



## Management of super refractory status epilepticus

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### ABSTRACT

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**Received:** 24 Oct 2018

**Reviewed:** 28 Oct 2018

**Accepted:** 6 Nov 2018

Super refractory status epilepticus (SRSE) is the status epilepticus in which the seizures continue for 24 hour or more after anesthetic medications to control and reappear when the patient is weaned from the anesthetic agent. Characteristic seizures are distinguished, by the presence and/or absence of motor seizure, into convulsive and non-convulsive status epilepticus (NCSE). An aggressive therapy is often needed after diagnosis is confirmed. Continuous monitoring during therapy is very important. The management for SRSE includes pharmacological and non-pharmacological treatment. Clinical and electrographic seizure suppression is the treatment goal. After that we need to find and treat the cause of seizures. Clinical judgement by the clinician is needed to identify the risks of excessive suppression of the nervous system, so as the morbidity and mortality is reduced for those patients who can survive but often have difficult and prolonged recovery.

**Key words:** Super refractory status epilepticus; Management, Seizures; Pharmacological treatment; Non- pharmacological treatment

**Citation:** Kurniawan D, Machin A, Hidayati HB, Islamiyah WR. Management of super refractory status epilepticus. *Anaesth Pain & Intensiv Care* 2018;22 Suppl 1:S67-S72

## INTRODUCTION

The description of status epilepticus (SE) was first found on the *Sakikku cuneiform tablets*. SE was defined clinically by Bourneville in 1876. SE is defined as a seizure sustained for longer than 5 minutes or two or more seizures without recovering to the neurological baseline in between seizures. SE is said to be super refractory status epilepticus (SRSE) when the seizures persist or recurs for 24 hours or more after the anesthetic medications and reappear when the patient is weaned from the anesthetic agents.<sup>1</sup>

SRSE can be found in two clinical situations: severe acute brain injury with no history of epilepsy before, or with no obvious cause. This condition has been known as new onset RSE (NORSE) found uncommonly. It is characterised by long periods of refractory seizures without a cause and it can be found in healthy people.<sup>2,3</sup>

SE can be distinguished by the presence and/

or absence of motor seizure into convulsive and non-convulsive status epilepticus (NCSE). The accuracy of the clinical classification and diagnosis is important for the management and to prevent the possible systemic complications. NCSE patients are divided into two groups; in first group the patients with automatism and behavioural changes are included. Second group involves the patients with brain injury causing decreased of consciousness or coma. Convulsive status epilepticus (CSE) can also turn to NCSE.<sup>2</sup>

## EPIDEMIOLOGY

In Asia, a study was conducted in a neurointensive care unit in West China over a period of 4 years (2009 - 2012) in a total of 98 patients. The incidence of NRSE was 67.3%, RSE 20.4% and SRSE 12.2%.<sup>5</sup> mortality, and risk factors of super-refractory status epilepticus (SRSE) Out of SRSE patients, 67.7% suffered from encephalitis and compared with a

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general SE, the mortality was 7 %. The encephalitis was the most important cause for progression from NRSE to SRSE.<sup>6</sup> data of patients with convulsive SE admitted in neurointensive care unit (NICU In the other study, the incidence of patients with SRSE was about 4 % to 9 % of the SE cases.<sup>7</sup> super-refractory status epilepticus (SRSE<sup>8</sup> estimated RSE frequency is between 31% and 43% of patients presenting an SE episode; almost all seem to require a coma induction for treatment. We prospectively assessed RSE frequency, clinical predictors, and outcome in a tertiary clinical setting. **METHODS:** Over 2 years we collected 128 consecutive SE episodes (118 patients

### PATHOPHYSIOLOGY

Mitochondrial failure has been shown as an alternative pathophysiology for SRSE development.<sup>9</sup> Inflammation has also been recognized as a cause in the pathophysiology of SRSE.<sup>10</sup> From uncommon causes of SE found from 588 articles, the most common etiologic factors for SE are autoimmune disorders and inflammation.<sup>10</sup> In this condition, the major role for the preservation of seizures was the loosening of the blood brain barrier (BBB). The main mechanism was maladaptive response of the astrocytes which causes damage of BBB, leading to induced leukocyte–endothelial interactions, stimulating the innate immune system and disrupting extracellular potassium and homeostasis of glutamate, resulting

into BBB break-down which causes severe seizures.<sup>11</sup>

No genetic factor is known that may contribute to lack of successful termination of the seizure, even though it has been known that changes in gene expression are responsible to keep up the maladaptive response that leads to SRSE. Changes in gene expression are the conjunctive effects of recurrent seizures, of neuronal death., and of the next neuronal reorganization.

### DIAGNOSIS

The diagnosis of convulsive SRSE is mainly clinical, investigations should be done quickly. First, any people who witnessed the events are interviewed; next, after convulsive SRSE is stopped, neurological examination is conducted to see any nuchal rigidity or other focal neurological deficit. We must rule out a differential diagnosis, like rigors related to sepsis, tremors, dystonia, and myoclonus. Non convulsive SRSE can happen with refined clinical signs and could be suspected as acute encephalopathy. Neuroimaging is also needed (for structural lesions that can be the cause for the seizures). Head CT scan with or without contrast, (or head MRI with or without contrast) can easily identify intracranial hemorrhage, vascular malformation, brain tumor, stroke, brain abscess etc., but the MRI is more sensitive for identifying the structural lesions Next modality is electroencephalography (EEG); especially

continuous electroencephalography with visual live monitoring, to know the response to therapy, has been described as the best diagnostic method. Immuno-serology test for autoimmune disease, infection, paraneoplastic agents should also be done. The levels of anti-epileptic drugs in the blood are checked (including free levels, if available). Tests for toxicology (heavy metals), and genetic analysis may be needed (if there is a family history that has the same or similar symptoms).<sup>1,2,12</sup>

After completing neuroimaging (CT scan and MRI with and without contrast) and there is no contraindication, lumbar puncture is done and cerebrospinal fluid is checked to find etiologies such as infections (viruses, bacteria, parasites, fungi) or a paraneoplastic condition.

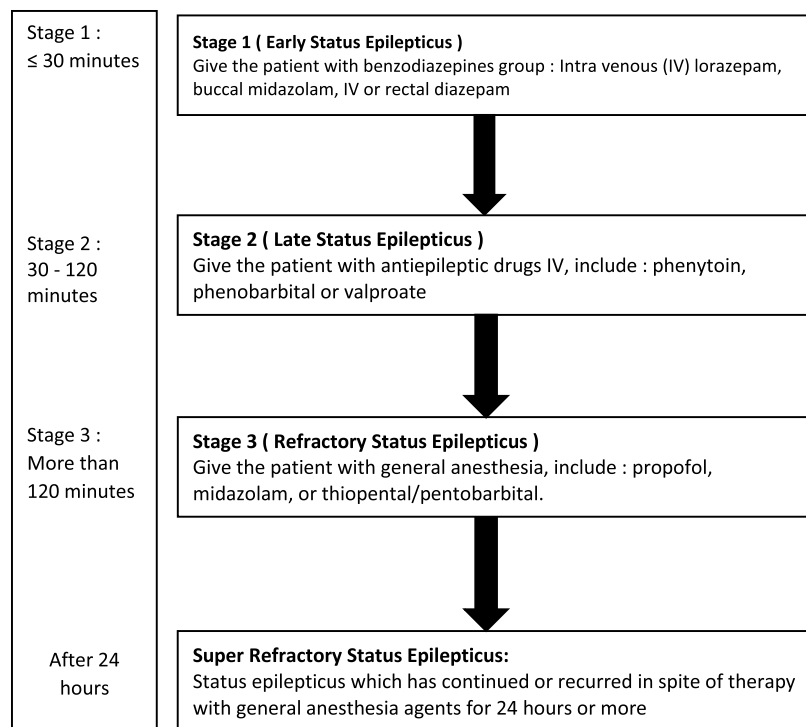


Figure 1. The stages of treatment of status epilepticus<sup>4</sup>

## MANAGEMENT APPROACH

Patients with SRSE should be treated in the intensive care unit. Patients treated in neuro intensive care unit showed better results than those treated in the general ICU. Aggressive therapy was needed in SE. There is increasing excitatory activity and decreased inhibitory activity, which happened at the same time. If this progresses, the seizures seem to become resistant with antiepileptic drug discontinuation (AED), especially drug which have action on GABA system, like benzodiazepine and barbiturates,<sup>13</sup> with emphasis on epidemiology, etiologies, therapeutic approaches, and clinical outcomes. Methods: Narrative review of the medical literature using MEDLINE database. Results: RSE is defined as status epilepticus (SE because of that SE can become RSE and SRSE.

The management approach includes four stages;

**Stage 1:** The patient is intubated, mechanically ventilated, full cardiovascular monitoring and continuous EEG. Intravenous anesthetic agents have been very useful for the symptomatic treatment in patients with SRSE.<sup>14</sup> These include midazolam, propofol, thiopental or pentobarbital. Dosage for midazolam: 0.2 mg/kg IV bolus, could be repeated every 5-10 min up to a total of 2 mg/kg, begin for infusion 0.1 - 0.2 mg/kg/h; propofol 2 mg/kg bolus IV and 150 µg/kg/min for infusion; thiopental 4 mg/kg loading dose IV and 0.3-0.4 mg/kg/min infusion; pentobarbital 10 mg/kg loading dose IV, it can be repeated till burst-suppression effect on EEG. Starting infusion is 1 mg/kg/h and is titrated up to 10 mg/kg/h. AEDs are continued if these had been started earlier. AEDs are usually given concomitantly with anesthetic agents for SRSE treatment. This is to prevent seizures after weaning from anesthesia that usually occurs 24 to 48 hour after the therapy. Regarding AEDs there has been no data for their precise role, and the effectiveness of each AED. There are no randomized trials comparing different AEDs for the SRSE cases. However, there are various studies that explain the usefulness of AEDs for SE cases.<sup>15</sup>

**Stage 2:** If seizures fail to control or there are recurrent seizures after decreasing the dosage, same drug is used in a dose used 1 week back, or go directly to stage 3.

**Stage 3:** If seizures still occur, use alternative therapies, including: ketamine 0.5 – 4.5 mg/kg bolus IV and start infusion up to 5 mg/kg/h, magnesium 4 g bolus IV and 2-6 g/h infusion (keep serum levels < 6 mEq/L); pyridoxine (vitamin B6) 100-600 mg/day IV or via naso/orogastric tube; methylprednisolone 1 g/

day IV for 5 days, followed by prednisone 1 mg/kg/day for 1 week. Other regimens include immunoglobulin (IG) 0.4 g/kg/day IV for 5 days, plasmapheresis for 5 sessions, hypothermia with temperature 33-35 °C for 24 to 48 h and rewarming 0.1-0.2 °C/h, ketogenic diet 4:1, electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and neurosurgical resection for epileptogenic focus.

**Stage 4:** If weaning has failed several times and within a few weeks, end-of-life decisions are discussed with family or the person who has the right to make decision.<sup>15</sup>

## PHARMACOLOGICAL TREATMENT

### 1. Midazolam

Midazolam is an anesthetic agent that is used to treat patients with RSE and SRSE. It quickly penetrates into the central nervous system, the onset of action is fast, and duration of action is adequate without the risk of accumulation, the half-life being 0.8-2.8 hours.<sup>2 13</sup> The mechanism of action of midazolam is binding at and enhancing the action of GABA alpha receptors. The main advantage is its strong anti-epileptic effect. The disadvantage is predisposition to recurrent seizures; the occurrence of seizure again in 47% to 57%.<sup>16,17</sup> In another study, midazolam controlled seizures in 78%, but failed in 16% of patients. Mortality using midazolam was reported at 2%. The adverse effects of midazolam include: respiratory depression and hypotension.<sup>1,18</sup>

### 2. Propofol

Propofol is an anesthetic agent that used to the treatment of RSE and SRSE. The main action was through modulation of GABA alpha receptor and N-methyl-D-aspartate (NMDA) antagonism. Propofol is short-acting, the onset of action is rapid. The advantage: lowers intracranial pressure and lowers cerebral metabolism. The main disadvantage is the risk of suffering from propofol infusion syndrome (PRIS).<sup>18</sup> Other side effects are involuntary movements, lactic acidosis, hypertriglyceridemia and rhabdomyolysis. The involuntary movements occur due to lowered inhibition in cortical areas or it might possibly be peripheral in nature. Propofol is effective in control seizures in 68% patients with RSE and SRSE, and the incidence of therapy failure was 11% and recurrent seizures were seen in 1% and withdrawal seizures in 6%, respectively.<sup>18,19</sup>

### 3. Ketamine

Ketamine is an anesthetic agent that has dual effect,

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binding to the GABA alpha receptor and as NMDA receptor antagonist. Effect as cardiac depressant was minimal. From a study in 58 patients, ketamine controlled seizure in 12% of the patients. For infusion > 0.9 mg/kg/h there was no response, or when it was given for 8 days or more after onset of SE, or after failure of treatment with seven or more drugs.<sup>20</sup> Long-term complication of brain atrophy may be related to excitotoxicity caused by ketamine, so the clinicians must be careful while using it for a long time.<sup>21</sup>

### 4. Barbiturates

Barbiturates are the most effective in aborting SE, but for withdrawal seizures on weaning, barbiturates are not the choice. Thiopental is the choice barbiturate in Europe, but in North America, pentobarbital is preferred for treatment of SRSE. It has neuroprotective effect and acts by enhancing the action of the GABA receptor. It lowers core body temperature, which may improve the antiepileptic effect of barbiturates. The disadvantages: it has rapid redistribution, have a profound predisposition to accumulation resulting in a long half-life in anesthesia, long recovery time, causes hypotension and cardiorespiratory depression, risk of pancreatic and hepatic dysfunction, and risk of toxicity especially in the elderly.<sup>4</sup> Some clinicians have found that RSE and SRSE was controlled by barbiturates in 64% of the patients, and it failed in only 5% of the patients and was unable to control seizures.<sup>4,19</sup> Out of all patients discharged from hospital, after one year 74% were dead or were in a condition of unresponsive wakefulness, 16% were severely disabled, and only 10% had minimal or no disability.<sup>22</sup>

### 5. Magnesium

Magnesium is the drug of choice for patients with preeclampsia and eclampsia. The mechanism of action is by blocking NMDA receptors. This drug has low incidence of the most severe side effects. From 9556 women who were given magnesium, the side effect for affected patellar reflex was 1.6% and respiratory depression 1.3%. But a blood level of magnesium > 8 mEq/L, has a risk of cardiovascular system failure.<sup>23,24</sup>

### 6. Pyridoxine

Pyridoxine (vitamin B6) has been advised for the supportive treatment of SRSE.<sup>15</sup> It is a coenzyme for conversion of glutamic acid to become GABA by glutamic acid decarboxylase. But for patients with epilepsy and without pyridoxine dependency there was not enough evidence that it can help reduce the seizures in patients with non vitamin B6-dependent refractory seizures when given vitamin B6

supplementation.<sup>25</sup>

## 7. Steroids and Immunotherapy

The immunological and immunogenetic abnormalities are often found in patient with epilepsy, and it has been recognized that SRSE may be caused by antibodies directed against neuron element. It was thought that many cryptogenic cases might be caused by immunological diseases due to antibodies that have yet to be identified, or perhaps the persistence of the status epilepticus is due to immunological processes. Because of that the steroids were used together with the AEDs. The dose for corticosteroids was 1 gram methylprednisolone IV for 5 days, followed by 1 mg/kg prednisone/day) with or without IG (2 g/kg over 5 days) or with plasmapheresis.<sup>2,26</sup>

## NON-PHARMACOLOGICAL TREATMENT

### 1. Hypothermia

Hypothermia has been used for patients with SRSE. Hypothermia has been suggested to reduce excitatory transmissions, decrease the global cerebral metabolic demand for glucose and oxygen, to reduce the breakdown of ATP, and to provoke glycolysis which can increase energy production. Hypothermia is induced and maintained using special blanket and a temperature of 34–35°C is achieved within 5 hour. It is not a harmless treatment and should be used in ICU with experience and care. Hypothermia safety monitoring protocol must be obeyed. The parameters to be checked include: metabolic status, respiratory status, cardiovascular status, renal status, hematological status, infectious diseases. Complications of hypothermia therapy include acid–base disturbances, cardiac arrhythmias, coagulopathy, and ischemia of the gastrointestinal tract.<sup>2,27</sup>

### 2. Ketogenic Diet

Ketogenic diet 4:1 has been recommended, with total avoidance of glucose. Ketogenic diet in one case of status epilepticus was reported by *Cervenka et al.*, it was indicated for patient refractory to medical and surgical treatment; it was stopped after induction of the diet, then switched after 29 days and continued as a modified Atkins diet.<sup>28</sup> Another case reported was treated successfully with the modified Atkins diet alone. The antiepileptic effect and the effectiveness of the ketogenic diet in SRSE may have been caused by a possible anti-inflammatory action.<sup>29</sup>

### 3. Electrical and Magnetic Stimulation

Various forms of electrical stimulation for seizures

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was reported in case reports or small case series.<sup>30</sup> A 26 years old woman was given cortical stimulation with low frequency via subdural electrodes for seven consecutive days. She had been on two anesthetic agents and enteral AEDs (two to four drugs) with high doses. The response was checked after one day and one anesthetic agent was successfully stopped. Seizures only recurred on the 4th day when the second anesthetic agent was reduced by 60%.<sup>31</sup> Three sessions of electroconvulsive therapy (ECT) were given per week (total 6 times) in a patient with SRSE and not responding with pentobarbital, patient had been in coma for 40 days. After the second session, the pentobarbital wasn't used anymore and finally the patient recovered in one month. In a systematic review, the result of retrospective studies showed seizure reduction or seizure control with ECT in 11 out of 19 patients (57.9%), with 4 (21%) having partial response and 7 (36.8%) complete response respectively.<sup>32</sup> Another treatment modality was low frequency repetitive transcranial magnetic stimulation (TMS) which has been used in a patients with focal SRSE. The stimulation was given on the epileptogenic focus in 60 minute sessions daily for 8 days; the patient had clinical and electroencephalographic improvement.<sup>33</sup>

### 4. Vagal Nerve Stimulation

Vagal nerve stimulation could be considered. In a case report, a 30 year old man, who suffered from SRSE was applied left vagal nerve stimulator after he failed to respond to pentobarbital, and was in coma for 9 days. The EEG result revealed resolution of earlier observed periodic lateral epileptiform discharges and he had no seizure again.

If the epileptogenic focus is found, the resection

of this focus with Durante surgery under EEG monitoring was very useful.<sup>34</sup>

## TREATMENT GOALS

Clinical and electrographic seizure suppression is the treatment goal. When suppression is complete, e.g. an iso-electric or flat EEG, then we opt to reverse the cause of seizures. Decide that how much to suppress, for clinician, clinical judgement needed to know the risks of increased suppression ( high doses of anesthetic or AED drugs are sometimes needed to achieve a burst suppression or iso-electric EEG background, but increased risk for hypotension, and other systemic complications). Continuous EEG monitoring helped clinicians, because when seizures may still appear from a burst suppression pattern, so the next step needed to do greater suppression that the result better for seizure control.<sup>18</sup>

## SUMMARY

Patients with SRSE treated with aggressive was rationale, modality treatment with pharmacological and non pharmacological. For using pharmacological treatment and non pharmacological treatment which can control the seizures and the underlying cause of the seizures. Multiple AED ( non anesthetic ) at high therapeutic levels are necessary to stop the anesthetic agents. There was important too carefully maintenance the organ function normally and early identification and management of systemic complications to decrease the degree of morbidity for those patients who can survive and often difficulty and prolonged recovery.<sup>18</sup>

**Conflict of Interest:** Nil declared by the authors

**Authors' contribution:** All authors took equal part in literature search and manuscript preparation

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