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REVIEW ARTICLE

Emergency Neurological Life Support: Status Epilepticus

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Abstract Patients with prolonged or rapidly recurring convulsions lasting more than 5 min are in status epilepticus (SE) and require immediate resuscitation. Although there are relatively few randomized clinical trials, available evidence and experience suggest that early and aggressive treatment of SE improves patient outcomes, for which reason it was chosen as an Emergency Neurologic Life Support protocol. The current approach to the emergency treatment of SE emphasizes rapid initiation of adequate doses of first line therapy, as well as accelerated second line anticonvulsant drugs and induced coma when these fail, coupled with admission to a unit capable of neurologic critical care and electroencephalography monitoring. This protocol not only will focus on the initial treatment of SE but also review subsequent steps in the protocol once the patient is hospitalized.

Keywords Seizures · Anticonvulsant · Pharmacological coma · EEG monitoring · Protocol

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Introduction

Each year in the United States, emergency departments (EDs) experience an average one million seizure-related visits based on International Classification of Diseases (ICD)-9 coding. These visits represent approximately 20 % of ED visits for neurologic problems and 1 % of all ED visits [1–3]. Approximately 200,000 US patients per year have prolonged or rapidly recurring convulsions lasting more than 5 min—the defining features of status epilepticus (SE).

The 30-day mortality of patients with generalized convulsive SE ranges from 19–27 % [4–8], while more recent randomized controlled trials suggest that this rate might be lower (hospital discharge mortality of 9.4 %) with more inclusive definitions of SE [9]. Prolonged seizures are associated with higher mortality and worse clinical outcomes [7, 8, 10–12]. Adverse effects of SE include both indirect systemic problems arising from the convulsive state (e.g., impaired ventilation, pulmonary aspiration, and metabolic aberrations) and direct neuronal cellular injury from excitotoxicity, causing both immediate neuronal loss and delayed programmed cell death.

Rapid control of seizures is fundamental to the emergency treatment of SE (Fig. 1) [13]. Earlier termination of SE reduces neuronal injury in experimental models of SE in laboratory animals, and it is associated with improved clinical outcomes in human observational studies. In experimental SE, benzodiazepines are more likely to terminate seizures when given closer to the seizure onset and they decrease in effectiveness as seizure duration increases, most likely related to changes in the neuronal gamma-aminobutyric acid (GABA) receptor subunit composition as a function of time [14]. Rapid seizure cessation may also prevent duration-dependent kindling and adverse cytokine-mediated effects in experimental models [15, 16].

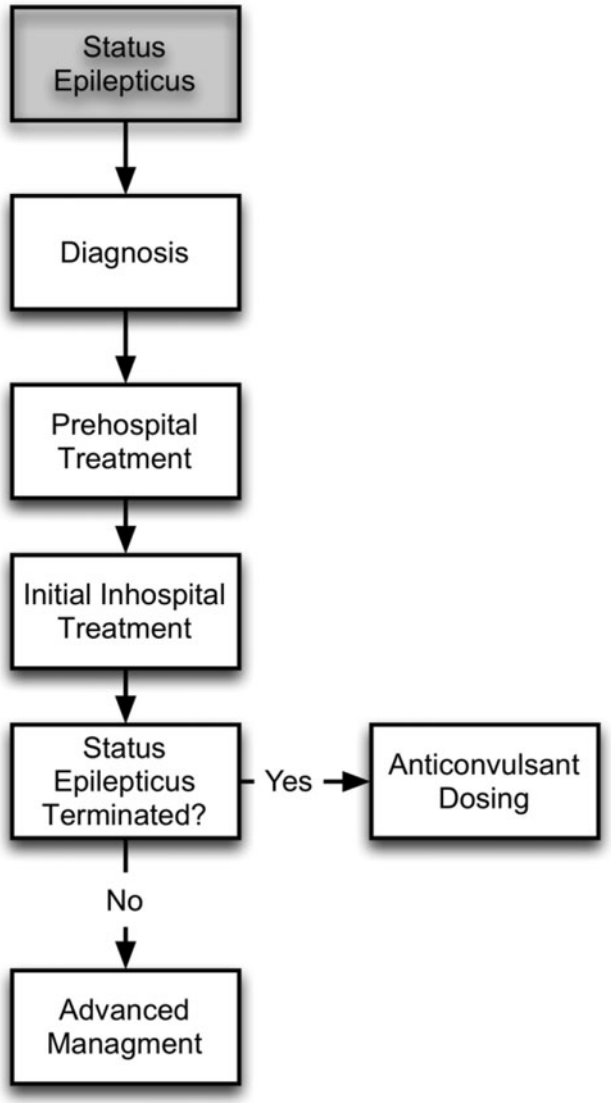

Fig. 1 ENLS status epilepticus protocol

The emergency neurologic life support (ENLS) suggested algorithm for the initial management of SE is shown in Fig. 1. Suggested items to complete within the first hour of evaluating a patient with SE are shown in Table 1.

Table 1 Status epilepticus checklist for the first hour

☐ Fingerstick glucose
☐ Obtain IV access
☐ Obtain IV access
☐ Pulse oximetry, BP monitor, supplemental O_2 and fluid as needed, cardiac monitor
☐ Labs: CBC, BMP, CA, Mg, AED levels
☐ Brain CT
☐ Continuous EEG (if available)

Diagnosis

The importance of more rapid treatment of prolonged convulsions is reflected in the current definitions of SE. Outdated definitions of SE required that convulsions persist or recur for greater than 30 min without a return to the pre-seizure neurologic baseline. The rationale for this definition has been challenged, and the more useful and clinically relevant duration of greater than 5 min of unrelenting seizure is more appropriate [13, 17, 18].

As in patients with any other critical illness, diagnostic evaluation of patients with SE is pursued concurrently with treatment and stabilization. However, it is important to ensure that diagnostic testing does not interfere with or delay control of seizures in the ED.

Approximately, two-thirds of patients evaluated in the ED for SE have a history of prior seizure. Approximately, half of these patients will be found to have poor adherence to anti-epileptic drugs (AEDs) or withdrawal from AEDs or other substances, and half will have idiopathic breakthrough seizures. A smaller portion has other diagnoses which lower seizure threshold.

Confirming this perspective is the demonstration that in the pre-hospital phase, intramuscular (IM) administration of midazolam is more successful in stopping seizures than the intravenous (IV) route; this was simply the result of delay in starting the IV access [19]. The pre-hospital treatment of SE is discussed further below.

In the ED, a detailed neurologic evaluation including descriptions of ongoing convulsions, automatisms, focal deficits, pupillary changes, and level of arousal are also useful. Hypoglycemia, hypoxia, and hemodynamic instability are addressed during the patient's initial evaluation and stabilization. Oxygen saturation and cardiac monitoring are typically initiated during this phase.

Blood and serum laboratory evaluation typically includes a complete blood count, basic metabolic panel, and calcium and magnesium determinations. Selected laboratory studies that may be useful in some patients include liver enzymes, cardiac injury markers, toxicology screen, and arterial blood gas determinations. Certain AED levels that are typically obtainable on an acute basis such as for phenytoin, valproate, and carbamazepine can also be useful.

The need for neuroimaging should be determined for each individual, but is generally warranted in patients who do not return to a normal level of consciousness, have new focal neurologic findings, or have new onset SE without an otherwise obvious identifiable etiology. Non-contrast computed tomography (CT) of the brain will identify most immediate threats and is the most typical initial imaging study obtained in the ED. Chest X-rays and

electrocardiograms should also be obtained selectively. A lumbar puncture should be performed in febrile patients and in whom there is suspicion of central nervous system infection or subarachnoid hemorrhage, preferably after obtaining the CT scan.

As noted in the "Initial Inhospital Treatment" section below, electroencephalography (EEG) is necessary to identify non-convulsive SE [20] in patients who do not return to a normal level of consciousness. EEG may also guide therapy in these patients and provide other diagnostic information.

Non-epileptic spells-simulating SE ("pseudostatus") occur mainly in patients with genuine seizure disorders and may be difficult to differentiate from SE. These may represent volitional behavioral problems or non-volitional somatization disorders. Indicators suggestive of non-epileptic spells include preserved consciousness or purposeful movements, poorly coordinated thrashing, back arching, eyes held shut, head rolling, and pelvic thrusting. Benzodiazepines are usually effective therapy for non-epileptic spells.

Pre-Hospital Treatment

The initial minutes after seizure onset likely offer the best opportunity for pharmacological termination of SE seizures. The pre-hospital treatment of status epilepticus (PHTSE) trial randomized SE patients to paramedic treatment with IV diazepam, lorazepam, or placebo. PHTSE demonstrated that emergency medical services (EMS) delivery of benzodiazepines resulted in a higher rate of cessation of seizures before arrival in the ED than compared to placebo. Early termination of seizures was associated with better clinical outcomes in PHTSE, and there was also a trend toward better clinical outcomes with EMS benzodiazepines compared to placebo [9]. More recently, IM administration of midazolam was compared to IV administration of lorazepam in a randomized, pre-hospital, prospective trial [21]. Midazolam administered IM was at least as good as IV-administered lorazepam in terminating SE.

Airway adjuncts and/or supplemental oxygen may be needed. An IV or intraosseous (IO) line should be established with fluid resuscitation if needed for profound hypotension. Hypoglycemia should also be rapidly excluded as the cause of seizure or immediately treated. Although 4 mg of IV lorazepam was more effective in the PHTSE trial [9], it is usually impractical for EMS use because of a short shelf life out of refrigeration. The IM route of midazolam may eclipse the previously recommended 10 mg of IV diazepam.

IO lines provide rapid access to the vascular space when IV access is difficult to achieve. Other alternatives include midazolam given intravenously, intramuscularly, or across the nasal or buccal membranes, or diazepam given rectally.

The most important modifiable element of therapy determining successful termination of seizures is time elapsed before initiating benzodiazepines. When treatment with IV agents was begun within 30 min of seizure onset, the initial AED was successful in terminating SE patients' seizures in 80 % of cases, yet this rate decreased to 40 % if treatment was started 2 h after seizure onset [22]. This was amply documented in the recent trial of field-administered midazolam in which IM administration was superior to IV, but almost entirely on the basis of the extra time expended in inserting an IV catheter.

Paramedics should be prepared to treat respiratory depression in patients with SE. Benzodiazepine doses recommended for SE are relatively higher than those used for many other indications in the ED and may contribute to respiratory depression. However, continued seizures are more likely to cause respiratory problems than are side effects of the benzodiazepines [9].

Initial Inhospital Treatment

Initial treatment of SE in the ED continues or completes the elements that should have been initiated by EMS. Airway, breathing, and circulation should be re-evaluated and supportive care continued. If IV access has not already been obtained, it should be achieved now. If hypoglycemia has not been excluded either clinically or by measuring blood glucose, this should occur upon ED arrival.

In patients who continue to convulse or do not regain consciousness and have electrographic seizures, additional benzodiazepines may be administered. The Veterans administration (VA) cooperative trial identified 4 mg of IV lorazepam as the preferred initial AED, but IV diazepam was also efficacious in terminating seizures [4]. If adequate doses of benzodiazepines had already been administered by EMS, then in the ED, lorazepam can be immediately followed by a second line AED, as noted in the "Secondary Inhospital Treatment" section below. If the patient did not get benzodiazepines before ED arrival and is still seizing, the first dose of lorazepam can be followed by a repeat dose 5–10 min after the first, which in turn is immediately followed by a second line AED.

First line benzodiazepines are frequently under-dosed because the labeled 4 mg initial dosing of lorazepam for SE is greater than the initial dose used for most other indications in the ED. Initial treatment failure is often a result of using inadequate initial doses of IV benzodiazepines and then waiting too long to repeat benzodiazepine doses and advance to second line agents or general anesthesia and induced coma.

Secondary Inhospital Treatment

The best choice of second line AEDs for patients with refractory SE is uncertain since the second line AED has not been adequately compared in randomized controlled trials. Options include phenytoin/fosphenytoin, phenobarbital, valproic acid, continuous infusions of midazolam, and levetiracetam [4].

Among second line AEDs, the preferred medications in most units have been IV 20 mg/kg of phenytoin or fosphenytoin, the latter given up to 150 mg/min [23–25]. Phenytoin and fospheyntoin are FDA labeled for the treatment of SE. They act at the sodium channel rather than the GABA receptor, and thus represent a rational choice for treating patients whose seizures do not seem to be terminating with the diazepine GABA agonists. The phenytoins can cause hypotension when given at rapid infusion rates, especially in the elderly.

Some physicians who treat SE prefer alternative approaches. A small randomized study suggested that IV valproic acid may have similar efficacy in SE when compared to phenytoin [23]. Valproic acid 20–40 mg/kg of IV is given over 10 min with an additional 20 mg/kg subsequently over 5 min if the patient is still seizing.

IV phenobarbital is also FDA labeled for the treatment of SE and remains a reasonable option, but it is now less commonly chosen in adults unless other agents are contraindicated or unavailable. Phenobarbital 20 mg/kg of IV is given at up to 50–100 mg/min with an additional 5–10 mg/kg given if needed. Phenobarbital also acts at the GABA receptor and may be a less rational choice in those who have not responded to benzodiazepines although there are few data to address this concern. Levetiracetam is often used off-label as a second line agent to treat SE and can be given as 1–3 g IV over 5 min or 2–5 mg/kg/min [26]. Some experts recommend using continuous infusions of midazolam at this stage starting with a dose of 0.2 mg/kg bolus and then maintenance doses of 0.05–2 mg/kg/hr [13].

Second line AEDs are also typically used in the ED, in the same doses, to suppress recurrent seizures in patients after SE has ended. If a patient stops convulsing but does not wake up or does not return to the pre-convulsive state, an EEG should be obtained to detect continuing non-convulsive SE.

Anticonvulsant Dosing

If seizures have stopped and the patient has awakened, loading doses of anti-epileptic medications with longer half-lives should be undertaken. Fosphenytoin 20 mg/kg IV at a rate not exceeding 150 mg/min, or valproate 40 mg/kg IV over 10 min and an additional 20 mg/kg over 5 min if still seizing can be used.

EEG monitoring is useful if the patient has not awakened. The reasons for persistent seizures should be established by determining AED levels, imaging if needed, urine toxicology, and other appropriate testing. The most important cause of persistent stupor after convulsive SE is ongoing electrical seizures that can only be detected by EEG monitoring.

Advanced Management

SE will typically be terminated by the primary and secondary drugs described above. If the patient remains in the ED and seizures have not stopped, SE is considered refractory. General anesthesia and induced coma are recommended in these circumstances.

It is not necessary, and is usually not advisable, to delay advanced therapy with repeated trials of alternative second tier AEDs. Some period, generally shorter than an hour and perhaps even 30 min, is adequate to determine if the above-described conventional approach will be successful.

Endotracheal intubation is necessary to safe induction of coma and should be quickly performed when patients remain convulsing. Particularly in patients that received long-acting paralytics for intubation, there should be a low threshold to obtain EEG monitoring as convulsions may not be seen.

The agents most commonly used to induce a general anesthesic state of coma are continuous infusions of midazolam or propofol [27–30]. IV midazolam infusions usually are preceded by a loading dose of 0.2 mg/kg at 2 mg/min, with repeated boluses of 0.2–0.4 mg/kg every 5 min until the seizures stop, up to a maximum loading dose of 2 mg/kg and then maintaining the infusion at 0.05–2 mg/kg/hr. IV propofol infusions usually include a loading dose of 1–2 mg/kg IV over 3–5 min, with repeated boluses of the same amount every 3–5 min until the seizures stop, up to maximum total loading dose of 10 mg/kg, then maintaining 30–100 mcg/kg/min.

Pentobarbital (or thiopental in some countries) is an alternative agent for the treatment of refractory SE that is less commonly used in the US. It has adverse side effects, including hypotension, and has a prolonged effective half-life, but it is still a reasonable option when other agents have failed or are contraindicated. If needed, pentobarbital will most typically be initiated in the intensive care unit (ICU), but ED use is also possible.

IV pentobarbital infusions usually include a loading dose of 5–15 mg/kg IV at up to 50 mg/min with repeated 5–10 mg/kg boluses until seizures stop and then maintenance of 0.5–10 mg/kg/hr. Anesthetics may have a number of side effects and will frequently be associated with dose-dependent hypotension requiring IV pressors [27]. Hypotension may be more frequently seen with pentobarbital, while prolonged use of propofol is associated with propofol infusion syndrome [30].

Table 2 Status epilepticus communication regarding assessment and referral

☐ Clinical presentation
☐ Duration of status
☐ Relevant PMH/PSH
☐ Prior medications, medications given so far
☐ Neurologic examination
☐ Brain imaging/LP results (if available)

Valproate may be the preferred choice particularly for patients with refractory status epilepticus who cannot or should not be intubated [31–33]. Other potentially useful but unproven therapeutic options in refractory SE include, but are not limited to, ketamine, lacosamide, and induced mild hypothermia.

In the ED, any of these IV agents will usually be titrated to the cessation of clinical manifestations of convulsive or subtle SE. When continuous EEG monitoring is available, the administration rate can be titrated to the desired electroencephalographic findings, ranging from suppression of frank seizures to burst suppression or a completely suppressed background. Few data are available to identify the optimal treatment level of suppression.

It is appropriate to continue second line AEDs to attain therapeutic serum levels during the treatment of refractory SE. Expeditious admission to an intensive care setting, preferably with continuous EEG monitoring, is advisable for patients treated for refractory SE.

Communication

When communicating to an accepting or referring physician about this patient, consider including the key elements listed in Table 2.

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