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1.0 Introduction:


Status Epilepticus is a major medical emergency associated with significant morbidity and mortality rate of up to 76% in elderly patients with refractory status epilepticus. This clinical entity requires prompt management. The complications of status epilepticus include cardiac dysarrhythmias, derangements of metabolic and autonomic function, neurogenic pulmonary edema, hyperthermia, rhabdomyolysis and pulmonary aspiration. Permanent neurologic damage occurs with prolonged uncontrolled convulsive activity.

The longer status epilepticus remains untreated, the greater the neurologic damage. In addition, the longer an episode of status continues, the more refractory to treatment it becomes and the greater is the likelihood of chronic epilepsy. The management of status epilepticus involves the rapid termination of seizure activity, airway protection, the taking of measures to prevent aspiration, the management of potential precipitating causes, the treatment of complications, the prevention of recurrent seizures and the treatment of any underlying conditions. ^(1, 2)

2.0 Definitions:

Status epilepticus is usually defined as continuous seizure activity lasting 30 minutes or as two or more discrete seizures between which consciousness is not fully regained. Lowenstein et al. have proposed that status epilepticus be defined as a continuous, generalized, convulsive seizure lasting > 5 min, or two or more seizures during which the

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patient does not return to baseline consciousness. The rationale for this revised definition is based on the fact that a typical, generalized tonic-clonic seizure rarely lasts >5 min, that spontaneous termination becomes less likely in seizures of >5 min, and that the longer the seizure continues, the more difficult the seizure becomes to control with antiepileptic drugs, and the greater the degree of neuronal damage. This definition is consistent with common clinical practice in which it would be unreasonable to wait 30 minutes before initiating antiepileptic drug therapy. (1, 2, 3)

Refractory status epilepticus is usually defined as seizures lasting >2 h, or seizures recurring at a rate of two or more episodes per hour without recovery to baseline between seizures, despite treatment with conventional antiepileptic drugs. However, from a clinical perspective, it is preferable to consider refractory status epilepticus in any patient who has not responded to first-line therapy. (2, 3, 4)

3.0 Classification:

Using electroclinical features, status epilepticus may be classified simply by the presence of motor convulsions (*convulsive status epilepticus*) or their absence (*non-convulsive status epilepticus*). They may be further divided into status epilepticus that affects the whole brain (*generalized status epilepticus*) or only part of the brain (*partial status epilepticus*). The generalized convulsive status epilepticus is the form most commonly observed in clinical practice. (3, 4, 5)

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4.0 Generalized Convulsive Status Epilepticus

Diagnosis:


The diagnosis of generalized convulsive status epilepticus is straightforward in patients with witnessed generalized convulsive tonic-clonic seizures as the diagnosis is clinical. Electroencephalography is not required for diagnosis. ⁽¹⁾

Management:

General Measures:

1. Ensure an adequate airway and to provide respiratory support. ⁽¹⁾
2. The patient should be positioned so that they cannot harm themselves during the seizure activity. ⁽¹⁾
3. Two large-gauge IV catheters should be inserted to allow fluid resuscitation and pharmacotherapy. Should peripheral venous access be difficult, the placement of a central venous catheter is recommended? ⁽¹⁾
4. Despite the periods of apnea and cyanosis that occur during the tonic or clonic phases of their seizure, most patients in status epilepticus breathe sufficiently well as long as the airway remains clear. An oral airway may be required once the seizure


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has terminated to prevent airway obstruction. Once the seizures are controlled, and if the patient is oxygenating and ventilating adequately, endotracheal intubation may not be required for airway protection, even if the patient remains comatose. However, in this situation precautions should be taken to avoid aspiration, and a nasogastric tube should be placed to ensure that the stomach is empty. Endotracheal intubation will be required in patients who continue to experience seizures despite receiving first-line therapy. There are no available data as to the pharmacologic agents that are preferred for achieving endotracheal intubation. As these patients will be comatose and would already have received therapy with lorazepam, a hypnotic agent is usually not required. However, an anesthetic induction dose of propofol, midazolam, or etomidate may terminate the seizure activity and facilitate intubation. Neuromuscular blockade will be required to facilitate intubation in patients who continue to have tonic-clonic seizure activity despite these pharmacologic interventions. Rocuronium (1mg/kg), a short-acting, non-depolarizing muscle relaxant that is devoid of significant hemodynamic effects and does not increase intracranial pressure, is the preferred agent. Succinylcholine should be avoided, if possible, as the patient may be hyperkalemic as a consequence of experiencing rhabdomyolysis. Prolonged neuromuscular blockade should be avoided.⁽¹⁾

5. Hypoglycemia must be excluded rapidly, and corrective measures must be instituted if serum levels of glucose are low. If the prompt measurement of blood glucose

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levels is not possible, the patient should receive 100 mg IV thiamine followed by a 50-mL bolus of 50% dextrose. ⁽¹⁾

6. BP, ECG, and temperature should be monitored. If the patient develops significant hyperthermia (*i.e.*, temperature > 40°C), then passive cooling is required. ⁽¹⁾
7. Blood specimens should be obtained for the determination of serum chemistry levels. (Complete blood count, Random blood glucose, Urea and Electrolytes, Liver function test, Calcium, Magnesium and serum PH, drug toxicology and anti epileptic drug levels if the patient is epileptic). ⁽¹⁾
8. Continuous motor seizures may lead to muscle breakdown, with the release of myoglobin into the circulation. The maintenance of adequate hydration is necessary to prevent myoglobin-induced renal failure. Forced saline solution diuresis and urinary alkalization should be considered in the presence of myoglobinuria or significantly elevated serum creatine kinase levels (*i.e.*, > 5,000 to 10,000 U/L). ⁽¹⁾
9. Brain imaging with a CT scan and/or MRI as well as a lumbar puncture will be required in patients presenting with a previously undiagnosed seizure disorder once the seizure activity has been controlled. It is important to emphasize that the first priority is to control the seizures. Imaging studies should be performed only once the seizure activity has been controlled. Endotracheal intubation and neuromuscular paralysis for the sole purpose of imaging the patient may increase morbidity and is strongly discouraged. ⁽¹⁾

5.0 Pharmacotherapy:

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Goals of pharmacologic therapy are:


1. To achieve the rapid and safe termination of the seizure.
2. To prevent its recurrence without adverse effects on the cardiovascular and respiratory systems or altering the level of consciousness. (1, 2, 3)

Step I:

Time	Drug	Route	Preparation	Loading Dose
0-5 min	*Lorazepam (first choice)	Intravenous	Bolus (over 5 min)	2-4 mg (0.1 mg/kg)
	Or Diazepam (second choice)		Intravenous (over 5 min)	5-10 mg (0.15mg/kg)
5-60 min	**Phenytoin (first choice)	Intravenous	***Infusion	20-30 mg/kg
	Or **Phenobarbitone (second choice)		Intravenous ****Infusion	15-20 mg/kg

*Refrigeration or storage in lightproof containers is recommended for lorazepam, but not for diazepam, to maintain efficacy for 4-6 months.

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**If the patient is already on phenytoin or phenobarbitone maintenance doses, you may give ½ loading dose until the drug levels are available.

*** The phenytoin loading dose is mixed in 250 cc of 0.9% saline to be infused at a rate that does not exceed 50 mg/min. Avoid mixing in dextrose containing solutions. Blood pressure and heart rate monitoring is mandatory during the infusion.

**** The phenobarbitone loading dose is mixed in 250 cc of 0.9% saline to be infused at a rate that does not exceed 50 mg/min. Avoid mixing in dextrose containing solutions. The loading dose may be divided into 3 portions to minimize the need for endotracheal intubation. Blood pressure, heart rate and respiratory monitoring are mandatory during the infusion.

An electroencephalogram EEG is recommended at this stage to assess the control of the status epilepticus. (1, 2, 3, 4, 5)


Where can the patient be treated in Step I management?

The patient can be managed in the ambulance, emergency room, general ward or in the ICU as long as the blood pressure and pulse rate can be monitored.

Who can conduct Step I management?

Any physician or trained paramedical staff can conduct Step I management of status epilepticus. If phenobarbitone is to be used facilities for endotracheal and intubation and

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a physician capable of endotracheal intubation should be standby to manage the patient if he/she develops respiratory depression.

Step II:


If the status epilepticus fails to respond to first line therapy then we have a refractory status epilepticus.

Refractory status epilepticus RSE: SE that fails to respond to optimal doses of first and second line therapy. (>60 min despite optimum Benzodiazepine + Phenytoin). RSE occurs in one third of patients with SE (9-31%).

EEG Monitoring is mandatory during this step of treatment.

Time	Drug	Route	Preparation	Dose
60-90 min	*Phenobarbitone (first choice)	Intravenous	Infusion	*L.d. 15-20 mg/kg
>90 min	Midazolam	Intravenous	Infusion	*L.d.0.2 mg/kg over 5-10 mins, followed by an infusion of 0.1 to 2.0 mg/kg/h
	Or Propofol	Intravenous	Infusion	*L.d.3-5mg/kg 3-10mg/kg/h over 5-10 mins, followed by an infusion

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*L.d. =Loading dose

The maintenance dose of Medazolam or Propofol is titrated to produce EEG seizure suppression by continuous EEG monitoring. (1, 5, 6, 7, 8, 9, 10)

Where can the patient be managed in Step II?

In the Intensive Care Unit.

Who can manage the patient in Step II management?


A neurologist and or an intensive care physician.

Step III:

High-dose barbiturate therapy is associated with hemodynamic instability and immune paresis. Due to their side effects, therapy with barbiturates is reserved for those patients who do not respond to midazolam or propofol.

Time	Drug	Route	Preparation	Dose
>120 min	Pentobarbital	Intravenous	Infusion	*Ld of.10-15mg/kg/h, followed by an infusion

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>180 min	Kentamine	Intravenous	Infusion	of 0.5 to 1 mg/kg/h 1mg/kg bolus then 10-15 microgram/kg/min
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*Ld =Loading dose.

The maintenance dose of Pentobarbital is titrated to produce EEG seizure suppression by continuous EEG monitoring. (1, 3, 10, 11)

Where can the patient be managed in Step III?

In the Intensive Care Unit.

Who can manage the patient in Step III management?


A neurologist and or an intensive care physician.

Step IV:

A variety of other agents have been used for the treatment of refractory status epilepticus, including, high-dose thiopentone, IV valproate, topiramate, tiagabine, ketamine, isoflurane, and IV lidocaine. (10, 11, 12)

Prevention of seizure recurrence after termination of the status epilepticus:

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Once status epilepticus is controlled, attention turns to preventing its recurrence. The best regimen for an individual patient will depend on the cause of the seizure and any history of antiepileptic drug therapy. The following steps are recommended to prevent seizure recurrence after termination of SE.

1. Maintain the patient on appropriate doses of suitable antiepileptic drug.
2. Keep the Medazolam, propofol or pentobarbital maintenance infusions for a minimum of 72 h or until high therapeutic blood levels of antiepileptic drugs is reached.
3. Gradual withdrawal of maintenance Medazolam, Propofol or Pentobarbital under EEG monitoring i.e. the maintenance dose is gradually titrated by 50% over the next 12 h and then titrated to 0% over the subsequent 12 h. If seizure recurs at any stage the dose is gradually escalated up to the minimum dose that suppresses the seizure. Gradual withdrawal is attempted again after 12 h and so on till the maintenance dose is 0%.^(1,3,11)

Important Points to Remember:

1. Medazolam accumulates with prolonged infusion, which may result in a prolonged time to awakening of the patient.

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2. Midazolam may be accompanied with tachyphylaxis specifically after 24 to 48 hours, the dose of the drug must be increased several folds to maintain seizure control.
3. "Propofol infusion syndrome" a very rare complication reported predominantly in pediatric patients and associated with high-dose propofol infusion. The propofol infusion syndrome is characterized by severe metabolic acidosis, rhabdomyolysis, and cardiovascular collapse frequently leading to death. Circumstantial data suggest that this disorder is due to interference with mitochondrial respiration. It is possible that the full-blown propofol infusion syndrome occurs only in those individuals with a genetic susceptibility. However, the risk appears to be higher in children.
4. High-dose barbiturate therapy is associated with hemodynamic instability and immune paresis. ^(1, 10, 11)

Where can the patient be managed in Step IV?


In the Intensive Care Unit.

Who can manage the patient in Step IV management?

A neurologist and or an intensive care physician.

6.0 Management of Non-Convulsive Status Epilepticus

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Diagnosis:

Non-convulsive status epilepticus constitutes approximately 20 to 25% of status epilepticus cases, occurring in about 8% of all comatose patients without clinical signs of seizure activity, and persisting in 14% of patients after generalized convulsive status epilepticus. The diagnosis of non-convulsive SE requires an EEG for confirmation. (12, 13)


Classification:

Absence Status Epilepticus ASE: A form of non convulsive generalized status epilepticus occur with certain generalized epileptic syndromes such as childhood absence epilepsy, juvenile absence epilepsy, myoclonic astatic epilepsy, De nuvo absence status epilepticus in adults...etc. Absence status epilepticus is a benign condition that does not require aggressive therapy. Seizure control is often accomplished with intravenous lorazepam or diazepam and or Intravenous or oral Valproate. (12, 13, 14)

Complex Partial Status Epilepticus CPSE: A form of non-convulsive status epilepticus that complicates temporal and frontal lobe epilepsies. Experimental and clinical data suggest that this form of non-convulsive status epilepticus may cause ongoing neuronal injury. Complex partial status epilepticus should be treated aggressively as outlined above for convulsive status epilepticus. (15)

Electrical Status Epilepticus in the comatosed patients and electrical status Epilepticus following convulsive SE:

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These two entities are different forms of electrical status epilepticus ESE. However, the prognosis of both entities of ESE depends on the etiology and the level of consciousness. These are associated with significant morbidity in those patients with a depressed level of consciousness. Furthermore, experimental and clinical data suggest that non-convulsive status epilepticus may cause ongoing neuronal injury. Comatose patients with non-convulsive status epilepticus and non-convulsive status epilepticus following generalized convulsive status epilepticus should be treated aggressively as outlined above for refractory convulsive status epilepticus. ^(14, 15)

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