

Status epilepticus: Having treatment paradigms in place in Neurosurgical settings

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ABSTRACT

Status epilepticus (SE) is an emergency situation, which needs immediate and prompt treatment. Lack of early treatment often leads to permanent neuronal damage and poor long-term neurological outcome. Among the known neurosurgical causes of SE are central nervous system (CNS) tumors, subarachnoid and intracerebral hemorrhage (ICH), head trauma and post-operative states. Given the frequency of SE events in neurosurgical wards, it is essential that the neurosurgical teams and intensive care unit staff are adequately sensitized to the prompt detection and management of SE. Uniform, easily understandable and logical algorithms are needed as part of care pathways to enable satisfactory management. Such measures are imperative in improving long-term patient outcome.

Key words: Algorithm, antiepileptic, neurosurgical, refractory, status epilepticus

INTRODUCTION

The first description of status epilepticus (SE) was given as '*état de mal*' by Calmeil in 1824, the Latinized version SE, was mentioned in Bazire's translation of Trousseau's lectures.^[1,2]

SE is a neurological emergency, which needs immediate and prompt treatment. There is evidence that convulsive SE leads to significant metabolic and circulatory disturbances and can even lead to neuronal damage, if prolonged and untreated. The incidence of SE ranges from 10- 41/100,000 based on population based studies.^[3,4] Most important causes leading to SE are antiepileptic drug (AED) withdrawal, alcohol intoxication, acute cerebrovascular insults, central nervous system (CNS) infections, cerebral tumors, head injury.^[5,6] Among neurosurgical causes of SE, important are CNS tumors, subarachnoid and intracerebral hemorrhage, head trauma and post-operative state. Various tumors such as astrocytoma, malignant lymphoma, metastasis of sarcomas, corpus callosum glioma have been mentioned in the etiology of SE.^[6]

There has been a change in the definition of SE over a period of years. The original description given by International League against Epilepsy (ILAE) refers to "a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition."^[7] Various studies have shown that 30 min of uncontrolled seizure activity can lead to significant neuronal damage.^[8] Hence, SE was defined as seizure activity that continues for at least 30 min.^[9]

Furthermore, it was noticed that most seizures terminate spontaneously after 5-10 min. It has also been observed that early treatment is associated with good outcome.^[10] The current accepted working definition for SE mentions 'continuous, generalized, convulsive seizures lasting >5 min (in an adult or child older than 5 years), or two or more seizures during which the patient does not return to baseline consciousness.'^[11]

SE can be divided into convulsive and non-convulsive. Convulsive SE can be further divided into generalized, simple partial, complex partial and secondarily generalized. Non-convulsive SE (NCSE) refers to continuous seizure activity without minimal or absent motor activity. It is described as a change in behavior and mental processes when compared to baseline with continuous electroencephalography (cEEG) discharges.^[12] It is an important cause of coma and is missed in the absence of high degree of suspicion in a

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comatose patient. NCSE can be further divided into focal and generalized. Subtle SE is a form of NCSE that develops from generalized convulsive SE if the latter has been treated insufficiently or not treated at all.^[12]

Refractory SE is defined as seizures lasting longer than 60 min despite treatment with two drugs including a benzodiazepine and an adequate loading dose of a standard intravenous (iv) anticonvulsant drug.^[13] Super-refractory SE can be defined as SE that continues or recurs beyond 24 h despite the administration of general anesthesia.^[14]

Animal studies have shown that SE can become self-sustaining and can continue for hours if untreated, hence, there is a need for early intervention to prevent irreversible cerebral damage. SE can have varied systemic manifestations including arrhythmias, hypoxia, respiratory acidosis, rhabdomyolysis and lactic acidosis.^[15-17] If seizures continue for more than 30 min, hypotension, hyperthermia and respiratory compromise can ensue.^[8] The pathophysiologic mechanism behind SE is due to inhibition failure in initial stages, when it is gamma-aminobutyric acid (GABA) responsive, followed by excitotoxic damage and GABA unresponsiveness with persistent seizure activity beyond 30 min, explaining the need for non-benzodiazepine AED's.

TREATMENT

Immediate management: As soon as the patient is suspected to be in status, evaluation on a war footing should take place and airway, breathing and circulation should be secured immediately. Iv access should be obtained and pulse oximetry with oxygen supplementation and oral suction should be performed. Blood tests for complete blood count, glucose, electrolytes, arterial blood gas, blood and urine toxicology screen and AED levels (if patient is already on antiepileptic medication) should be sent. Cardiac monitoring should be started. If glucometer blood sugar levels are low or history of alcoholism is present, 100 mg thiamine followed by dextrose should be administered.

Considering the importance of time in management of SE, it is imperative to divide the management of SE according to various stages, i.e. (a) Premonitory stage (b) established SE (c) refractory SE and (d) superrefractory SE the algorithm for treatment of SE is described in Figure 1.

Impending SE

In the initial 5 min, seizures can become prolonged or can happen in clusters without recovery in between. The mainstay of treatment in this stage is benzodiazepines. Iv lorazepam, midazolam or diazepam can be given. Iv lorazepam is preferred due to its favorable pharmacokinetic

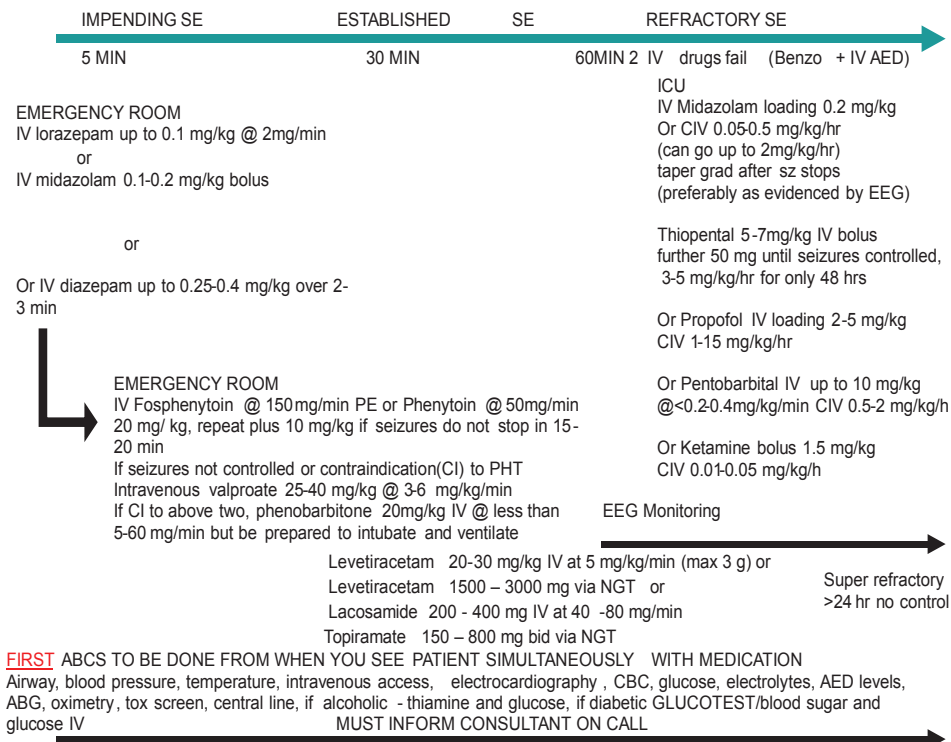


Figure 1: Treatment algorithm for status epilepticus management

profile. The half-life of lorazepam is much longer when compared to diazepam and midazolam, with a stronger affinity for receptors.^[18] The initial dose of lorazepam is up to 0.1 mg/kg at the rate of 2 mg/min.

Iv midazolam can be given as 0.1-0.2 mg/kg bolus or as continuous iv infusion with 0.05-0.5 mg/kg/h. Midazolam has a rapid onset of action and has the added advantage of intramuscular administration in case iv access is not being obtained initially.^[19] Iv diazepam can be administered as 0.25-0.4 mg/kg over 2-3 min. All the benzodiazepines carry the risk of respiratory depression; hence intubation may be needed if required.

If iv benzodiazepines are unable to completely control the SE, patient should be loaded with iv phenytoin or fosphenytoin. Over the years, phenytoin has been the benchmark for treatment of SE, unless contraindicated. Phenytoin should be administered as 20 mg/kg with infusion rates at 50 mg/min. However, it carries the risk of arrhythmias and hypotension and extravasation with tissue necrosis (purple glove syndrome). Fosphenytoin is a water soluble prodrug, which can be given at 150 mg/min phenytoin equivalent. It is a better option in view of faster infusion rates and less chances of infusion reactions, though costlier as compared to phenytoin. If seizures are not controlled within 15-20 min, another dose of 10 mg/kg phenytoin or equivalent fosphenytoin can be given.

If seizures are not controlled with phenytoin, Iv sodium valproate should be considered as the next option, administered as 25-40 mg/kg at the rate of 3-6 mg/kg/min. Valproate was studied as second line drug in seizures refractory to benzodiazepines and found to be as effective as phenytoin in terms of clinical efficacy and tolerability.^[20] Adverse effects include hyperammonemia, dose dependent thrombocytopenia and elevated liver enzymes, hence avoided in liver disease patients.^[21] If there is any contraindication to above two AED's, phenobarbitone can be given as 20 mg/kg at the rate of less than 5-60 mg/min. However, it carries the risk of significant respiratory depression and hence intubation and ventilator support may be needed.

Iv levetiracetam has emerged as an important treatment alternative in seizures not contained or responding to first line drugs. It binds to synaptic vesicle protein SV2A, involved in synaptic vesicle exocytosis. It has fewer side-effects and is not associated with respiratory and cardiac complications. The efficacy of levetiracetam has been found to be comparable to valproate, in cases of long lasting seizures not responding to initial drugs.^[22] It can be given at dose of 20-30 mg/kg intravenously at 5 mg/kg/min (maximum 3 gm). In cases without secure

iv line, 1500-3000 mg can be given by nasogastric tube in liquid preparation.

Another important antiepileptic that has recently entered the AED assemblage is lacosamide, which acts by selectively enhancing slow inactivation of voltage gated sodium channels. A recent study shows lacosamide as an effective drug for control of SE, not responding to standard treatment. It can be given at dose of 200-400 mg, at 40-80 mg/min. There are no significant side-effects except for potential PR interval prolongation.^[23]

When seizures persists for more than 60 min, without response to two main iv AED's, stage of refractory SE sets in, where seizures become more pharmacoresistant, self-propagatory and are associated with significant neuronal damage and systemic complications. Early recognition of treatment failure in initial stages of SE and timely management of refractory SE is essential to minimize further complications.^[24]

Patient should be shifted to intensive care unit (ICU) and cEEG monitoring, with the cooperation of a neurologist, is advisable along with monitoring of other vital parameters. Anesthetic agents remain the mainstay of treatment in refractory SE. It is necessary that neurosurgical ICUs have cEEG available with them.

Midazolam acts rapidly and can be given at loading dose of 0.2 mg/kg or as continuous infusion at 0.05-0.5 mg/kg/h (maximum up to 2 mg/kg/h). Patient may require vasopressor and ventilator support. Another concern is tachyphylaxis attributed to secondary downregulation of GABA receptors. Iv infusion can be stopped gradually after sustained seizure control for at least 24 h, preferably as evidenced on EEG.

Thiopental can be given at dose of 5-7 mg/kg iv bolus dose with further 50 mg increment if needed. Continuous iv infusion can be given as 3-5 mg/kg/h up to 48 h. Pentobarbital can also be given as loading dose 0.2-0.4 mg/kg/min up to 10 mg/kg, followed by continuous iv infusion as 0.5-2 mg/kg/h. Both these drugs have a long duration of action due to accumulation in adipose tissue. In view of significant cardiorespiratory depression, intubation and ventilation and vasopressor support is usually required while continuing on barbiturate infusions.

Propofol is lipid soluble, fast acting and has a short duration of action. It can be given at loading dose of 2-5 mg/kg, along with continuous iv infusion as 1-15 mg/kg/h. An important side-effect is propofol infusion syndrome, initially described in children, but

may also be found in adults receiving high doses for more than 48 h, especially in head injury cases.^[25] It presents as hypertriglyceridemia, lactic acidosis and rhabdomyolysis.

However, there has been no significant difference in mortality while using these above mentioned agents for refractory status epilepticus (RSE).^[26] The primary goal while administering barbiturates and propofol is to achieve a burst suppression for a period of at least 24-48 h.

Another anesthetic agent of choice in managing RSE is ketamine. Ketamine is an N-methyl-D-aspartate (NMDA) antagonist and its sympathomimetic action prevents hypotension as seen while administering other anesthetic agents. Isoflurane and desflurane have also been described in treatment of RSE.

Super refractory SE is defined as SE which continues even after initiating anesthetic therapy. It also comprise of those cases which recurs 24 h or more after commencing anesthetic therapy, including cases where SE reappears on withdrawal or reduction of anesthetic agents.^[14] Various treatment modalities for treatment of superrefractory SE are mentioned in Table 1.

If medical management fails, emergency resective neurosurgery has been tried and shown to be successful for control of seizures.^[27] Various surgical procedures including focal resection, multiple subpial resection for partial seizures and corpus callosotomy, hemispherotomy, vagal nerve stimulation can be done and are found to be effective on a case to case basis.^[28]

An important and potentially reversible cause of SE, noticed recently, is autoimmune encephalitis, with antibodies against neural tissue including NMDA receptor, voltage-gated potassium channel, antiglutamic acid decarboxylase antibodies, where steroids and immunotherapy like immunoglobulin and plasma exchange provides a good response. A recent study showed, around 30% of patients diagnosed as autoimmune encephalitis presented with SE and showed significant

improvement with immunotherapy.^[29] These patients present with a subacute course, associated behavioral features and may mimic bilateral Mesial temporal sclerosis on magnetic resonance imaging brain, a fact which neurosurgeons should be aware of.

NCSE presents as unexplained, undiagnosed or fluctuating coma in ICU patients, where patient has continuous epileptic activity without any visible motor signs. Diagnosis can be made with cEEG monitoring which shows an electrographic SE, however EEG changes due to associated encephalopathy and medications should also be taken into consideration. An important diagnostic practice is to administer benzodiazepines, usually lorazepam and look for electroclinical response. Low Glasgow coma scale score, remote risk factors for seizures and ocular movement abnormalities are found to be more associated with NCSE than other encephalopathies while evaluating comatose patients.^[30] A recent study evaluating patients with altered sensorium showed that 12% of patients had NCSE and was found to be a factor highly predictor of poor outcome.^[31]

It is necessary that the neurosurgical ICU staff is sensitized to the prompt detection and management of overt and covert status, something which goes a long way in improving patient outcomes.

SE is frequently encountered in clinical practice and needs to be diagnosed early. Since time plays a crucial role, prompt and judicious use of AED's according to treatment algorithm is important in SE management, to prevent neuronal damage and systemic complications. The index of suspicion should be kept high for NCSE in undiagnosed coma; cEEG monitoring is an indispensable tool in detection and management.

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Table 1: Treatment modalities described in super refractory status epilepticus management

Anesthetic agents. e.g., ketamine, midazolam, barbiturates, propofol
Intravenous magnesium
Hypothermia
Electroconvulsive therapy
Pyridoxine
Vagal nerve stimulation
Steroids
Ketogenic diet
Immunotherapy

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