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Original Article

A Practical Approach to Super Refractory Status Epilepticus in Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesinde Süper Refrakter Status Epileptikus'a Pratik Yaklaşım

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ABSTRACT

Objective: In this study, we aimed to evaluate the demographic, clinical features, long-term electroencephalography (EEG) findings and treatment modalities of pediatric patients with super refractory status epilepticus (SRSE).

Method: A retrospective, observational study was conducted in patients diagnosed as SRSE between 1 June 2018 and 30 May 2021 in the pediatric intensive care unit. Patients with SRSE between 1 month and 18 years of age who underwent continuous electroencephalogram (cEEG) monitoring were included in the study. Demographic data, clinical, and electroencephalographic characteristics were collected.

Results: A total of 11 patients were included in the study. The median age of the patients was 31 months (IQR 8-72 months). Nine (81.8%) patients had symptomatic etiology. Of the symptomatic etiologies, 4 (36.3%) patients had acute symptomatic, 3 (27.2%) patients had remote symptomatic and 2 (18.2%) patients had progressive etiology. The most common etiology was immune-related. The median cEEG duration of the patients was 60 hours (IQR 52-72 hours). Midazolam infusion was given to 11 (100%) patients, ketamine infusion was given to 9 (81.8%) patients, thiopental infusion was given to 6 (54.5%) patients, and propofol infusion was given to 2 (18.1%) patients as coma induction treatment. Intravenous immunoglobulin, corticosteroid and plasmapheresis were administered to 3 (27.2%) patients with immune etiology. The overall mortality was 18.1%.

Conclusion: SRSE is a neurological emergency with high mortality and morbidity. cEEG monitoring is very important in diagnosis and treatment. Immune etiology should be considered in long-lasting seizures, especially if they are resistant to anesthetics. The immunomodulatory therapy should be started.

Keywords: Super refractory status epilepticus, continuous electroencephalographic monitoring, non-convulsive status epilepticus, febrile infection-related epilepsy syndrome, pediatric intensive care unit

ÖZ

Amaç: Bu çalışmada, süper refrakter status epileptikus'lu (SRSE) çocuk hastaların demografik, klinik özellikleri, uzun dönem elektroensefalografi (EEG) bulguları ve tedavi modalitelerini değerlendirmeyi amaçladık.

Yöntem: Bir Haziran 2018-30 Mayıs 2021 tarihleri arasında çocuk yoğun bakım ünitesinde SRSE tanısı konulan hastalarda retrospektif, gözlemsel bir çalışma yapıldı. Çalışmaya 1 ay-18 yaş arasında sürekli elektroensefalogram (cEEG) takibi yapılan SRSE'li hastalar dahil edildi. Demografik veriler, klinik ve el EEG özellikler toplandı.

Bulgular: Çalışmaya toplam 11 hasta dahil edildi. Hastaların medyan yaşı 31 aydı (IQR 8-72 ay). Dokuz (%81,8) hastada semptomatik etiyoloji mevcuttu. Semptomatik etiyolojilerden 4 (%36,3) hastada akut semptomatik, 3 (%27,2) hastada remote semptomatik ve 2 (%18,2) hastada progresif etiyoloji vardı. En sık etyoloji immün nedenli idi. Hastaların medyan cEEG süresi 60 saat (IQR 52-72 saat) idi. On bir (%100) hastaya midazolam infüzyonu, 9 (%81,8) hastaya ketamin infüzyonu, 6 (%54,5) hastaya tiyopental infüzyonu ve 2 (18,8) hastaya koma indüksiyon tedavisi olarak propofol infüzyonu verildi. İmmün etiyolojisi olan 3 (%27,2) hastaya intravenöz immünoglobulin, kortikosteroid ve plazmaferez uygulandı. Genel mortalite %18,1 idi.

Sonuç: SRSE yüksek mortalite ve morbiditeye neden olan nörolojik bir acildir. Sürekli elektroensefalogram takibi tanı ve tedavide çok önemlidir. Uzun süreli ve özellikle anesteziklere dirençli nöbetlerde immün etiyoloji düşünülmelidir. İmmünomodülatör tedavi başlatılmalıdır.

Anahtar kelimeler: Süper refrakter status epilepticus, sürekli elektroensefalogram izlemi, non-konvülzif status epilepticus, febril ilişkili epilepsi sendromu, çocuk yoğun bakım ünitesi

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INTRODUCTION

Status epilepticus (SE) is defined as a seizure lasting longer than 5 minutes, or 2 or more consecutive seizures without consciousness. Refractory status epilepticus (RSE) is defined as SE that does not respond to an adequate dose of benzodiazepines and another appropriately selected second-line antiepileptic therapy. Super refractory status epilepticus (SRSE) is defined as seizure activity lasting more than 24 hours despite the anesthetic drugs given and recurrent seizures during reduction of anesthetic drugs[1,2]. There are few epidemiological studies on SRSE in the pediatric age group; In a retrospective study, SRSE was reported to occur in 7.14% of 602 cases with SE[3]. The most commonly reported etiologies are acute symptomatic causes (infectious or immune-mediated encephalitis, central nervous system infections, traumatic brain injury, brain ischemia); remote symptomatic causes (e.g., lymphoproliferative disease, human immunodeficiency virus infection, hypoxic-ischemic encephalopathy, developmental delay, epilepsy), progressive encephalopathies (metabolic diseases, epileptic encephalopathies), and cryptogenic etiologies[1,3,4]. Low serum antiepileptic drug (AED) levels in children with epilepsy, acute symptomatic etiologies, and neurodegenerative diseases are common risk factors for SRSE[5-8].

SRSE mortality has been reported to be 15.4-39.9% in adult patients and 5-20% in pediatric patients. An irreversible serious neurological deficit may develop in the majority of survivors[3,7,9-11]. The most commonly used drugs for treatment in SRSE are anesthetics such as midazolam, barbiturates, ketamine, and propofol[12]. The response of patients with immune etiologies to anesthetics are poor and they respond better to immunomodulatory treatment [steroid, intravenous immunoglobulin (IVIG), plasma exchange][13]. However, to date, there is still no evidence of optimal treatment for the individual pediatric patient. Difficulties in treatment arise because the underlying etiologies are not always immediately recognized and treatment options are limited by prolonged seizures. Treatment decisions are mainly based on case series or expert opinions. The comparative efficacy of different treatment strategies has not been evaluated in large prospective serie or randomized clinical trials[2,11-13].

Our study aims to evaluate the demographic, clinical features, long-term EEG findings, and treatment modalities of patients with SRSE.

MATERIALS and METHODS

A retrospective, observational study was conducted at the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, in pediatric intensive care unit (PICU) from June 1, 2018, and May 30, 2021, in patients diagnosed with SRSE.

Inclusion criteria;

One month to 18 years old with SRSE,

Patients with SRSE undergoing continuous electroencephalogram (cEEG) monitoring

Exclusion criteria;

All patients aged 1 month ≤ >18 years,

Patients whose cEEG monitoring cannot be performed or whose data cannot be accessed for technical reasons, patients with deficiencies in demographic and clinical data.

SRSE was defined as seizure activity for more than 24 hours despite administration of anesthetic drugs or recurrent seizure during tapering of the anesthetic drug. In the follow-up of all patients; EEG monitoring lasting at least 24 hours was used. It was done using the Nihon Kohden (Neurofax EEG-1200) EEG system. EEG interpretation was done by a pediatric neurologist. Patients with electrographic findings without clinical seizures (without motor symptoms) were defined as non-convulsive SE, and patients with both clinical seizures (with motor symptoms) and electrographic seizures were defined as convulsive SE. cEEG findings are divided into 4 different localizations: lateralized epileptic activity, bilateral independent epileptic activity, multifocal epileptic activity, and generalized epileptic activity[14]. Age, gender, previous neurological diseases, other etiologies, length of hospital stay, number of AEDs for prophylaxis, irregular use of AED, mechanical ventilator support, positive microbial cultures (blood, urine, and cerebrospinal fluid (CSF), bronchoalveolar lavage, nasopharyngeal aspirate), magnetic resonance findings, the pediatric risk score of mortality (PRISM III) and mortality were recorded. Treatments were administered and recorded within the framework of the protocol of our PICU (Table 1).

The ethics committee approval for the study was obtained from Ethics Committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (decision no: 2019/356, date: 02.01.2020).

Statistical Analysis

Descriptive statistics were given as mean ± standard deviation for normal distribution, medians and interquartile ranges (IQR) for abnormally distributed parameters, and numbers and percentages for categorical variables. Statistical analysis was performed using SPSS statistical software (version 22; SPSS, Chicago, IL, USA).

RESULTS

A total of 11 patients, 4 (36.4%) boys, and 7 (63.6%) girls were included in the study. The median age of the patients was 31 months (IQR 8-72 months) and 5 patients were under 2 years of age. Nine (81.8%) patients had symptomatic etiology (Table 2). Of the symptomatic etiologies, 4 (36.3%) patients had acute symptomatic, 3 (27.2%) patients had remote symptomatic and 2 (18.2%) patients had progressive etiology. Immune etiology was the most common among symptomatic etiologies. Two (18.2%) patients were diagnosed as non-convulsive SE after cEEG activity was detected in the comatose state without clinical seizures. Four of the patients were hospitalized with the diagnosis of febrile SE. Blood, urine, and CSF, bronchoalveolar lavage, nasopharyngeal aspirate cultures were taken for the etiology of fever. In one patient with a diagnosis of hypoxic-ischemic encephalopathy, *Klebsiella pneumonia* was grown in blood culture and it was defined as SRSE triggered by infection with the clinic of sepsis. Herpes virus was detected in CSF viral polymerase chain reaction of 1 patient followed up for encephalitis and herpes encephalitis was diagnosed. The cultures of the patients who were given SRSE treatment, who had complaints of high fever and impaired consciousness, were found to be negative in terms of infectious. For etiology and differential diagnosis, viral antibody tests in serum (toxoplasma, rubella, cytomegalovirus, and herpes simplex), antinuclear antibody, thyroid antibody tests, oncological evaluation, limbic encephalitis panel, methyl-d-aspartate (NMDA) receptor antibodies in CSF, and serum and neuroradiological imaging were performed and NMDA encephalitis was diagnosed in 1 patient. Cranial MR imaging was found to be abnormal in 3 of 4 patients diagnosed with encephalitis, while it was found to be normal in a 6.5-year-old patient with a diagnosis of FIRES. Mechanical ventilator support was given to all patients. While 4 patients were intubated with respiratory failure in the course of refractory SE,

Table 1. Status epilepticus protocol of our pediatric intensive care unit

0-5 minutes Emergency stabilitizion Airway protection Breathing support Monitoring Check glukose and electrolytes	**Midazolam IV:** 0.1- 0.2 mg/kg/dose (max 5 mg) **Midazolam IM:** 0.1- 0.2 mg/kg/dose (If vascular access no available)
5-15 minutes	**Midazolam IV/IO:** 0.2 mg/kg/dose (may repeat if seizures persist) If vascular access no available, use intraosseous vascular access
15-30 minutes	**Phenytoin IV:** 20 mg/kg/dose (max 1,000 mg) **Sodium valproate IV:** 20 mg/kg/dose (If >2 years, max 3,000 mg) **Levetiracetam IV:** 30 mg/kg/dose (max 4,500 mg) **Phenobarbital IV:** 15-20 mg/kg/dose (max 1,000 mg) If there are antiepileptics used by the patients, a loading dose is given, and if necessary, the drug that the patient does not use one of the AED selected according to according individual characteristics of the patient as a second-line treatment
30-60 minutes	**Midazolam:** After 0.2 mg/kg bolus, 0.1 mg/kg/h infusion is started. An additional bolus of 0.2 mg/kg is given every 10-15 minutes and titrated by increasing the infusion rate by 1 mg/kg/h EEG monitoring is started
Refractory SE & Super refractory SE	**Ketamine IV infusion:** 1 mg/kg IV loading dose, after 1-6 mg/kg/h continuous IV infusion **Thiopental sodium IV infusion:** 3 mg/kg IV loading dose, after 1-6 mg/kg/h continuous IV infusion. Titrate by 1 mg/kg/hour every 10 minutes **Propofol IV infusion:** 1-2 mg/kg loading dose, 1-12mg/kg/h continuous IV infusion **Pyridoxine:** <3 years patients 100 mg/dose IV

AED: Antiepileptic drugs, SE: Status epilepticus

7 patients progressed to SRSE and were intubated electively with titration of anesthetic drugs.

Benzodiazepines (IV 2 doses of midazolam) were initially given to all of our patients as first-line therapy except for patients with FIRES, herpes encephalitis, and NMDA encephalitis, all patients had a previous diagnosis of epilepsy and had a history of multiple AED use. In patients diagnosed with epilepsy, a loading dose was applied to the drugs used as second-line therapy, and/or another AED was added to the treatment. As second-line therapy, phenytoin 5 (45.5%), levetiracetam 8 (72.7%), phenobarbital 7 (63.6%), sodium valproate 3 (27.3%), topiramate 2 (18.2%), clonazepam 2 (18.2%) and clobazam 2 (18.2%) patients were given. cEEG monitoring was started in refractory and super-refractory SE patients with ongoing seizures. Midazolam infusion was given to 11 (100%) patients, ketamine infusion was given to 9 (81.8%) patients, thiopental infusion was given to 6 (54.5%) patients, and propofol infusion was given to 2 (18.1%) patients as coma induction treatment. IVIG, high-dose corticosteroids and were administered to 3 (27.2%) patients with immune etiology. Antiviral agents were started in patients with encephalitis. In addition, intravenous pyridoxine was given to 5 (45.4%) patients and magnesium sulfate infusion to 9 (81.8%) patients. It was not given because the other 2 patients had high serum magnesium levels (>3 mg/dL). After clinical seizure or electrographic seizure was controlled for at least 24 hours (by providing burst suppression), anesthetics were started to be decreased every 4-6 hours according to cEEG monitoring and increased again in those who developed seizure activity again. The median cEEG duration of the patients was 60 hours (IQR 52-72 hours). When we evaluate the cEEG data; 2 (18.1%) had lateralized, 3 (27.2%) multifocal, and 5 (45.5%) generalized epileptic activity. The median time to burst suppression after induction of anesthetic was 4 hours (IQR 2-7 hours). All patients developed medical complications during their intensive care stay. Inotropic therapy was initiated as a result of pneumonia in 3 patients, urosepsis in 1 patient, electrolyte disturbance in all patients, and cardiovascular dysfunction in 4 patients with prolonged seizure duration. In 1 patient; mechanical ventilator-associated lung injury and severe ARDS developed (Table 3). Two patients died after multiorgan dysfunction and the overall mortality was 18.1%. One patient could not tolerate weaning from the mechanical ventilator for a long time and was discharged with a tracheostomy. Th median length of stay in the PICU was 13 days (8-20 days), and the median PRISM score was 10[6-17].

Table 2. Etiological classification of case

Etiologies	n (%)
Structural disorders	1 (9.1%)
Hypoxic-ischemic encephalopathy	1 (9.1%)
Genetic epilepsy syndromes	2 (18.2%)
West syndrome	1 (9.1%)
Dravet syndrome	1 (9.1%)
Metabolic disorders	2 (18.2%)
Pyruvate dehydrogenase deficiency	1 (9.1%)
GLUT 1 deficiency	1 (9.1%)
Immunologic etiology	3 (27.3%)
Anti-N-methyl-d-aspartate receptor encephalitis	1 (9.1%)
FIRES	2 (18.2%)
Infectious etiology	1 (9.1%)
Herpes encephalitis	1 (9.1%)
Unknown (cryptogenic)	2 (18.2%)
Idiopathic generalized epilepsies	2 (18.2%)
Structural disorders	1 (9.1%)
Hypoxic-ischemic encephalopathy	1 (9.1%)
Genetic epilepsy syndromes	2 (18.2%)
West syndrome	1 (9.1%)
Dravet syndrome	1 (9.1%)
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Anti-N-methyl-d-aspartate receptor encephalitis	1 (9.1%)
FIRES	2 (18.2%)
Infectious etiology	1 (9.1%)
Herpes encephalitis	1 (9.1%)
Unknown (cryptogenic)	2 (18.2%)
Idiopathic generalized epilepsies	2 (18.2%)

GLUT: Glucose transporter, FIRES: Febrile infection-related epilepsy syndrome

DISCUSSION

Super refractory status epilepticus (SRSE) is a neurological emergency with high mortality and morbidity. Studies for SRSE are limited and generally based on case reports or small series[2-4]. SRSE presents in different age groups according to the etiology. In a study conducted in the PICU, the mean age was 5.4 years[15], and in another study, the median age was 7 years[11]. In our study, we found a lower median age (31 months) compared to other studies, and 4 (36.3%) patients were under the age of 2 years. Common risk factors are that the dose of

Table 3. Clinical characteristics of all patients

Patient no/ gender/age (month)	Etiology	MR findings	AED(s)	Convulsive/ non-convulsive	Complication	cEEG findings before treatment	Mortality	Treatments (induction and immunomodulatory)
1/F/6	Hypoxic-ischemic encephalopathy	Diffuse hypomyelinated areas in the cerebral hemispheres	3	Convulsive	Urosepsis, multiple organ dysfunction syndrome, electrolyte disturbance	Sharp-wave discharges in fronto centro temporal regions	Non-survivor	Midazolam Ketamine Pyridoxine
2/F/8	West syndrome	Areas of hyperintense gliosis in T2A-FLAIR in the basal ganglionic localization in the parietooccipital region	3	Convulsive	ARDS, electrolyte disturbance	Active multifocal epileptic activity	Survivor	Midazolam Ketamine Thiopental Pyridoxine
3/F/72	Dravet syndrome	Atrophy of cerebral sulci, leukoaraiosis in cerebral white matter	3	Convulsive	Electrolyte disturbance	Active generalized epileptic disorder	Survivor	Midazolam Ketamine Thiopental Propofol
4/M/10	Pyruvate dehydrogenase deficiency	In white matter, T2A is high at basal ganglionic levels, T1A isointense pathological signal intensity foci	3	Convulsive	Electrolyte disturbance, pneumonia	Focal epileptic activity in the bilateral frontotemporal region	Survivor	Midazolam Ketamine Thiopental Propofol Pyridoxine
5/M/31	Glucose transporter protein type 1 deficiency	Diffuse atrophy of cerebral cortical sulci	3	Non-convulsive	Multiple organ dysfunction syndrome, electrolyte disturbance	Generalized spike-wave bursts in the temporo-parieto-occipital regions	Non-survivor	Midazolam Ketamine Thiopental Pyridoxine
6/F/164	Anti-N-methyl-d-aspartate receptor encephalitis	Right posterior parietal region T2-FLAIR hyperintense focal focus. diffusion bilateral thalamic region acute ischemia	0	Non-convulsive	Cardiovascular dysfunction, electrolyte disturbance	Sharp spike-wave discharges in bilateral temporooccipital regions	Survivor	Midazolam Ketamine Corticosteroids IVIG Plasmapheresis

Table 3. Continued

Patient no/ gender/age (month)	Etiology	MR findings	AED(s)	Convulsive/ non-convulsive	Complication	cEEG findings before treatment	Mortality	Treatments (induction and immunomodulatory)
7/F/60	Febrile infection-related epilepsy syndrome	Mild leukomalacia changes in white matter	0	Convulsive	Electrolyte disturbance, pneumonia	Significant generalized spike-wave discharges in bilateral temporo-parietal regions	Survivor	Midazolam Ketamine Corticosteroids IVIG Plasmapheresis
8/M/80	Febrile infection-related epilepsy syndrome	Normal	0	Convulsive	Electrolyte disturbance,	Pronounced generalized spike-wave discharges in bilateral temporo parieto areas	Survivor	Midazolam Ketamine Corticosteroids IVIG Plasmapheresis
9/F/80	Herpes encephalitis	Hyperintense signals in the left frontotemporal region on T2 images	2	Convulsive	Electrolyte disturbance,	Slow-wave activity in the left hemisphere	Survivor	Midazolam Ketamine
10/M/13	Idiopathic generalized epilepsy	Atrophy of cerebral sulci Chronic leukomalacia changes in periventricular white matter	3	Convulsive	Electrolyte disturbance, pneumonia	Very active generalized epileptic activity	Survivor	Midazolam Ketamine Thiopental Pyridoxine
11/M/60	Idiopathic generalized epilepsy	Normal	2	Convulsive	Cardiovascular dysfunction, electrolyte disturbance	Sharp spike-wave activity in the right hemisphere fronto sentro temporoparietal region	Survivor	Midazolam Thiopental

AED used in patients with epilepsy is not given at an appropriate dose, that the dose is reduced, and that the serum AED level is low[6,8]. In our study, serum AED levels of 4 patients were significantly lower than the therapeutic range. The etiologies of SRSE patients differs in many studies, and the most common acute symptomatic causes (infectious or immune-mediated encephalitis, traumatic brain injury, brain ischemia) are observed[4]. In another study, the most common etiology was progressive encephalopathy[3]. In our study, immune etiologies were found to be the most common acute symptomatic etiologies. Among them, 2 patients were diagnosed with FIRES and 1 patient was diagnosed with anti-NMDA-receptor encephalitis. FIRES is a variant of NORSE that previously affected completely healthy children and was thought to be immune-mediated, but the pathogenesis was not known clearly[13-16]. It is typical for a febrile episode to occur between 24 hours and 2 weeks before the onset of the refractory seizure. Fever was described a few days ago in 2 patients aged 5 years and 6.5 years without any known disease. Another important disease among immune etiologies is anti-NMDA-receptor encephalitis. Patients clinically; may present with fever, headache, behavioral disorder, and RSE/SRSE. Immunomodulation therapy (steroid, intravenous immunoglobulin, plasma exchange) was also applied in anti-NMDA-receptor encephalitis[17]. EEG monitoring has a very important place in the diagnosis of SRSE and the evaluation of treatment. Non-convulsive SE, characterized by electrical activity without motor findings, can be seen in 15% of comatose patients[18]. In our study, two (18.1%) patients were diagnosed with nonconvulsive SE in EEG monitoring performed by presenting in a comatose condition. EEG monitoring also plays an important role in the titration of anesthetic infusions. In our practice, we dose anesthetic infusions to induce burst suppression in cEEG. In a multicenter study, the median cEEG duration was 30 hours[19], and in a study with a high number of FIRES patients, the median cEEG duration was 9 days[11]. In our study, the median cEEG duration was 60 hours. In general, we perform cEEG monitoring until the anesthetics are discontinued after creating burst suppression and following at least 24 hours without seizures. The treatment approach in SRSE aims to prevent neuronal excitotoxicity, neuroprotection and prevent systemic complications, and to provide seizure control[2]. Although coma induction is the most common treatment, there are no randomized controlled studies to guide clinical practice[11,20]. Our general approach for coma induction; under the guidance of cEEG monitoring, anesthetics are started to be reduced in the follow-up of seizure-free monitoring for at least 24 hours. If electrographic or clinical seizures are observed again during reduction, anesthetics are increased again and cEEG monitoring is continued. Benzodiazepines are used as first-line therapy in SRSE. In our study, intravenous midazolam was given to all patients as first-line treatment. Second-line treatment selection was planned following our intensive care protocol. It was determined according to the age of the patient, the antiepileptic he used, and the seizure type. For example we didn't prefer valproate under 2 years of age. Among this group of drugs, we used levetiracetam, phenobarbital, phenytoin, and sodium valproate, respectively. In the literature, no superiority has been shown in terms of the effectiveness of second-line treatments[21]. The main treatment in SRSE is coma induction and immunomodulatory (corticosteroids, intravenous immunoglobulin, plasmapheresis) treatments. Among the anesthetics inducing a coma, midazolam is the most commonly used, followed by barbiturates, ketamine, and propofol[12,13]. In some studies, it has been shown that SRSE can be controlled with a ketogenic diet[15]. In our study, midazolam infusion was applied to all patients by starting cEEG monitoring. After then ketamine infusion was given to 81.8% of the patients. Thiopental was used in 54.5% and propofol in 18.1% of patients. In our study, midazolam infusion was found to be the most common agent, similar to the literature[22]. In some studies, the most commonly used agents after midazolam failure were found to be barbiturates[11,23]. In our study, we detected more frequently ketamine, which also acts on the NMDA receptor and is frequently used as a sedo-analgesia in our intensive care unit. In our practice, we see that the side effect profile is lower than other coma-inducing agents, apart from seizure control. It is used with increasing frequency in the treatment of SE, especially in pediatric intensive care units[24,25]. We think that it will be included in the guidelines for earlier step treatments with future studies. All of the anesthetics used for coma induction have serious side effects. With the induction of midazolam, hemodynamic instability and suppression of the respiratory system are common[12,24]. Barbiturates may cause stronger cardiorespiratory suppression, arrhythmia, immunosuppression, renal failure, and multiple organ failure[24]. Ketamine may cause cardiac side effects, increased secretion, and signs

of laryngospasm[25]. Propofol, on the other hand, may cause propofol infusion syndrome characterized by heart failure, rhabdomyolysis, metabolic acidosis, and renal failure[26,27]. Complications may occur with the prolongation of the SRSE period, apart from the side effects of anesthetic drugs. In our study, it was observed that inotropic therapy was initiated in all patients as a result of electrolyte disturbances and cardiovascular dysfunction in 4 patients, severe ARDS developed in 1 patient, and 2 patients with multiple organ dysfunction syndrome (MODS) were found to have died. Immunological treatments such as IVIG, corticosteroid, and plasmapheresis have been reported in many studies. However, there are no randomized studies in the literature, but small series and case reports[28,29]. It is used especially in autoimmune encephalitis because it is held responsible for seizures[30]. In our study, IVIG, steroids, and plasmapheresis were applied to 2 patients diagnosed with FIRES and 1 patient diagnosed with NMDA encephalitis due to immune etiology. All patients received IVIG 1 gr/kg for 2 days, methylprednisolone 3 days pulse 30 mg/kg, then maintenance 2 mg/kg and was discontinued depending on the clinic. Plasmapheresis treatment was applied to all patients for 10 days. Patients with immune etiology had longer seizure control and hospital stay. However, mortality did not develop in the patients, except for comorbidity. The mortality rate of SRSE varies between 5-20% in pediatric patients[3,9,11]. In our study, the mortality rate was found to be 18.1%. When the patients who died were evaluated, it was observed that although seizure control was achieved, the patients died due to sepsis and subsequent MODS.

Study Limitations

The most important limitation of the study is the small number of cases and its retrospective design. Since the data in our study were analyzed retrospectively, long-term neurological outcomes were not included.

CONCLUSION

In our study, we evaluated the clinical features of patients diagnosed with SRSE. Since there are no studies in the literature to guide treatment management, we planned the treatments within the framework of our intensive care protocol. cEEG monitoring should be used in the recognition of seizures and titration of anesthetic drugs. Immune etiologies should be considered and immunomodulatory treatment should not be delayed, especially in SRSE patients with history, clinical course, cEEG findings, and seizures resistant to anesthetics.

Ethics

Ethics Committee Approval: The ethics committee approval for the study was obtained from Ethics Committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (decision no: 2019/356, date: 02.01.2020).

Informed Consent: Retrospective study.

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Author Contributions

Surgical and Medical Practices: A.G., M.Ç., Concept: E.S., G.C., M.Ç., Ö.S.S., H.A., A.Ü., Design: E.S., A.G., Ö.S.S., H.A., A.Ü., Data Collection or Processing: Y.A., Y.G., P.S., M.Ç., S.T., Analysis or Interpretation: Y.A., Y.G., P.S., M.Ç., S.T., U.K., Literature Search: E.S., G.C., G.A., Ö.S.S., S.T., U.K., Writing: E.S., G.A., Ö.S.S., U.K., H.A. A.Ü.

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