Treatment of Convulsive and Nonconvulsive Status Epilepticus

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Opinion statement

Status epilepticus (SE) should be treated as quickly as possible with full doses of medications as detailed in a written hospital protocol. Lorazepam is the drug of choice for initial treatment. If intravenous access is not immediately available, then rectal diazepam or nasal or buccal midazolam should be given. Prehospital treatment of seizures by emergency personnel is effective and safe, and may prevent cases of refractory SE. Home treatment of prolonged seizures or clusters with buccal, nasal, or rectal benzodiazepines should be considered for all at-risk patients. Nonconvulsive SE is underdiagnosed. An electroencephalogram should be obtained immediately in anyone with unexplained alteration of behavior or mental status and after convulsive SE if the patient does not rapidly awaken. Delay in diagnosis of SE is associated with a worse outcome and a higher likelihood of poor response to treatment. For refractory SE, continuous intravenous midazolam and propofol (alone or in combination) are rapidly effective. Randomized trials are needed to determine the best treatment for SE after lorazepam.

Introduction

Status epilepticus (SE) is a medical and neurologic emergency. Overall, mortality is approximately 17% to 23% [1,2]. An additional 10% to 23% of patients who survive SE are left with new or disabling neurologic deficits [2,3]. The varied presentation of nonconvulsive SE (NCSE) can lead to misdiagnosis or delayed treatment. This article will review the recent literature pertaining to early, efficient recognition and management of SE.

DEFINITION AND CLASSIFICATION

Status epilepticus has traditionally been defined as continuous or repetitive seizure activity persisting for at least 30 minutes without recovery of consciousness between attacks [4]. Recent revisions of this definition gradually shortened the duration of SE. Because isolated seizures rarely last more than 5 minutes, the current operational definition of SE is 5 minutes or more of continuous seizures or two or more discrete seizures with incomplete recovery of consciousness between seizures [5]. From a clinical standpoint, the most practical definition is any patient who is still seizing.

There are many different types of SE. The simplest classification scheme divides SE into two major types: convulsive and nonconvulsive, based on whether or not there is rhythmic jerking. Generalized convulsive status epilepticus (GCSE), including generalized tonic-clonic, myoclonic, tonic, and clonic, is more easily recognized than NCSE. However, as GCSE continues, the overt symptoms usually evolve into subtler features, such as subtle twitching of the face or limbs, or nystagmus [6]. Some patients may not show any motor symptoms of seizure and therefore have nonconvulsive status epilepticus. It is this group of patients who often evade early diagnosis because NCSE has protean manifestations, ranging from slight alteration of consciousness to coma. In the intensive care unit (ICU), most seizures are nonconvulsive and would not be noticed without electroencephalography

based on its site of onset; however, practically, it often is not possible to distinguish between NCSE of generalized onset and NCSE of partial onset with bilateral spread.

ETIOLOGY

The most frequent cause of SE is a prior history of epilepsy (22% to 26%). However, more than half of episodes of SE occur in patients without prior seizures. In these patients, stroke (19% to 20%) is the most frequent cause, followed by remote causes (16%), toxic-metabolic encephalopathy (12% to 18%), alcohol and/or drugs (8% to 15%), tumor (4% to 20%), cardiac arrest or hypoxia-ischemia (4% to 12%), infection of the central nervous system (CNS) or other infection (4% to 7%), traumatic brain injury (2% to 5%), and idiopathic or unknown causes (2% to 15%) [2;8, Class III; 9]. Metabolic etiologies include: low glucose, calcium, sodium, magnesium and phosphate (the latter particularly in alcoholic patients); high glucose, osmolality, blood urea nitrogen or creatinine; medication toxicity (theophylline, imipenem, isoniazid [treat with pyridoxine], clozapine, cyclosporine and related drugs, fentanyl, meperidine, propoxyphene, bupropion, and high dose intravenous [IV] beta-lactam antibiotics); withdrawal from medications and drugs (benzodiazepines, barbiturates, alcohol); and acute intoxication from illicit drugs, especially cocaine.

DIAGNOSIS OF STATUS EPILEPTICUS AND NONCONVULSIVE STATUS EPILEPTICUS

Early recognition of SE allows for prompt treatment and increases the likelihood of treatment success. Typically, patients who present with GCSE are expected to awaken gradually after the motor features of seizures disappear. If the mental status remains depressed 20 to 60 minutes after the convulsions cease, NCSE must be considered and urgent EEG is advised.

Nonconvulsive seizures and NCSE are much more common than previously recognized, particularly in patients who are in the intensive care unit. Risk factors for nonconvulsive seizures or NCSE include severely impaired mental status of any cause, young age (<18 years), prior clinical seizures or remote epilepsy risk factors, and ocular movement abnormalities (sustained deviation, nystagmus, or hippus) [7••,10]. In one study, more than 50% of 96 comatose patients undergoing continuous EEG monitoring had nonconvulsive seizures [7••].

Any fluctuating or unexplained alteration in behavior or mental status warrants an EEG and consideration of NCSE. Delays in the recognition of NCSE are associated with poor outcome and lessen the likelihood of successful seizure control [11•].

CONSEQUENCES OF STATUS EPILEPTICUS

Patients who present with a first episode of SE are at increased risk for development of epilepsy compared with those with a single, brief first episode of seizure [12]. Status epilepticus after stroke has been shown to be associated with a much higher mortality, independent of stroke size and location [13]. In GCSE and NCSE, long seizure duration and delay to diagnosis are independent predictors of poor outcome after controlling for etiology [11•,14]. There are several reported cases of prolonged nonconvulsive seizures alone causing permanent CNS injury or worsening [15, Class III]. In patients with intracerebral hemorrhage, nonconvulsive seizures are associated with increased mass effect and shift after controlling for hemorrhage size [16•, Class II]. SE also can cause nonneurologic abnormalities, including acidosis, rhabdomyolysis, renal failure, arrhythmias, and aspiration. Fever, hypotension, hypoxia, and metabolic abnormalities accelerate seizure-related neuronal injury and should be corrected aggressively. The best way to prevent these adverse effects is to stop the seizure activity as soon as possible.

Treatment

General principles

- Early cessation of seizures is the key in the management of SE. Treatment strategies should focus on several aspects: early termination of seizure, identification of the cause, prevention of seizure recurrence, and treatment of secondary complications.
- As summarized in Table 1, initial steps in the management of SE involve basic life support. Patients should receive 100% oxygen by nasal cannula or nonrebreather mask, and may require intubation if there is evidence of respiratory failure. Patients should not be pharmacologically paralyzed for intubation unless continuous EEG is being recorded, or unless absolutely necessary. IV access should be established quickly to administer drugs necessary for seizure control and resuscitation, but rectal, buccal, or nasal benzodiazepines should be given if there is any delay in obtaining IV access (see below). Fever and hypotension should be treated concurrently. Labora

Table 1. Treatment protocol for status epilepticus in adults

Time, *min*	Action
0 to 5	Diagnose; give supplemental O2; check ABC; obtain IV access; begin EKG and blood pressure monitoring; draw blood for basic metabolic panel: Mg, Ca, phosphate, CBC, LFTs, AED levels, arterial blood gas; do toxicology screen.*
6 to 10	Thiamine 100 mg IV; give 50 mL D50 IV unless adequate glucose known. Lorazepam 4 mg IV over 2 min; if the patient is still seizing, repeat once in 5 min. If there is no rapid IV access, give diazepam 20 mg rectally or midazolam 10 mg intranasally, buccally, or intramuscularly.†
10 to 20	If seizures persist, begin fosphenytoin 20 mg/kg IV at 150 mg/min, with blood pressure and EKG monitoring.
20 to 60	If seizures persist, give one of four options:‡ 1) give cIV midazolam at a loading dosage of 0.2 mg/kg; repeat 0.2 to 0.4 mg/kg boluses every 5 minutes until seizures stop, up to a maximum total loading dose of 2 mg/kg. Initial cIV rate is 0.1 mg/kg/hr. cIV dose range: 0.05 - 2 mg/kg/hr. If still seizing, proceed to cIV propofol or pentobarbital; or 2) give cIV propofol at a loading dosage of 1 to 2 mg/kg. Repeat 1 to 2 mg/kg boluses every 3 to 5 minutes until seizures stop, up to maximum total loading dose of 10 mg/kg. Initial cIV rate is 2 mg/kg/h. cIV dose range is 1 to 15 mg/kg/h. If the patient is still seizing, proceed to cIV midazolam or pentobarbital; or 3) give IV valproate 40 mg/kg over approximately 10 minutes. If the patient is still seizing, give an additional 20 mg/kg over approximately 5 minutes. If the patient is still seizing, proceed to cIV midazolam or propofol; or 4) give IV phenobarbital 20 mg/kg IV at 50 to 100 mg/min. If the patient is still seizing, proceed to cIV midazolam, propofol, or pentobarbital.
60	Give cIV pentobarbital at a loading dosage of 5 to 10 mg/kg at up to 50 mg/min; repeat 5 mg/kg boluses until seizures stop. Initial cIV rate should be 1 mg/kg/h. cIV dose range is 0.5 to 10 mg/kg/h; traditionally titrated to suppression-burst on EEG. Begin EEG monitoring as soon as possible if patient does not rapidly awaken or if any cIV treatment is used.

*Urine and blood
†The IV solution of diazepam can be given rectally if Diastat is not available; the IV solution of midazolam can be given by any of these routes
‡Intubation necessary except for valproate
ABC— airway, breathing and circulation; AED—antiepileptic drug; CBC—complete blood count; cIV—continuous intravenous; EEG—electroencephalogram; EKG—electrocardiogram; IV—intravenous; LFT—liver function test

tory studies should be sent (see Table 1). A bedside glucose level should be obtained, and 100 mg thiamine and 50 mL 50% glucose should be administered if hypoglycemia is present or if glucose level is unknown. Other components of management include determining whether there is a history of alcohol or drug use, previous epilepsy, or neurologic insult. A description of the seizure at onset should be obtained if witnessed, and brain imaging should be done after the patient is stable and seizures are controlled. For seizures caused by a metabolic abnormality, correcting the metabolic problem is more effective than antiepileptic drugs (AEDs).

Initial pharmacologic therapy

- First line medications control SE in 80% of patients when initiated within 30 minutes, but in 40% if started after 2 hours of onset [3;8, Class III]. For practical purposes, treatment should be started after 5 minutes of continuous seizure activity. Our protocol for treatment of SE in adults is shown in Table 1.

Benzodiazepines

- Benzodiazepines are potent, parenterally available medications with a rapid onset of action and are the preferred initial therapy. Their mechanism of action involves binding to high affinity sites on the γ-aminobutyric acid (GABA) receptor, resulting in hyperpolarization of the neuronal cell membrane and decreased neuronal firing [17].

Lorazepam

Standard dosage	4 to 8 mg given intravenously (0.1 mg/kg). Onset of action is 3 to 10 minutes Duration of antiepileptic effects is 12 to 24 hours (slower redistribution than diazepam). Elimination half-life is 14 hours.
Contraindications	Hypersensitivity to drug.
Main drug interactions	Increased sedation with other CNS depressants. Lorazepain is highly protein-bound.
Main side effects	Sedation of several hours, occasional respiratory depression, hypotension.
Special points	Lorazepam is the drug of choice in the initial management of SE. It has several important advantages over diazepam, which has been used traditionally. Diazepam has a much shorter duration of antiepileptic action (approximately 15 to 30 minutes), but its elimination half life of 30 hours is twice that of lorazepam, making it less optimal. However, the rectal preparation of diazepam can be valuable when IV access is not available.

Midazolam

	Give when there is no immediate IV access; see below for continuous IV drip for refractory SE.
Standard dosage	0.2 to 0.3 mg/kg intramuscular (IM), intranasal (IN), or buccal. Onset of action is 1 to 5 minutes.
Contraindications	Hypersensitivity to drug.
Main drug interactions	Increased sedation with other CNS depressants
Main side effects	Sedation, occasional respiratory depression, cardiac arrest, hypotension.
Special points	Midazolam is a water-soluble drug in acidic environments, thereby allowing for an intramuscular preparation in addition to the IV form [18]. It is lipid-soluble in physiologic pH ranges and is able to penetrate the brain to exert its anticonvulsant effects. When IV access cannot be established, buccal, IN or IM midazolam plays an important role in seizure control. Buccal and IN forms in particular are good alternatives for out-of-hospital settings. Continuous IV midazolam also plays a key role in refractory SE (discussed below).

Alternative routes of administration of benzodiazepines

- Alternative modes of administration are particularly important in patients without IV access in various settings. Prompt treatment by caregivers outside the hospital can shorten the duration of seizure, prevent progression to SE, and possibly reduce the need for emergency room visits (potentially lowering health care costs). Rectal, IM, buccal, and IN all are alternatives which have been shown to effectively and rapidly control seizures [19•, Class I; 20;21,22, Class III; 23;24–26, Class I]. Currently, rectal diazepam gel (Diastat, Xcel Pharmaceuticals, San Diego, CA) available in prefilled syringes, is the only version approved by the United States Food and Drug Administration. In a randomized trial involving patients with seizure clusters, a single dose of rectal diazepam gel decreased seizure frequency significantly and increased the chance of seizure freedom after treatment compared with placebo (55% vs 34%) [26, Class]. In children, IM midazolam has been shown to stop seizures more rapidly than IV diazepam because of earlier administration [24, Class I].
- Buccal and IN midazolam are easier to administer than rectal medications and are more socially acceptable. Two prospective studies have shown that IN or buccal midazolam is effective in aborting prolonged seizures in adults and children [22, Class III; 27•, Class I]. Scott *et al.* [19•, Class I] found that in children with seizures lasting more than 5 minutes, buccal midazolam was as effective as rectal diazepam. In a recently presented randomized trial in children presenting to the emergency room with acute tonic-clonic seizures, buccal midazolam was more likely to stop seizures in

less than 10 minutes than rectal diazepam, and had a similar (slightly lower) rate of respiratory depression [28, Class I]. In select patients, these forms of benzodiazepines also can confer the ability of patients to treat themselves during prolonged auras, simple partial seizures, or clusters with recovery between seizures.

Comparison of benzodiazepines

- Recent studies investigating out-of-hospital treatment of SE found benzodiazepines to be safe and effective when administered by paramedics for out-of-hospital SE in adults [29••, Class I]. In this study, 59% of patients with SE treated with IV lorazepam in the field were no longer seizing on arrival at the emergency department, compared with 43% of patients treated with IV diazepam, and 21% in the placebo group. Respiratory and circulatory complications were higher in the placebo group (22.5%) than in the diazepam and lorazepam groups (10% to 11%). In an older randomized trial comparing 4 mg IV lorazepam to 10 mg IV diazepam, SE was controlled in 89% of patients in the lorazepam group, compared with 76% in the diazepam group, and there were no significant differences in side effects [30 Class I].
- The clinical bottom line is that when IV access is available, IV lorazepam should be initiated as first-line therapy, and if possible, in the prehospital phase. If widely practiced, this type of treatment could have a major impact on the prevention of refractory status epilepticus. Whenever obtaining IV access would delay administration of AEDs significantly, diazepam should be given rectally (0.2 to 0.5 mg/kg for SE; usually 20 mg for an adult), or midazolam should be given nasally, buccally, or intramuscularly (0.2 to 0.3 mg/kg; usually 10 to 15 mg for an adult). Patients with a history of prolonged seizures or acute repetitive seizures should be offered rectal diazepam, or nasal or buccal midazolam for out-of-hospital use.

Second-line pharmacotherapy

- Most patients who respond to first-line agents also will require maintenance therapy with a second-line agent because the risk of recurrence is high. Additionally, second-line therapy must be initiated quickly when patients continue to seize despite treatment with benzodiazepines. The longer SE persists, the higher the risk for developing refractory status epilepticus. If convulsions are successfully abated but patients fail to improve in their mental status, there is a high probability of ongoing subclinical seizures or NCSE. Such cases warrant additional treatment. DeLorenzo *et al.* [31, Class II] found subclinical electrographic seizure activity in 48% of patients after control of convulsive SE, including NCSE in 14%. Towne *et al.* [32•, Class III] found that among 236 comatose patients with no current or past evidence of seizures, 8% showed electrographic seizures. In the Veteran Affair Cooperative study, 20% of convulsive SE patients whose movements stopped with treatment still were seizing as shown by EEG [33••, Class I]. Therefore, EEG is mandatory for all patients who do not wake up quickly after cessation of clinical SE, and for all patients with unexplained coma.

Phenytoin

The primary mechanism of action of phenytoin is inhibition of high-frequency repetitive neuronal firing by blocking voltage-dependent sodium channels [34]. It is the most commonly used second-line therapy in status epilepticus.

Standard dosage 20 mg/kg load given intravenously. The maximum infusion rate is 50 mg/min. Maximal effect is achieved in 20 to 25 minutes

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