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 if the SE remains unresolved. It is vital that the critical care clinician understands the potential aetiology, pathophysiology, appropriate investigations as well as the pharmacological management of patients with SE. This article will arm the critical are trainee with the theoretical knowledge required to effectively manage this particularly vulnerable cohort of patients.

Keywords Epilepsy; intensive care; status epilepticus

Royal College of Anaesthetists CPD Matrix: 2F00, 3F00

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)
- describe the 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

Status epilepticus (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 9% and 27% for convulsive status epilepticus (CSE), 18–65% for non-convulsive status epilepticus (NCSE) and 23–61% for refractory status epilepticus (RSE). This wide variation reflects the importance of the underlying aetiology as a determinant of outcome (i.e. post-anoxic SE traditionally had a mortality rate approaching 100% but following new ACLS guidelines advocating hypothermia post cardiac arrest the prognosis may have improved).

There are many different classifications of SE (WHO and ILAE, see Box 1) and the potential aetiology of SE in adults (see Box 2) is extensive. The most recent consensus states that SE should be defined as 5 minutes or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures. This definition allows for more prompt administration of treatment, and hence minimization of neuronal damage and development of refractoriness.

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 (epilepsiapartialis continua)

Complex partial attacks

Unilateral SE: hemiclonic SE

Erratic SE

Non-classifiable SE

Abbreviations: World Health Organization (WHO) and the Commission Classification of the International League Against Epilepsy (ILAE).

Box 1

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Aetiology of SE

CNS infection (meningitis, encephalitis)
Sepsis
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)
Pre-existing epilepsy (± subtherapeutic levels of AEDs)
Idiopathic/cryptogenic

Box 2

SE should be classified as either convulsive SE (convulsions that are associated with rhythmic jerking of the extremities) or non-convulsive SE (seizure activity seen on EEG without the clinical findings associated with convulsive SE). Refractory SE should be defined as SE that does not respond to the standard treatment regimens, such as an initial benzodiazepine followed by another anti-epileptic drug (AED).

Pathophysiology

SE may occur due to an imbalance between neuronal excitability (mainly glutamatergic neurotransmission) and inhibition (mainly γ-aminobutyric acid (GABA) mediated). Failure of inhibitory processes is increasingly thought to be the major mechanism leading to status epilepticus. 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. Pathological neuronal changes occur after 30 minutes and neurons begin to die after 60 minutes. The hippocampus contains the most sensitive neurons to damage. Interestingly, after this time pharmacoresistance also develops to many of the first- and second-line therapeutic 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 are NDMA agonists, even late in the course of SE.

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

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, calcium and potassium), serum anti-epileptic drug (AED) levels (especially if the patient has a history of epilepsy), blood glucose level, 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 CNS infection is suspected as a cause of SE, or where no other obvious cause is found. Of note, CSF 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 non-convulsive status epilepticus (NCSE) (estimated to account for up to 15% of SE) and should be suspected in patients with impaired consciousness without obvious cause. NCSE is defined as 'seizure activity seen on EEG without the clinical findings associated with convulsive SE'. 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).

Treatment

The main goals of treatment are the initial stabilization of the patient (i.e. airway, breathing and circulation), terminating the seizure (clinically and electrographically) 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,