TREATMENT OF REFRACTORY STATUS EPILEPTICUS

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Definition

Refractory status epilepticus (RSE) is defined as seizure activity which persists for over 2 hours and after failing two first line treatments, usually a benzodiazepine and a conventional intravenous antiepileptic medication. The established status epilepticus trial which started enrollment 2015 will address the question which second line intravenous antiepileptic agent, phenytoin, valproate or levetiracetam, may be favorable. For patients in refractory convulsive status epilepticus, general anesthesia is usually recommended after failing two first line drugs with the goal to achieve EEG to stop electrographic seizure activity and to prevent excitoxicity associated with prolonged convulsive seizure activity.

Super-refractory status epilepticus (SRSE) is defined as status epilepticus that continues or recurs 24 hours or more after the onset of anesthetic therapy (Shorvon S and Ferlisi M, Brain 2011).

Refractory Status Epilepticus (RSE)

A standardized and timely treatment protocol for patients in refractory convulsive status epilepticus is highly recommended (Brophy GM et al, Neurocrit Care 2012). The three first line anesthetic agents are pentobarbital, propofol and midazolam.

Barbiturate anesthesia with pentobarbital is the traditional first line agent and has a strong anti-epileptic effect, is relatively safe and may provide neuroprotection by lowering body temperature. Barbiturate act by enhancing GABA(A) receptor function. The major two disadvantages is their zero order kinetics leading to rapid redistribution and tendency to accumulate associated with a long half-life and prolonged recovery over days even after only a short infusion for 12-24 hours. The second disadvantage is hypotension and cardiorespiratory depression often requiring additional vasopressor therapy. Other disadvantages are drug interactions, autoinduction, pharmacologic tolerance, pancreatic and hepatic toxicity.

Propofol increases GABA(A) receptor function and has a remarkable quick onset and recovery even after prolonged infusion which allows relatively instant control of the anesthesia level. The major disadvantage is the risk of a propofol infusion syndrome (PRIS) which is seen with more prolonged anesthesia but which can occur even during short-term anesthesia (Iyer VN, 2009). PRIS is heralded by metabolic acidosis, lactic acidosis, rhabdomyolysis, hyperkalemia, cardiac arrhythmia and dysfunction, and renal failure with a potentially lethal outcome due to mitochondrial and metabolic dysfunction.

Midazolam has become a widely used short acting benzodiazepine suitable for prolonged infusion without accumulation. It acts by binding and enhancing GABA(A) receptor function and has a strong anti-epileptic effect. Major disadvantage is the often rapid onset of tolerance and seizure relapse. It is a cardiorespiratory depressant, although the effect is usually less pronounced than with barbiturates.

Drug	Initial Dose (adults)	Continuous infusion
Pentobarbital	5-15 mg/kg (at <50mg/min)	0.5-5 mg/kg/h
Thiopental	2-7 mg/kg (at < 50mg/min)	0.5-5 mg/kg/h
Propofol	1-2 mg/kg load; Start at 20mcg/kg/min	30-200 mcg/kg/min
Midazolam	0.2 mg/kg (at 2mg/min)	0.05-2 mg/kg/hr

General anesthesia is often avoided or delayed in patients with RSE which did not initially present with generalized convulsions, including patients in absence status, partial status epilepticus, and postanoxic status epilepticus. Several alternative antiepileptic medications have been used in this situation including valproic acid, levetiracetam, clonazepam, topiramate, lacosamide and phenobarbital.

Ketamine (bolus: 0.5-3 mg/kg in adults; continuous infusion: up to 5 mg/kg/h) can be considered as an alternative anesthetic agents in patients who cannot tolerate the cardiodepressant effect and hypotension associated with the first line anesthetics. Ketamine acts as an NMDA receptor antagonist which is potentially neuroprotective and has a sympathomimetic effect which may lead to a raise rather than fall in blood pressure. A neurotoxic effect cannot be ruled out given the limited available data.

Commonly, patients who undergo general anesthesia for RSE are kept on antiepileptic medications to provide adequate coverage when anesthesia is tapered. Anesthesia is initially reversed 24-48 hours after burst suppression and seizure cessation was achieved and re-established in progressively longer cycles if seizures recur. During that time, additional antiepileptic medications are often added to optimize the chance of anesthesia weaning. More than two antiepileptic medications in high therapeutic dose range are usually not recommended and frequent and rapid changes should be avoided.

Super-Refractory Status Epilepticus (SRSE)

A systematic approach to patients in SRSE is paramount and has to include a diligent workup for an underlying, potentially treatable cause. In the majority of patients, the etiology is readily apparent, often including severe brain insults from a trauma, stroke or infection (Neligan A, 2010; Tan RYL, 2010).

Rare causes of SRSE

Immunologic (Davis R, 2013)	Intracellular paraneoplastic: Hu, CV2/CRMP5, Ma2, Amphyphysin Cell surface: NMDA, LGIl, Caspr2, GABA(B), AMPAR (GluR I/2), mGluR5, DPPX, GAD Unclear significance: AMPAR (GluR3), VGKC other than LGIl/Caspr2, TPO
Mitochondrial disorders	Alpers, MELAS, Leigh, MERRF, NARP
Uncommon infections	Atypical bacteria, prion disease, fungal, viral
Drugs/Toxins	AEDs, antimicrobials/antiviral drugs, antipsychotics, contrast media, chemotherapeutics, toxins.
Genetic disorders	Chromosomal abnormalities, malformation of cortical development, neurocutaneous syndromes, channelopathies

CRMP5 - collapsin response mediator protein-5; GAD - glutamic acid decarboxylase; NMDAR - N-methyl-D aspartate receptor, LGI1 - leucine rich glioma inactivated protein 1, Caspr2 - contactin-associated protein-like 2, GABA(B) receptor, c-aminobutyric acid-B receptor, AMPAR - alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptor, mGluR5 - metabotropic glutamate receptor 5, DPPX - dipeptidyl-peptidase-like protein-6.

Magnesium sulfate and in children pyridoxine infusion can be considered given the minimal side effect risk, despite lack of evidence for efficacy of magnesium sulfate outside peri-partum seizures and in children without pyridoxine deficiency syndrome.

GABAA receptor positive allosteric modulator neuroactive steroids, such as allopregnanolone, potentiate synaptic GABAA receptors and may enhance extrasynaptic GABAA receptors. A trial using allopregnanolone as adjunctive therapy for patients with SRSE is currently under way.

The next step after failure of general anesthesia is to consider steroids and immunotherapy and, in patients with an amenable lesion, epilepsy surgery (Shorvon SD, 2011). The efficacy of steroids and immunotherapy without evidence for an immune-mediated etiology is low. Steroids may be helpful to reduce the inflammatory cascade associated with prolonged status epilepticus and there is experimental evidence suggesting that early administration within the first week may be more beneficial even for patients without an immunologic cause.

Immunotherapy often includes plasmapheresis or immunoglobulins after an initial steroid trial and after sending off autoimmune antibody panels in serum and if necessary CSF. If those treatments fail, cyclophosphamide and rituximab should be considered in patients with evidence of an autoimmune process.

Patients in SRSE attributable to a circumscribed epileptogenic lesion with corroborating semiologic and neurophysiologic and functional imaging data can be considered for epileptic surgery, as early as two weeks after onset of the SE (Lhatoo SD, 2007). According to the limited literature, the outcome has been promising.

If those measures fail, ketogenic diet, brain stimulation and hypothermia can be considered as last resorts for patients in SRSE.

The ketogenic diet is theoretically easy to administer in a controlled environment such as the intensive care unit. However, collaboration not only of the nutritionist but also the nursing staff and pharmacologist are mandatory to restrict any glucose administration particularly through intravenous fluids. Contraindications are patients with pyruvate carboxylate and β-oxidiation deficiencies. A 4:1 ketogenic diet is usually recommended. Blood glucose should be checked regularly and once ketosis is obtained, urinary ketosis should be measured daily and β-hydroxybutyrate weekly.

The results of transcranial magnetic stimulation, deep brain stimulation and vagal nerve stimulation for SRSE have been largely anecdotal. Electroconvulsive therapy was first used for status epilepticus in the 1930s. The effect is attributed to release of presynaptic GABA and increase of the postictal refractory period. Anesthetic drugs and antiepileptic medications may have to be weaned to allow successful stimulation which is carried out daily for a period of a week.

Hypothermia is typically induced by endovascular cooling. Mild hypothermia (32-35°C) is recommended to avoid side effects and maintained for 24-48 hours as a trial and can be continued if the response is positive.

Summary

The treatment of refractory and super-refractory convulsive status epilepticus is a neurological emergency and a standardized protocol is highly recommended and should be applied expediently. SRSE is defined by the failure of general anesthesia to stop the seizure activity within 24 hours and is associated with a mortality of 30-50%. For patients with evidence for an immunologic etiology or a resectable epileptogenic lesion, specific therapy can improve outcome. A number of trials are under way to determine the best second line treatment for status epilepticus and the usefulness of adjunctive therapies.

References

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