

Management of status epilepticus

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ABSTRACT

Status epilepticus (SE) is defined as a condition characterized by an epileptic seizure that is so frequently repeated or so prolonged as to create a fixed and lasting condition. Any type of epileptic seizure can develop into SE. Status epilepticus can be classified as generalized convulsive, non-convulsive and simple partial. Generalized convulsive SE includes tonic clonic seizures with either a partial or a generalized onset. Generalized tonic clonic status is defined when consecutive seizures occur without recovery of consciousness between them. Generalized tonic clonic SE is a medical emergency associated with a high morbidity and mortality if untreated. The most common etiology of SE is non-compliance to antiepileptic drugs. Other causes include alcohol withdrawal, cerebrovascular lesions, drug intoxication, central nervous system infections, neoplasms and acute metabolic derangements. The metabolic-biochemical complication of SE includes respiratory and metabolic acidosis, anoxia, hyperazotemia, hyperkalemia, hypoglycemia, hyponatremia and autonomic and endocrine dysfunctions. Prognosis of SE depends on the duration and etiology of SE. Vigorous treatment of SE is recommended. Effective medical treatment of SE includes Benzodiazepines, Phenytoin, Barbiturates and several other new antiepileptic drugs. In this presentation, we discuss the updated management of SE and propose a protocol for management of convulsive SE.

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Status epilepticus (SE) is a medical emergency that requires early diagnosis and treatment.¹⁻³ Prolonged seizures are accompanied with significant morbidity and mortality. During the first 30 minutes of convulsive SE, compensatory mechanisms of the brain are able to prevent central nervous system damage.^{1,2} If convulsive SE exceeds 30 minutes the compensatory mechanisms fail to correct the metabolic derangement and subsequently metabolic acidosis, anoxia, hypoglycemia, rhabdomyolysis, aspiration pneumonia, neurogenic pulmonary edema and respiratory failure follow. In addition, the longer the SE the more difficult it will be to treat.¹⁻³ The objectives of this syllabus are to alert physicians to the classification and pathophysiology of SE and to propose a management protocol for convulsive and nonconvulsive SE.

Definitions. Status epilepticus is defined as continuous seizure activity lasting for more than 30 minutes or recurrent seizures for more than 30 minutes without regaining consciousness in between. The duration of a convulsive seizure is usually less than 2 minutes.¹ Therefore some definitions of SE include any

seizure of duration that exceeds 5 minutes. However, a recent epidemiological study has shown a significant statistical difference in morbidity and mortality between seizures lasting for 1-29 minutes and seizures lasting 30 minutes or more.³

Classification of status epilepticus. Any seizure type can evolve into SE. Therefore some authors classify SE into generalized SE, partial SE and non-epileptic status.³ The generalized status includes generalized tonic clonic SE, tonic SE, myoclonic SE, clonic SE, astatic SE and generalized electrographic SE. Partial SE includes simple partial SE, complex partial SE and secondary generalized SE.³ Other authors simply classify SE into convulsive and nonconvulsive SE. Convulsive SE includes overt and subtle convulsive SE.^{3,4} The overt convulsive SE indicates convulsive status with frank tonic clonic component and the subtle convulsive status indicates a state of confusion or delirium with minor clonic jerks.^{3,4} The definition of subtle convulsive SE overlaps with the definition of nonconvulsive SE.^{3,4} Nonconvulsive SE includes complex partial SE, which is usually of temporal lobe origin or less commonly of

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frontal lobe origin,⁵ generalized absence SE and partial or generalized electrographic seizures.³ Special SE syndromes include neonatal SE, epilepsia partialis continua, prolonged febrile seizures and electrical SE during sleep.³

Pathophysiology of status epilepticus. To develop SE there is failure of the seizure termination mechanisms. These include calcium dependant potassium current, N-Methyl-D-aspartate (NMDA) channels blockade by magnesium, gamma-aminobutyric acid (GABA) and adenosine inhibition. Some reports indicate that SE at any age can lead to mesial temporal sclerosis. Although the morbidity of convulsive SE is well recognized, significant morbidity subsequent to prolonged partial onset nonconvulsive SE is reported.⁶

Management of status epilepticus. Once SE is diagnosed prompt treatment should be started as soon as possible.^{1,2} The indications for electroencephalography (EEG) in SE include establishment of the diagnosis of nonconvulsive SE, evaluation of the effect of therapy, and assessment of prognosis, otherwise EEG is not necessary to initiate treatment of convulsive SE.² Treatment of SE should aim for rapid termination of SE, prevention of recurrence of seizures, correction of possible etiologies and complications if they occur.^{1,2,4,6}

Supportive therapy. Supportive therapy of convulsive SE includes maintenance of vital signs and airways, the patients head should be turned to one side to prevent aspiration, insertion of intravenous lines possibly 2 to extract blood and to start parenteral antiepileptic drug therapy. At least 50 cc of blood should be extracted to study serum electrolytes, renal function, liver function, calcium, magnesium, glucose, anticonvulsant drug level if any, complete blood count, alcohol level, toxicology screen and arterial blood gases. After the blood is withdrawn, an infusion of normal saline should be started. If hypoglycemia is suspected 50 ml of 50% glucose is given. Intravenous thiamine at 100mg should be given with the glucose to prevent precipitation of Wernicke encephalopathy. During this initial period, a brief history and physical examination is advised to provide clues for systemic diseases, trauma or focal neurological signs.² Baseline electrocardiography (ECG) should be carried out and ECG monitoring during parenteral antiepileptic drug infusion is advised.² Several parental antiepileptic drugs are useful for treatment of convulsive SE. These include the following:

Benzodiazepines. Boluses of intravenous Lorazepam at 4 mg (0.1mg per kilogram) at 1-2mg per minute, or Diazepam at 10 mg (0.2 mg per kilogram). Lorazepam is superior to diazepam because of the longer antiepileptic half-life. The major side effect of benzodiazepines is respiratory depression.^{2,4,6}

Phenytoin. A loading dose of 20-30 mg per kilogram diluted in normal saline (10-20 mg per milliliter) and infused at a rate that does not exceed 50 mg per minute. Hypotension or cardiac arrhythmia's may result from the propylene glycol vehicle used for parenteral phenytoin.^{2,4,6} A new phenytoin formula is now available

Fosphenytoin, which is a disodium phosphate ester of phenytoin. It has better solubility than phenytoin, therefore it can be given via the intramuscular route and has less hypotensive effect and therefore can be given safely to patients with unstable hemodynamic functions. Intravenous Fosphenytoin is given at 150 mg per minute. Each 150 mg of Fosphenytoin is equal to 100mg of phenytoin.^{2,6}

If seizures persist after these measures then we are justified to consider SE as a refractory SE. Electroencephalogram monitoring is justified and the objective of successful treatment is to obtain burst suppression pattern on EEG (**Figure 1**). Antiepileptic drug therapy used in refractory SE includes:

Phenobarbitone. A loading dose of 15-20 mg per kilogram at a rate of 50-100 mg per minute. Phenobarbitone acts through enhancement of GABAergic receptors. Successful treatment is achieved by a burst suppression pattern on EEG (**Figure 1**). Respiratory depression is a major side effect so the treatment should be conducted where the patient can be intubated if required. Some reports suggest the use of phenobarbitone as a first line treatment in nonconvulsive SE of partial onset.¹

Benzodiazepines. Medazolam at a loading dose of 0.15-0.2 mg per kilogram followed by a maintenance dose of 0.1-2mg per kilogram per hour. Medazolam is better tolerated in children than phenobarbitone. The patient often requires intubation during therapy. An alternative is intravenous infusion of lorazepam at 1-2 mg per hour.^{2,4,6-8}

Propofol. A short acting barbiturate at a loading dose of 3-5 mg per kilogram followed by maintenance dose of 1-18 mg per kilogram per hour. It is well tolerated by children. Intubation is required for therapy. Lactic acidosis is a recognized complication. Short series on the use of propofol in SE are available in the literature.^{2,4,6,9}

Other parenteral drugs used in refractory SE include Pentobarbital at a loading dose of 4-12 mg per kilogram followed by a maintenance dose of 3-5 mg per kilogram per hour, Lidocaine at a loading dose of 100-200 mg per

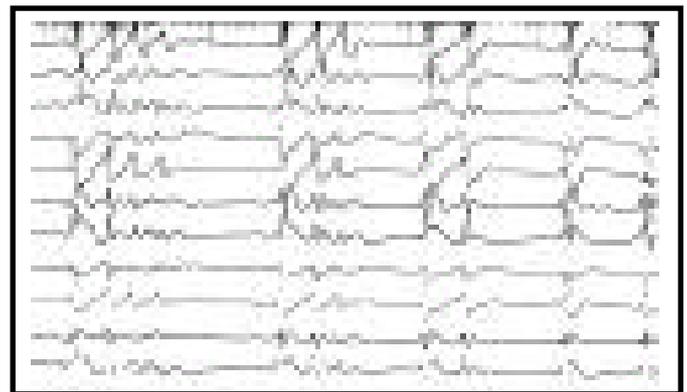


Figure 1 - Burst suppression pattern.

kilogram followed by maintenance dose of 1.5-3.5 mg per kilogram per hour.¹⁰ A new formula that is tried successfully in the treatment of SE includes the parenteral form of valproic acid (Depacon) at a loading dose of 15 mg per kilogram followed by maintenance dose of 1 mg per kilogram per hour. Controlled studies are needed to compare the efficacy of Depacon to standard antiepileptic drugs used in SE.⁶ Other therapies used in the treatment of SE include electroconvulsive therapy, parenteral pyridoxine phosphate injections and neurosurgery.⁴

Treatment of special forms of status epilepticus.

Tonic SE is often precipitated by benzodiazepines so it is preferred to avoid intravenous diazepam in the treatment of tonic SE associated with Lennox Gastaut syndrome. Tonic SE associated with anoxic encephalopathy is often refractory to most therapies and carries poor prognosis.² Myoclonic SE associated with primary generalized epilepsies responds very well to sodium valproate and benzodiazepines. Myoclonic SE associated with anoxic encephalopathy is usually refractory to most forms of therapies and carries poor prognosis.² Absence SE seen in primary generalized epilepsies responds well to intravenous benzodiazepines and the patient recovers his consciousness immediately.² The Armed Forces Hospital, Riyadh protocol for the management of convulsive SE is summarized in **Table 1**.

Discussion. Status epilepticus is a medical emergency that should be promptly treated to avoid undesirable neurological sequelae.^{1,2} During the first 30 minutes of convulsive SE compensatory mechanisms appear to prevent central nervous system (CNS) damage. If SE lasts longer than 60 minutes compensatory mechanisms begins to fail and CNS damage may result.^{2,6} Although several antiepileptic drugs can be

used effectively as first line therapy in convulsive SE recent studies showed no significant statistical differences between lorazepam (67%), phenobarbitone (63%) and diazepam with phenytoin (59.6%).¹ At the Armed Forces Hospital, Riyadh we use phenytoin and diazepam as first line therapy. This is because of the wide range availability of these medications in the emergency room, general wards and intensive care units. Convulsive SE responds to first line antiepileptic drug therapy in 80-90% of cases after administration of adequate doses according to body weight.^{1,2,4,6} Phenytoin administration should be slow at a rate of 50 mg per kilogram per minute or less to avoid unnecessary hemodynamic instability. Blood pressure and ECG should be monitored during phenytoin administration.² The definition of refractory SE is justified if the first line drug therapy fails to control the seizures.⁶ In our consideration the choice of a second line antiepileptic drug therapy is influenced by several factors, such as the age of the patient. Children tolerate medazolam and propofol better than phenobarbitone.⁷⁻⁹ In intubated and ventilated patients such as those referred from the intensive care units probably the choice of propofol or medazolam as the drug for the second line therapy or even as a first line treatment is justified because there is no risk of respiratory depression as the patient is already ventilated, they can be used as sedative agents as well and the dose of the continuous parenteral infusion can be titrated according to the response and the hemodynamic stability of the patient.⁷ In a patient with refractory convulsive SE who is not intubated, or in a patient with a nonconvulsive SE of partial onset the use of phenobarbitone as the first second line therapy is justified.^{1,6} The administration of parenteral phenobarbitone should be slow at a rate of 50-100mg per hour to minimize the need for ventilation. The administration of phenobarbitone should be carried out in a unit where intubation and ventilation can be carried out immediately if respiratory depression occurs. From our experience and some reports from the literature nonconvulsive SE may respond better to phenobarbitone than other agents. If maximum doses of phenobarbitone, medazolam, or propofol as a second line therapy fails to control SE a third, or more, medication may be added as necessary, so medazolam and or propofol can be added to phenobarbitone and vice versa.^{2,6} If SE continues despite the use of all the above medications parenteral pentobarbital is added.² During the control of refractory SE using medazolam, propofol, or pentobarbital EEG monitoring should be performed so the drugs are titrated to produce an EEG without electrographic seizures or a pattern of burst suppression (**Figure 1**).^{2,4,6,7,9-11} In nonconvulsive and electrographic SE EEG monitoring is advised to assess therapeutic response. Most patients with refractory SE have either metabolic, anoxic or major structural abnormality, and is usually associated with high morbidity and mortality.² With prolonged convulsive SE systemic consequences must be prevented or treated effectively. This may

Table 1 - Armed Forces Hospital, Riyadh protocol for the management of convulsive status epilepticus.

Time	Action
0-5 min	Supportive therapy (see management of SE)
0-30min	IV phenytoin 15-20 mg per kilogram + Diazepam 0.2 mg per kilogram.
30-60 min	IV phenobarbitone 15 mg per kilogram
*60-90 min	IV medazolam Ld = 0.2mg per kilogram and Md = 0.1-2 mg per kilogram per hour Or IV propofol Ld = 3-5mg per kilogram and Md = 1-12 mg per kilogram per hour
+*>90 min	IV pentobarbital Ld = 4-12mg per kilogram and Md = 0.5-5mg per kilogram per hour
min - minute; IV - intravenous; Ld - loading dose; Md - maintenance dose *EEG monitoring is mandatory +Correction of acidosis, volume monitoring and maintenance of body temperature	

require correction of acidosis, monitoring of volume by pulmonary artery catheter to ensure proper volume correction. The body temperature should be kept near normal to prevent irreversible CNS damage.² The duration of parenteral infusion of medazolam, propofol or pentobarbital is controversial. From our experience we like to keep the patient on parenteral drug infusions for not less than 72 hours or more and our objective is to achieve high normal serum levels of concomitant maintenance antiepileptic drugs. It is reported that some patients with refractory SE may take a few weeks on parenteral medazolam or propofol infusions before successful control of the SE.⁷⁻¹¹ Larger series and longer experience with the use of propofol and medazolam in adults and children with SE are required.⁷⁻¹¹ There is an improved understanding of basic pathophysiology associated with prolonged convulsive SE and the subsequent neuronal loss that results from both neurotransmitter excitatory response as well as the elevated intracellular calcium levels.⁶ These facts have thrown light on possible new treatment strategies in SE such as the use of neuroprotective agents using glutamate antagonists or targeted at preventing the apoptotic cascade that results in neuronal death. However these are future prospective for the treatment of SE.^{2,6}

In conclusion, SE is a medical emergency that requires prompt treatment to prevent irreversible neurological sequelae. Pharmacological treatment depends on the availability of therapeutic agents. First line therapy controls SE in the majority of cases. Failure of response to first line therapy is usually due to inadequate dosage, incorrect route of drug

administration, or misdiagnosis. True refractory SE is usually due to metabolic, anoxic or major structural etiologies and usually carries poor prognosis.^{2,6}

References

1. Treiman DM, Meyers PD, Walton NY. Treatment of generalized convulsive status epilepticus, a randomized double blind comparison of four intravenous regimens. *N Engl J Med* 1998; 339: 792-798.
2. Reutecki P, Sutula T. Status Epilepticus. In: Johnson R, Griffin R, editors. *Current Therapy in Neurologic diseases*. 5th ed. USA: Mosby; 1997. p. 41-46.
3. DeLorenzo RJ. Clinical syndromes and epidemiology of status epilepticus. In: Luders H, Noachtar S editors. *Epileptic Seizures 2000*. Philadelphia (PA): Churchill Livingstone Publishers; 2000. p. 697-710.
4. Treiman DM. Treatment of Status Epilepticus. In: Engle JE, Pedley T, editors. *Epilepsy A Comprehensive Textbook*. Philadelphia (PA): Lippincott-Raven Publishers; 1997. p. 1317-1323.
5. Thomas P, Zifkin B, Migneco O, Lebrun C, Darcourt J, Andermann F. Nonconvulsive status epilepticus of frontal origin. *Neurology* 1999; 52: 1174-1183.
6. Treiman DM. Therapy of status epilepticus in adults & children. *Current Opinions in Neurology* 2001; April: 203-210.
7. Hanley DF, Pozo M. Treatment of status epilepticus with medazolam in the critical care setting. *Int J Clin Pract* 2000; 54: 30-33.
8. Pellock JM. Use of medazolam for refractory status epilepticus in paediatric patients. *J Child Neurol* 1998; 13: 581-587.
9. Stecker MM, Kramer TH. Treatment of refractory status epilepticus with propofol clinical and pharmacological findings. *Epilepsia* 1998; 39: 18-26.
10. Holmes GL. Medazolam and pentobarbital for refractory status epilepticus. *Paediatric Neurology* 1999; 20: 259-264.
11. Rosenow F, Arzimanoglou A, Baulac M. Recent developments in treatment of status epilepticus: A review. *Epileptic Disorders* 2002; 4 Suppl 2: S41-S51.