Review Article

Status Epilepticus and its Management: A Review Article

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Abstract

Status epilepticus (SE) is a common neurological emergency affecting 65 million people worldwide with considerable associated health-care costs, morbidity, and mortality. There is a need for redefinition of status epilepticus to set up better management guidelines to avoid neuronal injury and pharmaco-resistance associated with prolonged seizures. Despite the availability of traditional treatment algorithms there is need for further research to establish universal treatment strategies based on sound data.

Key Word: seizures, status epilepticus, management, anti-epileptic drugs.

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Received Date: 22/11/2015 Revised Date: 06/12/2015 Accepted Date: 12/01/2016

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 22 January 2016

INTRODUCTION

SE has an annual incidence of 28-61 per 100,000 [1,9-13] and an estimated mortality of 20 %.[6,7] It is most prevalent in the population with structural brain damage, occurring as first or second unprovoked seizure 65% of the time, early in the course of epilepsy. It confers 3·3-times higher risk of a subsequent unprovoked seizure after symptomatic SE.[2] There is a need for more practical definition to identify and deliver emergent and targeted treatment as prolonged seizure activity has profound neuropsychological consequences like chronic encephalopathy with marked global and hippocampal atrophy.[3] Research findings in the last decade have been translated into new conceptual definition, revised diagnostic criteria, classification and design of treatment trials. Status epilepticus (SE) treatment strategies vary substantially due to lack of

- clear definition leading to a high degree of variability in the current literature
- data to support one treatment over another

In this Review, we discuss the current knowledge about status epilepticus in adults, focus on definitions, pathophysiology, epidemiology, outcomes and treatment of generalised convulsive status epilepticus (GCSE), and emphasise the importance of early termination of status epilepticus.

METHODS

A PubMed/Medline, Cochrane literature search was performed for relevant articles published from 1980 to 2015, using the following search terms: status epilepticus, recent trends in treatment, anticonvulsive therapies. Clinical trials, meta-analyses, review articles, and practice guidelines were all eligible for inclusion.

Status Epilepticus

Status epilepticus is broadly defined as a prolonged seizure or multiple continuous clinical and/or electrographic seizure activity for 5min or more, with incomplete return to baseline.

Definition of status epilepticus by International League Against Epilepsy (ILAE) in 1981:

A seizure that "persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur".[4]

The absence of a definitive timeframe of seizure duration made it difficult to accurately define and treat SE. SE was redefined as a seizure lasting 30 min on the basis of the

How to site this article: Vijaya Lakshmi Koduri. Status Epilepticus and its Management: A Review Article. *International Journal of Recent Trends in Science and Technology.* January 2016; 17(3): 317-322. http://www.statperson.com (accessed 24 January 2016).

time needed to sustain neuronal injury from a prolonged seizure.[5]

Classification of Status Epilepticus

Status Epilepticus can be classified by semiology, duration and underlying etiology. The following is a typical classification based on semiology:

(a) Generalised Convulsive Status Epilepticus (GCSE)
- Generalized tonic–clonic movements of the extremities
- Mental status impairment
- Focal neurological deficits in the post ictal period (e.g., Todd's paralysis)

(b) Non-convulsive SE (NCSE)
- seizure activity seen on electroencephalogram (EEG) without clinical findings associated with GCSE.
- Complex partial SE (CPSE), common form of NCSE, starts focally and spreads rapidly to involve other portions of the brain. Patients may present in confused/combative/''twilight state'' characterized by bizarre behavior and automatisms.[6]

(c) Refractory SE (RSE)

Patients who do not respond to standard treatment regimens for status epilepticus are considered to be in RSE [7]

Epidemiology

SE has an annual incidence of 28-61 per 100,000 population. There is a bimodal distribution of SE, with most cases occurring in patients less than 1 year of age or older than 60 years of age. The mortality associated with GCSE is about 45-74% of all cases.[9,10]

Etiology

Chronic epilepsy and low anti-epileptic drug levels
Chronic aetiologies : delayed effects tumours, stroke, and traumatic brain injury,

Pathophysiology

SE is initiated by excessive excitatory stimulation but is maintained through the lack of g-aminobutyric acid (GABA)–mediated neuronal suppression due to the development of changing GABA isoforms. It is sustained through excitatory N-methyl-D-aspartate (NMDA)–mediated neuronal stimulation. [14]

Clinical presentation

- convulsive
- non-convulsive
- electrographic

The initial presentation of GCSE is characterised by unresponsiveness and tonic, clonic, or tonic-clonic movements of the extremities.
NCSE has not been precisely defined, but is characterised by prolonged seizure activity evidenced by epileptiform discharges on EEG [47]
History to be elucidated:
- Past history of epilepsy
- details surrounding the onset and initiation of the seizure
- Changes in medication or alcohol or illicit drug use
- Trauma.

Table 1: Clinical course of Status Epilepticus[8]

Stage 1	5 to 10 min	Early phase – Premonitory SE, Impending SE
Stage 2	10 to 30 min	Established SE
Stage 3	30 to 60 min	Refractory SE : SE that continues despite stage I/II treatment subtle SE, stuporous SE
Stage 4	>24 hrs	Super-refractory SE : SE that continues despite treatment with anaesthetics >24 hrs

STESS

Status Epilepticus Severity Score (STESS)[34] predicts reliably which patients have a favourable chance of surviving an episode of SE(ie, reliable negative predictive value).[35]
It is measured at the time of presentation from:
- level of consciousness,
- SE type,
- Age in years
- Past seizure history

Table 2

Investigations :
complete blood count
blood glucose
basic metabolic panel
calcium (total and ionized)
magnesium
AED levels
Head (CT) scan
Continuous electroencephalograph (cEEG) monitoring
Based on clinical presentation consider :
Brain MRI
Lumbar puncture
Comprehensive toxicology panel
LFT, serial troponins, type and hold, coagulation studies, arterial blood gas,

Treatment of Status Epilepticus

Management Principles

Evidence shows that early seizure control improves long-term outcome[15,16,17] and hence the primary focus of treatment should be immediate termination of the seizure. Treatment needs to be initiated by whatever route is available as several medications can be given intramuscularly, rectally, or sublingually. A secure intravenous access is imperative.

Pre-hospital

Experimental evidences have proved that seizures can be terminated with relatively low doses of medications if treated early. Almost 60% of SE can be controlled with 2-4 mg of lorazepam if given as pre-hospital treatment medication, reported Alldredge *et al*.[18]

Findings from a randomised double-blind trial[33] in children and adults with prolonged (>5 min) convulsions showed that intramuscular midazolam given by paramedics is safe and effective as intravenous lorazepam to suppress seizures.

Table 3

Drugs	No. of patients treated	No. of pts seizure free	95% CI
Midazolam – IM / Buccal	448	329 (73%)	4.0 – 16.1
Lorazepam	445	282 (63%)	

Rapid Anticonvulsant Medications Prior to Arrival Trial (RAMPART)[33] study of the pre-hospital administration of intramuscular midazolam has shown that midazolam(IM) was as effective as lorazepam (IV) in the timely termination of status epilepticus without an increase in respiratory compromise or seizure recurrence. [47]

Regardless of the clinical manifestations of generalized SE, aggressive supportive care and prompt termination of electrical seizure activity are the goals. GCSE is managed as a true medical emergency.

Table 4

Critical care treatment outline for convulsive and non-convulsive SE [46]

Critical care treatment	Timing (minutes postseizure onset)	Goals
Airway protection and gas exchange with head positioning	Immediate (0–2 min)	To maintain patency of airway, administer O_2
Intubation (compromised airway/gas exchange or raised ICP suspected)	Immediate (0–10 min)	Establish adequate and secure oxygenation
Vital signs: O_2 saturation, BP, HR	Immediate (0–2 min)	Baseline vital signs to be maintained
Vasopressor support of BP if SBP <90 mmHg or MAP <70	Immediate (5–15 min)	Support CPP
Blood glucose (finger prick)	Immediate (0–2 min)	Diagnose hypoglycaemia
Peripheral IV access 1. Emergent initial AED therapy (i.e. benzodiazepine) 2. Fluid resuscitation 3. Nutrient resuscitation (thiamine given before dextrose; dextrose)	Immediate (0–5 min)	Establish medication route 1. Stop seizure 2. Establish euvolemia 3. Reverse thiamine deficiency, treat hypoglycaemia
Urgent SE control therapy with AED	Immediate after initial AED given (5–10 min)	Stop seizure
Neurologic exam	Urgent (5–10 min)	Evaluate for mass lesion, acute intracranial process. Expert opinion.
Triage lab test	Immediate (5 min)	Diagnose life threatening metabolic condition. Expert opinion
Refractory SE	treatment Urgent (20–60 min after 2nd AED)	Stop seizures; treatment strategies based on individual patient response and AED concentrations (if applicable) .Expert opinion

EEG

Continous EEG should be initiated within one hour of suspected SE in all patients. The duration of cEEG monitoring should be at least 48 hours following acute brain insult in comatose patients [39]

Pharmacological Treatment

First-Line Medications[8]

Benzodiazepines - diazepam, lorazepam, and midazolam are the mainstay of treatment. They function by stimulating $GABA_A$ receptor subunits. This leads to inhibition of neural transmission through chloride channel–induced hyperpolarization of the resting cell membrane.[14] Diazepam has high relapse rate. Midazolam can be given through various routes and hence used out of hospital. Lorazepam with duration of action for 12 hrs is the benzodiazapine of choice. The results of the Veterans Affairs Status Epilepticus Cooperative Study Group suggested improved seizure control with lorazepam.[19]

Second-Line Medications[8]

Phenytoin

- supratherapeutic levels (25-30 µg/mL) should be achieved before considering additional medication.[20]

- Patients previously on phenytoin should be given half of the loading doses.
- The side effects :
  - **a.** hypotension,
  - **b.** bradycardia,
  - **c.** QT prolongation, which correlates with the infusion rate (maximum rate 50 mg/min).
  - **d.** phenytoin extravasation results in severe tissue necrosis -''purple glove syndrome'', reported in 6% of patients.[21]

Fosphenytoin (phosphate-ester prodrug) is now preferred over phenytoin despite the increased cost as it can be given intramuscularly and at a faster rate with fewer side effects.[22] Valproic acid decreases seizure activity by prolonging the recovery of voltage-gated sodium channels and through effects on GABA metabolism.[23] Experience in SE is limited to small series.[24,25] In one series valproic acid was as effective in terminating SE as phenytoin.[26] Valproate may serve as a second-line drug in SE /recalcitrantSE prior to giving Phenobarbital or initiating treatment for RSE as it has few cardiovascular effects.[27] Levetiracetam has neuropsychiatric and few cardiovascular side effects.[28] Use in SE has been limited to a few case reports.[29,30] Doses of 2500 mg are safe and effective when used as an additional drug to treat SE.[31] Levetiracetam is particularly effective in absence seizures and CPSE.[32]

Table 5: Medication Dosages and Routes of Administration for the Treatment of Status Epilepticus [36]

Drug	Medication Route	Dose
Lorazepam	Intravenous (IV)	4-8 mg initial 0.1-0.2 mg/kg loading
Diazepam	IV	5-20 mg initial 0.15 mg/kg loading
Diazepam	Rectal gel	0.2-0.5 mg/kg initial
Midazolam	Intramuscular(IM)	0.07-0.3 mg/kg initial
Phenytoin	IV	20-30 mg/kg loading
Fosphenytoin	IV	20-30 Phenytoin Equivalents (PE)/kg loading
Fosphenytoin	Intramuscular	500-1500 PE initial
Phenobarbital	IV	20-30 mg/kg loading
Valproate	IV	20 mg/kg loading
Levetiracetam	IV	1000-2500 mg initial

Pregnancy

There are known risks of birth defects with first trimester exposure to AEDs, particularly valproate sodium, phenobarbital, and phenytoin. Lorazepam / fosphenytoin are recommended as emergent initial therapy /urgent control therapy. [37] Data from recent pregnancy registries suggest less risk with newer AEDs like levetiracetam. [38] Eclampsia must be considered in patients with SE during pregnancy. [40] Vitamin B6 deficiency should be ruled out as it is not uncommon in pregnancy.

PROGNOSIS

TABLE 6

SE Types	Mortality at discharge	Mortality at 30 days
GCSE	9 – 21%	19 – 27%
NCSE	18 – 52%	65%
RSE	23 – 61%	39%

DISCUSSION

Summary of Treatment Recommendations

1) The treatment of convulsive SE should be rapid and continue sequentially until clinical and electrographic seizures stop (strong recommendation, high quality).
2) Critical care treatment and monitoring should be started simultaneously with emergent initial therapy and continued until further therapy is consider successful or futile (strong recommendation, moderate quality).
3) Treatment options :
   a) Benzodiazepines are the first line/emergent initial therapy (Strong recommendation (SR), Moderate Quality{MQ}).
      - Lorazepam : drug of choice for IV administration (SR, MQ).
      - Midazolam : drug of choice for IM administration (SR, MQ).
      - Rectal diazepam can be given when there is no IV access and IM administration of midazolam is contraindicated (SR, MQ).
   b) Second line/Urgent control AED therapy
      IV fosphenytoin / phenytoin, valproate sodium, or levetiracetam (SR, MQ).

CONCLUSIONS

Early and rapid administration of anticonvulsant medications, mobilization of available resources is essential for successful treatment / prevention of status epilepticus. Recent studies have proven the efficacy of administering drugs by whatever routes of administration are immediately available to prevent very recalcitrant forms of SE.

The treatment of SE should follow a staged protocol to enable prompt and appropriate treatment. Prospective studies are needed to establish a cost-effective approach for the early identification and treatment of status epilepticus.

The Established Status Epilepticus Treatment Trial (ESETT; NCT01960075) has started in 2015 and is set to compare the efficacy of second-line AEDs fosphenytoin, valproic acid and levetiracetam for the treatment of benzodiazepine-refractory status epilepticus in a randomised, blinded fashion.[41]

The research gap is due to scarce funding opportunities, despite the fact that, in terms of disability weight, severe epilepsy ranks fourth among 220 health states surveyed by the Global Burden of Disease study[42], an issue recently addressed by the WHO's evidence-based recommendations for epilepsy care in resource-limited settings.[43] There is a need to develop biomarkers to predict the development of epilepsy, identify the presence of tissue capable of generating spontaneous seizures, and measure progression.[44, 45]

Some antiepileptic and neuro-protective compounds and interventions as preventive tools under trial / research :

a) Ketogenic diet
b) Brain cooling
c) Antioxidants and free radical scavengers
d) Antiapoptotic agents
e) Transplantation of neuronal precursor cells and embryonic stem cells
f) Suppression of respiratory alkalosis
g) Modulators of glutamatergic transmission
h) Activators of neurotrophic receptors
i) Immunosuppressive treatments and agents targeting brain inflammation

Future care of patients with SE can be better managed by raising awareness of the dangers of ongoing SE, develop new drugs, faster and more reliable diagnostic techniques including advanced monitoring algorithms.

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Source of Support: None Declared
Conflict of Interest: None Declared