

# How Refractory is Super-Refractory Status Epilepticus- A Personal View!



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## Abstract

Super-refractory status epilepticus is named for those continuous un-abated ,prolonged seizure activity, despite aggressive treatment including general anesthesia, lasting more than 24 hours. There is ongoing serious damage to the neuraxis, in such cases, if seizures continue, over longer time and the important issue in the management is to prevent the damage by interfering its activity, liberally in the initial stage of the seizures, itself. As the seizures prolong, structural as well molecular changes of the neurons could interfere in the management profile also, however aggressive, it could be.

## Introduction

The word, super-refractory is coined recently in status epilepticus (SE) when the seizures continue unabated for a day or more, despite rigorous management , leading to subsequent neuronal injury, most of the times and even death [1]. The Super-Refractory Status Epilepticus is a rare but not uncommon type of ongoing seizure activity and the exact pathophysiology is still not yet studied well. This type of seizure activity is commonly encountered in intensive care units but the exact frequency is not yet known. There were many retrospective studies in the recent past, revealing approximately 15% of cases admitted with status epilepticus, became refractory and Holktemp [2] reported 20% of his patients with SE had recurrence of ongoing SE after even general anesthesia was withdrawn and in some other studies nearly 50% of the those requiring anesthesia became super refractory in the various settings. In the ideal management protocol of SE, in staged approach, seizures of less than 30 minutes (early SE).

Benzodiazepines are administered by intravenous/rectal/intranasal/buccal and sometimes intramuscular routes, but the main aim is to rapidly abort the seizures by any means in order to arrest seizure propagation, further. In stage 2 seizure continuation (established SE), long acting anticonvulsants namely Phenytoin, sodium valproate and sometimes phenobarbitone are given by intravenous route and control is anticipated up to 2hrs. Beyond this period, if patient reaches stage 3 (refractory SE) within 120 mts, one should resort to general anesthesia, muscle relaxants to achieve burst suppression in EEG wherein seizures are aborted

both by clinical but also by electrographic al methods. Many protocols have been laid down as algorithm flow charts in many centers , approved by international bodies and the main aim of such aggressive management is to abort the seizure propagation and avoid further neuronal damage [3].

Despite all these aggressive measures, then why some of the patients go on to develop resistance to treatment and become super refractory SE (24 hrs or more)? Although often encountered in patients with established epilepsy with underlying cryptogenic or secondary etiology (head trauma, infection, infarction, cerebral bleed) it is not uncommon to see this in previously healthy people also. Probably the normal physiological process that could terminate the seizure activity has failed in them, mostly the receptors of the axonal surface becoming externalized rather than internalization. In this process, there is considerable reduction in GABA receptors (inhibitory) and substantial increase in glutaminergic (excitatory) receptors.

Once the GABAergic receptors levels are reduced the GABAergic drugs (phenobarbitone, benzodiazepines) are likely to become ineffective in this ongoing process of seizure activity. Moreover, normal inhibitory GABA-A mediated currents in the external ionic milieu become excitatory with changes in extra cellular chloride concentrations. Besides, inflammatory cascade activation during ongoing seizure propagation, blood-barrier leakage leading to increase in extracellular potassium and mitochondrial failure with oxidative stress could also

perpetuate the process of continued insult [4]. Additionally gene expression within few minutes of seizures and lack of synchrony of neuronal network could prevent seizure termination however aggressive the treatment is given. The underlying damage to the cerebral internal milieu is devastating with necrosis, gliosis and network reorganization, ultimately leading into cell death.

This is initiated first by excitotoxicity and further driven by glutaminergic receptor over-activity. Once the damage initiated, calcium influx into the cell triggers cascade of chemical reactions and lead to cell necrosis or apoptosis. This chain of events usually takes place after the continuation of the seizure process and lead to neuronal remodeling, activation of several molecular signal pathways to activate programmed cell death. As a result, in the long term histological structural changes namely neurogenesis, angiogenesis are seen. In order to prevent these irreversible events, aggressive management to the extent of general anesthesia to induce electrographic burst suppression is highly recommended and several neuro protective measures (barbiturate coma, hypothermia, steroids, intravenous immunoglobulins, ketamine) are attempted to prevent sequel of excitotoxicity although the efficacy of later measures is unknown.

### Discussion

The management of super refractory SE is very challenging and always managed in intensive care units with general anesthesia, endotracheal intubation and ventilation, cardio pulmonary monitoring. Maintaining the hemodynamic status is the main stay in the management portfolio as drugs used to control seizures at maximum doses would invariably give rise to hypotension, bradycardia and respiratory arrest. Midazolam infusion, thiopental, pentobarbital and propofol are preferred to induce deep sedation and burst suppression although there is low threshold for the later drug usage in many centers for children because of its potential lethal side effects (propofol infusion syndrome) [5].

Selection of the above medications depend upon the availability, personal experiences and acceptable limit of side effects. Midazolam is a safe medication as continuous infusion because of its strong and established anti-epileptic action but tachyphylaxis and rapid tolerance is the main disadvantage; as a result, seizure emerge in nearly 50% of the patients. Barbiturates infusion have been used conventionally in the past in SE and apart from its known anti epileptic action, hypothermia induced by this drug could be theoretically beneficial as neuro-protection. However, due to long half-life, the prolonged anesthetic effect even after the drug has been withdrawn may be a major problem of extubation. Ketamine, a NMDA receptor antagonist is used in some centers because of it least cardiac depressant effect and could be considered as second choice, if the anesthetic drugs fail.

What about anti epileptic drug armamentarium, apart from above? Many patients end up taking cocktail of several drugs

namely carbamazepine, phenytoin, phenobarbitone, valproate, topiramate, levetiracetam, but there is no evidence that single drug is superior to other medications [6]. So it's the choice for the treating neurologists to decide about the combinations as most of the times, these patients are on polytherapy. However, it is recommended not to use more than two anti-epileptic medications with different mode of actions at higher doses and to avoid frequent and abrupt switch-over of the drugs. Magnesium sulfate infusion is a safe and least toxic medication and must be attempted in every patient with super refractory SE. what about steroids and immunomodulators? Recent evidence prove that inflammation play an important role in seizure propagation and moreover the recently evolved autoimmune encephalitis with increase in N methyl D aspartate antibody and status epilepticus, steroids or immunomodulators could only control seizure activity [7].

With this background, many centers use these medications, even inadvertently, in refractory SE with varying results. Other measures namely, ketogenic diet, hypothermia, electroconvulsive therapy are available and being tried as experimental modes of therapy with no conclusive evidence of its use. So in conclusion, super refractory SE is a grave situation in the stages of SE evolution with relatively high mortality and morbidity. Yet, there is no consensus opinion regarding effective management of this and one has to be aggressive and rational in the initial stages of treatment of SE and theoretically prevent patients progressing to this serious stage of SE. Treatable causes of SE must be identified early and managed appropriately. An acceptable treatment protocol and guidelines should be formulated in every center, agreed upon by the governing committee in concurrence with the neurologists and effectively treat the condition [8].

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