Review Article

TRENDS AND STRATEGY TOWARDS THERAPIES FOR STATUS EPILEPTICUS: A DECISIVE REVIEW

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ABSTRACT

Status epilepticus (SE) is defined as any seizure lasting for 30 minutes or longer or intermittent seizures lasting for greater than 30 minutes from which the patient did not regain consciousness. It may cause death or severe sequelae unless terminated promptly. SE is divided into convulsive and non-convulsive types; both are associated with significant morbidity and mortality. There are a limited number of well-designed studies to support the development of evidence-based recommendations for the management of SE, especially for the management of non-convulsive status. This review expresses modern knowledge on the definition, classification, diagnosis, and treatment of SE.

Keywords: Epilepsy, Management, Convulsive status epilepticus, Non-convulsive status epilepticus, Benzodiazepines.

INTRODUCTON

The definition of status epileticus (SE) is evolving and debate persists as to what constitutes this entity. This has lead to some heterogeneity between studies in methodology and inclusion criteria particularly with regard to seizure duration. The 1981 International League against Epilepsy's (ILAE) define the SE as whenever a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur. This definition has not been officially updated, remains unsatisfactory from a research viewpoint because the duration is not specified. Subsequently, the Epilepsy Foundation of America working group and several major recent studies have defined SE as "any seizure lasting for 30 minutes or longer or intermittent seizures lasting for greater than 30 minutes from which the patient did not regain consciousness"[1, 2].

This time frame is based on an estimate of duration necessary to cause damage to cerebral neurons[3]. However the practical experience of clinicians has been that seizures need to be controlled much earlier than 20 minutes, and therefore, an operational definition for SE has been proposed: either continuous seizures lasting at least ten minutes or two or more discrete seizures between which there is incomplete recovery of consciousness[4, 5]. A modern definition should be statistical and should take account the different stages, types and age specific feature of SE. The average tonic clonic seizure last about a minute whereas complex partial seizure last generally 2-3 minute[6].

CLASSIFICATION OF STATUS EPILEPTICUS

A classification of SE according to clinical information including pathophysiology, epilepsy syndrome, and seizure semiology combined with EEG data within various age groups (neonatal, infancy/childhood, childhood/adult, and adult) has been proposed but as yet has not been utilized in any study[7]. It can be classified as generalized convulsive status epilepticus (GCSE) and nonconvulsive status epilepticus (NCSE). GCSE is the most common and severe form of SE and is characterized by repeated primary or secondary generalized seizures that involve both hemispheres of the brain and are associated with a persistent postictal state. It can be further divided into primary generalized SE (tonic-clonic, tonic, clonic, myoclonic and erratic) and secondary generalized SE (tonic and partial seizures with secondary generalization). NCSE occurs in approximately 25% of those with SE and is characterized by a fluctuating or continuous "twilight" state that produces altered consciousness and/or behaviour (e.g., lethargy, decreased mental function). An altered EEG is the most important diagnostic and management tool. It also can be divided in absence, complex partial SE and subtle SE[8]. Table 1 shows clinical presentation of SE.

Table 1: Clinical Presentation[9-11]

Symptoms	Impaired consciousness (e.g., lethargy to coma) Disorientation once GCSE is controlled Pain associated with injuries (e.g., tongue lacerations, shoulder dislocations, head trauma)
Early Signs	Generalized convulsions Acute injuries or CNS insults that cause extensor or flexor posturing Hypothermia or fever suggestive of intercurrent illnesses (e.g., sepsis or meningitis) Incontinence Normal blood pressure or hypotension and respiratory compromise
Late Signs	Clinical seizures may or may not be apparent Pulmonary oedema with respiratory failure Cardiac failure (dysrhythmias, arrest, cardiogenic shock) Hypotension or hypertension Disseminated intravascular coagulation, multi system organ failure Rhabdomyolysis Hyperpyremia

EPIDEMIOLOGY AND ETIOLOGICAL FACTOR

The incidence of SE has been estimated at 10 to 41 cases per 100,000 people per year, accounting for approximately 100,000 to 160,000 individuals per year in the United States, most of who are patients with epilepsy and approximately 5% of adults and 10% to 25% of children[12]. Most episodes that occur in known epileptics occur because of acute anticonvulsant withdrawal, a metabolic disorder or concurrent illness, or progression of a pre-existing neurological disease. Common etiologies are infection of CNS or other infection, metabolic, low anti epileptic drug levels, alcohol, idiopathic type II (structural lesion), anoxia/hypoxia, CNS tumour, cerebrovascular accident, drug overdose, haemorrhage, trauma, remote causes. The most frequent precipitating events in adults are cerebrovascular disease, withdrawal of anticonvulsants, and low anticonvulsant serum concentrations. Cerebrovascular disease is the leading cause of GCSE in those who have their first seizures after age 60[13].

PATHOGENESIS

Seizures occur when the excitatory neurotransmission overcomes inhibitory impulses in one or more brain regions. Although the exact cellular mechanisms responsible for the production of abnormal neural impulses are unknown, it appears that seizure initiation is caused by an imbalance between excitatory (e.g., glutamate, calcium, sodium, substance P, and neurokinin B) and inhibitory neurotransmission [e.g., GABA (γ-Amino butyric acid), adenosine, potassium, neuropeptide Y, opioid peptides, and galanin][14]. Repeated seizures produce complex pathophysiologic and biochemical changes in the brain. The first milliseconds to seconds are dominated by the release of neuro-transmitters and modulators, the opening and closing of ion channels, receptor phosphorylation, and desensitization. In seconds to minutes, receptor trafficking, mainly of the GABA and glutamate receptors, is responsible for key adaptations. Receptors can move from the synaptic membrane into endosomes where they are inactive but ready for recycling, or be mobilized from storage sites to the synaptic membrane where they become active. This changes brain excitability by decreasing the number of inhibitory receptors and increasing the number of excitatory receptors in the synaptic membrane[15].

PATHOPHYSIOLOGY

Status epilepticus represents a failure of inherent cellular mechanisms to prevent sustained seizure activity[16]. Two distinct and predictable phases have been identified. Phase I occurs during the first 30 minutes of seizure activity, and phase II begins 60 minutes later. Although these systemic complications affect the prognosis of GCSE, a prolonged seizure can destroy neurons independent of these systemic events[17]. During phase I, each seizure produces marked increases in plasma epinephrine, nor-epinephrine, and steroid concentrations that can cause hypertension, tachycardia, and cardiac arrhythmias. Although blood pressure returns to normal within 60 minutes, mean arterial pressure does not fall below 60 mm Hg[18]. There also may be metabolic and biochemical complications, including respiratory and metabolic acidosis, hyperkalemia, hyponatremia, and azotemia. There is increased sweating and salivation. This has important clinical ramifications in that a patient's seizures can seem to terminate without treatment or when an ineffective therapy is given[19].

MANAGEMENT OF SE WITH FUTURE PERSPECTIVE

Management of status epilepticus depends on severity of situation and urgency. Depend on situation mono-therapy or combination therapy is given and 'Alter gene expression' would be a good target to treat SE as we know that SE changes the expression of genes which can trigger the causes of SE[20]. Important drugs to treat SE:

Benzodiazepines as an initial treatment drug therapy

These drugs act through GABA (A) receptor and causes hyper-polarization of the resting cell membrane[21]. Diazepam has faster onset of action with short duration due to its high lipid solubility and redistributed phenomena[22]. Lorazepam came to limelight due to its long duration of action approx 12 hrs[23]. Lorazepam has safer profile in comparison to diazepam, as confirmed in some clinical studies[24, 25]. These drugs cause some side effects like respiratory depression, hypotension and decreased level of consciousness while lorazepam may have least respiratory depression[26]. Midazolam has both characteristics as it is water soluble at pH 4 due to ring opening structure and is lipid soluble at physiological pH because of its ring closing structure; due to these belongings it has rapid cerebral penetration and short duration of action. Midazolam is complemented with long acting anti status epileptic drugs due to its short acting nature[27]. Table 2 highlights the clinical presentation of SE.

Table 2: Availability of routes and its impact on drug administration[28-33]

Drugs	Route of administration
Lorazepam	Intravenous, rectal, sublingual, intramuscular
Diazepam	Intravenous, rectal, intramuscular(It should not be administered intramuscularly (IM) due to muscle necrosis and sterile abscesses)
Midazolam	Intravenous, rectal, sublingual, intramuscular, buccal and nasal (Good drug for out-hospital treatment or when IV is not available)

Phenytoin and Fosphenytoin

Phenytoin is good for rapid control of seizure with prolong effect and works well where benzodiazepines fail. Phenytoin loading dose for SE is 20 mg/kg with maximum rate of 50 mg/min but sometime it is insufficient and additional 10 mg/kg should be given to patient[34, 35].

Phenytoin causes cardiovascular side effects, hypotention and QT prolongation with added problems of drug interaction. This can be minimized by reducing the infusion rate[36]. Fosphenytoin is a prodrug of phenytoin for parenteral use and its water soluble ability makes it easier and faster administration. It is cleared by serum and hepatic phosphatises to form phenytoin with a conversion half-life of 8 to 15 minutes[37].

Other Agents

Phenobarbital

Phenobarbital has same mechanism of action as benzodiazepines act through GABA (A) receptor but it has more adverse effect like profound respiratory depression, hypotention and decrease cardiac contractility with low blood pressure[38, 39].

Sodium Valproate

Valproate act through prolonged recovery of activated voltage-gated sodium channels and other mechanisms may be mediated through neuronal calcium channels or through its effects on GABA metabolism[40]. Loading doses of 15 to 20 mg/kg in dextrose-containing solutions have been administered safely in SE at a rate of 3 to 6 mg/kg/min with mild-to-moderate and reversible adverse effects[41, 42]. Some case studies revealed valproic acid uses as a second line drug after benzodiazepines to avoid proceeding to a general anaesthetic because of its safety profile and ease of administration[43].

Topiramate

This drug has multiple preventive actions on status epilepticus mediated through receptors. Topiramate act through GABA mediated transmission independently of the benzodiazepine antiepileptic action. It also inhibits excitatory glutamatergic transmission and shows beneficial effects on RSE (Refractory Status Epilepticus). It has been noticed that it delayed neuronal death in prolonged SE with some adverse effects like lethargy[44].

Promising Levetiracetam and Lacosamide

Benzodiazepines and phenytoin impart GABA receptor internalization and traffic result in a prolong SE. Levetiracetam (LEV) act on SV2A receptor, also thought to interact with GABAergic transmission and enhance benzodiazepine efficacy mainly at the early phase of SE in addition it should be given as early as possible in SE . Delay in treatment could be harmful in SE. Most side effects related to LEV are signs or symptoms associated with the central nervous system like somnolence, dizziness, headache and fatigue. The bioequivalence of oral and intravenously administered doses of 1500 to 4000 mg LEV has been demonstrated in human's steady state was reached after 48 hours for the oral and intravenous forms and rapid infusion rates of up to 4000 mg in 15 minutes or 2000 mg in 5 minutes have been well tolerated. LEV is not metabolized hepatically might be a good treatment option in SE with hepatic failure. More clinical investigations are needed on the effectiveness of

LEV in SE. The mechanism of action of lacosamide (LCM) is thought to involve enhancement of slow inactivation of sodium channels. In a study of intravenous and oral administration of lacosamide has showed the LCM was well tolerated and a good promising agent to treat SE but still clinical evaluation of LCM is necessary to treat SE [45, 46].

AMPA receptor antagonist like GYKI 52466

GYKI52466 is a non-competitive AMPA (alpha-amino-3-hydroxy-5-methyl-4- isoxazole-propionic acid) receptor antagonist with good bioavailability[47]. AMPA receptor antagonist may have a broader anticonvulsant spectrum due their blocking action cannot be overcome by high synaptic glutamate levels that may be associated with intense seizure activity [48].

A case study revealed that Adenosine monophosphate receptor antagonist effective in stopping early status epilepticus as well as in late and benzodiazepine-refractory SE. It also minimizes the risk of recurred SE and may act as single agent therapy for SE. It would avoid the cardiovascular side effects which is a major problem of current standard two-agent regimen – one benzodiazepine followed by phenytoin with mild sedative and muscle relaxant side effects. AMPA receptor antagonist is good to cure SE but more clinical study and research necessary for its efficacy and safety towards SE.

MANAGEMENT OF SE IN CHILD

Reasons of SE depend on child age; common cause in child less than five years is febrile SE while trauma and infections are major cause in older children. Table 3 shows management of SE in child.

Table 3: Management of SE in child [49, 50]

Management	Outcome
Initial step: • Maintenance of vital parameters. • Adequate brain oxygenation. • Maintain low blood glucose level.	Prevent further complication of SE
Next step: • Lorazepam 0.05-0.1 mg/kg (i.v.) or 0.1-0.4 mg/kg (rectal). • Diazepam 0.1-0.3 mg/kg at rate not greater than 2 mg/min for a maximum of 2 doses(i.v.) or 0.5-1 mg/kg to a maximum of 10 mg(rectal). • Midazolam 0.1 to 0.2 mg/kg to a maximum of 5mg (mainly intranasal and buccal route). • Phenytoin loading dose of 20 mg/kg and maintenance dose of 5-8 mg/kg/day can be given in two divided	Lorazepam is drug of choice for initial treatment. Diazepam is used if lorazepam is not available and Midazolam is good for out and in patient but further evaluation is needed. Phenytoin is drug of choice when lorazepam and diazepam are ineffective to treat SE. Phenobarbital is long-acting potent drug but may depress respiration and level of consciousness and give that time when benzodiazepines and phenytoin are ineffective to treat SE.

doses after 12-24 hours. • Phenobarbital loading dose of 15-20 mg/kg over 10-30 min with repeated dose of 10 mg/kg every 30 minutes until seizure control.	
Steps for RSE: EEG and blood pressure monitoring with ventilator support might be necessary during RSE. Available drugs are: • **Midazolam** 0.15 mg/kg stat, infusion 0.75-18 µg/kg/minute. • **Diazepam** 0.3 mg/kg stat, infusion 0.01-0.04 mg/kg/minute. • **Propofol** 1-3 mg/kg stat, infusion 2-10 mg/kg/hr. • **Pentobarbital** 5-15 mg/kg stat, infusion 0.5-5 mg/kg/hr. • **Thiopental infusion** 3-4 mg/kg stat, infusion 1-10 mg/kg/min.	If Midazolam is not available Diazepam should be used and propofol can be used as alternative treatment. Pentobarbital and thiopental can be used if conventional drug therapy fails to control RSE

CONCLUSION

SE is a life threatening disease. Conventional therapies may treat SE successfully but more work would be done in some areas like efficacy and side effects of drugs, further understanding of SE mechanism to discover new path for treating SE, awareness among people and practitioners for out and in hospital treatment with better implementation of guidelines. Moreover, new agents like levetiracetam, lacosamide, AMPA receptor antagonist and emerging 'Alter gene expression' come to limelight but more clinical trials should be conducted with regulations to approve these approach for the treatment of SE.

REFERENCES

1. Delorenzo RJ, A prospective, population based epidemiologic study of status epilepticus in Richmond, Virginia, Neurology, 46, 1996, 1029-1035.

2. Hesdorffer DC, Incidence of status epilepticus in Rochester, Minnesota, 1965-1984, Neurology, 50, 1998, 735-745.

3. Foundation of America's Working Group on Status Epilepticus, Treatment of convulsive status epilepticus: recommendations of the Epilepsy, JAMA, 270, 1993, 854-859.

4. Bleck TP, Convulsive disorders: Status epilepticus, Clin Neuropharmacol, 14, 1991, 191-198.

5. Trieman DM, A comparison of four treatments for generalized convulsive status epilepticus cooperative study group, N Engl J Med, 339, 1998, 792-798.

6. Shorvon S, Status epilepticus: its clinical features and treatment in children and adults, Cambridge, England: Cambridge University Press, 1994.

7. Knake S, Rosenow F, Vescovi M, et al, Incidence of status epilepticus in adults in Germany: a prospective, population-based study, Epilepsia, 42, 2001, 714–718.

8. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA, Incidence of status epilepticus in Rochester, Minnesota, 1965 and 1984, Neurology, 50, 1998, 735-741.

9. DeLorenzo RJ, Pellock JM, Towne AR, Boggs J, Epidemiology of status epilepticus, J Clin Neurophysiol, 12, 1995, 316–325.

10. Working Group on Status Epilepticus. Treatment of convulsive status epilepticus: Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus, JAMA, 270, 1993, 854–859.

11. Goodkin HP, Joshi S, Mtchedli~hvili Z, Kapur J, Subunit-specific trafficking of GABA A receptors during status epilepticus, J Neumsci, 50(9), 2009, 2011-2018.

12. Coulter DA, DeLorenzo RJ, Basic mechanisms of status epilepticus, Adv Neurol, 79, 1999, 725-33.

13. Pitkanen A, Efficacy of current antiepileptics to prevent neurodegeneration in epilepsy models, Epilepsy Res, 50, 2002, 141–60.

14. Lothman E, The biochemical basis and pathophysiology of status epilepticus, Neurology, 40, 1990, 13–23.

15. Lothman EW, Bertram EH III, Epileptogenic effects of status epilepticus, Epilepsia, 34, 1993, 59-70.

16. Pitkanen A, Lukasiuk K, Molecular and cellular basis of epileptogenesis in symptomatic epilepsy, Epilepsy Behav, 14, 2009,16-25.

17. Hoppu K, Santavuori P, Diazepam rectal solution for home treatment of acute seizures in children, Acta Paediatr Scand, 70, 1981, 369-372.

18. Greenblatt DJ, Divoll M, Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action, Adv Neurol, 34, 1983, 487-491.

19. Smith BJ, Treatment of status epilepticus, Neurol Clin, 19, 2001, 347-369.

20. Levy RJ, Krall RL, Treatment of status epilepticus with lorazepam, Arch Neurol, 41, 1984, 605-611.

21. Dooley JM, Rectal use of benzodiazepines, Epilepsia, 39, 1998; 24-27.

22. Edward M.Manno, New Management Strategies in the Treatment of Status Epilepticus, Mayo Clin Proc, 78, 2003, 508-518.

23. Rey E, Treluyer JM, Pons G, Pharmacokinetic optimization of benzodiazepine therapy for acute seizures: focus on delivery routes, Clin Pharmacokinet, 36, 1999, 409-424.

24. Bongard FS, Sue DY, Current critical care diagnosis & treatment. 2nd ed. New York: Lange Medical Books/McGraw–Hill; 2002, p.119.

25. Yoshikawa H, Yamazaki S, Abe T, Oda Y, Midazolam as a first line agent for status epilepticus in children, Brain Dev, 22, 2000, 239-242.

26. Towne AR, DeLorenzo RJ, Use of intramuscular midazolam for status epilepticus, J Emerg Med, 17, 1999, 323-328.

27. Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus, JAMA, 270, 1993, 854-859.

28. Lowenstein DH, Alldredge BK, Status epilepticus, N Engl J Med, 338, 1998, 970-976.

29. Schumacher GE, Barr JT, Browne TR, Collins JF, Veterans Administration Epilepsy Cooperative Study Group- Test performance characteristics of the serum phenytoin concentration (SPC): the relationship between SPC and patient response, Ther Drug Monit, 13, 1991, 318-324.

30. Browne TR, Kugler AR, Eldon MA. Pharmacology and pharmacokinetics of fosphenytoin, Neurology, 46(6), 1996, 3-7.

31. Graves N, Pharmacoeconomic considerations in treatment options for acute seizures, J Child Neurol, 13, 1998, 27-29.

32. O'Brien TJ, Cascino GD, So EL, Hanna DR, Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin, Neurology, 51,1998,1034-1039.

33. Mazarati AM, Baldwin RA, Sankar R, Wasterlain CG, Time dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus, Brain Res, 814, 1998, 179-185.

34. Goldberg MA, McIntyre HB, Barbiturates in the treatment of status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Porter RJ, editors. Advances in neurology Vol. 34 Status epilepticus: Mechanisms of brain damage and treatment. New York: Raven Press; 1983 p. 499-503.

35. Mc Namara JO, Drugs effective in the therapy of the epilepsies. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's The Pharmacologic Basis of Therapeutics. 10th Ed. New York, 2001:521-547.

36. Ramsay RE, Cantrell D, Johnson ME, Safety of high-dose rapid infusion of intravenous valproic acid, Neurology, 54(3), 2000, 11.

37. Venkataraman V, Wheless JW, Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients, Epilepsy Res, 35, 1999, 147-153.

38. Petroff OA, Hyder F, Rothman DL, Mattson RH, Topiramate rapidly raises brain GABA in epilepsy patients, Epilepsia, 42, 2001, 543-548.

39. Gibbs JW, Sombati S, DeLorenzo RJ, Coulter DA, Cellular actions of topiramate: Blockade of kainate-evoked inward currents in hippocampal neurons, Epilepsia, 41, 2000, S10-S16.

40. Niebauer M, Gruenthal M, Topiramate reduces neuronal injury after experimental status epilepticus, Brain Res, 837, 1999, 263-269.

41. Chen JWY, Naylor DE, Wasterlain CG, Advances in the pathophysiology of status epilepticus, Acta Neurol Scand, 115, 2007, S7-S15.

42. Rigo J-M, Nguyen L. Rochcr Y, Belachew S, Malgrange B, Lcprime P, Mooncn G, Sclak I. Matagne A, Klitgaard H, The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents, Hr J Pharmacol, 136, 2002, 659-667.

43. Lynch BA, Lambeng N, Nocka K, Kcnsel-Hammes P, Bajjalieh SM, Matagne A, Fuks B, The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levcliracetam, Pmc Natl Acad Sci USA, 101, 2004, 9861-9866.

44. Mazarali AM, Baldwin R, Klilgaard H, Matagne A, Waslerlain CG, Anticonvulsant effects of levetiracetam and levetiracetam diazepam combinations in experimental status, Epilepsy Res, 58, 2004, 167-174.

45. Towne AR, Waterhouse EJ, Boggs JG, Prevalence of nonconvulsive status epilepticus in comatose patients, Neurology, 54, 2000, 340-345.

46. H. Meierkord, EFNS guideline on the management of status epilepticus in adults. European Journal of Neurology, 17, 2010, 348–355.

47. G Rajshekher, Recent trends in the management of status epilepticus, 9, 2005, 52-63.

48. Mishra, et al, Status epilepticus in central nervous system infections: An experience from a developing country, The American journal of medicine, 121, 2008, 618-623.

49. Singhi S, Singhi P, Dass R, Status epilepticus: Emergency management, Indian J Paediatric, 70, 2003, 1–22.

50. Behera MK, Rana KS, Kanitkar M, Adhikari KM, Status Epilepticus in Children, MJAFI, 61, 2005, 174-178.

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