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Treatment of Status Epilepticus

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Status epilepticus is a serious and potentially life-threatening medical emergency that requires prompt intervention. The traditional definition of status epilepticus is any seizure lasting longer than thirty minutes regardless of whether consciousness is impaired, or recurrent seizures without an intervening period of consciousness between seizures.[1] Clinically, the average seizure is less than two minutes; however, only 40% of seizures that last 10 to 29 minutes cease without treatment. Given that status epilepticus can be associated with significant morbidity and mortality, the definition has been expanded to include prolonged seizures lasting longer than five minutes in order to promote early and adequate intervention to reduce complications.

Current Status Epilepticus Treatment Guidelines

Over the past two decades, a number of guidelines have been released to provide physicians with a consistent, rational approach for the treatment of status epilepticus. In 2016, the American Epilepsy Society released the evidence-based guideline, "Treatment of Conclusive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society." The goal of the guideline was to analyze efficacy, tolerability, and safety data for anticonvulsant treatment for children and adults with convulsive status epilepticus.[1] A literature search was performed for relevant articles published between January 1940 and September 2014. A total of 38 randomized controlled trials were identified and contributed to the development of an evidence-based treatment algorithm. An algorithm was developed from these studies to provide a framework for the evaluation and management of a patient with status epilepticus using four phases: stabilization, initial therapy, second therapy, and third therapy.

Stabilization Phase: 0-5 minutes

The stabilization phase consists of interventions for emergency department, inpatient setting, or prehospital setting with trained paramedics. Management during the first five minutes of seizure activity includes stabilization of the patient (airway, breathing, circulation, and disability), monitoring vital signs, initiating electrocardiogram monitoring, and obtaining intravenous access for laboratory studies.

Initial Therapy Phase: 5 -20 minutes

The initial therapy phase begins when the duration of the seizure lasts at least five minutes. The recommended initial therapy choice is a benzodiazepine (Table 1).

Table 1: Therapeutic Options in Status Epilepticus

Phase of Treatment	Therapeutic Options
Initial Phase	• Benzodiazepines
Second Therapy Phase	• Fosphenytoin • Levetiracetam • Valproic acid • Phenobarbital
Third Therapy Phase	Repeat second-line therapy agents **OR** continuous infusion of: • Pentobarbital • Midazolam • Propofol

Benzodiazepines bind to a stereospecific benzodiazepine binding site (between then α and γ subunits) on postsynaptic $GABA_A$ neurons leading to an increase in frequency of channel opening and inhibition of neurotransmission. Intramuscular (IM) midazolam (0.2 mg/kg/dose, maximum single dose: 6 mg), intravenous (IV) lorazepam (0.1 mg/kg/dose, maximum single dose: 4 mg), or intravenous diazepam (0.1-0.3 mg/kg/dose, maximum single dose: 10 mg) are the preferred benzodiazepines. If none of these options are available, intravenous phenobarbital (15 mg/kg/dose, single dose), rectal diazepam (0.2-0.5 mg/kg/dose, maximum single dose: 20

mg) or intranasal or buccal midazolam can be considered. The most common adverse events associated with benzodiazepine use include sedation, hypotension, and respiratory depression.

Available Pediatric Literature

Chamberlain and colleagues evaluated the efficacy and safety of lorazepam compared to diazepam for the treatment of pediatric status epilepticus.[2] Two-hundred and seventy-three patients, aged 3 months to younger than 18 years were included in the trial. Patients received either IV diazepam 0.2 mg/kg or IV lorazepam 0.1 mg/kg, with half this dose repeated at 5 minutes if necessary. The primary outcome was cessation of status epilepticus by 10 minutes without recurrence within 30 minutes. There was no statistically significant difference between the two groups with 72.1% in the diazepam group and 72.9% in the lorazepam group having met the primary outcome. The authors concluded that there was no evidence to support the preferential use of lorazepam.

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) was a double-blind randomized trial comparing IM midazolam to IV lorazepam.[3] Eight hundred and ninety-three patients, including 120 children, were randomized to receive either IM midazolam dose via auto-injector or IV lorazepam administered prior to emergency department arrival. The primary efficacy endpoint, absence of seizures at the time of arrival to the emergency department, was achieved in 73% of subjects in the IM midazolam group compared with 63% in the IV lorazepam group ($P < 0.001$ for non-inferiority and superiority). IM midazolam was shown to have a shorter time to administration (1.2 versus 4.8 minutes); however, onset after administration favored IV administration (1.6 versus 3.3 minutes).

Arya and colleagues performed a non-inferiority, randomized, open-label study comparing the efficacy and safety of intranasal versus IV lorazepam in children aged 6 to 14 years presenting with acute seizures.[4] Patients were randomized to receive either IV or intranasal lorazepam (0.1 mg/kg, maximum 4 mg). For the primary outcome of clinical seizure remission within 10 minutes of drug administration, there was no statistically significant difference between the IV and intranasal groups at 80% versus 83.1%, respectively. The authors concluded that intranasal administration is an acceptable alternative to IV administration of lorazepam.

Moretti and colleagues conducted a retrospective review evaluating the differences in terms of immediate management and subsequent outcome when comparing the use of rectal diazepam versus buccal midazolam.[5] A total of 33 children were included in the subgroup analysis with 17 and 16 who received effective administration of rectal diazepam and buccal midazolam, respectively, for the treatment of a subsequent seizure. Seizure duration was significantly shorter (10.3 versus 48.4 minutes, $p = 0.004$) and risk of status epilepticus was decreased (1 versus 11, $p = 0.0008$) in those who received buccal midazolam. Admission rate was not statistically significantly different between the two subgroups (8 versus 2 patients, $p = 0.06$). Buccal midazolam may offer some advantages over rectal diazepam; however, further studies are necessary to confirm these results.

Second Therapy Phase: 20-40 minutes

The second therapy phase begins when a benzodiazepine fails to terminate seizures or approximately 20 minutes after the onset of the seizure. Reasonable options in therapy to consider at this point include IV forms of fosphenytoin, valproic acid, and levetiracetam. If these agents are unavailable, phenobarbital can be considered.

Fosphenytoin is a pro-drug of phenytoin which is converted to phenytoin by phosphatases in the liver and red blood cells. Fosphenytoin works by binding to voltage-gated sodium channels leading to stabilization of neuronal membranes and decreased seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex during generation of nerve impulses. Fosphenytoin is preferred over phenytoin due to differences in the formulation which allow for a faster rate of administration and reduced incidence of adverse events (e.g., phlebitis, hypotension). The dose of IV fosphenytoin is 20 mg Phenytoin Equivalents (PE) per kg (maximum single dose: 1500 mg PE).

Valproic acid has a similar mechanism of action to fosphenytoin, binding to voltage-gated sodium channels leading to a prolonged recovery phase. It also causes increased availability of GABA to brain neurons or may enhance the action of GABA and mimic its action at postsynaptic receptor site. The usual dose of IV valproic acid in the setting of status epilepticus is 40 mg/kg/dose (maximum single dose: 3000 mg). The most common adverse events associated with valproic acid administration include central nervous system (CNS) depression and hepatic dysfunction.

Levetiracetam binds selectively to the synaptic vesicular protein SV2A; however, the function of this protein is unknown. The presumed mechanism of action is through modifications in the production of GABA and glutamate. Most institutions currently use a levetiracetam dose ranging from 20 to 60 mg/kg for the initial management of status epilepticus, with a

maximum single dose of 3000 mg. There have been relatively few serious adverse events associated with the administration of levetiracetam.

Phenobarbital binds to $GABA_A$ receptors increasing the time the chloride channel is open leading to membrane hyperpolarization and inhibition of action potentials. The recommended dose for phenobarbital in this setting is 15 to 20 mg/kg, with a maximum single dose of 1000 mg. Rapid IV administration, greater than 30 mg/minute in children and 60 mg/minute in adults, should be avoided due to risk of severe respiratory depression, hypertension, or vasodilation with hypotension. The most common adverse event related to phenobarbital administration is CNS depression.

Available Pediatric Literature

Limited clinical trials have evaluated the use of second-line therapy agents for the treatment of status epilepticus. Agarwal and colleagues compared the efficacy of phenytoin and valproate in patients with benzodiazepine-refractory seizures.[6] Patients were randomized to receive IV phenytoin 20 mg/kg or IV valproate 20 mg/kg with both groups receiving initial therapy with a single dose of IV diazepam 0.2 mg/kg. Successful treatment was defined as cessation of all motor or electroencephalogram seizure activity within 20 minutes following the beginning of the drug infusion. A total of 100 patients were included in the study, matched for age and sex. Of those, 22 patients in the valproate group and 16 in the phenytoin group were less than 18 years of age. The overall efficacy was similar between valproic acid and phenytoin (88% vs 84%) in patients whose seizures did not respond initially to diazepam. There was not a statistically significant difference in the total number of adverse events between the two groups. The authors concluded valproate is as effective as phenytoin for the treatment of benzodiazepine-refractory seizures.

Third Therapy Phase: 40-60 minutes and Refractory Seizures

The third therapy phase begins when the duration of seizure reaches 40 minutes. There is no clear evidence or consensus to guide selection of anticonvulsant at this point during status epilepticus. In addition to repeating the second-line therapy options, continuous infusions of midazolam, pentobarbital, or propofol may be considered. A patient's condition is considered refractory when seizures continue despite initial treatment with a first- and second-line drug or the seizure duration has been greater than 1 hour, or there is a need for general anesthesia. Although not specifically mentioned in the AES guideline, ketamine has emerged as a potential option for refractory status epilepticus.

Similar to other benzodiazepines, midazolam works via the $GABA_A$ receptors. The typical dose used for a midazolam continuous infusion is a loading dose of 0.15 to 0.2 mg/kg followed by a rate of 0.06 to 0.12 mg/kg/hour titrated until seizure activity ceases. Pentobarbital works via $GABA_A$ receptors, similar to phenobarbital. When used for the treatment of refractory seizures, the dose of pentobarbital is a loading dose of 5 mg/kg followed by a maintenance infusion of 1 mg/kg/hour (up to 3 mg/kg/hour). The most common adverse events related to pentobarbital infusions are CNS depression and profound hypotension necessitating initiation of a vasopressor, such as norepinephrine. Propylene glycol, the vehicle for pentobarbital, can be associated with cardiotoxic effects leading to sinus tachycardia, myocardial depression, and cardiac arrest.

Although not specifically known, propofol is thought to work through stimulation of $GABA_A$ receptors and inhibition of NMDA receptors. The dose of propofol when used as a continuous infusion is a loading dose of 1 to 2 mg/kg followed by a rate of 20 mcg/kg/minute titrating to desired effect. The most common adverse events are CNS depression and hypotension.

Similarly, ketamine is a NMDA receptor antagonist that reduces glutamatergic activity. The dose of ketamine for continuous infusion is a starting rate of 10 mcg/kg/minute titrating to desired effect with a maximum infusion rate of 100 mcg/kg/minute. The most common adverse events are tachycardia, increased secretions, and emergence reaction.

Available Pediatric Literature

There are no randomized, controlled trials comparing agents for the third therapy phase or for the treatment of refractory seizures. Kim and colleagues evaluated the safety and efficacy of IV levetiracetam for the treatment of refractory status epilepticus in the pediatric population.[7] A total of 14 patients were included in the retrospective analysis. Treatment success was defined as the complete cessation of the seizure activity. The standard protocol for the treatment of status epilepticus used benzodiazepines as initial therapy followed by phenobarbital, phenytoin, and/or valproic acid. If the seizure activity continued, levetiracetam was considered. The dose for IV levetiracetam was 20 to 30 mg/kg. Seizure termination occurred in 6 (43%) of the 14 patients with no immediate adverse events. The authors concluded that levetiracetam should be considered a safe and effective treatment option.

Barberio and colleagues conducted a retrospective chart review to describe the dosing regimens and outcomes in children who received

continuous pentobarbital therapy for refractory status epilepticus.[8] Thirty patients were included in the analysis. All patients achieved some period of burst suppression after initiation of pentobarbital with 33% achieving sustained burst suppression without relapse. The most common adverse event documented was hypotension requiring intervention, with 50% requiring fluid boluses and 93% requiring vasoactive support.

Gaspard and colleagues conducted a multicenter retrospective analysis to examine patterns of use, as well as efficacy and safety of intravenous ketamine for the treatment of refractory status epilepticus.[9] A total of 60 episodes were included in the analysis, involving 46 adults and 12 children. Response was defined as "likely" if permanent control of status epilepticus occurred within 24 hours of initiation and if ketamine was the last drug added. "Possible" response was defined as permanent control of status epilepticus within 24 h of initiation when ketamine was not the last drug added. Ketamine was introduced after a median 9 days of status epilepticus. The dosing of ketamine included a median loading dose of 1.5 mg/kg (maximum 5 mg/kg) followed by a median continuous infusion of 2.75 mg/kg/hour (maximum 10 mg/kg/hour). Permanent control of status epilepticus was likely or possibly attributed to ketamine in 32% of episodes. Discontinuation due to possible adverse events occurred in five patients. The authors concluded that ketamine appeared to be safe and moderately effective for treatment of refractory status epilepticus; however, further prospective studies are necessary.

Currently, there is a multicenter, randomized, controlled, open-label study being conducted in Italy to assess the efficacy of ketamine compared with conventional anesthetics in the treatment of refractory status epilepticus in children.[10] The primary outcome is the resolution of status epilepticus up to 24 hours after withdrawal of therapy. The trial registration number is NCT02431663 and expected completion of the study was April 2016. As of publication of this article, no study results have been published.

Summary

Status epilepticus is a serious and potentially life-threatening medical emergency that requires prompt intervention. In 2016, the American Epilepsy Society released evidence-based guidelines and a treatment algorithm for status epilepticus in adult and pediatric patients. The treatment algorithm consisted of four phases laid out in a timeline format: stabilization, initial therapy, second therapy, and third therapy. Following stabilization, the initial therapy phase focuses on benzodiazepines as the treatment of choice. For the remaining phases of therapy and treatment of refractory seizures, there is a paucity of evidence to guide the optimal approach. Reasonable agents to consider following first-line agents include fosphenytoin, levetiracetam, valproic acid, or phenobarbital. For third-line treatment, continuous sedative infusions of pentobarbital, midazolam or propofol can be considered. Although not included in the guideline, ketamine has emerged as another potential option for the treatment of refractory status epilepticus. Further studies are necessary to evaluate the efficacy and safety of these agents and determine their place in therapy.

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