Status epilepticus: an intensive care medicine problem

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Abstract

Status epilepticus (SE) is a major neurological emergency associated with significant morbidity and mortality. Whilst there are many definitions of SE, the operational definition as a seizure lasting greater than 5 minutes is widely implemented to ensure there is no delay in emergency treatment. After initial resuscitative assessment and first-line treatment these patients frequently require admission to the intensive care unit for both continuing physiological support and specific second- and third-line therapies of the SE if still unresolved. It is vital that the critical care clinician understands the potential aetiology, pathophysiology, appropriate investigations and the pharmacological management of patients with SE.

Keywords Epilepsy; intensive care; status epilepticus

Learning objectives

After reading this article, you should be able to:

- define status epilepticus (SE) and identify the various aetiologies
- instigate resuscitative treatment and perform emergent investigations (laboratory and radiological)
- become familiar with first-, second- and third-line pharmacological therapies for SE, as well as rescue therapies including neurosurgical intervention. Additionally, the reader should gain an appreciation of the mechanism of action and adverse effects of these treatments
- recognize the significant morbidity and mortality of SE, especially if there is progression to refractory SE

Currently, first-line therapy involves administration of a benzodiazepine, with phenytoin and sodium valproate promoted as second-line therapies. Propofol, midazolam and thiopental infusions are commenced as third-line therapies for refractory status epilepticus (SE); however, there is no evidence to suggest superiority of a particular agent, and no randomized control trials (RCTs) have been performed comparing the third-line therapies. In addition, in exceptional cases of refractory SE rescue therapies such as neurosurgical intervention are occasionally used.

This article will arm the critical care trainee with the theoretical knowledge required to effectively manage this particularly vulnerable cohort of patients.

SE is a neurological emergency associated with significant morbidity and mortality, which frequently requires admission to an intensive care unit (ICU) for supportive care, treatment and further investigation of the underlying aetiology. Reported mortality rates in adults are high and have been estimated between 3 and 49%. This wide variation reflects the importance of the underlying aetiology as a determinant of outcome (i.e. post-anoxic SE confers a mortality risk close to 100%).

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SE was defined by the World Health Organization (WHO) and the Commission Classification of the International League Against Epilepsy (ILAE) as persistent seizures over time, or when recovery of consciousness does not occur between attacks. Studies have demonstrated that after 30 minutes neuronal injury occurs, spontaneous resolution is less likely to ensue, and pharmacological resistance becomes established. Furthermore, an 'operational definition' which reclassifies an episode of SE as a seizure persisting beyond 5 minutes, allows for more prompt administration of treatment, and hence minimization of neuronal damage and development of refractoriness.

There are many different classifications of SE (WHO and ILAE, see Table 1) and the potential aetiology of SE in adults (see Box 1) is extensive.

Pathophysiology

SE may occur due to an imbalance between neuronal excitability (mainly glutamatergic neurotransmission) and inhibition (mainly γ-aminobutyric acid (GABA) mediated). The early physiological changes in SE include increased blood flow and increased serum glucose and lactate; this compensation, for the increased cerebral metabolic activity, protects against neuronal injury. However, ongoing seizures (>30 minutes) will result in decompensation, with failure to meet ongoing cerebral metabolic demands with associated neuronal injury. Interestingly, after this time pharmacoresistance also develops to many of the first- and second-line agents. The mechanisms underlying this include a decrease in GABA-mediated inhibition, which may explain the loss of response to benzodiazepines. Translocation of calmodulin from the membrane to the cytosol is thought to explain phenytoin resistance; notably, excessive N-methyl D-aspartate (NMDA) receptor activation and increase of these receptors supports the observations that SE responds well to agents which NDMA agonists, even late in the course of SE.

Systemic effects of SE include hyperglycaemia, hypertension, tachycardia and lactic acidosis initially; later, in the decompensated stage, hypotension, hypoglycaemia, hyperthermia, rhabdomyolysis, hypoxia and cardiac arrhythmias ensue.

Classification of SE according to WHO and ILAE

- Generalized SE
- Convulsive
  - Tonic–clonic
  - Tonic
- Clonic
  - Myoclonic
- Non-convulsive
  - Absence status
- Partial or focal SE
- Simple partial attacks: partial elementary
  - Motor
  - Sensory
- Somatomotor
  - Dysphasic
  - Continuous partial epilepsy
- Complex partial attacks
- Unilateral SE: hemiclonic SE
- Erratic SE
- Non-classifiable SE

Abbreviations: ILAE, International League Against Epilepsy; SE, status epilepticus; WHO, World Health Organization.

Table 1

Investigations

Laboratory, electrophysiological and radiological investigations are aimed at determining the aetiology, efficacy of treatment and the development of complications. Blood tests should include electrolyte levels (particularly sodium, magnesium and potassium), serum anti-epileptic drug (AED) levels (especially if the patient has a history of epilepsy), full blood count (infection), hepatic and renal function tests. A serum toxicology screen and ethanol level should be added. Blood cultures should be performed and a lumbar puncture should be considered in patients where a central nervous system infection is suspected as a cause of SE, or where no other obvious cause is found. Of note, cerebrospinal fluid pleocytosis can occur in patients with SE in the absence of infection, hence cautious interpretation of the result is required. In general, if encephalitis or meningitis is clinically suspected, empiric antimicrobial/antiviral therapy should be commenced prior to lumbar puncture.

CT brain and MRI provide valuable information, particularly in excluding a space-occupying lesion. Whilst MRI is more sensitive in revealing intracranial abnormalities, CT brain can be performed faster in most institutions and should be performed once the patient is stabilized.

An EEG is mandatory for diagnosing NCSE (estimated to account for up to 15% of SE) and should be suspected in patients with impaired consciousness without obvious cause. NCSE is a subtype of SE, and includes a range of conditions characterized by prolonged electrographic seizure activity which results in non-convulsive symptoms. Continuous EEG monitoring (cEEG) is ideal, particularly in the ICU setting; however, many factors limit its application, such as cost, availability of staff to perform and interpret the EEG, as well as lack of studies to demonstrate a positive impact on outcome. Intermittent EEG should be performed in the absence of cEEG monitoring, particularly in diagnosing SE (and also excluding pseudoseizures as a differential diagnosis).

Aetiology of SE

- CNS infection (meningitis, encephalitis)
- Traumatic brain injury
- Stroke (ischaemia, intracerebral haemorrhage, subdural haemorrhage)
- Space-occupying lesions
- Anoxic brain injury
- Substance misuse/recreational drugs (e.g. alcohol withdrawal)
- Medications that lower seizure threshold (e.g. cefepime in renal failure)
- Metabolic abnormalities (e.g. hyponatraemia, hypoglycaemia)
- Subtherapeutic levels of AEDs
- Idiopathic/cryptogenic

CNS, central nervous system; SE, status epilepticus.

Box 1

Treatment

The main goals of treatment are the initial stabilization of the patient (i.e. airway, breathing and circulation), terminating the seizure as soon as possible and avoiding seizure recurrence. Simultaneously, any systemic complications arising from the SE should be identified and treated.

Initial treatment of SE begins with assessment and management of the patient's airway and ventilation, which may require intubation in some cases. It is important to note that the use of neuromuscular blocking agents may cause the convulsions to cease, but the patient will have ongoing neuronal firing and still be at risk of neuronal damage in the absence of obvious seizure activity. Attention to the cardiovascular state would include close monitoring of heart rate (HR) and blood pressure (BP). Also, as hypoglycaemia is a potential cause of SE, intravenous (IV) glucose can be given (50 ml of 50% dextrose) followed by 100 mg IV thiamine (to prevent possible Wernicke encephalopathy). Correction of electrolyte disturbances should be performed in a timely fashion.

Pharmacological treatment

Benzodiazepines (BZD) are the first-line agents used in SE. The Veteran's Affairs Study (Treiman et al,- comparing lorazepam, phenobarbital, diazepam followed by phenytoin, and phenytoin alone for GCSE) recommended lorazepam as the initial drug of choice; although it was no more efficacious than phenobarbital or than the combination of diazepam and phenytoin together, the authors recommended that it was easier to use. Furthermore a systematic review noted that compared with diazepam, lorazepam has a significantly lower risk of non-cessation of seizures and continuation of SE requiring a different drug or general anaesthesia, compared with diazepam.

Hence it is recommended that first-line treatment of SE is lorazepam 0.1 mg/kg at an infusion rate of 2 mg/minute; if this is