Current Treatment for Generalized Convulsive Status Epilepticus in Adults

Li-Kai Tsai, Horng-Huei Liou

Abstract

Status epilepticus (SE) is defined as a seizure lasting longer than 5 min, or at least two seizures without full recovery of consciousness between them. Early emergent medical management consists of life support and an etiology survey, and subsequent treatment can be classified into 4 stages: (1) early SE, (2) established SE, (3) refractory SE, and (4) super-refractory SE. For early SE, benzodiazepines, such as lorazepam and diazepam, are the agents of choice, given to terminate the seizure activity rapidly. For established SE (20-30 min after SE onset), the therapeutic strategy is to give parental antiepileptic drugs, such as phenytoin, valproic acid, and levetiracetam. At the stage of refractory SE (1-2 hours after SE onset), the conventional treatment is induction of general anesthesia using midazolam or propofol. Super-refractory SE is defined as SE that continues, or recurs, for at least 24 hours after the onset of anesthetic therapy. In addition to treatments used in established and refractory SE, other potentially effective therapies include ketamine, magnesium, inhalational anesthetics, immunotherapy, ketogenic diet, induced hypothermia, and neurosurgery. The principle of SE therapy is rapid seizure control and correction of underlying problems. Future well-designed clinical trials are mandatory to establish the standard treatment, especially in settings of established, refractory, and super-refractory SE.

Key Words: antiepileptic drug, convulsion, seizure, status epilepticus

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between seizures \( ^{(4)} \).

SE is the second most frequent neurological emergency (the most frequent is acute stroke) \( ^{(5)} \). In recent years, neurocritical care has been emphasized and many medical centers and general hospitals in Taiwan, and throughout the world, have neurological intensive care units. Familiarity with current management of SE is important and useful particularly for emergency physicians, neurologists, and intensive care specialists—all of whom work together to provide optimal care for patients with SE. Types of SE include generalized convulsive SE, focal convulsive SE, and non-convulsive SE. Of these three SE types, focal convulsive SE is relatively less harmful and treatment for non-convulsive SE is still controversial. Generalized convulsive SE is the most common and pernicious type of SE, and its management is the focus of this article.

**EPIDEMIOLOGY, PROGNOSIS, AND ETIOLOGY**

The annual incidence rates of SE of all types have been reported to range from 10 to 41 per 100,000 \( ^{(6-7)} \). For generalized convulsive SE, annual incidence rates have been reported to range from 3.6 to 6.6 per 100,000 \( ^{(8)} \). The 30-day mortality rates of generalized convulsive SE have been reported at approximately 19-27% \( ^{(9)} \). The mortality rate was 38% for in elderly patients (age > 60 years) compared with 14% in young adults \( ^{(6)} \). Among SE patients, 23-43% suffered from refractory SE \( ^{(5)} \), which is the SE persisting despite adequate administration of benzodiazepines and at least one antiepileptic drug.

The prognosis of SE depends strongly on the underlying etiology, age, seizure duration, and response to treatment \( ^{(6,10)} \). Patients with anoxia or multiple medical problems suffered high mortality rates \( ^{(6)} \). Generally, the elderly showed a higher risk of poor prognosis compared with younger subjects \( ^{(10,11)} \). Prolonged SE and refractoriness to treatment were associated with poor outcome \( ^{(10)} \). The prognosis of SE may be predicted using the Status Epilepticus Severity Score (STESS), which is based on assessment of 4 factors: (1) severity of the disturbance in consciousness, (2) type of epileptic seizure, (3) age, and (4) history of the presence or absence of epileptic seizures \( ^{(12)} \). High STESS scores were shown to correlate with high mortality.

The main causes of SE included low concentrations of anti-epileptic drugs (AED) in patients with chronic epilepsy (34%), remote symptomatic causes (24%), cerebrovascular accidents (22%), anoxia or hypoxia (~10%), metabolic causes (~10%), and alcohol and drug withdrawal (~10%) \( ^{(10)} \). Since treatment of the underlying etiology is crucial for SE control, SE management depends strongly on rapid work-up and correction of essential problems.

**PATHOPHYSIOLOGY**

SE results from reduced inhibition and persistent excessive excitation of epileptogenesis, and subsequent failure of the normal mechanisms that terminate seizures. The neuronal density has been shown to be decreased in the hippocampus of patients after SE \( ^{(13)} \). Studies using nonhuman animal models have demonstrated that sustained SE induces widespread neuronal death, due to excessive neuronal firing damaging neurons via excitotoxic mechanisms. Massive glutaminergic receptor over-activity causes calcium influx into cells and triggers a cascade of harmful processes resulting in necrosis or apoptosis \( ^{(3,14)} \). In addition to neuronal damage, SE also causes many systemic complications, such as cardiac arrhythmias, temperature disturbances, electrolyte and glucose imbalances, rhabdomyolysis, and pulmonary edema \( ^{(15)} \).

During prolonged seizure activity, dynamic changes occur in gamma-aminobutyric acid (GABA) \(_{A}\) and N-methyl-D-aspartate (NMDA) receptors \( ^{(3)} \). Seconds to minutes after onset of SE, GABA\(_{A}\) receptors at the synaptic membrane are internalized into the neuronal cytoplasm, followed by endocytosis and subsequent degradation \( ^{(16)} \). The decrease in the number of GABA\(_{A}\) receptors on the synaptic membrane may lead to the failure of GABA\(_{A}\) inhibition in SE and progressive pharmacoresistance to benzodiazepines \( ^{(10)} \). At the same time, NMDA receptors are progressively transported to the synaptic membrane, resulting in increasing density of excitatory NMDA receptors \( ^{(17)} \). This may partly explain why antagonists of the NMDA receptor become particularly efficacious in the late phase of SE, while SE becomes progressively resistant to benzodiazepines \( ^{(18)} \). The phenomenon of receptor
trafficking highlights the importance of early management for SE.

Management of Convulsive Status Epilepticus

The principal goal of SE management is to stabilize vital signs and stop seizure activity as soon as possible, while correcting of the underling problems rapidly. Early emergency medical management of SE consists of life support and an etiology survey. Subsequent treatment can be classified into 4 stages: (1) early SE, (2) established SE, (3) refractory SE, and (4) super-refractory SE. Frequently used medications, dosing, and features of drugs in SE treatment are summarized in Table 1.

Early medical management

The initial treatment for generalized convulsive SE includes the emergent elements of routine critical care, such as airway protection, hemodynamic resuscitation, and intravenous access. Noninvasive methods for airway protection and oxygen supplement are required at first, but early intubation is necessary, if patients develop respiratory compromise, or if continuous intravenous anesthesia is to be prescribed. Vital signs should be monitored carefully, and a vasopressor should be given to support cerebral perfusion pressure if systolic blood pressure is < 90 mmHg, or if mean arterial pressure is < 70 mmHg\(^9\). Rapid peripheral intravenous access is mandatory, not only for fluid resuscitation and creation of a route for medication therapy, but also for collection the blood samples in order to assess SE etiology.

The essential diagnostic work-up for SE includes fingerstick glucose testing, laboratory testing (blood glucose, complete blood count, liver/renal function, electrolytes, creatine phosphokinase, and drug levels for AEDs), and head computed tomography (CT) scanning (especially for patients with de novo SE). Additional tests that are advisable for individual SE patients include magnetic resonance imaging (MRI) of the head, lumbar puncture, toxicology screening, arterial blood gas testing, and electrocardiography\(^9\). If the seizure persists despite aggressive treatment, continuous EEG monitoring is recommended\(^9\), especially when the convulsive SE evolves into subtle nonconvulsive SE, or if patients undergo continuous anesthesia therapy.

Treatment during the first stage: early status epilepticus

For rapid termination of seizure activity during early SE, benzodiazepines are the agents of choice, according to expert opinion and the results of a few clinical trials\(^8\).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dosing</th>
<th>Administration rates or continuous infusion dosing</th>
<th>Mechanisms</th>
<th>Serious adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg IV up to 4 mg per dose, may repeat after 10 min</td>
<td>Rate up to 2 mg/min</td>
<td>GABA receptor agonist</td>
<td>Respiratory depression, hypotension, sedation</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.15 mg/kg IV up to 10 mg per dose, may repeat after 5 min</td>
<td>Rate up to 5 mg/min</td>
<td>GABA receptor agonist</td>
<td>Respiratory depression, hypotension, sedation</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>15-20 mg/kg IV, may give an additional 5-10 mg/kg 10 min after loading</td>
<td>Rate up to 50 mg/min</td>
<td>Sodium channel blocker</td>
<td>Arrhythmia, hypotension</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>20-40 mg/kg IV, may give an additional 20 mg/kg 10 min after loading</td>
<td>Rate of 3-6 mg/kg/min</td>
<td>Unknown</td>
<td>Hyperammonemia, pancreatitis, hepatotoxicity, thrombocytopenia</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000-3000 mg IV</td>
<td>Rate of 2-5 mg/kg/min</td>
<td>Unknown</td>
<td>Somnolence, pancytopenia</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg IV</td>
<td>0.05-0.4 mg/kg/hr continuous infusion</td>
<td>GABA receptor agonist</td>
<td>Respiratory depression, hypotension</td>
</tr>
<tr>
<td>Propofol</td>
<td>2-3 mg/kg IV</td>
<td>2-10 mg/kg/hr continuous infusion</td>
<td>Modulation of GABA receptor</td>
<td>Propofol infusion syndrome</td>
</tr>
</tbody>
</table>
Benzodiazepines (GABA receptor agonists) have the advantages of rapid onset of action and high efficacy for controlling seizures during early SE. In Taiwan, lorazepam (Anxicam, Ativan) and diazepam (Valium) are the most frequently used benzodiazepines for SE control. Three clinical trials have compared the efficacy of lorazepam and diazepam directly or indirectly as initial treatment for SE (19-21). A randomized control trial evaluating 81 episodes of SE has demonstrated seizure control rates of 89% and 76% for lorazepam (4 mg i.v.) and diazepam (10 mg i.v.), respectively (19). In another study, this one involving 192 patients with generalized convulsive SE, 0.1 mg/kg lorazepam i.v. was associated with a success rate of 65%, while the success rate for 0.15 mg/kg diazepam combined with 18 mg/kg phenytoin i.v. was 56% (20). One randomized control trial compared the effects of lorazepam and diazepam administered by paramedics prior to hospital entry. The results showed seizure control rates of 59% in the lorazepam group (2 mg i.v., n = 66) and 43% in the diazepam group (5 mg i.v., n = 68) (21). Although the efficacies of lorazepam and diazepam are similar, lorazepam is the preferred agent for intravenous SE therapy, primarily because the duration of the anti-seizure effect for lorazepam is longer (12 to 24 hours) compared with that of diazepam (15 to 30 minutes) (8,9,22).

The main side effects of benzodiazepines are respiratory depression, hypotension, and sedation, especially in cases of overdose, and following excessively rapid administration of the drug. For intravenous benzodiazepines, the drug should be injected slowly (up to 2 mg/min for lorazepam and 5 mg/min for diazepam), and injection should be accompanied by close monitoring of respiratory rate, heart rate, and blood pressure. Other benzodiazepines recommended for SE treatment include midazolam (intramuscular, intranasal/buccal, or intravenous), intrarectal diazepam, and intravenous clonazepam. Some of these are preferred for children. A recent, randomized control trial (n = 893) demonstrated that intramuscular midazolam (10 mg) was significantly better than intravenous lorazepam (4 mg) for seizure control in the setting of SE prior to arrival at the hospital (23). However, pre-hospital, paramedic administered benzodiazepine for patients with SE is still not permitted in Taiwan.

Treatment during the second stage: established status epilepticus

If seizure persists despite adequate benzodiazepine treatment, SE enters the established phase (approximately 20-30 min after SE onset). The therapeutic goal is stopping SE using parental antiepileptic drugs. In Taiwan, frequently used antiepileptic medications include phenytoin (Dilantin), valproic acid (Depakine), and levetiracetam (Keppra). Three clinical trials have compared the efficacy of phenytoin (18-20 mg/kg) and valproic acid (20-30 mg/kg) head-to-head for SE (24-26). Each study enrolled 68 to 100 patients and demonstrated similar seizure control rates for phenytoin (42-88%) vs. valproic acid (66-88%). Thus far, there has been no direct comparison trial for levetiracetam and other antiepileptic drugs in the setting of SE. However, one recent meta-analysis demonstrated overall seizure termination rates of 50.2%, 75.7%, and 68.5% for phenytoin, valproic acid, and levetiracetam, respectively (27). One randomized control trial will be initiated to compare the efficacies of fosphenytoin (a prodrug of phenytoin), valproic acid, and levetiracetam in the setting of established SE (ESETT trial), and to determine optimal treatment parameters of these antiepileptic drugs (28).

For many physicians, phenytoin, a sodium channel blocker, is the first-line drug of choice for treating established SE (29). Probably, this is because of the long-term experience in its administration. During intravenous infusion of phenytoin (max. 50 mg/min), monitoring of the cardiovascular system is necessary in order to avoid hypotension and bradyarrhythmia (9). The main advantage of valproic acid is a relative lack of respiratory or hemodynamic complications. Because of its multiple therapeutic mechanisms, valproic acid produces antiepileptic effects against various types of SE, including generalized convulsive SE, partial nonconvulsive SE, status myoclonicus, and absence status. The adverse effects include dizziness, hypotension, thrombocytopenia, hyperammonemia, pancreatitis, and hepatotoxicity (9,30). Levetiracetam is a second-generation antiepileptic drug, and pharmacokinetic and bioequivalence data show convincingly that it is non-sedating and has almost no interactions with other drugs. Many open studies have demonstrated good efficacy and low toxicity of levetiracetam in SE settings (31). However, there has been
no randomized controlled study until now. Phenobarbital is also a recommended antiepileptic drug for SE treatment, but is used infrequently in Taiwan. A new antiepileptic drug, lacosamide has shown a 56% (76/136) success rate in controlling SE\(^{(32)}\). However, lacosamide is not available in Taiwan, and the efficacy in settings of SE require confirmation.

**Treatment during the third stage: refractory status epilepticus**

Refractory SE is defined as SE that continues despite treatment with benzodiazepines and one antiepileptic drug (1-2 hours after SE onset\(^{(3)}\)). Conventional therapy at this stage is induction of general anesthesia, and there has been no comparative trial to determine optimal treatment. The most frequently used anesthetic agents for refractory SE in Taiwan include midazolam (Dormicum) and propofol (Propofol, Fresofol, Recofol). Patients need to be treated in the intensive care unit and must be intubated and given respiratory support. A meta-analysis has found seizure control rates of 78% for midazolam (n = 585) and 68% for propofol (n = 143)\(^{(33)}\). Seizure breakthrough rates (recurring after initial control) were 3% with midazolam and 1% with propofol. Therapy failed due to side effects in less than 1% of patients treated with midazolam and 6% of patients treated with propofol.

Midazolam acts by enhancing the action of the GABAA receptor and shows strong antiepileptic action. Since tolerance of midazolam tends to develop, the risk of seizure relapse is relatively high\(^{(34)}\). Midazolam may cause respiratory depression and hypotension; therefore, respiratory support is mandatory and an inotropic agent is usually needed during high dose midazolam infusion. Antiepileptic effects of propofol are produced via modulation of the GABAA receptor. Propofol features very rapid onset and recovery, no serious drug-drug interactions, and a relatively low possibility of cardiocirculatory depression. However, prolonged use (> 2 days) of propofol at high dose increases the risk (7%) of propofol infusion syndrome, which is a potentially lethal toxic effect on mitochondrial and cellular metabolic function\(^{(34)}\). Clinical manifestations of propofol infusion syndrome include metabolic acidosis, bradycardia, renal failure, rhabdomyolysis, and hyperkalemia.

When general anesthesia is used, it is recommended that the dosage of the drug be titrated, not only to terminate the clinical and electrophysiological seizure activity, but to achieve an adequate level of burst-suppression by EEG\(^{(3,9)}\). The dosage of anesthetic drugs can then be tapered after 24 hours of adequate anesthesia. Since rapid tapering is associated with high rates of recurrent seizure, it is reasonable to wean patients from anesthetic drugs over periods of days. If seizures recur during tapering, infusion should be reinstated and an adequate dose of anesthesia maintained for intervals of 24 to 48 hours. Over time, in highly relapsed seizures, the duration of individual cycles may be increased.

**Treatment during the fourth stage: super-refractory status epilepticus**

Super-refractory SE is defined as SE that continues or recurs for at least 24 hours after the onset of anesthetic therapy, including cases in which SE recurs on the reduction or withdrawal of anesthesia\(^{(34)}\). It is estimated that approximately 15% of all SE patients will become super-refractory\(^{(34)}\). Current available literature regarding therapy for super-refractory SE consists of only case reports and case-series studies; there is a lack of controlled and randomized trials. In addition to administration of treatments used in established and refractory SE (described above), potentially effective pharmacological and non-pharmacological therapies for patients with super-refractory SE include ketamine, magnesium, inhalational anesthetics, immunotherapy, ketogenic diet, induced hypothermia, and neurosurgery\(^{(33)}\).

Ketamine is an NMDA receptor antagonist featuring no cardiac depressant properties and an absence of hypertensive side effects. A meta-analysis found a seizure response rate of 56.5%\(^{(35)}\). Previous studies have used bolus doses of ketamine ranging from 0.5 to 5 mg/kg, followed by infusion at doses of 0.12-10 mg/kg/h. Neurotoxicity and hypertension are potential side effects of prolonged ketamine usage. Magnesium sulfate is a current standard medication for treatment of eclamptic seizures\(^{(36)}\). The effect of magnesium sulfate is likely to involve multiple factors. For instance, an anticonvulsive effect may work through NMDA receptor antagonism, protection of the blood-brain barrier may limit cerebral edema formation, and vasodilatation may relieve vasoconstriction. Although the role on SE therapy is unclear, magnesium sulfate is
an attractive drug due to its high safety profile. For SE treatment, the recommended magnesium serum level is 3.5 mmol/L (34).

Inhalational anesthesia, using isoflurane or desflurane, is an alternative approach to the treatment of super-refractory SE. This tactic features a rapid onset of action and good efficacy. In one small retrospective study, isoflurane and desflurane suppressed refractory SE in seven out of seven cases (100%), and prolonged treatment was well-tolerated (37). The identification of autoimmune encephalitis as a mechanism for SE raises the possibility of immune therapy as a potential SE treatment (38). For example, anti-NMDA receptor encephalitis often responds to immunotherapy (eg. Corticosteroids, immunoglobulins) and, if applicable, tumor removal (eg. ovarian teratoma) (39). The ketogenic diet is a high fat, low carbohydrate, and adequate protein diet. Treatment with a ketogenic diet achieved resolution of super-refractory SE in 9 of 10 critically ill patients (40). Administration of a ketogenic diet may cause acidosis, hypoglycemia, constipation, and hypercholesterolemia.

In addition to an antiepileptic effect, hypothermia is neuroprotective and can reduce the intensity of brain edema caused by SE (41). One small study demonstrated that mild hypothermia (31-35°C), induced using an endovascular cooling system, could suppress seizure activity in 4 patients with super-refractory SE (42). However, coagulopathy, venous thromboembolism, infection, cardiac arrhythmia, and acid-base and electrolyte imbalance may occur as side effects of hypothermia. If there is a clearly definable focal epileptogenesis in patients with super-refractory SE, and if other therapies fail to control seizures, neurosurgical intervention may be a treatment of choice. Operations that may be carried out include focal cortical resection, lobar and multi-lobar resection, and corpus callosotomy. According to the results of a meta-analysis, 33 of 36 surgeries (91.7%) resulted in successful control of the SE (33). However, SE usually features widespread epileptogenic areas; thus, neurosurgery is considered generally only after weeks of SE, if other treatment has failed to control seizures (34).

Other potential management for super-refractory SE includes vagal nerve stimulation, electroconvulsive therapy, deep brain stimulation, transcranial magnetic stimulation, cerebrospinal fluid drainage, pyridoxine, lidocaine, verapamil, and classical music (5,34). These therapies have been described in a few reports and these reports cover just a small number of participating patients. These treatments require further investigation to confirm their utility in the setting of SE.

**Status Epilepticus in Pregnancy**

The therapeutic goal for pregnant women with SE is rapid seizure control to achieve better maternal and fetal outcome. Throughout the treatment, continuous fetal heart monitoring and obstetric and pediatric assistance are required to enhance the safety of both mother and child. The drug choice for SE is similar for pregnant and non-pregnant patients, but teratogenicity of medications should always be considered. Medications for SE and their classification in pregnancy are lorazepam [D], diazepam [D], midazolam [D], phenytoin [D], valproic acid [D], and levetiracetam [C]. Therefore, lorazepam and levetiracetam are usually the drugs of choice for pregnant women with early SE and established SE, respectively. For patients with seizures and eclampsia, magnesium sulfate is superior to antiepileptic drugs according to results of a meta-analysis (43). The dosage of the antiepileptic drugs may be adjusted, because their volume of distribution and clearance may increase during pregnancy.

**CONCLUSION**

SE is an emergent clinical situation with heterogeneous etiology. The principle of SE therapy centers on rapid seizure control and correction of underlying problems. Although treatment is given in stages, treatment is a continuum and urgent cessation of seizure activity is the goal in each stage. At the same time, the etiology of SE should be investigated extensively. Emergency physicians, neurologists, and specialists in intensive care should work together to provide optimal care. Additionally, current treatment consensus and guidelines for SE are usually based on expert opinions and case series studies. Future well-designed clinical trials are mandatory to establish the standard treatment, especially for established, refractory, and super-refractory SE.

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