Chapter

Advances in the Treatment of Status Epilepticus

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Abstract

The management of status epilepticus (SE) emphasizes early identification, support of vital functions, quick implementation of pharmacotherapy, and recognition of acute etiologies. Prompt administration of a benzodiazepine, often followed by an intravenous antiseizure medication, has been supported by multiple high-quality studies. SE evolving into a refractory stage may require the initiation of anesthetic agents, such as midazolam or propofol. The contribution of autoimmune encephalitis to the burden of refractory SE cases has led to the introduction of immune-modulatory agents, such as steroids and IVIG, in the treatment protocols for refractory SE appearing de novo without prior history of epilepsy. This chapter summarizes the pharmacological agents proposed in the treatment of SE and the stepped approach to their implementation.

Keywords: status epilepticus, convulsive and nonconvulsive status, management, treatment protocols, antiseizure medications, anesthetics, immune-modulatory agents

1. Introduction

Status epilepticus (SE) is a common emergency with severe consequences, both systemic and neurologic. It occurs when biological mechanisms that terminate a seizure fail. Unfortunately, mortality attributed to convulsive status epilepticus (CSE) has not changed for over 30 years.

Immediate therapeutic intervention is required to minimize the risk of short- and long-term morbidity. Delayed treatment increases the risk of a self-sustained seizure and pharmacologic failure (Altered Mental Status (AMS) [1–7].

Treatment involves quick administration of benzodiazepines followed by antiseizure medications to terminate, not only the clinical motor component, but also the electrographic seizure activity. It is also essential to screen for rapidly identifiable etiologies, address them, and provide supportive care as needed. The initial management highlights also the adequacy of airway, breathing, and circulation basics [3, 7].

Most of the treatment trials and algorithms are based on studies of CSE. But in practice, these guidelines are also applied to a certain extent to the nonconvulsive type of SE (NCSE).

An episode of SE can be divided into four stages based on its treatment responsiveness and the escalation of applied therapeutic agents [2].

Evidence-based treatment guidelines derived from high-quality studies are only available for the initial stages of SE.

2. Stage 1 (early or emerging SE): benzodiazepines

Multiple studies confirmed benzodiazepines as the mainstay of treatment for early CSE, thus a benzodiazepine is usually the first administered agent (**Table 1**). It is typically given when a seizure lasts more than 5 minutes. If IV access is already established, IV lorazepam is typically used (4 mg) with another repeated dose for ongoing seizures if needed. IV lorazepam is superior to phenytoin in the treatment of early SE according to the landmark veterans affairs cooperative SE study. IV diazepam is another alternative. Lorazepam has a smaller volume of distribution than diazepam, thus it may contribute to a longer antiseizure effect and a lower rate of seizure recurrence [3, 8, 9].

If IV access is not available, IM midazolam should be administered as a 10 mg dose. This route of administration is feasible due to midazolam's water solubility.

Benzodiazepines can also be delivered in the prehospital setting by trained EMS personnel as the patient is being transported to the emergency room (ER) [10, 11].

A majority of patients in CSE are still facing delays before treatment initiation, and suboptimal benzodiazepine dosing out of fear of drug-induced respiratory depression. The "RAMPART" study showed that the latter is more likely to occur due to ongoing seizure activity rather than as an adverse event due to benzodiazepines [11, 12].

IV thiamine should be given early also, especially for patients with a history of heavy alcohol use [3].

3. Stage 2 (established SE): anti-seizure medications (ASMs)

After first-line therapy with a benzodiazepine, randomized controlled trials have established IV fosphenytoin (fPHT), levetiracetam (LEV), and valproic acid (VPA) as equivalent second-line treatments (**Table 2**). These treatments are applied in the event of ongoing seizure activity, but also even after seizure cessation to maintain a longer seizure control unless a seizure-provoking factor has been identified and addressed. An adequate loading dose (20 mg/kg for fPHT, 20–40 mg/kg for VPA, 40–60 mg/kg for LEV) should be administered to achieve a rapid effect with an appropriate therapeutic serum level. fPHT carries some advantages over phenytoin IV; it can be given at a faster infusion rate and is compatible with a dextrose solution. IV phenobarbital is still considered an alternative choice and is included in SE treatment algorithms, but caution about respiratory

Drug	Mechanism of action	Dosing	Remarks
Lorazepam	Enhances GABA	0.1 mg/kg IV up to 4 mg	May repeat once
Diazepam	Enhances GABA	0.2 mg/kg IV up to 10 mg	May repeat once
Midazolam	Enhances GABA	10 mg IM if >40 kg	Single-dose

Table 1.
Commonly used benzodiazepines in early SE.

Drug	Mechanism of action	Dosing	Remarks
IV fosphenytoin	Prolongs Na channel inactivation	20 mg/kg maximum 1500 mg	Monitor for bradycardia and hypotension
IV valproate	Na channel inactivation and enhancing GABA	40 mg/kg up to 3000 mg	Caution about hyperammonemia & hepatotoxicity
IV levetiracetam	Binds to SV2A protein	60 mg/kg up to 4500 mg	Minimal drug interactions, caution in renal failure
IV phenobarbital	Enhances GABA	15–20 mg/kg	Sedation, respiratory depression

Table 2.
Commonly used ASMs in established SE.

depression needs to be taken into account when this agent is combined with a benzodiazepine. The newer ASM lacosamide is available in IV formulation and has also been used to treat SE, but it is less rigorously studied. The typical adult loading dose is 400 mg. Potential cardiac side effects include bradycardia, hypotension, PR interval prolongation, etc. [13–16].

4. Stage 3 (refractory SE, RSE): ASMs & anesthetics

If the seizure continues despite the implementation of the above-mentioned treatments and measures (initial benzodiazepine + one ASM), the efficacy of additional ASMs decline, and the SE episode can be classified as refractory. Up to 40% of SE cases reach this stage. High-quality randomized trials comparing the different RSE treatments are lacking. Trials in such critically ill patients have proven to be very difficult. Another ASM can be loaded if the first choice administered earlier failed to arrest ongoing seizures. An anesthetic agent can be initiated instead or follow the second failed ASM. There is no consensus governing such a decision at this time. The "ConSEPT" trial showed that successive use of IV ASMs in children is successful in the majority (instead of recourse to anesthetics). This approach is probably feasible also in NCSE and focal SE in adults to avoid intubation and ventilatory support [3, 14, 17].

When an anesthetic agent is contemplated, usually IV midazolam or propofol are such first-choice agents. Pentobarbital is an accepted alternative (**Table 3**).

Drug	Mechanism of action	Dosing	Remarks
IV midazolam	Enhances GABA	Loading: 0.2 mg/kg Maintenance: 0.05–2 mg/kg/hour	Tachyphylaxis with prolonged use
IV propofol	Enhances GABA	Loading: 1–2 mg/kg Maintenance: 5–10 mg/kg/hour	Propofol infusion syndrome
IV pentobarbital	Enhances GABA and inhibits glutamate	Loading: 5–15 mg/kg Maintenance: 1–10 mg/kg/hour	Hemodynamic instability, ileus

Table 3.
Commonly used anesthetics in RSE.

These drugs act through the modulation of GABA receptors. An IV loading dose is administered followed by continuous infusion, titrated to complete clinical and electrographic seizure cessation or burst suppression pattern on EEG. Propofol should not be infused for more than two to three days preferably, to minimize the risk of propofol infusion syndrome. The latter can be potentially fatal and consist of a constellation of heart and renal failure, acidosis, and rhabdomyolysis [2, 3, 17, 18].

5. Stage 4: Super refractory SE (SRSE)

This stage is reached when seizures, clinical or electrographic, continue for more than 24 hours despite the use of anesthetic agents and pharmacologically induced coma.

Therapeutic suggestions at this stage are based on open-label or retrospective case series and reports, thus their evidence for benefit is rather weak. In addition to the anesthetic agents detailed for the previous stage, suggested agents and procedures include the following to name a few: ketamine, magnesium, pyridoxine, immunomodulating agents/procedures (steroids, IVIG, and plasmapheresis), therapeutic hypothermia, ketogenic diet, etc (**Table 4**).

ASMs not deployed in the early stages can be tried, even through a nasogastric tube, if the chosen drug is not manufactured in an IV formulation [2, 7, 18, 19].

Ketamine acts as a noncompetitive NMDA glutamate receptor antagonist. It has a neuroprotective effect in animal models of SE. A loading dose of 1–3 mg/kg is suggested followed by a continuous infusion of 1–10 mg/kg/h. In a report on 58 patients started on ketamine after a median of nine days of SE, the drug apparently contributed to the control of SE in up to a third of cases. A more recent metanalysis suggested success with ketamine in 74% of adult cases and rare adverse events. A potential advantage of this drug is the lack of significant hypotension compared to other anesthetics [18, 20, 21].

Magnesium sulfate may be especially effective in the context of eclampsia [2, 19].

An open-label small study for SRSE treated with a ketogenic diet noted that 73% of patients (11 out of 14) had resolution of SRSE after a median of five days [22].

An autoimmune etiology for SE is becoming increasingly recognized. It is suspected, especially in patients with new-onset refractory SE (NORSE). NORSE occurs in patients without antecedent epilepsy and clear structural, infectious, metabolic, or toxic causes. Treatment with classical ASMs is often unsuccessful. Some patients require multiple anesthetic drugs, often with recurrence of SE once these are weaned off. Small case series have suggested that steroids, IVIG, and plasmapheresis may be beneficial in NORSE. Patients can be given IV methylprednisolone 1000 mg/day for five days, followed by IVIG 2 gram/kg divided over five days or plasma exchange every other day for a total of five to seven sessions. Identification of an autoantibody (anti-GAD, anti-NMDA ...) proves the autoimmune etiology in some NORSE cases, but this is not a prerequisite for considering immune therapies; a delay in starting one of these therapies may contribute to a worse outcome. In other words, it is recommended to not delay treatment, while waiting for the results of the autoantibody screening. In addition to the immunotherapies mentioned above, tocilizumab, an IL-6 receptor inhibitor, was used in six patients with NORSE. It terminated SE after an interval of three days from initiation. Other proposed second-line immune therapies include rituximab, cyclophosphamide, and anakinra. Through suggested anti-inflammatory mechanisms, the ketogenic diet may also play an adjunctive therapeutic role in NORSE and FIRES [23–27].

Drug/procedure	Mechanism of action	Dosing/use	Remarks
Ketamine	NMDA antagonist	Loading: 0.5–3 mg/kg Maintenance: 1–10 mg/kg/h	Tachycardia and acute elevation in blood pressure
Magnesium Sulfate	Inhibits NMDA receptor	Loading: 50 mg/kg Maintenance: 20–40 mg/kg/hour	Most relevant in the context of eclampsia
Pyridoxine	Co-factor in metabolic pathways of multiple neurotransmitters	180–600 mg/day	Empiric treatment for pyridoxine-dependent seizures
Methylprednisolone	Immune modulation	1 g IV, for 3–5 days	Hyperglycemia, fluid retention, GI ulceration
IVIG	Immune modulation	0.4 g/kg daily for 5 days	Acute renal failure, thrombosis, aseptic meningitis

Table 4.
A sample of reported treatments for SRSE.

Neurostimulation methods have been explored in refractory and super refractory SE, but the evidence supporting their use is of low quality. In a recent systematic review, acute implantation of VNS is reported to result in SE cessation in 74% of cases. These results should be interpreted with caution due to the high risk of reporting bias [28, 29]. Although successful treatments with electroconvulsive therapy, responsive neurostimulation, deep brain stimulation, and other neuromodulation procedures are reported, the data remains sparse and inconclusive. As such patients are typically receiving numerous ASMs and anesthetics concomitantly, the contribution from the neuromodulator procedure specifically is not always obvious [18, 19].

6. Non-convulsive seizures/SE

NCSE can follow partially treated CSE or develop independently. It is also common in critically ill patients treated in an ICU setting [7]. Very limited data exist addressing its specific management, thus treatment protocols are typically borrowed from CSE guidelines. One study compared fPHT (20 mg/kg) and lacosamide (400 mg) for the treatment of recurrent NC seizures and found lacosamide to be non-inferior to fPHT. Both agents achieved grossly comparable seizure cessation and adverse events rates. However, this study addressed the use of these drugs for recurrent NC seizures, not NCSE [30].

7. Supportive care

Securing and stabilizing the subject's airway, breathing and circulation represent the earliest steps in proposed treatment algorithms. Initial management include the administration of oxygen, ECG monitoring, finger stick glucose measurement, IV access, blood work (electrolytes and hematology), and toxicology screening. One

hundred mg of thiamine IV is typically administered early, and before IV dextrose in the event of hypoglycemia [2, 3, 7]. Appropriate work-up should also be tailored specially to screen for life-threatening etiologies (meningitis/encephalitis, stroke, intracranial tumors, etc.).

Treatment typically involves acute monitoring in the ICU.

EEG monitoring, rather than routine EEG, is recommended in the management of patients with SE. It is the only means to recognize the epileptic nature of subclinical non-convulsive seizures. It is also essential in monitoring the treatment response and titrating therapy with anesthetics to achieve burst suppression or seizure cessation. Some EEG patterns can be difficult to interpret as they may be classified within the ictal-interictal continuum. Expert EEG readers and interpretation within the clinical context are needed to solve such scenarios [31–33].

Cancer screening with a CT of the chest, abdomen and pelvis, testicular ultrasound, and whole-body PET are recommended when an autoimmune or paraneoplastic etiology is suspected. ASMs and immunotherapy are less effective if the tumor is not addressed [7, 23].

8. Conclusion

Status epilepticus represents a neurological emergency. Rapid and adequate treatments have the potential to modify prognosis and decrease neuronal injury. There is reasonable evidence dictating the initial treatments in CSE, but later stages and NCSE have scarce data directing their management. The risks and morbidity related to the administered treatments should be accounted for by the treating clinicians. After the immediate stabilization of the patient, possible etiologies behind the SE should be investigated and treated.

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