Practice parameters in management of status epileptics

Usha Kant Misra, Jayantee Kalita, Sanjeev Kumar Bhoi

Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Abstract

Status epilepticus (SE) is an emergency neurological problem, more common in the developing countries due to high incidence of infection, stroke and head injury. The protocol for management of SE is intravenous benzodiazepine, followed by phenytoin, valproate (VPA) and phenobarbitone and if uncontrolled general anesthesia (GA). World Federation of Neurology recommends special guidelines for resource poor countries. Use of GA results in hypotension and respiratory depression needing intensive care management. There is a paucity of intensive care facilities hence the recommended antiepileptic drugs (AEDs) which have inherent toxicity of hypotension and respiratory failure cannot be given safely. Under these situations AEDs such as VPA, levetiracetam and lacosamide may be evaluated in SE because of cardiovascular and respiratory safety profile. In this review, the limitations of existing guidelines in the developing countries have been discussed and a way forward has been suggested.

Key words

Anesthetic agent, antiepileptic drug, refractory status, status epilepticus, respiratory failure, hypotension

For correspondence:

Dr. Usha Kant Misra, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareily Road, Lucknow - 226 014, Uttar Pradesh, India. E-mail: ukmisra@sgpgi.ac.in

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Introduction

Status epilepticus (SE) is a common and important neurological emergency faced not only by neurologist but also by pediatricians, general physician and family physician. The incidence of SE is variable depending on the population studied. In the developing countries, SE is likely to pose a more common and a more serious problem, because of a higher frequency of central nervous system (CNS) and systemic infections, infestations, stroke, malnutrition, injury, treatment gap and poor compliance to antiepileptic drug (AED).[1-3] Though there are no epidemiological data, but SE is estimated to be more common in India. Extrapolating the incidence of SE in USA which is 18.3/100,000 population, about 124,600 cases of SE annually may occur in India.[4] The variability in definition, investigations and treatment protocols and outcome of patients necessitate careful analysis and defining the special management issues which are important in a specific geographic area. In this review, we discuss the case definition, etiological and pathophysiological issue of SE in India and limitations of management guidelines and suggest a way forward.

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Definition of SE

Contemporary SE protocols adapt a staged approach. SE is categorized into four stages [Table 1].

Stage I

Early SE refers to first 30 min of SE and is treated by benzodiazepines. If seizures persist in a patient more than 30 min, SE is categorized into stage II.

Stage II

Established SE is defined if SE persists for 30 min to 2 h and is treated with intravenous (IV) phenytoin (PHT), phenobarbitone (PB) or sodium valproate (VPA). If seizure persists longer than 2 h the patient is categorized into stage III.

Stage III

Stage III SE is refractory SE refers to SE lasting for more than 2 h. Refractory SE is treated by general anesthesia (GA) in a dose that results in electroencephalography (EEG) burst suppression. At this level of anesthesia, the seizures are generally controlled.

Stage IV

Supra refractory SE is defined if SE persists longer than 24 h in spite of GA and requires inhalational anesthetics.

There are many reasons for refractoriness of SE. SE following CNS infection, trauma and stroke is more severe than due to drug default or metabolic abnormalities; however, refractory and supra refractory SE can also occur in previously healthy persons without any obvious precipitating cause.[1] In the developing countries, CNS

Table 1: Stage of status epilepticus (SE) and the recommended treatment option

Time	Stage	Treatment
30 min	Stage I-early SE	IV benzodiazepines-lorazepam, midazolam, diazepam
30-120 min	Stage II-established SE	IV phenobarbitone, phenytoin or valproate
>120 min	Stage III-refractory SE	IV general anesthesia, propofol, midazolam, phenobarbitone
>24 h	Stage IV-supra refractory SE	Inhalation anesthesia

SE = Status epilepticus

infection, arterial and venous stroke and trauma are more common.[2,5] Moreover the delay in starting treatment may also contribute to refractoriness of SE. In our study on 117 patients, the median duration of SE before coming to the hospital was 19.6 h (0.25-72)[6] highlighting the delay in starting therapy in the developing countries. Associated hypoxia, metabolic alterations and toxic drugs may aggravate the SE and render it refractory.

The receptors on the surface of neurons are highly dynamic-externalization and internalization occurs along the axonal membrane. This receptor transferring increases during SE. In later stage of SE, there is a reduction in the number of functional gamma-aminobutyric acid (GABA) receptors in the cells affected in seizure discharge.[7] Since GABA is the principal inhibitory neurotransmitter, a reduction in GABA receptors may be one of the mechanisms for refractoriness especially if the primary GABAergic drugs (benzodiazepine, PB) are used. Moreover, reduction of GABA receptor triggers activation of glutaminergic receptors. Other contributing factors for refractoriness may be mitochondrial insufficiency. Mitochondrial failure may contribute to failure of seizure termination and cellular damage, apoptosis and necrosis.[8] Ongoing inflammatory response and damage to the blood brain barrier may also result in the perpetuation of seizures and refractoriness of SE especially in SE due to inflammation.[9] This may justify the use of steroids in some patients with SE.

Cerebral damage by SE

SE results in neuronal degeneration, apoptosis and cell death which is associated with gliosis and neuronal re-organization. Excitatory neurotoxicity is also important in SE and is triggered by glutamate receptor over activity. Glutaminergic over activity is more important than hypoxia and hypoglycemia.[10] This cascade is initiated within a few hours of seizure onset. This is the basis of recommendation of anesthesia if seizure persists for 1-2 h. The initiation of this cascade comprising of mitochondrial dysfunction, oxidative stress, release of neurotrophins, neurohormones, inflammatory reactivation, dendritic remodeling, neuromodulation, immunosuppression and activation of several molecular signaling pathways that moderate apoptosis[11] which occur at variable interval ranging from minutes to days to weeks.

To prevent the above mentioned changes of excitotoxicity, it is recommended that all the EEG activity should be suppressed using an anesthetic agent to achieve burst suppression; the other strategies are hypothermia, barbiturates, steroids and ketamine on the theoretical basis, but their role in clinical practice needs to be evaluated.

Treatment of SE

Establishing the cause of SE

The underlying cause of SE determines its outcome to a great extent.[1] When possible the etiology of SE should be treated promptly. The etiology of SE depends on the geographical region; in the Veterans Administration co-operative study, the etiology of SE was remote neurologic cause in 69.5% and acute neurologic cause in 27.5%.[12] In a study from India, on 117 patients with SE, the most common etiology was CNS infection in 63 (53.8%), stroke in 11 (6.5%), metabolic factors in 12 (10.2%) and miscellaneous disorders in the remaining.[2] High prevalence of infection in SE has also been reported from Africa.[3] High frequency of CNS infection and stroke are common in the developing countries, but all of these do not have specific treatment. However in a small percentage of treatable disorders such as herpes simplex encephalitis, cerebral venous sinus thrombosis and pyogenic infection, treatment of primary disorder may improve the outcome of SE.

Investigations

In SE, a large number of investigations are recommended such as blood counts, blood sugar, blood culture, serum electrolyte, serum chemistry, AED level, cerebrospinal fluid (CSF) examination, coagulation parameters, imaging and EEG. All the investigations are not necessary in every patient.

American academy of neurology practice parameters for diagnostic evaluation

In a systematic review, the role of investigation in changing the outcome of SE was evaluated for the quality of evidence and the diagnostic yield of different investigations.[13] The investigation should be done in the clinical context. If infection is suspected, blood culture and CSF examination may be appropriate. AED levels should be ordered if the patient was on drug prophylaxis and there is suspicion of non-compliance or toxicity as a cause of SE. Serum tests for toxins are recommended if no cause of SE is apparent. Screen for inborn error of metabolic or genetic abnormalities would be cost-effective if there is a family history.

EEG is especially useful for the diagnosis of non-convulsive SE or in focal abnormality. Imaging is especially useful in the evaluation of first seizure/SE or if the clinical setting suggests CNS infections or a mass lesion.[13]

Refractory SE is usually due to severe brain insult such as infection, trauma and stroke and can be established by history, examination and investigation. However, there are a range of rare causes of SE which could be due to immunogenic, mitochondrial, uncommon infections, drugs, toxins or rare genetic disorder. There is a group of idiopathic disorders which result in SE or there may be de novo SE. Every effort is justified in establishing the cause of SE and treating the underlying cause to prevent refractoriness of SE.

Intensive care management

Ideally all patients with SE should be managed in intensive care unit (ICU) and especially those who have not responded to 2-3 AEDs and/or have persisted SE for 2 h (refractory SE). The management of refractory SE is by anesthetic drugs such as midazolam (MDL), propofol or PB. The drugs used for management of SE and especially anesthetic drug cause hypotension and cardiorespiratory depression which are sometimes severe and is the limiting factor. Artificial ventilation and vasopressor drugs therefore are essential.

Invasive BP monitoring

Intra-arterial BP monitoring and pulmonary artery catheterization and invasive EEG recording have been proposed recently. Continuous EEG monitoring is necessary for titrating the dose of anesthetic to burst suppression or monitoring the epileptiform activity especially in subtle or non-convulsive SE.

There have been questions to what extent the physiological information helps in improving the outcome, e.g., pulmonary artery pressure or intra-arterial BP monitoring, though provides continuous objective documentation of BP and help in titrating the dose of vasopressor drugs but has associated risks due to frequent withdrawing of blood for investigations resulting in anemia and need for blood transfusion, risk of vascular injury and thrombosis and high frequency of blood borne bacterial and fungal infections. In a systematic review, the odds ratio for bloodstream infection by intra-arterial catheter was 1.7 (95% confidence interval [CI] 1.2-2.3), venous catheter 0.5 (95% CI 0.2-0.7) and central venous catheter 2.7 (95% CI 2.6-2.9)[14] and there has been appeal for a moratorium on pulmonary artery catheterization.[15]

In the developing countries, there is a paucity of ICUs; these are mostly available in big cities in teaching and private hospitals only. The ICU facilities are either unaffordable or unavailable. The recommended practice parameters therefore are not applicable to the majority of patients in the developing countries.

Managing SE in Resource Poor Countries

The patients with SE should ideally be managed in ICU with facilities for artificial ventilation. The mechanical ventilators however are scarce in the resource poor countries outside large teaching hospitals. In India, the estimated number of ICU was 7000.[16] Our conservative estimate of ICU beds in India is 8700.[17] During monsoon period the need for ICU beds increases many fold due to annual meningoencephalitis outbreaks. Moreover, the high cost of ICU in private hospitals also renders them unaffordable to poor patients.

WFN guidelines for management of SE in resource poor countries

The neurologists in the developing countries have to work with primary physicians to develop appropriate protocols for management of SE.

Initial evaluation and management: After ensuring airway, ventilation and circulation a quick physical examination including had injury, pregnancy and comorbidities should be carried out. If a patient is already receiving AED that should be restarted through nasogastric tube unless contraindicated because of frequent seizures. In pregnant females, eclampsia should be considered and relevant evaluation (BP, pedal edema, albuminuria and fundus examination) should be done. The patient with seizures due to eclampsia should be treated with magnesium sulfate 2 g IV and continuous infusion of 2 g/h in 5% dextrose. Since magnesium sulfate is a muscle relaxant it can mask convulsive SE if EEG monitoring is not available. Tendon reflexes can be used to monitor magnesium toxicity. The rate of infusion should be decreased if tendon reflex becomes unelicitable. A maximum dose of magnesium sulfate is 40 g/24 h. Rapid delivery of the fetus should be considered.

In patients with SE, IV line is maintained with normal saline and rapidly acting AED (diazepam, lorazepam (LOR) or MDL) may be administered. Two co-administered agents are recommended — phosphenytoin and MDL may be ideal; LOR requires refrigeration though ideal but may not be widely available. Through the IV line 1 ml/kg 25% glucose with 100 mg thiamine is administered. Blood is collected after the IV line for cell counts, malarial parasite and serum chemistry. If the seizures continue after 5-10 min of short acting anti-seizure treatment such as LOR, MDL, diazepam or paraldehyde another dose of the same group may be repeated.

The respiratory rate is counted for full 1 min. If the respiratory rate is 8 bpm (10 bpm in children) a third dose of short acting anti-seizure drug is administered and is prepared to administer a long acting AED. If the respiratory rate is below 8 bpm (10 bpm in children) it is recommended to directly administer long-acting AED (PHT, fosphenytoin, PB). If the respiratory rate is severely depressed (<4 bpm), delay the administration of long-acting AED for 30 min and provide supplementary oxygen and artificial manual breathing unit ventilation. If ventilator is available and SE is refractory, GA is administered.[18]

A detailed history and examination is done to investigate the possible cause of SE such as malaria, meningoencephalitis, alcohol withdrawal or AED withdrawal. Antibiotics such as quinolones, third-generation cephalosporins, cefepime and carbapenem can result in seizure and SE especially in patients with impaired renal or hepatic functions and were responsible for SE in 10% of our patients.[19]

EEG monitoring

Ideally the patients with SE undergo continuous EEG monitoring. We recommend EEG if the patient's seizures have been controlled, but the consciousness does not become normal. It answers the question of sedation due to AED, ongoing subtle or non-convulsive SE and predicts the seizure recurrence within 24 h.[20]

For infants and children rectal diazepam (0.5 mg/kg in 13-30 s) is preferred if IV is not available or in pre hospital setting. This dose may be repeated within 30 min. If IV line is available diazepam is given in a dose of 0.5 mg/30 s to a maximum of 05 mg/kg total dose.

Tight rope walk

Management of SE in resource poor setting is a tightrope walk; suboptimal treatment results in brain damage due to SE whereas administration of AED often results in hypotension and respiratory depression necessitating artificial ventilation which is not easily available.

Indication for artificial ventilation is restricted in infants and children. It is recommended that artificial ventilation in children should be for respiratory failure because of underlying brain damage and not for administering respiratory suppressing AEDs and general anesthetic.[18]

Search for Safer AED

VPA

Valproic acid is a short chain fatty acid with anticonvulsant properties. It acts through activated sodium channel, neuronal calcium channels or through GABA metabolism. The safety and tolerability of VPA have been reported and upto 6 mg/kg/min has been administered to a total loading dose of 45 mg/kg without adverse reaction.[21,22] The chief advantage is safety and ease of administration and its efficacy range between 58% and 83% respectively.[23,24] In a study, 68 patients with convulsive SE were randomized to VPA and PHT. Seizures were aborted in 66% in VPA and 42% in PHT group. As a second choice also VPA was more effective (79% vs. 25%) than PHT[25] and was considered non-inferior to PHT in another study.[26] In another study VPA was effective in 65% (15/23) patients as first line therapy.[27]

Levetiracetam (LEV)

IV formulation of LEV was recommended earlier for those patients in whom oral therapy was not possible and up to 1500 mg IV was recommended to be safer if given in 15 min. Later studies reported safety of up to 2500 mg in 5 min and 4000 mg in 15 min in normal volunteer.[28] Safety and efficacy of LEV was reported in 17/18 episodes in 16 patients who were refractory to benzodiazepine and intubation was avoided.[29] In a randomized controlled trial on 79 patients with SE, LEV 20 mg/kg over 15 min was as effective as LOR 0.1 mg/kg in 2-4 min (76.3% vs. 75.6%) and 24 h seizure freedom was also comparable (79.3% vs. 67.7%). However, LOR was associated with significantly higher need for artificial ventilation and insignificantly higher hypotension. The authors feel that LEV was an alternative to LOR and may be preferred to LOR in patients with respiratory compromise and hypotension or in non ICU setting.[6]

Lacosamide

Lacosamide is a N_2-acetyl-N-benzyl-D-homoserinamide, a functional aminoacid and its mechanism of action is selective enhancement of slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. The IV formulation of lacosamide is now available and its efficacy has been evaluated in refractory SE in some studies.[30,31] More studies with the well-defined end points are needed. The dose and side-effects of various AEDs used in the management of SE are summarized in the Table 2.

Comparative study, systematic review and meta-analysis revealed comparable efficacy of LEV, PHT and VPA, and VPA has been reported to be safer than PB.[32-34] There are limited studies evaluating these drugs as first-line AED in SE. More studies are needed to evaluate the efficacy and safety of these drugs compared with benzodiazepines which may have wider implication especially in resource poor countries. Recently the adverse events of intravenous antiepileptic drugs (IV AED) in SE have been highlighted in a report from an academic medical center in Switzerland. In a retrospective review of ICU cases during 2005-2011, out of 171 patients 37% were treated with IVAEDs and death occurred in 18%. The patients with IVAED had more frequent intubation (90% vs 25%), severe hypotension requiring vasopressor (6% vs 1.9%), more infection (43% vs 11%) and 2.9 fold relative risk of death. The authors suggested the need of a randomized controlled trial (Sutter et al 2013)

Table 2: Antiepileptic drugs used in status epilepticus (SE)

Drugs	Dose	Side effects
Short acting		
Lorazepam	0.1 mg/kg @ 2 mg/min (adult) rate	Respiratory depression, hypotension, decreased level of consciousness
Midazolam	0.2 mg/kg at 0.2-5 mg/kg	Hypotension, respiratory depression, decreased level of consciousness
Diazepam	0.2 mg/kg at 5 mg/min	Sedation, respiratory depression
Propofol	2 mg/kg at 2-10 mg/kg/h (up to 200 mg/kg/min)	Sedation, hypotension, respiratory depression Infusion syndrome
Ketamine	1.5 mg/kg IV every 5 min maximum dose 4.5 mg/kg	Hypertension, possible raise in intracranial pressure
Paraldehyde	0.8 ml/kg deep IM	Muscle necrosis
Long acting		
Phenytoin	20 mg/kg IV, maximum 50 mg/min	Hypotension, QT prolongation, purple glove syndrome
Phosphenytoin	20 mg/kg at 150 mg/min	Hypotension, cardiac arrhythmia
Phenobarbitone	15-20 mg/kg at 100 mg/min	Hypotension, respiratory depression
Levetiracetam	Up to 20 mg/kg (usually 2 g) over 5-15 min	Mild sedation
Valproate	25-45 mg/kg up to 6 mg/kg/min	Severe encephalopathy if a patient has hyperammonemia or mitochondrial disorder
Lacosamide	400 mg IV over 5 min	No major adverse reaction, but may prolong PR interval

SE = Status epilepticus

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