Refractory status epilepticus (RSE) is a common problem in intensive care units and emergency departments. The important risk factor predisposing patients with SE to RSE is delay in receiving treatment. Self-sustaining SE is associated with progressive, time-dependent development of pharmacoresistance. Early termination of convulsive SE by aggressive treatment is the best way to prevent RSE. RSE once develop, requires more aggressive treatment as it is associated with higher mortality and morbidity. To date, no randomized controlled trials have been done for RSE. The most experience exists with coma inducing agents like pentobarbital, midazolam and propofol. New evidence suggests for the possible role of newer AEDs.

**Key words:** Anesthetic agents, burst suppression, midazolam, pentobarbital, propofol, refractory status epilepticus.

Status epilepticus (SE) is a frequent neurological emergency associated with an annual incidence between 3.86-38 per 100,000 individuals. The incidence of SE has a bimodal distribution with peaks in children aged less than a year and the elderly.[1] Although conventional antiepileptic drugs (AED) can terminate SE in most cases, a substantial minority of patients develop medically refractory SE (RSE). In Veteran Administrative (VA) Cooperative study[2] first treatment regimen was successful in 55.5% of patients with “overt” SE, but in only 14.9% of those with “subtle” SE. Subsequent treatments of patients, who did not respond to first-line agent, indicates that the aggregate response rate was 7% to second-line agents and 2.3% to third-line agents. Only 5% of patients with SE who did not respond to lorazepam and phenytoin therapy, responded to phenobarbital administration.[2,3]

**Definition**

Although the entity of RSE is widely recognized and discussed, a standard definition has not yet been evolved and is usually defined as seizure activity that continues after first- and second-line therapy has failed.[4] However the proposed criteria vary in the number of AEDs (e.g., 2[5-9] or 3[10-13]) failed and in the duration of seizure activity (e.g., ranging from <1[5,9,11,13] at least 1[7] or 2[6,8] hours).

Recently Holtkamp and colleagues[14] have coined the term “malignant” SE for the most severe variant of SE with persistent epileptic activity even after high dose anesthetics.

**Epidemiology**

RSE is a common problem in intensive care units and emergency departments. Estimates of the frequency of RSE in patients with SE have ranged from 31 to 44%.[15,16] The proportion of patients with RSE in the cohort reported by Rossetti et al.[17] was 38% when considering all episodes and was 44% when considering only incidence cases. In the VA Cooperative Study, 38% of patients with “overt” SE and 82% of patients with “subtle” SE continued to have seizures after receiving 2 AEDs.[2]

RSE is associated with high mortality and a significant morbidity; only about a third of patients return to their pre-morbid state.[18] In the VA Cooperative study[2] outcomes 30 days after treatment were significantly worse for patients with “subtle” SE. At 30 days, only 8.8% of patients had been discharged from the hospital and 26.5% were still in the hospital and the mortality was 64.7%. In the recent studies the reported mortality rates varied between 16 to 23%.[15-17] In a retrospective study the outcome was independent of specific coma inducing agents used and the extent of EEG burst suppression, suggesting that the underlying cause represents its main determinant.[17]

**Risk factors**

RSE is more prevalent in incident than in recurrent SE.[17] Risk factors predisposing patients to RSE include delay in receiving treatment, infections of central nervous system (CNS), metabolic encephalopathy and hypoxia.[15,18] Encephalitis is a predictor for RSE, which is associated with markedly poor

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**JMK Murthy**

Department of Neurology, The Institute of Neurological Sciences, CARE Hospital, Nampally, Hyderabad 500 001, India. E-mail: jmkmurthy@satyam.net.in
outcome, in particular, the development of post-SE symptomatic epilepsy.[15] The patient at risk for malignant SE is typically young and suffers from encephalitis.\textsuperscript{[16]}

**Pathophysiology**

SE refers to a condition in which there is a failure of the “normal” factors that serve to terminate a typical seizure. \(\gamma\)-Aminobutyric acid (GABA) receptor-mediated inhibition may be responsible for the normal termination of a seizure. In addition, the activation of the N-methyl-D-aspartate (NMDA) receptor by the excitatory neurotransmitter glutamate may be required for the propagation of seizure activity.\textsuperscript{[20]} SE that is refractory to treatment may be the result of several processes [Table 1] and has been attributed to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive NMDA excitatory receptor-mediated transmission.\textsuperscript{[21-26]} In experimental models, resistance to both benzodiazepines and barbiturates develops during prolonged seizures and it has been hypothesized that prolonged seizure activity alters the structure and/or function of \(\text{GABA}_A\) receptors.\textsuperscript{[27]}

SE induced neuronal death is morphologically necrotic and is initiated by excessive glutamate release, which activates postsynaptic NMDA receptors and triggers receptor-mediated calcium influx (excitotoxicity). This results in a cascade of events and cell death.\textsuperscript{[28]}

The alterations in inhibitory and excitatory pathways have important implications for the pharmacological management of SE. Another important aspect of self-sustaining SE is the progressive, time-dependent development of pharmacoresistance.\textsuperscript{[29]} Currently recommended agents acts primarily through the \(\text{GABA}_A\) receptor and have been shown to become less effective in SE of longer duration. Drugs shown to be effective in RSE act at different receptor sites other than benzodiazepine receptor site, propofol acts at a site distinct from the benzodiazepine and barbiturate binding sites, isoflurane acts by potentiation of inhibitory postsynaptic \(\text{GABA}_A\) receptor-mediated currents, although effects on thalamo-cortical pathways also have been implicated.\textsuperscript{[27-31]}

**Continuous EEG Monitoring**

Though continuous EEG monitoring (cEEG) has a definite place in the diagnosis and management of nonepileptic status epilepticus (NCSE), its place in the management of convulsive SE is still unclear.\textsuperscript{[32]} However EEG is useful in determining whether seizures have completely stopped, as well as in diagnosing electrographic seizures or nonconvulsive status epilepticus (NCSE) in patients who do not regain consciousness after clinical seizure stops. Electrographic seizures may persist in patients after convulsive SE. In one study cEEG demonstrated electrographic seizures in 48% of patients and 14% manifested NCSE.\textsuperscript{[33]} In the VA study, 20% of clinically controlled convulsive SE patients were still seizing on EEG.\textsuperscript{[2]} Mortality in patients in whom cEEG demonstrates electrographic seizures and NCSE is high.

cEEG monitoring is required in patients with RSE during continuous intravenous therapy to monitor seizure activity and to titrate the drug dosage to achieve burst suppression pattern and during the withdrawal of anesthetic therapy. However the major limiting factor may be lack of EEG monitoring facility in many intensive care units.

**Management - General Measures**

RSE requires more aggressive treatment and however, the optimal treatment has not been defined. Patients should be treated in intensive care unit, as artificial ventilation and hemodynamic support is required. These patients generally require intravenous fluids and vasopressors to treat hypotension associated with high dose intravenous use of anesthetic agents. In a third of adults in SE, arterial pH falls below 7;\textsuperscript{[34]} the main contribution to this change is lactate acidosis from skeletal muscle,\textsuperscript{[35]} which responds well to oxygen and control of convulsive activity. Mild acidosis might be an anticonvulsant\textsuperscript{[36]} and neuroprotective.\textsuperscript{[37]} The usual practice is to treat with bicarbonate if the patient is hypotensive and arterial pH if it is < 7 due to metabolic acidosis. Control of hypothermia is neuroprotective.\textsuperscript{[38,39]}

**Pharmacological treatment**

To date, no randomized controlled trials have been done for SE refractory to first- and second-line therapy. The most experience exists with \(\text{cIV}\) of pentobarbital, midazolam and propofol.\textsuperscript{[35-41]} [Table 2]. The best comparative information comes from the systematic review by Claassen and colleagues.\textsuperscript{[19]} No difference was found in mortality among the groups treated with \(\text{cIV}\) propofol, \(\text{cIV}\) midazolam and \(\text{cIV}\) pentobarbital. Mortality was related to patient’s age and duration of SE rather than AED choice. A recent retrospective study investigated the effect on RSE prognosis of various coma-inducing pharmacologic options.\textsuperscript{[17]} Mortality and likelihood of the patient’s condition returning to clinical baseline at discharge did not differ significantly among the three arms, barbiturates (pentobarbital and phenobarbital), propofol and midazolam. This study did not find any evidence for mortality related to propofol infusion syndrome.

Traditionally, barbiturates such as pentobarbital or thiopental have been used to terminate RSE, inducing coma and EEG

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**Table 1: Refractory status epilepticus – Possible mechanisms**

| • Changes in GABA receptor composition and loss of benzodiazepine efficacy |
| • Excessive glutamate excitation |
| • Activation of drug resistance genes |

**Table 2: Refractory status epilepticus-anesthetic agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Load dose</th>
<th>(\text{cIV}) rate</th>
<th>(\text{cIV}) dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg</td>
<td>0.1 mg/kg/h</td>
<td>0.05-2.9 mg/kg/h</td>
</tr>
<tr>
<td>Propofol</td>
<td>1-2 mg/kg</td>
<td>2 mg/kg/h</td>
<td>1-15 mg/kg/h</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>5 mg/kg</td>
<td>1 mg/kg/h</td>
<td>0.5-10 mg/kg/h</td>
</tr>
</tbody>
</table>
High dose phenobarbital

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High dose of phenobarbital with serum levels of 100 to 200 µg/ml has been found effective and safe in the treatment of RSE in children. In another study a very high dose phenobarbital at accumulated daily doses up to 80 mg/kg, with a resulting serum level of more than 1000 µmol/l has been shown to effective in achieving seizure control in children with RSE. In this study the adverse effects were milder compared with thiopental infusion.

Ketamine

Ketamine, a NMDA antagonist, has been proved useful in RSE and it is also a neuroprotective. However, because ketamine can raise intracranial pressure, the absence of intracranial mass lesion should be confirmed by neuroradiology. The experience with this agent in RSE is very limited.

Inhalational Anesthetics

Inhalational anesthesia (IA) is an alternative approach to the treatment of RSE. Its attractive feature include efficacy, rapid onset of action and the ability to titrate the doses according to the effects demonstrated on the EEG. Of the various agents, isoflurane and desflurane are the two agents that have been administrated for RSE because of their safety associated with long-term administration. In a recent retrospective study, seven patients with RSE were initiated to IAs (all patients to isoflurane and one patient in addition to desflurane) after 1 to 103 (mean, 19) days. They received multiple AEDs (mean 10, range 7-15) in addition to IAs. Regardless of seizure type, isoflurane and desflurane consistently stopped epileptic discharges with adequate, sustained electrographic burst suppression within minutes of initiating IA therapy. Four patients had good outcomes. Prolonged use of IAs was well tolerated.

Newer AEDs

The use of newer AEDS in the treatment of RSE has not been studied systematically. In 6 patients with RSE unresponsive to sequential trials of multiple agents, a suspension of topiramate administered via nasogastric tube was effective in aborting RSE. Effective dosages ranged from 300 to 1,600 mg/d.
terminated in three children with topiramate loading, 5 mg/kg/day. Seizure control has been achieved in patients with RSE by administration of levetiracetam (500–3000 mg/day) by nasogastric route. Injectable levetiracetam formulation is available and the pharmacokinetics of levetiracetam administered by IV infusion was comparable across all dose groups and infusion rates and the pharmacokinetic profile was consistent with that for levetiracetam administered orally. Well designed studies are needed to determine the place of newer AEDs as the use of drugs can avoid pharmacologic coma.

**Target of treatment-burst suppression**

Experimental studies demonstrated maximal depression of cerebral metabolism with barbiturates with burst suppression intervals of 30 seconds. Burst suppression and isoelectric background EEG have been shown to be accompanied by fewer recurrent seizures than simply stopping seizures. There is uncertainty about the optimal extent of EEG suppression in RSE. Several authors used different burst suppression intervals. Kofke et al used 15 to 30 seconds as burst suppression interval. Van Ness used 3 to 9 bursts per minute during pentobarbital treatment. Mirsattari and colleagues considered the maintenance of burst suppression for burst duration of less than 1 second and suppression duration longer than 10 seconds as the goal of therapy. Where as Bleck advocates a more aggressive approach using isoelectric EEGs. In a recent retrospective study the outcome was independent of the extent of EEG burst suppression and probably related to the underlying cause of RSE.

**Maintenance therapy**

In parallel with emergency treatment attention must be given to maintenance AED therapy to prevent recurrence of seizures. In patients known to have epilepsy, their usual AEDs should be maintained and dose adjustments may be required depending on AED levels. In patients presenting *de novo* the AEDs, phenytoin/fosphenytoin or valproate, used to control the status can in principle be continued as oral maintenance therapy. In others, unless relatively short-lived treatment is anticipated, the preference is to initiate oral maintenance therapy, valproate or carbamazepine, starting immediately at standard doses. If additional medication is needed, the most appropriate AEDs are topiramate and levetiracetam as these drugs can be started at high doses with a low risk of idiosyncratic reactions.

**Conclusions**

The important risk factor predisposing patients with SE to RSE is delay in receiving treatment. Self-sustaining SE is associated with progressive, time-dependent development of pharmacoresistance. Early termination of convulsive SE by aggressive treatment is the best way to prevent RSE. RSE once develop, requires more aggressive treatment as it is associated with higher mortality and morbidity. To date, no randomized controlled trials have been done for RSE. The most experience exists with coma inducing agents like pentobarbital, midazolam and propofol. New evidence suggests for the possible role of newer AEDs [Figure 1].

![Figure 1: Refractory status epilepticus – Treatment algorithm](image)

**Figure 1: Refractory status epilepticus – Treatment algorithm**

AEDs: antiepileptic drugs; TPM: topiramate, LEV: Levetiracetam

**References**


40. Murphy JM, Naryanian TJ. Continuous EEG monitoring in the evaluation of nonconvulsive seizures and status epilepticus. Neurol India 2004;52:430-5.


Appendix I

A literature search was performed for relevant articles published from 1990 to August 2006 using following key words: status epilepticus, refractory status epilepticus, pathogenesis of status epilepticus and refractory status epilepticus and treatment of status epilepticus. Standard search procedures were used and subheadings were applied as appropriate. In addition standard text books on epilepsy and status epilepticus were also referred.

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