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Refractory status epilepticus

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Abstract

Status epilepticus is a life threatening neurological emergency. In persons with status epilepticus, if administration of a benzodiazepine and at least one antiepileptic drug has failed then management protocols for refractory status epilepticus should be put into effect. The article summarises the causes, effects, pathophysiology and treatment protocols for refractory status epilepticus.The concept of super refractory status and newer etiologies and therapeutic options are also discussed.

INTRODUCTION

Status epilepticus (SE) is the second most common neurological emergency after acute stroke having an incidence of 10-40 per 100,000.[1-3] Irrespective of the timeframe, SE that persists despite adequate administration of benzodiazepines and at least one antiepileptic drug (AED) is labelled refractory status epilepticus (RSE).[4,5] The reported incidence of RSE is estimated at 31–43% of all SE episodes[6-8], however one prospective study reports lower incidence at 24.6%.[5] Commonest cause of RSE are encephalitis, massive stroke, rapidly progressive brain tumours.[5,6,9] The short-term fatality rates for RSE is between 16%-39%. Mortality in RSE occurs after the cessation of seizures and is mostly related to the underlying clinical problem highlighting the fact that underlying cause of SE is the most important predictor of clinical outcome.[7] Functional outcome after RSE is very poor and the chances of returning to baseline clinical status is approximately 21% as compared to 63% for non refractory SE.[5]

PATHOPHYSIOLOGY OF REFRACTORY STATUS EPILEPTICUS

RSE patients have many systemic complications which includes arrhythmias, pulmonary edema, metabolic acidosis, and rhabdomyolysis.[10] Rat models have shown that SE responds to benzodiazepine (GABAa agonists) or phenytoin (sodium channel blocker) when administered early. As time passes by RSE becomes more resistant to these drugs, because of internalization of GABAa receptors (inhibitory) in the neuronal cytoplasm, and the overexpression of NMDA receptors (excitatory).[11,12] However the clinical evidence for the refractoriness cannot be fully accounted by loss of inhibition or overexpression.

TREATMENT OF REFRACTORY STATUS EPILEPTICUS

There are 3 distinct steps in controlling SE; benzodiazepines for early seizure control, conventional AED for early resistance and anaesthetics for RSE. Benzodiazepines have the best available evidence.[13] (Figure 1). The validated clinical SE severity score (STESS) can help to decide treatment strategy. With four variables (age, seizure semiology, extent of consciousness impairment, and history of previous seizures as a surrogate for cause), STESS is readily applicable in clinical settings, relies on straightforward clinical criteria, and has a robust negative predictive value for mortality (ie, patients with a low score are very unlikely to have a fatal outcome.[14] As SE becomes refractory to therapy[15,16], coma induction with an anaesthetic, mostly a barbiturate, propofol or midazolam, is usually required (Table 1).[17] The optimal agent for refractory SE should exert a GABAa agonistic and NMDA antagonistic action, be fast acting, with a short elimination half-life, and have a favourable risk profile.

Midazolam is a benzodiazepine with a short half-life after a single bolus but on repeated administrations, it increases to 6-50 hrs. Constant monitoring and dose changes need to be made because of the concern of tachyphylaxis and adverse effects.[18]

Propofol has a very short half-life allowing for rapid titration and withdrawl. It primarily acts by modulating GABAa receptors however it also acts on sodium and calcium channels

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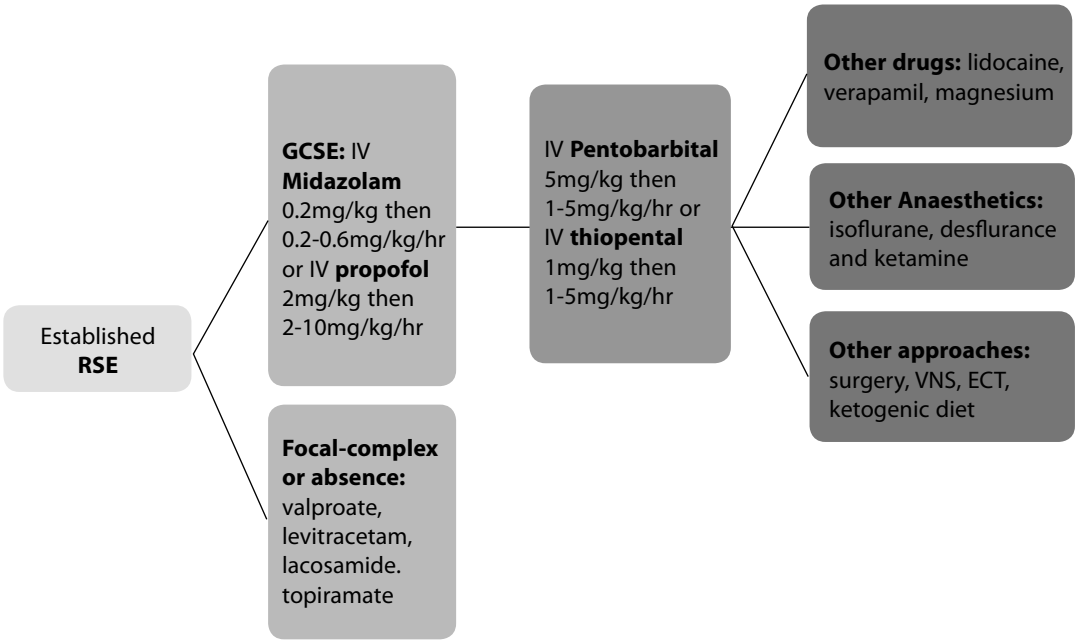
Figure 1. Algorithm for refractory status epilepticus (RSE) treatment. Increased refractoriness is indicated by background shading intensity; third line drugs are on the right column.



RSE, refractory status epilepticus; GCSE, generalized convulsive status epilepticus; VNS, vagus nerve stimulation; ECT, electroconvulsive therapy

and probably on NMDA receptors. Since it is administered as an oil emulsion, it carries a risk of propofol infusion syndrome (PIS), which consists of cardiocirculatory collapse with hypertrigleridemia, rhabdomyolysis and lactic acidosis.[19,20] (Table 2) This has mainly been reported in young children as it results mainly from the impairment of mitochondrial activity and use of free fatty acids. Retrospective series estimated the incidence of PIS in RSE as 7% (fatal) and 38% (non-fatal).[21]

Barbiturates are the oldest compounds used in RSE. They have a tendency to accumulate in the adipose tissues accounting for the increased half-

Table 1: Pharmcacological characteristics of anesthetics used in refractory status epilepticus[22]

	Barbiturates	**Propofol**	**Midazolam**
Used since	Before 1960	End of 1980	Early1990
Mechanism of action:			
GABAa agonistic	+++	+++	+++
NMDA antagonistic	+	+	-
Ca channel modulation	+	+	-
Na channel modulation	-	+	-
Elimination half-life			
(hrs)	THP:14-36; PTB:15-22	1-2	6-50
Accumulation	+++	+	++
Tachyphylaxis	-	+	+++
Hypotension	+++	+++	++
Other adverse effects	Immunological suppression	Infusion syndrome	
Loading dose (mg/kg)	THP:1-2; PTB:5	2	0.2
Maintenance dose (mg/kg/h)	THP:1-5; PTB:1-5	2-5	0.2-0.6

THP: thiopental, PTB: pentobarbital

Table 2: Features of propofol infusion syndrome (PIS)

Metabolic acidosis:	pH≤7.35 or anion gap ≤15 or measured serum bicarbonate ≤22
Cardiac changes:	Asystole, unexplained cardiac failure, cardiac arrest, pulseless electrical activity, increased PVC,new LBBB/RBBB, prolonged QTc, bradycardia (heart rate ≤55 beats/min or decrease in HR ≤30 beats/min),
Rhabdomyolysis:	Elevated creatine kinase (≥176 units/L), hyperkalemia (≥5.2), or myoglobinuria
Lipid/hepatic changes:	Hypertriglyceridemia (≥150 mg/dL), splenomegaly/hepatomegaly, hepatic steatosis, transaminitis, lipemia
Renal changes:	Renal failure, anuria, oliguria, hyperkalemia

life (up to 36 hours). This accumulation can be specially troublesome in patients with underlying cardiovascular problems.

EVIDENCE OF AVAILABLE TREATMENT IN REFRACTORY STATUS EPILEPTICUS

A meta-analysis of the use of barbiturates, propofol, or midazolam in RSE, mostly based on retrospective and heterogeneous case series, did not show any significant difference in short-term mortality, although barbiturates were more effective in controlling clinical seizures and preventing breakthrough seizures when compared to midazolam and propofol.[23] (Table-3). Results of another single-centre retrospective analysis failed to show any outcome difference between different anaesthetics, used alone or in combination.[8] A Survey conducted among Epileptologists and Critical Care Specialists regarding the management of refractory generalized convulsive SE and complex partial refractory SE using a postal questionnaire showed great variability of practice. Majority of the responders used a non-anaesthetic agent after the failure of first line anticonvulsants. Time period of starting anaesthetizing agents after the onset of SE also varied, and the drug most commonly used was barbiturates followed by propofol and then midazolam.[24] A multicentre randomised, unblinded trial assessing propofol and barbiturates in RSE was interrupted because of insufficient recruitment. The enrolled patients receiving barbiturates had a substantially increased need for mechanical ventilation, whereas long-term outcome and complications were the same.[25] Thus inspite of inadequate evidence, midazolam appears to be the safest compound but if seizure control is not reached it often needs to be combined with propofol. Barbiturates should be used as a salvage therapy because of longer elimination time.

OTHER PHARMACOLOGICAL AND NON-PHARMACOLOGICAL APPROACHES IN TREATMENT OF REFRACTORY STATUS EPILEPTICUS

Other non-sedating pharmacological approaches are available and can be administered intravenously or orally (through the nasogastric tube) as add-on compounds to optimise control of RSE. Topiramate[26], pregabalin[27],levetiracetam[28], and lacosamide[29] have different and potentially synergistic pharmacodynamic actions. Tripathi *et al*. conducted at a tertiary care hospital in a developing country with the hypothesis of using a anticonvulsant with no anaesthetizing property. RSE patients were divided into 2 groups; one

Table 3: Meta-analysis in refractory status epilepticus

	Barbiturates	Propofol	Midazolam
Mortality	48%	52%	46%
Acute failure in SE control (first 6 hours)	8%	27%	20%
Breakthrough seizures	12%	15%	51%
Withdrawal seizures	43%	46%	63%
Hypotension requiring vasopressors	77%	42%	30%

SE, status epilepticus

group received valproate and the other group received levitracetam; 68.3% patients in valproate group and 73.2% in levitracetam group were relieved from their status.[30] Non-pharmacological approaches are last resort approaches and cannot be generalized because of lack of quality evidence. Resective brain surgery, mild hypothermia, classical music, ECT and transcranial magnetic stimulation are some of the examples of non-pharamacological treatment.

EFNS GUIDELINES FOR MANAGEMENT OF REFRACTORY GENERALIZED CONVULSIVE STATUS EPILEPTICUS AND SUBTLE STATUS EPILEPTICUS

The EFNS (EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES) published guidelines on management of status epilepticus in 2011. In generalised convulsive and subtle SE, the EFNS advocated to proceed immediately to the infusion of anaesthetic doses of midazolam, propofol or barbiturates because of the progressive risk of brain and systemic damage. Because of poor evidence, no recommendation is made regarding choice of anaesthetic drug. Depending on the anaesthetic used in the individual in-house protocol, titration against an EEG burst suppression pattern with propofol and barbituratesis recommended. If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 hours.[31]

SUPER-REFRACTORY STATUS EPILEPTICUS

Super-refractory SE has been defined as SE that continues or recurs 24 hours or more after the onset of anesthesia, including those cases in which SE recurs on the reduction or with drawl of anesthesia. It occurs in 10-15% of all presenting to hospital with status epilepticus. It has a high morbidity and mortality rates. Super-refractory SE is often seen in patients with underlying severe acute brain injury. It is sometimes also seen in patients with no history of epilepsy in whom SE develops *de novo* with no overt cause (NORSE: new-onset refractory status epilepticus)[32] A varieties of therapeutic measures has been used, the outcome has been reviewed by Shorvon & Ferlisi.[33] Immunosupression with intravenous steroids and immunomodulation with immunoglobulins has also been used, even if antibodies causing epilepsy cannot be detected or afforded, based on presumed immune etiology.

In conclusion, early recognition of treatment failure in early status epilepticus and management of emerging refractory status on a war footing would go a long way in managing patients with epilepsy.

REFERENCES

1. Delorenzo RJ, Hauser WA, Towne AR, *et al*. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996; 46: 1029-35.
2. Knake S, Rosenow F, Vescovi M, *et al*. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. *Epilepsia* 2001; 42:714-8.
3. Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 2000; 55:693-7.
4. Holtkamp M. Treatment strategies for refractory status epilepticus. *Curr Opin Crit Care* 2011; 17:94-100.
5. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia* 2010; 51:251-6.
6. Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Arch Neurol* 2002; 59:205-10.
7. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 2005b; 76:534-9.
8. Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol* 2005; 62:1698-702.
9. Holtkamp M, Othman J, Buchheim K, Masuhr F, Schielke E, Meierkord H. A malignant variant of status epilepticus. *Arch Neurol* 2005; 62:1428-31.
10. Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology* 1990; 40(suppl 2):13-23
11. Mazarati AM, Baldwin RA, Sankar R, Wasterlain CG. Time-dependent decrease in the eff ectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. *Brain Res* 1998; 814:179-85.
12. Mazarati AM, Wasterlain CG. N-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. *Neurosci Lett* 1999; 265: 187-90.
13. Prasad K, Al-Roomi K, Krishnan PR, Sequeira R. Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev* 2005; 4: CD003723
14. Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 2008; 255:1561-6.
15. Fountain NB, Lothman EW. Pathophysiology of status epilepticus. *J Clin Neurophysiol .1995;* 12:326-42.
16. Treiman DM, Walton NY, Collins JF. Treatment of status epilepticus if first drug fails. *Epilepsia 1999;* 40(Suppl 7):243.
17. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998; 388:970-6.
18. Claassen J, Hirsch LJ, Emerson RG, Bates JE,

Thompson TB, Mayer SA. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology* 2001; 57:1036-42.
19. Marik PE. Propofol: therapeutic indications and side-eff ects. *Curr Pharm Des* 2004; 10: 3639-49.
20. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med* 2003; 29:1417-25
21. Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. *Crit Care Med* 2009; 37:3024-30
22. Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus, *Epilepsia* 2000; 48(Suppl. 8):52-5.
23. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2000; 43:146-53.
24. Holtkamp M, Masuhr F, Harms L, Einhäupl KM, Meierkord H, Buchheim K. The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists *J Neurol Neurosurg Psychiatry* 2003;74:1095-9.
25. Rossetti AO, Milligan TA, Vullie´moz S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care* 2011; 14:4-10.
26. Stojanova V, Rossetti AO. Oral topiramate as an add-on treatment for refractory status epilepticus. *Acta Neurol Scand* 2011 published online June 29. DOI:10.1111/j.1600-0404.2011.01562.x.
27. Novy J, Rossetti AO. Oral pregabalin as an add-on treatment for status epilepticus. *Epilepsia* 2010; 51:2207-10.
28. Knake S, Gruener J, Hattemer K, *et al*. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. *J Neurol Neurosurg Psychiatry* 2008; 79: 588-9.
29. Kellinghaus C, Berning S, Immisch I, *et al*. Intravenous lacosamide for treatment of status epilepticus. *Acta Neurol Scand* 2011; 123:137-41.
30. Tripathi M, Vibha D,Choudhary N, *et al*. Management of refractory status epilepticus at a tertiary care centre in a developing country. *Seizure* 2010;19:109-11.
31. Meierkorda H, Boon P, Engelsen B, *et al*. EFNS guideline on the management of status epilepticus in adults *Eur J Neurol 2010*; 17:348-55
32. Shorvon S. Super-refractory status epilepticus: An approach to therapy in this difficult clinical situation. *Epilepsia* 2011; 52(Suppl. 8):53-6.
33. Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendation for therapy. *Brain* 2012.