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Treating status epilepticus in adults

CLINICAL REVIEW

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This clinical review examines the treatment of status epilepticus, a condition in which epileptic seizures are prolonged and pose a significant risk of brain damage and death. International guidelines recommend the use of benzodiazepines as first-line treatment, and these should be administered promptly and in appropriate doses. Second-line treatment involves the use of high-dose anti-seizure medications to stop and prevent seizures. If seizure activity persists, general anaesthesia should be administered as soon as possible. All neurological hospital departments should have established and rehearsed protocols for treating status epilepticus.

Status epilepticus is a neurological condition characterised by prolonged epileptic seizures that require prompt medical treatment to avoid permanent brain damage or death. Aetiology of the condition is varied (1, 2). Status

epilepticus is typically triggered by cerebrovascular diseases, brain tumours, infections, alcohol, medications, neurodegenerative conditions and failure to take epilepsy medication. The article is based on international and national guidelines for the treatment of status epilepticus, as well as relevant literature and our own clinical experiences. It is written by a group of neurologists from Bergen, Trondheim and Oslo university hospitals, who have a special interest in status epilepticus.

Classification and epidemiology

Status epilepticus can be classified according to seizure type, aetiology, electroencephalogram (EEG) findings, age and treatment response (1). The most common and most severe form is generalised convulsive status epilepticus, where the patient experiences tonic-clonic seizures. Other forms include focal status epilepticus, absence status epilepticus and non-convulsive status epilepticus.

Status epilepticus was previously defined as prolonged seizures lasting more than 30 minutes. In 2015, a new classification (1) was introduced, where the time limit for convulsive status epilepticus was reduced from 30 to 5 minutes for ongoing seizures, and to 10 minutes for focal and absence status epilepticus.

Another classification delineates the most severe forms of status epilepticus: if there is no treatment response following use of two different anti-seizure medications, including benzodiazepines, the condition is called refractory status epilepticus. Status epilepticus that persists or recurs despite treatment with general anaesthesia for more than 24 hours is called super-refractory status epilepticus. The latter is particularly challenging to treat and often raises difficult ethical questions. In cases of refractory and super-refractory status epilepticus, clinicians should look for unusual aetiology, such as immunological conditions, mitochondrial diseases, unusual infectious conditions, genetic disorders and toxins (2).

The incidence of status epilepticus varies from 10 to 40 per 100 000 adults per year. Mortality ranges from 9 to 37 %, depending on aetiology and duration (2–4). In refractory and super-refractory status epilepticus, the mortality rate is approximately three times higher than for non-refractory status epilepticus (3, 4). Status epilepticus leads to higher long-term mortality (5), and 30–40 % of patients have lower functional levels upon discharge (3).

Treatment and management in the emergency room

In principle, the treatment strategy follows the same plan for all forms of status epilepticus (Stages 1–4, Figure 1), but in focal status epilepticus, more medications can be considered before administering anaesthesia (2, 6–8). The threshold for administering anaesthesia should be particularly high for patients with focal status epilepticus with intact consciousness.

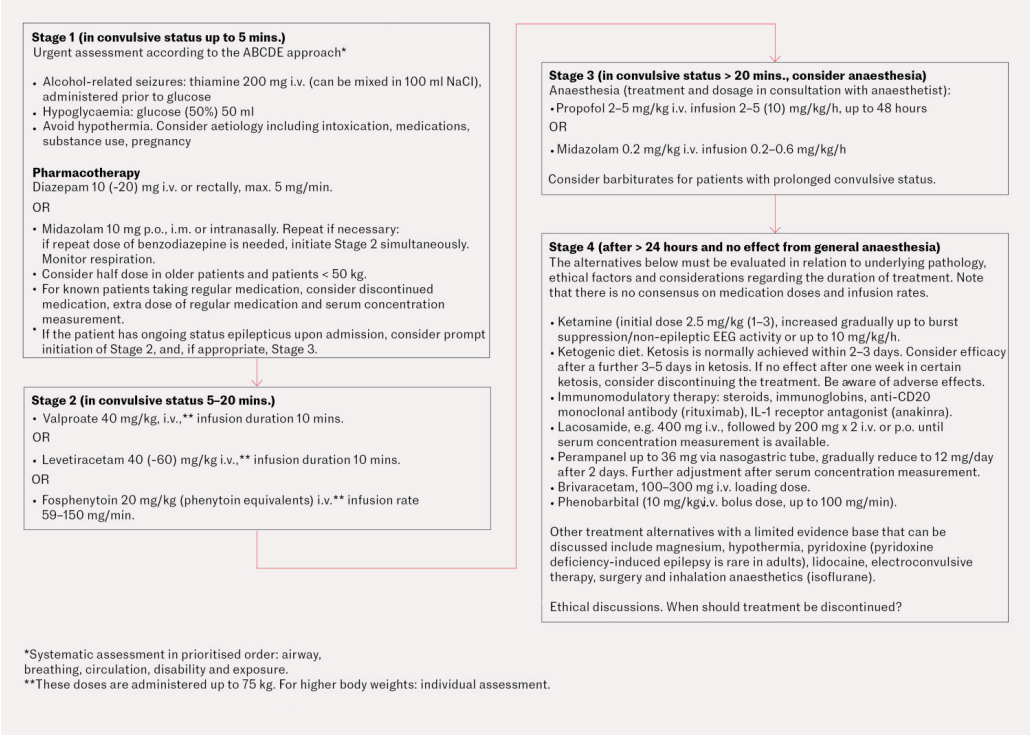

Figure 1 Treatment of status epilepticus and super-refractory status epilepticus based on national and international guidelines (Stages 1–4) and clinical experience (Stage 4) (2, 6–8).

Benzodiazepines are normally administered in pre-hospital settings by ambulance personnel. If the patient continues to have seizures without waking up in the emergency room, an established standardised protocol should be followed.

The first stage in the emergency room is examination and assessment according to the ABCDE approach (Stage 1), establishing intravenous access, measuring body temperature and performing blood tests, including blood glucose, CRP, leukocytes and serum concentration measurement of any anti-seizure medication. A targeted medical history is recorded and examination should be conducted with a view to establishing aetiology, including substance use, psychogenic non-epileptic seizures or seizures related to pregnancy. Comparative information about previous diagnoses, diabetes mellitus, or other comorbidities should be gathered.

If the seizures have not stopped after arrival in the emergency room, a new dose of benzodiazepine is administered (Stage 1). In such cases, anti-seizure medication is administered simultaneously, without waiting for the seizures to stop (Stage 2).

The anaesthesia team should be notified at an early stage. The importance of rapid seizure control is based on evidence of cellular changes that can prolong seizures (9, 10). The longer a seizure lasts, the greater the risk of neuronal damage or death – and the more difficult it becomes to stop the seizure.

Every minute is critical. However, delays often occur in practice, including insufficient dosing of anti-seizure medications. We have therefore recently proposed that the term 'time to control' be introduced as a quality measure for the period from seizure onset to clinical seizure cessation (11).

Medications for status epilepticus

The different stages of treatment are summarised in Figure 1, Stages 1–4.

Stage 1: Benzodiazepines

International guidelines recommend the use of benzodiazepines as first-line treatment for status epilepticus. Diazepam and midazolam are most commonly used in Norway, and have the same efficacy in practical terms (6, 12). Diazepam can be administered intravenously or rectally. Midazolam is given either buccally, intramuscularly or intranasally. Intramuscular administration of midazolam can be beneficial where intravenous access is not possible, and is increasingly being used in pre-hospital settings in Norway (12). Benzodiazepines can usually be re-administered after 2–5 minutes if the seizure does not stop. It is essential to give a sufficient dose of benzodiazepine promptly.

Stage 2: Anti-seizure medications

The most commonly used are valproate, levetiracetam and fosphenytoin. These medications are initially given as a bolus/loading dose, followed by a maintenance dose. These three medications have shown equally good efficacy at the following doses: 40 mg/kg for valproate, 60 mg/kg for levetiracetam and 20 mg/kg for fosphenytoin up to a body weight of 75 kg. In a large-scale randomised controlled trial, no improvement in efficacy was detected with doses exceeding those equivalent to 75 kg body weight (7).

Valproate is rapidly redistributed in the body fat, requiring close monitoring of serum concentration. We suggest measuring serum concentration once or twice daily, one to two days after initiation. Maintenance dosing is initiated immediately after the loading dose, usually in the form of continuous infusion, typically 100–200 mg/hour for the first 12–24 hours, followed by intermittent intravenous or oral dosing (a suggested 600 mg × 2–3 with the first dose after 6 hours, guided by serum concentration).

Valproate should not be administered to patients with diagnosed liver disease or a predisposition to liver failure, such as established or suspected mitochondrial disease. As a general rule, valproate should not be given to pregnant women. Ammonia levels may increase with valproate use, but the clinical significance of values up to 100–120 mmol/l is uncertain (13).

Levetiracetam is given as a loading dose, starting at 40 mg/kg (6, 7), then intermittently intravenously or orally, with a suggested 1000 mg × 2–3 with the first dose after 6 hours. Levetiracetam can cause psychological adverse effects and behavioural changes. This is of secondary concern in a phase where the priority is to stop seizures, but should be considered if the patient remains on the medication after discharge from hospital.

Fosphenytoin is a phenytoin prodrug that is less of an irritant to tissue, and doses are specified in phenytoin equivalents. Fosphenytoin is administered intravenously as a loading dose based on body weight. The maintenance dose is

usually given 2–3 times daily, with the first dose typically administered 6–8 hours after the loading dose (6). Fosphenytoin has proarrhythmic properties and can lead to hypotension, and should therefore be administered with caution, and under telemetry monitoring, to patients with diagnosed cardiac arrhythmias.

Stage 3: General anaesthesia

In patients experiencing prolonged status epilepticus despite sufficient treatment in Stages 1 and 2, general anaesthesia should be administered as quickly as possible. Propofol is most commonly used because it allows for rapid awakening, unlike barbiturates. Propofol-related infusion syndrome is rare, but long-term use of propofol can lead to multi-organ failure. The need to continue propofol should therefore be assessed after two to three days.

After general anaesthesia is administered, it is not possible to control clinical seizure symptoms. The most important monitoring tool available is electroencephalogram (EEG). There is no clear understanding of the optimal anaesthesia depth with regard to EEG findings. Full burst suppression is an EEG pattern characterised by periods of high-voltage electrical activity alternating with periods of suppression with little or no activity in the brain. While not absolutely necessary, aiming for burst suppression for 12 to 24 hours can be a practical goal (14).

Stage 4: Treatment strategies for refractory and super-refractory status epilepticus

A wide range of alternative therapies have been tested in super-refractory status epilepticus, but systematic comparative studies are needed. These therapies should only be considered after conventional anti-seizure medications have been thoroughly explored. Medication is normally continued in Stage 2. It is important not to constantly change the treatment regimen but to try each regimen for at least a few days. Ketamine, immunotherapy and the ketogenic diet are the best-tested options (2). It may be appropriate to try lacosamide, perampanel and brivaracetam. More information is available in NevroNEL (8) and in various review articles (2, 3).

Ketamine is an NMDA receptor antagonist and has been effective in animal studies. Intravenous ketamine for super-refractory status epilepticus has shown highly variable anti-seizure efficacy, ranging from approximately 30 % to over 90 % (15). Ketamine acts as a mild vasopressor and can contribute to haemodynamic stability and a reduced need for vasopressor support.

Status epilepticus can occur due to autoantibody formation against ion channels or receptors in brain cells. In super-refractory status epilepticus, autoantibodies should be routinely measured, and anti-inflammatory treatment should be considered at an early stage. Steroids, intravenous immunoglobulins, plasmapheresis, rituximab, anakinra and several other medications have been tested in small-scale clinical trials (16). High-dose steroid therapy and immunoglobulins are normally considered first, followed by rituximab (in the case of confirmed or suspected autoantibodies) or anakinra or tocilizumab (if no autoantibodies are detected).

In some cases, the ketogenic diet has been shown to be effective in both children and adults, and it is administered in consultation with a nutritionist (6). The ketogenic diet can affect the serum concentration of epilepsy medications and increases the risk of fatal propofol-related infusion syndrome. The ketogenic diet is contraindicated in patients with liver failure, acute pancreatitis or metabolic acidosis.

In addition to the treatments mentioned here, there are other options that are rarely used, but they are not discussed here.

Ethical aspects of super-refractory status epilepticus

The aetiology of super-refractory status epilepticus is diverse and often multifactorial. There are no biomarkers that can predict super-refractory status epilepticus or its further clinical course. In cases of prolonged status epilepticus, continuous assessment of what is ethically appropriate for the patient, their family and intensive care capacity is crucial. Existing prognostic scoring systems such as STESS (status epilepticus severity score) and EMSE (epidemiology-based mortality score) lack sufficient sensitivity and specificity. Slightly better for a selected population is the recently published ACD (age, consciousness and duration) score (5), but such measurement tools are based on larger patient populations and are not always applicable at an individual level.

Conclusion

Most cases of status epilepticus are treatable. Considerably more challenging is the treatment of refractory and super-refractory status epilepticus. The most important aspect is to initiate treatment promptly and administer appropriate doses of benzodiazepines (Stage 1), immediately followed by anti-seizure medications (Stage 2). Furthermore, it is important to quickly try to identify underlying causes. The ethical aspects of treating refractory and super-refractory status epilepticus are a key factor and must be thoroughly discussed in each individual case, including how many alternative treatment options should be tried and when treatment should be discontinued. We recognise the benefit of being able to discuss particularly complicated cases in a forum of doctors with a special interest in and knowledge of status epilepticus, and we will initiate the establishment of such.

The article has been peer-reviewed.

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