[1] A more simplified and currently accepted definition is a state of prolonged or repeated seizure activity during which the patient does not fully recover. As most seizures rarely last more than a few minutes and therapy should be initiated well before 20 minutes have elapsed, an operational definition of SE specifies continuous seizures lasting at least 5 minutes or, 2 or more discrete seizures between which there is incomplete recovery of consciousness.[2] Various classifications of SE have been proposed which apply to both adults and children.[3] These are frequently based on the separation of SE to at least 2 groups: Generalized and partial or focal **(Table 1)**. Continuous or repeated convulsive activity presents straightforward and easily recognizable epileptic phenomena, while absence or partial complex SE may not be as easy to detect clinically. Altered cognitive function, particularly in younger children, may be subtle and challenge experienced clinicians. Electroencephalogram (EEG) confirmation is required in such cases to arrive at a correct diagnosis of non-convulsive SE. Epilepsia partialis continua refers to prolonged, refractory seizure activity which affects a specific anatomical location (commonly a distal extremity) and usually associated with structural focal lesions as in herpes or Rasmussen encephalitides. Electrographic status is the demonstration of continuous epileptiform activity during a recording period.

Although SE has a lower morbidity and mortality in children than in adults,[4] it is nevertheless a medical emergency and its effective management requires prompt recognition and treatment.[5,6] The accumulation of intracellular calcium and lactate result in neuronal injury and death. At a molecular level, endogenous potentiation of N-methyl-D-aspartate (NMDA) receptor function and nitric oxide-mediated neuronal excitotoxicity and damage contribute to the detriment of cortical function.[7] Systemic complications are multiple and varied **(Table 2)** and contribute significantly to mortality in adult patients. These metabolic derangements accumulate with time and, therefore, prompt diagnosis and treatment are imperative to reverse their noxious effects on brain. The rapid application of effective measures remains the mainstay for treatment of SE. In a major effort conducted in the

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Table 1 - Classification of status epilepticus.

Generalized
Tonic
Clonic
Tonic-Clonic
Absence
Myoclonic
Partial
Simple partial (includes epilepsia partialis continua)
Complex partial

Table 2 - Complications of status epilepticus.[3]

Cardiovascular	***Respiratory***
Tachycardia	Apnea
Bradycardia	Anoxia
Dysrhythmia	Hypoxia
Cardiac arrest	CO_2 narcosis
Conduction disturbance	DIC
Congestive heart failure	Metabolic acidosis
Hypertension	Respiratory acidosis
Hypotension	Altered respiratory pattern
	Pulmonary edema
Renal	Pneumonia
Oliguria	
Uremia	***Endocrine***
Renal tubular acidosis	Endocrine failure
Lower nephron nephrosis	Altered pituitary function
Myoglobinuria	Elevated prolactin
	Elevated vasopressin
Other	Hyperglycemia
Fever	Hypoglycemia
Increased CPK	Increased plasma cortisol
Autonomic dysfunction	

CPK - creatine phosphokinase, DIC - disseminated intravascular coagulation, CO_2 - carbon dioxide

Table 3 - Treatment of status epilepticus (Status Epilepticus Working Party Four-Step Protocol).[8]

Airway Breathing Circulation
Give high flow oxygen
Measure blood glucose
Confirm epileptic seizure
Immediate IV access
Lorazepam 0.1mg/kg IV
Lorazepam 0.1mg/kg IV
Phenytoin 18mg/kg IV
Thiopentone 4mg/kg IV

IV - intravenous

United Kingdom (UK), the Status Epilepticus Working Party reviewed the literature and found only 2 controlled studies on treatment of pediatric SE.[8] As a consequence, the treatment of SE in children remains mainly practice-based rather than evidence-based. The Status Epilepticus Working Party recommended a scheme or algorithm for treatment of SE which, consisted of 4 steps **(Table 3)**. The benefits of implementing such a protocol would be subsequently audited and altered as necessary.

The development of appropriate guidelines for the treatment of SE requires familiarity with the target patient population, taking into account not only the cultural, demographic and medical characteristics, but also availability of medical emergency services, personnel, medications and equipment. Therefore, a protocol such as proposed by the Status Epilepticus Working Party may be effective in the UK but not optimal for a different population. A recent study of SE in children seen in Jeddah, Kingdom of Saudi Arabia revealed important information regarding this population.[9] Comparable to other studies, delay in starting treatment, inappropriate selection and dosage of anticonvulsant medication, and lack of 2nd and 3rd-line drugs were major deficiencies. Of 59 episodes of SE treated, only 22 (37%) were appropriately diagnosed on initial assessment. Appropriate anticonvulsant treatment was given to only 18 (31%) of 59 SE episodes. Inappropriate treatment included administration of multiple doses of Benzodiazepine alone without using 2nd line or 3rd line medications, delay in administration of 2nd line or 3rd line drugs, and delayed treatment of underlying metabolic disturbances. Although a Benzodiazepine was given initially in 92% of episodes of SE, the dose was appropriate in only 48%. Similarly, appropriate dosing of 2nd line and third-line drugs, such as Phenobarbital or Phenytoin, was utilized in only 43%. Phenobarbital, Lorazepam and paraldehyde were not available in the hospital pharmacy during the study period.[9] These deficiencies may be improved by implementation of a protocol for the treatment of SE. Such a protocol will provide a framework for immediate response and hopefully lead to better results. As new information and results are analyzed, the protocol can be modified accordingly. Among the indispensable ingredients for a successful treatment protocol for SE in children are, prompt diagnosis and implementation of pharmacologic treatment. Protection of the airway and maintenance of sufficient systemic arterial pressure to provide oxygen to the brain and maintain effective cerebral perfusion pressure (CPP), or the so-called airway, breathing, circulation (ABCs), are also initially indispensable requirements and form part of any successful protocol. The selection of the first line anticonvulsants has also been well-studied and the use of benzodiazepines has become universally accepted.[10] More recently, comparison of Diazepam and Lorazepam suggests that the latter is more effective and associated with fewer complications.[11] The 2nd line anticonvulsant medications are also not difficult to select, as Phenytoin is less likely to cause depression of the level of consciousness than Phenobarbital.[12] The availability of aqueous soluble

Table 4 - Etiology of status epilepticus in children.

Etiology	Aicardi[1] n=239 %	Phillips & Shanahan[19] n=218%
Acute		
Infections	12	14
Toxic/metabolic	11	14
Head trauma	1	5
Neoplasm	0	1
Cerebrovascular	0	1
Other	3	6
Total	**27**	**41**
Chronic		
Anoxic/birth injury	5	1
Progressive encephalopathy	4	1
Non progressive/obscure encephalopathy	8	4
Brain malformation	2	5
Cerebral palsy	1	1
Other	1	3
Total	**21**	**15**
Idiopathic		
Febrile	28	29
Non-febrile	24	16
Total	**52**	**45**

n - number

Table 5 - Management of pediatric status epilepticus. A protocol proposal.

Definition
Continuous or repeated seizure activity during which child does not regain consciousness for at least 15 minutes.

Dose
Lorazepam (Ativan) 0.1mg/kg intravenously
Diazepam (Valium) 0.25mg/kg intravenously
Phenytoin (Dilantin, Epanutin) 18mg/kg (normal saline) intravenously (do not exceed 50mg/minute)
Phenobarbital 20 mg/kg intravenously (not to exceed 100mg/min)
Midazolam (Dormicum, Versed) 100microgram/kg loading dose intravenously, given over 1-2 minutes, may increase by 1-3 microgram/kg 5-10 minutes up to 20 microgram/kg
Thiopental (Pentothal) 3-5 mg/kg loading dose over 5 minutes may increase by 3 mg/kg per hour or 50 micrograms/kg/minute until seizures stop or EEG shows burst-suppression pattern. To achieve burst-suppression repeated boluses can be given, Beware of hypotension when loading and monitor blood pressure during treatment. Patient requires intubation and mechanical ventilation.

OUT OF HOSPITAL, AMBULANCE, EMERGENCY ROOM

DIAGNOSIS OF STATUS EPILEPTICUS

AIRWAY, BREATHING, CIRCULATION (ABC)

LORAZEPAM

LORAZEPAM

PHENYTOIN/PHENOBARBITAL

INTENSIVE CARE UNIT

MIDAZOLAM

THIOPENTAL

EGG-electroencephalogram

phenytoin may reduce the corrosive effect on few and small accessible portals for administration of medications in children.[13,14]

The initial scenario, whether it evolves in the ambulance, emergency room or in-patient ward, allows for the use of Benzodiazepines and a major anticonvulsant in appropriate doses. A lack of response or, more appropriately termed, refractory SE, will then require management in a more controlled setting, with skilled medical and nursing personnel as well as readily available intubation, ventilation, and monitoring equipment and rapid laboratory and radiology services response. The selection of the 3rd line anticonvulsant drugs is less clear. In a landmark article on treatment of status epilepticus in adults, a recommendation was made for the use of Propofol in this role.[2] Limited experience and incomplete information regarding adverse effects of propofol,[15] particularly in children, resulted in poor acceptance of these recommendations.

The efficacy and safety of use of Midazolam in treatment of refractory SE have been supported by numerous studies, including children.[16,17] In our hospital, implementation of intravenous Midazolam drip has been successfully carried out for a number of years. Intensivists have become familiar and adept at controlling SE with Midazolam. If necessary, EEG monitoring or daily sampling, may be used to modify dosage and, eventually, to determine the duration of treatment. Thus, Midazolam has taken priority over Barbiturates (Thiopental) in so-called Barbiturate-induced coma. Barbiturates may have a role as 4th or 5th line drugs for treatment of refractory SE.[18] The end point of burst suppression requires continuous or intermittent EEG sampling at the bedside, a requirement which may not be readily available.

When refractory SE is unresponsive to all these measures, it is important to recall that seizures are symptomatic manifestations of disease, just as fever is a symptom of infection. Proper investigations directed to identification of the etiology and direct efforts to counteract or reduce its epileptogenic effects become an essential component of the management of refractory SE. The various causes of SE in children have been enumerated in several series **(Table 4)**.[1,19] In the case of infection, hemorrhage, edema, intoxication or trauma, appropriate treatment or removal of the offending agent may provide the key to better control of SE.

The following protocol for management of SE in children is offered as a starting point **(Table 5)**. Hopefully, it will be adopted and modified as necessary according to individual circumstances. The ultimate goal is to improve our approach to this problem and, eventually, improve results and reduce the morbidity and mortality associated with SE in children.

References

1. Aicardi J. Status Epilepticus. In: Aicardi J, editor. Epilepsy in Children. New York (NY): Raven Press; 1986. p. 240-259.
2. Lowenstein DH, Allredge BK. Status epilepticus. *N Engl J Med* 1998; 338: 970-976.
3. Pellock JM. Status epilepticus. In: Swaiman KF, Ashwal S, editors. Pediatric Neurology Principles & Practice. 3rd ed. St. Louis (MO): Mosby; 1999. p. 683-691.
4. Maytal J, Shinnar S, Moshé SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. *Pediatrics* 1989; 83: 323-331.
5. Gilbert DL, Glauser TA. Complications and costs of treatment of refractory generalized status epilepticus in children. *J Child Neurol* 1999; 14: 597-601.
6. Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: A meta-analysis. *J Child Neurol* 1999; 14: 602-609.
7. Treiman DM. Therapy of status epilepticus in adults and children. *Curr Opin Neurol* 2001; 14: 203-210.
8. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The treatment of convulsive status epilepticus in children. *Arch Dis Child* 2000; 83: 415-419.
9. Mah JK, Mah MW. Pediatric status epilepticus: A perspective from Saudi Arabia. *Pediatr Neurol* 1999; 20: 364-369.
10. Treiman DM, Demeyers PD, Walton NY, Collins JF, Colling C, Rowan AJ et al. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998; 339: 792-798.
11. Allredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich SK et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001; 345; 631-637.
12. Wilder BJ. Efficacy of phenytoin in treatment of status epilepticus. *Adv Neurol* 1983; 34: 441-451.
13. Morton LD. Clinical experience with fosphenytoin in children. *J Child Neurol* 1998; 13 (Suppl 1): S19-S22.
14. Wheless JW. Pediatric use of intravenous and intramuscular phenytoin: lessons learned. *J Child Neurol* 1998; 13 (Suppl 1): S11-S14.
15. Hatch DJ. Propofol-infusion syndrome in children. *Lancet* 1999; 353: 1117-1118.
16. Igartua J, Silver P, Maytal J, Sagy M. Midazolam coma for refractory status epilepticus in children. *Crit Care Med* 1999; 27: 1982-1985.
17. Yoshikawa H, Yamazaki S, Abe T, Oda Y. Midazolam as a first-line agent for status epilepticus in children. *Brain Dev* 2000; 22: 239-242.
18. Goldberg MA, McIntyre HB. Barbiturates in the treatment of status epilepticus. *Adv Neurol* 1983; 34: 499-503.
19. Phillips SA, Shanahan RJ. Etiology and mortality of status epilepticus in children. A recent update. *Arch Neurol* 1989; 46: 74-76.