Case Report

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General Anesthesia Management of Super Refractory Status Epilepticus in Anti-N-Methyl-D-Aspartate-Receptor (NMDAR) Meningitis

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Abstract

Background: Super Refractory Status Epilepticus poses significant management challenges, requiring intensive therapeutic approaches including general anesthesia.

Objective: To discuss the management of Super Refractory Status Epilepticus (SRSE) with general anesthesia to control seizures.

Case Illustration: A 17-year-old female with tonic-clonic seizures, headache, unclear speech, and a change in behavior, who also appeared to be restless, was presented. She was admitted to the intensive care unit and administered anticonvulsant medication. A brain MRI with contrast showed the impression of meningitis, and cerebrospinal fluid examination showed a positive anti-NMDAR result. First-line therapy involved high-dose steroids and intravenous immunoglobulin for 5 days, followed by second-line therapy with rituximab. Patient received general anesthesia using sevoflurane volatile, dexmedetomidine, continuous rocuronium, propofol, ketamine, and fentanyl due to persistent seizures despite receiving anticonvulsant therapy. Monitoring was conducted for vital signs, seizure activity, and depth of anesthesia using the bispectral index (BIS). Tonic-clonic seizures in patients were successfully managed with general anesthesia. However, facial dyskinesia was still present despite the administration of general anesthesia. Facial dyskinesia worsened upon discontinuation of continuous rocuronium.

Conclusion: General anesthesia could be used in the management of SRSE with the aim of controlling seizures and preventing complications arising from continuous seizures.

Keywords: Anesthesia, Anti N-Methyl-D-Aspartate-Receptor, convulsion, super refractory status epilepticus

Introduction

Super Refractory Status Epilepticus (SRSE) is a severe and life-threatening medical condition characterized by seizures lasting 24 hours or more despite anesthesia treatment or when the anesthesia therapy dose is reduced. It affects 23–43% of patients and is linked to significant morbidity and mortality rates of 30–50%. SRSE can result from various central nervous system insults, including stroke, infection, or trauma.[1,2]

Encephalitis with anti-NMDAR antibodies can lead to the occurrence of SRSE. Therefore, in addition to immunotherapy, management for seizures is also required. Management of SRSE using general anesthesia may involve a combination of volatile and intravenous anesthesia.[2] Identifying the underlying cause of SRSE is also essential, along with the administration of general anesthesia to control seizures and to prevent potential

complications.[1,2] This case report presents a 17-year-old female patient with SRSE secondary to anti-NMDAR encephalitis, successfully managed with general anesthesia in the intensive care unit.. This study aims to explore the role of general anesthesia in managing SRSE due to anti NMDAR meningitis and the clinical challenges encountered.

Case

A 17-year-old female presented to the Emergency Department at Premier Bintaro Hospital in November 2023 with a one-week history of tonic-clonic seizures and headaches. The patient was also reported to be restless, speaking unclearly, and experiencing hallucinations. On physical examination, the patient was conscious and compos mentis, with blood pressure of 103/70 mmHg, pulse rate of 88 beats per minute, temperature of 36.9 degrees Celsius, and oxygen saturation of 100% on room air. Neurological examination did not reveal neck stiffness. Motor strength in both right and left extremities was 4/4, and no pathological reflexes were detected. Brain MRI without contrast was within normal limits. The patient was admitted to the intensive care unit and received intravenous phenytoin 200 mg in 50 mL of 0.9% NaCl, as well as oral valproic acid 3 times a day at 5 mL each.

On the seventh day of intensive care treatment, the patient experienced shortness of breath with desaturation and an increased work of breathing. The patient's consciousness became delirious, and vital signs revealed a blood pressure of 118/72 mmHg, a heart rate of 105 beats per minute, respiratory rate of 35-42 breaths per minute, and oxygen saturation of 81% with a non-rebreather mask (NRM) at 15 lpm. Arterial blood gas (ABG) analysis indicated venous impression with a pH of 7.41, pCO2 of 46.4 mmHg, pO2 of 39 mmHg, HCO3 of 30 mEq/L, BE of 5 mEq/L, and SaO2 of 73%. Subsequently, intubation and mechanical ventilation were initiated using PSIMV mode and sedation with midazolam at 2 mg/hour, along with analgesia using fentanyl at 300 mcg/day.

After the initiation of mechanical ventilation and sedation, there were no further tonic-clonic seizures, but there were still facial dyskinesia and myoclonic movements in both of the patient's hands. On the 12th day of treatment, spontaneous breathing efforts were observed in the patient, leading to a transition to spontaneous ventilation mode, and a decision was made to proceed with extubation. Following extubation, twitching movements were still observed. However, on the 13th day of treatment, the patient experienced focal seizures >7 times, leading to a diagnosis of status epilepticus. The patient was administered an additional anticonvulsant, intravenous phenobarbital at 700 mg over 30 minutes. Amidst the phenobarbital administration, there was another focal seizure lasting less than 1 minute, followed by oxygen desaturation. Consequently, endotracheal intubation was performed, and oxygen was administered via an endotracheal tube using the pressure support ventilation (PSV) mode, with a respiratory rate of 15 breaths per minute, PEEP of 6 cmH2O, FiO2 of 80%, tidal volume of 450 mL. Additionally, maintenance sedation was provided with fentanyl at 300 mcg/day and midazolam at 2 mg/hour.

While intubated, twitching persisted in the patient's eyelids and hands, prompting the decision to administer general anesthesia to manage the refractory seizures. On 14th day of treatment, the regiment of sedation changed into propofol 2mg/kg/hour and fentanyl 300 mcg/day. On the same day volatile anesthesia with sevoflurane at 9 mL/hour was initiated because the patient still has recurring seizures. On 17th day of treatment, dexmedetomidine 0.5 mcg/kg/hour was added to anesthesia regiment.

Despite general anesthesia, seizures continued, leading to the addition of continuous rocuronium at 30 mg/hour. Intravenous bolus doses of rocuronium at 10 mg were given if seizures persisted. Throughout general anesthesia, the depth of anesthesia was monitored using the Bispectral Index (BIS). The patient was diagnosed with super-refractory status epilepticus (SRSE) secondary to NMDAR meningitis. The patient was consulted to a hemato-oncology internal medicine specialist and planned to receive intravenous rituximab at 500 mg as a second-line therapy for NMDAR. During the administration of rituximab, the patient's condition remained stable, and there were no seizures. On the 20th day of treatment, continuous rocuronium was discontinued. When continuous rocuronium was stopped, the patient experienced twitching 16 times, prompting the administration of a 10 mg bolus of rocuronium, followed by the administration of ketamine at 2 mg/kg/hour. The administration of propofol and dexmedetomidine was stopped.

On the 23rd day of treatment, the patient

Table 1 Summary of Patient Progression

Day	Clinical Event
Day 0 (Admission)	17-year-old female presented with tonic-clonic seizures, headache, hallucinations; admitted to ICU; started on IV phenytoin and oral valproic acid.
Day 7	Developed shortness of breath and delirium; intubated and placed on mechanical ventilation; started sedation with midazolam and fentanyl.
Day 12	Spontaneous breathing observed; patient extubated; persistent twitching noted.
Day 13	Experienced >7 focal seizures; diagnosed with status epilepticus; reintubated; added IV phenobarbital.
Day 14	Seizures refractory to treatment; initiated general anesthesia with propofol, fentanyl, and sevoflurane.
Day 17	Dexmedetomidine added to anesthesia regimen; seizures persisted; continuous rocuronium infusion started.
Day 20	First dose of rituximab administered; seizures controlled; continuous rocuronium discontinued.
Day 23	Desaturation and apnea after rocuronium bolus; anesthesia adjusted; tracheostomy performed.
Day 29	Discontinuation of atracurium resulted in seizure recurrence; continuous atracurium restarted.
Day 31	Second dose of rituximab administered.
Day 33	Hypotension, fever, persistent twitching; vasopressor (norepinephrine) initiated; anesthesia regimen adjusted.
Day 34	Developed septic shock.
Day 36	Patient passed away.

experienced desaturation and apnea after receiving a bolus of rocuronium 10 mg. The patient's tidal volume on the ventilator was not achieved, leading to manual bagging, and the ketamine drip was stopped. A consultation with an Ear, Nose, and Throat (ENT) specialist was initiated for tracheostomy, and the anesthesia regimen shifted to volatile sevoflurane at 6.5 mL/hour titrated gradually, dexmedetomidine at 0.5 mcg/kg/hour, and continuous rocuronium at 30 mg/hour.

A tracheostomy was performed by an ENT specialist, and the ventilator was switched to an intelligent ventilator with iASV mode, MV 194%, PEEP 6 cmH2O, FiO2 41%, tidal volume of 499 mL, with desired target of EtCO2 35-40 mmHg, and oxygen saturation 96-100%. The anesthesia regimen was adjusted to volatile sevoflurane at 7.5 mL/hour titrated gradually, with a bolus of sevoflurane at 0.5 mL. Continuous atracurium was administered at 30 mg/hour, along with ketamine at 0.2 mg/kg/hour, and fentanyl at 400 mcg/day.

On the 29th day of treatment, continuous atracurium was discontinued, but seizures recurred >8 times. Consequently, continuous atracurium was resumed. On the 31st day of treatment, the patient received the second dose of rituximab. Subsequently, on the 33rd day of treatment, there was hypotension, fever, and persistent twitching in the patient. Vasopressor support with norepinephrine at 0.08 mcg/kg/minute was initiated. The anesthesia regimen was adjusted to include fentanyl at 400 mcg/day, ketamine at 1.5 mg/kg/hour, propofol at 2 mg/kg/hour, and continuous rocuronium at 30 mg/hour. In the event of seizures, a bolus of rocuronium at 10 mg was administered.

On day 34, the patient entered septic shock, with elevated creatine kinase (CK 540 U/L), lactate >20 mmol/L, and persistent clinical deterioration. Despite comprehensive treatment, the patient passed away on the 36th day of hospitalization.

Discussion

Status epilepticus that occurred despite the administration of first and second-line

anticonvulsants is referred to as refractory status epilepticus, requiring management with general anesthesia to control the ongoing seizures. However, if status epilepticus persists or recurs for ≥24 hours despite anesthesia treatment or when the anesthesia therapy dose is reduced, it is termed super-refractory status epilepticus (SRSE).[1]

In this case, a 17-year-old patient presented with tonic-clonic seizures lasting for 5 minutes before admission to the hospital, accompanied by a history of recurrent headaches for the past week. The patient was administered with anticonvulsant, and the seizures stopped. However, the patient experienced focal seizures >7 times, leading to the diagnosis of status epilepticus. Consequently, multiple anticonvulsants were administered to control the seizures. However, the seizure persisted despite the administration of the multiple anticonvulsants, and the patient was diagnosed with refractory status epilepticus. Then, this patient was given general anesthesia to manage the ongoing seizures. Nevertheless, despite receiving general anesthesia, the seizures still occurred, leading to the diagnosis of super-refractory status epilepticus (SRSE).

Encephalitis linked to anti-NMDAR antibodies is a rare autoimmune disorder characterized by antibodies that target the GluN1 subunit of the NMDAR. This condition can impair synaptic glutamatergic networks in the brain, which are essential for learning, memory, and neuroplasticity. Neurological symptoms associated with this disorder may include short-term memory issues, seizures, movement disorders, central hypoventilation, and reduced consciousness, often requiring intensive care.[2,3]

The causes of autoimmune encephalitis can include tumors, infections, or remain unknown (cryptogenic). This condition is often regarded as a classic paraneoplastic syndrome, prompting a thorough clinical evaluation for any hidden malignancy in suspected patients. Certain tumors can produce peptides resembling those in the nervous system, resulting in immune cross-reactivity and paraneoplastic neurological syndromes. The immune system responds to these tumors with cytotoxic and antibody-mediated actions that target not only the tumor but also the nervous system. Underlying malignancies are primarily found in individuals aged 12 to 45, with the majority being ovarian teratomas (94%), followed by extraovarian teratomas (2%) and other tumor types (4%).[4,5]

In this patient, a cerebrospinal fluid examination was conducted with positive results for anti-NMDAR antibodies. ANA profile, anti-Ds-DNA, and anticardiolipin antibody tests were also performed to rule out the possibility of other causes of autoimmune encephalitis. However, the results of these tests were negative. Treatments for this autoimmune disorder involve immunomodulation and tumor removal. In this patient, an abdominal ultrasound (USG) and CT scan were conducted, with normal results and no evidence of tumors found. First-line immunotherapy includes the administration of high-dose steroids through intravenous infusion, intravenous immunoglobulin, and/or plasmapheresis.[4] High-dose steroids can penetrate the blood-brain barrier, contributing to the control of persistent seizure activity. They also help reduce brain edema and intracranial pressure. The recommended high-dose steroid is intravenous methylprednisolone at 1 gram per day for 3-5 days, followed by intravenous methylprednisolone at 1 mg/kg per day for 7 days or longer.[2,6] For intravenous immunoglobulin (IVIG), a dose of 400 mg/kg/day for 5 days can be administered.[6] If the patient does not respond to first-line therapy, second-line treatment with rituximab is initiated at a dose of 375 mg/m^2 weekly for 4 weeks.[1,4]

Encephalitis with anti-NMDAR antibodies can lead to the occurrence of SRSE. Therefore, in addition to immunotherapy, management for seizures is also required. Seizures in this patient are managed with the administration of anticonvulsants such as valproic acid, phenytoin, levetiracetam, and phenobarbital. First-line anticonvulsants include benzodiazepines (lorazepam, diazepam), phenytoin, and intramuscular midazolam. Meanwhile, second-line options consist of valproic acid and levetiracetam.[6] Despite the administration of both lines of anticonvulsants, the patient continues to experience seizures indicates that they are facing refractory status epilepticus (RSE).

In this case, the patient experienced status epilepticus with altered consciousness and oxygen desaturation, leading to intubation and sedation. General anesthesia was induced to manage seizures. In this patient, seizures and twitching persisted even under the influence of general anesthesia or when the anesthesia drug doses were reduced. This supports the diagnosis of super-refractory status epilepticus (SRSE).

The goals of managing SRSE are: (1) control seizures to prevent early excitotoxicity. After

24 hours of continuous or recurrent seizures, the excitotoxic process that can cause brain damage may have already begun. (2) Neuroprotection, to inhibit the development of secondary processes triggered by early excitotoxicity. (3) Avoiding or Treating Systemic Complications: SRSE treatment often involves prolonged anesthesia.

Management of SRSE with general anesthesia is the foundation of therapy to achieve a burst suppression period, which aids in the remodulation of receptors, allowing antiepileptic therapy to become effective. Typically, anesthesia is continued for the first 24 hours, and then gradual attempts are made to reduce the administered anesthesia dosage once seizures are under control.[1] Midazolam, along with pentobarbital and propofol, is one of the three primary medications utilized when first- and second-line treatments are ineffective. It works by binding to the chloride ionophore complex of the gamma-aminobutyric acid (GABA) receptor in the central nervous system (CNS). This binding leads to membrane hyperpolarization and an increased frequency of chloride channel openings, enhancing GABA's inhibitory effects. Additionally, midazolam influences glycine receptors, acting as a muscle relaxant while exhibiting predictable anxiolytic, amnestic, hypnotic, anticonvulsant, and sedative properties. Its relatively short half-life, due to its water-soluble nature, makes it an effective choice for fast-acting pharmacokinetics with a lower risk of toxicity. However, midazolam's rapid onset can lead to tachyphylaxis and hypotension, and prolonged use often requires larger doses to sustain its therapeutic effects.[1]

Intravenous propofol is the third of the three most commonly used anesthetic agents for managing SRSE. It acts as a powerful depressant of the central nervous system (CNS), reducing the dissociation of GABA from its receptors, which extends the duration of chloride channel openings and enhances inhibitory effects on neurons. Propofol offers better control of anesthesia than midazolam and pentobarbital, thanks to its rapid onset of action and quick recovery, even with prolonged use. Additionally, propofol has minimal serious drug interactions and a lower incidence of hypotension and cardiorespiratory depression compared to midazolam and pentobarbital.[1,2,7]

Prolonged infusion of propofol carries a risk of propofol infusion syndrome (PRIS) especially in children and patients undergoing concurrent steroid or catecholamine therapy. PRIS can result in severe metabolic acidosis, hyperkalemia, hyperlipidemia, rhabdomyolysis, cardiac dysfunction, and renal failure. Therefore, during extended use of propofol, it is important to monitor laboratory values, including serum levels of creatinine kinase, lactate, and lipids.[2] In this patient, inhalation anesthesia with volatile sevoflurane was also administered when other therapies for SRSE were unsuccessful. Volatile inhalational agents offer deep sedation and act as strong anticonvulsants, typically reserved for patients experiencing seizures that do not respond to conventional intravenous medications like benzodiazepines, propofol, barbiturates, and standard antiepileptic drugs.

Sevoflurane is a versatile inhalational anesthetic known for its rapid induction, easy control of anesthetic depth, quick recovery, favorable hemodynamic responses, and minimal irritation to the airway. Sevoflurane also can alter neurotransmission by strongly enhancing GABAergic inhibition while reducing NMDA glutamatergic activity. Adverse effects of volatile anesthetics can include dose-dependent hypotension, increased intracranial pressure, and arrhythmias, along with rare but serious complications such as malignant hyperthermia..[8,9,10]

The patient was administered ketamine, a potent NMDA receptor antagonist with equal affinity for various NMDA receptor types. As an anesthetic agent, ketamine is effective in the advanced stages of SRSE. Ketamine also acts as neuroprotective agent by inhibiting glutamate excitotoxicity induced by NMDA receptors and a good alternative to propofol. Ketamine has a low risk of cardiac depression and hypotension, making it the preferred agent in emergencies involving cardiocirculatory instability.[1,2]

In a study involving seven critically ill with SRSE, the use of ketamine achieved electroencephalographic control of seizures in 50% of cases without causing hemodynamic instability. Additionally, a retrospective study found that ketamine treatment in refractory status epilepticus resolved seizures in 57% of cases, terminated them in 32% of cases, and provided seizure control in approximately 13% of cases when administered intravenously.[1]

Additionally, ketamine should be avoided in patients with cerebral damage because it can raise intracranial pressure (ICP). Beyond increasing ICP, ketamine also elevates cerebral oxygen consumption and cerebral blood flow. In patients with SRSE, earlier initiation and longer infusion of ketamine may enhance its effectiveness and improve clinical

outcomes..[1,2,11] Neuromuscular blocking agent (NMBA) used to optimize the use of mechanical ventilation during endotracheal intubation. NMBAs induce skeletal muscle relaxation by inhibiting impulse transmission at the neuromuscular junction. Rocuronium is an intermediate-acting NMBA and the only nondepolarizing agent currently used for rapid sequence induction and intubation. It does not trigger histamine release and has minimal effects on hemodynamics. Continuous infusions of NMBAs, as opposed to intermittent boluses, have been reported to reduce the risk of prolonged paralysis. Most significantly, neuromuscular blockade can lead to prolonged immobility, which may result in acquired weakness, myopathy, pressure ulcers, nerve injuries, and an increased risk of deep venous thrombosis (DVT).[12]

Electroencephalography (EEG) is essential for adjusting medication doses and confirming the cessation of electrographic seizures. Maximal therapy should be continued for 12 to 24 hours after the last clinical or electrographic seizure, after which the dosage can be tapered. If seizures reoccur, therapy can be resumed or modified as needed..[4,13] However, limitations in the hospital's facilities prevent continuous EEG monitoring from being performed in the intensive care unit.

Seizure activity in this patient is monitored using the bispectral index (BIS), a quantitative EEG device that assesses the effects of anesthetics and sedative medications. BIS values between 40 and 60 indicate an appropriate level of general anesthesia. It is particularly sensitive for patients undergoing invasive procedures in the ICU, such as intubation, tracheostomy, chest tube placement, and bronchoscopy. BIS can also aid in monitoring seizures in patients receiving neuromuscular blockade, where clinical detection of seizures may be challenging. A BIS value of 30 can detect burst suppression with a sensitivity of 99% and specificity of 98%. However, it may not identify regional epileptic activity.[14]

This patient is also monitored for esophageal pressure, levels of lactate and creatinine kinase are also examined. Esophageal pressure monitoring is a straightforward bedside technique for estimating changes in pleural pressure, which can enhance the cardiovascular performance of critically ill patients receiving assisted ventilation. It provides the most accurate estimate of pleural pressure. [15]

During the ICU stay, there is a significant increase in the levels of lactate and creatinine kinase in this patient. This could be caused by seizures leading to metabolic stress. Whole-body muscle contractions and catecholamine release elevate oxygen demands in the brain, muscles, and heart, while impaired breathing hinders the body's ability to compensate for this increased demand. Stressed tissues release metabolites like lactate, ammonia, and urea, while damaged skeletal muscles leak creatine kinase (CK) and myoglobin. Serum lactate levels are elevated in 90% case of seizures. A conducted retrospective study and meta-analysis showed a significant elevation in CK after 48 hours in epileptic seizures.[16]

In this patient, seizures recurred when the anesthesia dosage was reduced. The occurrence of seizures during the dosage reduction phase necessitated the reintroduction of anesthesia. This can prolong the stay in the ICU and may lead to complications and could complicate the management of the primary condition.[1,2,5] In conclusion, the management of SRSE associated with anti-NMDAR meningitis requires a multimodal therapeutic approach, where general anesthesia serves as a cornerstone in controlling refractory seizures. This case highlights the complexity and high mortality associated with SRSE and emphasizes that early aggressive seizure control, combined with targeted immunotherapy, is critical to improving outcomes.

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