Brain & Development 41 (2019) 359–366

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Treatment options in pediatric super-refractory status epilepticus

Palita Arayakarnkul [a], Krisnachai Chomtho [b,*]

[a] Department of Pediatrics, King Chulalongkorn Memorial Hospital, Thailand
[b] Division of Neurology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Thailand

Received 20 March 2018; received in revised form 26 November 2018; accepted 27 November 2018

Abstract

Background: Super-refractory status epilepticus (SRSE) is a seizure that continues >24 h after anesthesia, or recurs on the reduction of anesthesia. SRSE is extremely difficult-to-control and associated with poor outcome. To date, optimal therapy and outcome data in children is limited.

Objective: To assess etiology, treatment options and outcome in pediatric SRSE patients.

Method: We reviewed medical records of children <15 years old with SRSE during 2007–2017 at King Chulalongkorn Memorial Hospital. Demographic data, etiology, treatment, complications and discharge outcome were recorded.

Results: Seventeen patients, aged 1 month–13 years were included. The leading etiology was immune-mediated encephalitis (29.4%) and epilepsy (29.4%). The most common anesthetic agents were midazolam (94.1%) and propofol (52.9%) with the average maximal dose of 1.3 and 6.9 mg/kg/h respectively. Other treatments included immunological therapy (76.5%), ketogenic diet (76.5%), pyridoxine/pyridoxal-5-phosphate (70.5%). The most common complications were hypotension (61.5%), drug hypersensitivity (32.5%). Median length of anesthetic and intensive care were 9 and 23 days. The mortality rate was 17.6%, and 2 of 3 febrile infection-related epilepsy syndrome cases died. At discharge, all survivors were seizure free.

Conclusion: The majority of pediatric SRSE does not have epilepsy and the etiology is various. Treatment should expand from antiepileptic drugs to other modalities targeting different possible mechanisms such as immunomodulation or specific metabolic treatment. Multiple anesthetic drugs could be tolerated with close monitoring. Ketogenic diet, via enteral or parenteral route, could be considered early if requiring multiple anesthetic drugs. Initial outcome in children is relatively better than in adults.

Keywords: Super-refractory; Status epilepticus; Pediatric; Treatment; Intravenous immunoglobulin; Therapeutic hypothermia; Ketogenic diet; Ketogenic parenteral nutrition; Outcome

1. Introduction

Status epilepticus has been known as a common neurologic emergency in pediatric patients for several years. This condition is a life-threatening emergency that requires prompt recognition and management. The incidence of status epilepticus in children ranges from 10 to 58 per 100,000 per year for children under 18 years in the United States with mortality of 2–7% [1–3]. Refractory status epilepticus (RSE) and super refractory status epilepticus (SRSE) are even rarer, estimated in the USA brought 13/100,000 for SRSE in both adults and children [4].

A patient is considered to have RSE when seizures continue despite first- and second-line treatments, sei-

* Corresponding author at: Division of Neurology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, 11th Floor Sor Kor Building, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.
E-mail address: krisnachai.c@chula.ac.th (K. Chomtho).

https://doi.org/10.1016/j.braindev.2018.11.011
0387-7604/

zure duration is more than 1 h, or there is a need for general anesthesia [5]. The most frequent etiology of recurrent status epilepticus and RSE is progressive encephalopathy and remote symptomatic [6]. In normal healthy patients whom acute RSE were found, none returned to baseline neurological status [7] and overall mortality was 20% [4]. SRSE is defined as seizure that continues 24 h or more after the onset of anesthesia, including those cases in which status epilepticus recurs on the reduction or withdrawal of anesthesia. This is a new descriptive term, first appearing in 2011 in the summary of the Third London-Innsbruck Colloquium on Status Epilepticus [8]. SRSE is not a new entity, but naming it helps to clarify an approach to therapy in this difficult clinical situation. 10–15% of all those presenting to hospital in status epilepticus develop SRSE [9].

Therapy in this condition is difficult. To date, there are no randomized controlled studies of treatment option for SRSE. The published evidence bases largely on case reports or small series [8]. There is no clear guideline about dose or duration of therapy and little to no evaluation of effectiveness. In 2012, Shorvon and Fersili reviewed treatments and outcomes in 1168 adult SRSE patients and suggested treatment protocol [7]. First line therapy that should be used in those cases is general anesthesia and adequate antiepileptic drugs. Second line therapy that can be applied including hypothermia, Magnesium and pyridoxine infusion, immunological therapy (steroid, intravenous immunoglobulin (IVIG), plasma exchange) and ketogenic diet (KD) [9].

In this study, we mainly reviewed pediatric patients with SRSE who were admitted to Intensive Care Unit in King Chulalongkorn Memorial Hospital, a tertiary care hospital in Bangkok, Thailand. We assessed the clinical features, underlying etiology, treatment modalities and their duration, and the outcome of at discharge. The aim is to evaluate and adjust treatment protocol in pediatric SRSE patients.

2. Subjects and methods

2.1. Patients and clinical data

We retrospectively reviewed medical records of the patients aged 0–15 years who were diagnosed with SRSE and admitted to Pediatric intensive care unit (PICU) of King Chulalongkorn memorial hospital between January 2007–December 2017. All patients got continuous electroencephalography (EEG) monitoring to confirm diagnosis and monitor the response to treatment to ensure the termination of SRSE. Patients who solely had electrographic status epilepticus were excluded as they required less aggressive treatment protocol for non-convulsive nature. This study was approved by the Institutional Review Board at Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

The data was collected in a structured case record form, reviewing demographic data, underlying conditions, SRSE etiology, the number of antiepileptic drugs (AEDs) used, the detail of anesthetic agents used including their duration and maximum dose, the alternative interventions used for SRSE, duration until SRSE termination, side effects of all treatments, length of PICU stay and hospitalization, and treatment outcome at discharge.

2.2. Statistical analysis

Statistical analysis was performed with SPSS (version 19.0). The data was reported as median or mean for continuous variables and as proportions for categorical variables.

3. Results

Seventeen patients were recruited into this study. Clinical information regarding features, etiology, treatment detail and outcomes were collected as the following:

3.1. Clinical features

3.1.1. Demographic data

From all seventeen patients, ten cases (58.8%) were males and seven cases (41.2%) were female. The age range was between one month to thirteen years. The median age was 7 years, mean age was 6.1 years old. The majority of the subjects (64.7%) were in school age. Five patients (29.4%) have had underlying epilepsy. Twelve of the seventeen (70.6%), who were developmentally normal with no underlying condition, developed a new-onset SRSE.

3.1.2. Etiology

The cause of SRSE was identified in 14 patients (82.4%). The detail information of underlying condition and etiology for individual case is shown in Table 1. In five patients (29.4%), SRSE was the result of the incomplete control of their underlying epilepsy. Among those with a new onset SRSE, 6 cases (50%) had febrile SRSE. They were initially deemed acute encephalitis, which was defined here as an alteration of mental status >24 h with at least 2 of the following: fever, seizures, new onset of focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis, abnormal brain neuroimaging or compatible EEG, with no alternative cause identified [10]. Lumbar puncture revealed CSF pleocytosis in 2 cases (33%) and high opening pressure with no pleocytosis in 2 cases (33%). No pathogen was identified from routine bacterial culture but polymerase chain reaction technique

Table 1
SRSE etiology, treatment and outcome.

No.	Sex	Age (years)	Pre-existing epilepsy	Etiology	Number of AED	Continuous infusion type, duration (days)	Other treatment modalities	Treatment-related complications	Duration until SRSE termination (days)	PICU/total admission (days)	Seizure outcome at discharge
1	M	1.7	N	FIRES	8	Mid,14/Pro,13/Val,22/Ket,19	Steroid, ketogenic, pyridoxine, PLP	Hypotension, respiratory depression, transaminitis, hypercreatine phosphokinemia	16	56/83	No seizure
2	M	0.3	Y	PLP deficiency	9	Mid,14/Pro,7	Ketogenic, PLP, pyridoxine	–	10	13/80	No seizure
3	F	7.0	N	NPSLE	7	Mid,20/Pro,10/Dia,10	Phenobarbital coma, steroid, IVIG, pyridoxine	Propofol infusion syndrome, hypersensitivity	16	22/85	No seizure
4	M	0.1	Y	*SCN2A* mutation	3	Mid,16	Steroid, pyridoxine, PLP	–	10	23/50	No seizure
5	F	0.5	Y	PLP deficiency	6	Mid,22/Pro,3/Val,15	IVIG, ketogenic, pyridoxine, PLP	Hypotension, respiratory depression, propofol infusion syndrome, transaminitis	14	57/231	No seizure
6	M	9.8	N	Rasmussen encephalitis	6	Mid,14	IVIG, ketogenic, epilepsy surgery	Electrolyte imbalance, hypersensitivity	9	16/40	No seizure
7	M	3.8	N	Internal carotid artery occlusion	4	Mid,8	Hypothermia, steroid	–	4	17/37	No seizure
8	F	8.8	N	Herpes encephalitis	8	Mid,17	Steroid, ketogenic, pyridoxine	Hypercalciuria, hypersensitivity (DRESS)	6	51/87	No seizure
9	F	5.2	N	Rickettsia encephalitis	9	Mid,12/Thio,10/Ket,3	Steroid, IVIG, ketogenic, pyridoxine	Hypotension, transaminitis, heart block, hypercalciuria, hypersensitivity	8	15/15	Deceased, SRSE terminated
10	M	8.5	Y	Provoked SRSE	7	Mid,12	Phenobarbital coma, steroid, ketogenic, pyridoxine	Hypotension, electrolyte imbalance	9	25/57	No seizure
11	M	13.5	N	FIRES	3	Mid,17/Val,4	Steroid, ketogenic, pyridoxine	Hypotension, transaminitis	–	4/27	Deceased, SRSE uncontrolled
12	M	0.2	N	Child abuse, intracranial hemorrhage	4	Mid,11/Pro,9	Hypothermia, ketogenic, pyridoxine, PLP	Bradycardia	10	27/156	No seizure
13	F	10.7	Y	Lennox Gastaut syndrome	6	Pro,4/Ket,5	Steroid, ketogenic, pyridoxine	Hypotension, propofol infusion syndrome, hypersensitivity	6	33/66	No seizure
14	F	8.3	N	Anti-NMDA receptor encephalitis	6	Mid,19/Val,12	Steroid, IVIG, ketogenic, cyclophosphamide	Hypotension	13	49/149	No seizure
15	M	10.5	N	FIRES	7	Mid,34/Pro,8/Ket,4	Steroid, IVIG, isoflurane	Propofol infusion syndrome, hypersensitivity (DRESS), cardiac arrhythmia	–	27/27	Deceased, SRSE uncontrolled

Table 1 (*continued*)

No.	Sex	Age (years)	Pre-existing epilepsy	Etiology	Number of AED	Continuous infusion type, duration (days)	Other treatment modalities	Treatment-related complications	Duration until SRSE termination (days)	PICU/total admission (days)	Seizure outcome at discharge
16	M	3.4	N	SREAT	5	Mid,13/Pro,13	Steroid, IVIG, ketogenic, pyridoxine, PLP	Hypotension, prolonged PR interval, hypercalciuria	6	14/96	No seizure
17	F	11.4	N	SREAT	5	Mid,11/Pro,11	Steroid, IVIG, ketogenic, plasmapheresis	Transaminitis, electrolyte imbalance, propofol infusion syndrome	7	23/88	No seizure

GDD = global developmental delay, NPSLE = neuropsychiatric systemic lupus erythematosus, SREAT = steroid-responsive encephalopathy associated with autoimmune thyroiditis, DRESS = Drug reaction with eosinophilia and systemic symptoms Mid = midazolam, Pro = propofol, Val = sodium valproate, Ket = ketamine, Thio = thiopental, Dia = diazepam, PLP = pyridoxal-5-phosphate, IVIG = intravenous immunoglobulin, steroid = high dose methylprednisolone.

(PCR) identified herpes simplex virus and rickettsia in 2 cases (33%). Tests for CSF and systemic autoantibodies could unveil another case of immune mediated encephalopathy.

The leading cause was immune mediated encephalitis which were confirmed in five of all seventeen patient (29.4%) (two patients were confirmed with steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), one case had anti-N-methyl-D-aspartate Receptor (anti-NMDAR) encephalitis, one patient had Rasmussen encephalitis and the other one had neurological involvement and other criteria that fulfilled for the definite diagnosis of systemic lupus erythematosus (SLE). The second commonest cause was genetic disorders (3 cases, 17.6%), two of which has pyridoxal 5′-phosphate (PLP) dependent epilepsy confirmed by *PNPO* mutation and one case has *SCN2A* mutation detected by whole exome sequencing. Central nervous system infection was proven in two cases (11.7%) (one case with herpes encephalitis and the other with rickettsia encephalitis). The rest of definite causes were child abuse with intracranial hemorrhage in one case (5.8%), and the last one had ischemic stroke (5.8%) from internal carotid artery occlusion. However, three of 17 cases (17.6%) remained unknown of etiology despite extensive investigations. All of these 3 cases have febrile SRSE with no identified cause from bacterial culture, viral PCR or antibodies panel for immune mediated encephalitis so they fell into the category of febrile infection-related epilepsy syndrome (FIRES), which is defined following the consensus from the First International new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES) Symposium as a new onset of refractory status epilepticus without a definite cause, but having a prior febrile infection, with fever starting between 2 weeks and 24 h [11].

3.2. Treatment options of SRSE

3.2.1. Antiepileptic drugs

All patients were treated following standard guideline for treatment of status epilepticus and received multiple intravenous antiepileptic drugs and continuous infusion of anesthetic drug within the first few hours of the seizure onset [12]. Intravenous diazepam was used for the initial seizure termination. Intravenous phenobarbital, phenytoin and levetiracetam were then loaded and continued in all 17 patients. Sodium valproate was given intravenously in 16 cases except in case 3 with PLP dependent epilepsy whose SRSE was completely control with PLP administration. The additional antiepileptic drugs included intravenous lacosamide, oral topiramate, clobazam, clonazepam, vigabatrin, zonisamide, perampanel. The number of AEDs used ranged from three

to nine agents (median 6, mean 6.06) prior to an induced coma by anesthetic infusion.

3.2.2. Medically induced coma

All patients got continuous EEG monitoring to ensure the control of subclinical seizure. Continuous anesthetic infusion to induce coma with burst-suppression EEG pattern had been used in all seventeen patients, ranging from one to four agents in each patient. Midazolam was the first infusion agent used in sixteen patients (94.1%), in the dose range of 0.5–3.2 mg/kg/h and average maximal dose of 1.3 mg/kg/h. Other continuous infusion included propofol (nine cases, 52.9%), valproate (four cases, 23.5%), ketamine (four cases, 23.5%), thiopental (two cases, 11.8%) and diazepam (one case, 5.9%). The list and duration of anesthetic agents for individual case is shown in Table 1. Propofol infusion was used with an average maximal dose of 6.9 mg/kg/h (range 3–13 mg/kg/h) and mean duration 6.9 days (range 3–13 days). Every patient on propofol achieved complete seizure control but all got seizure recurrence when weaning in 48 h.

3.2.3. Adjunctive treatment

Other treatments comprised immunological therapy (15 cases, 88.2%), ketogenic diet (13 cases, 76.5%), pyridoxine and/or pyridoxal-5-phosphate (12 cases, 70.6%), therapeutic hypothermia (2 cases, 11.8%) and emergency neurosurgery (1 case, 5.9%) as shown in Table 1. All of the patients need multiple therapy to control SRSE.

3.2.3.1. Immunological therapy. Treatment with immunomodulation included pulse methylprednisolone in 13 cases, (76.5%), IVIG in 8 cases (47%), pulse cyclophosphamide in 1 case (5.9%) and plasmapheresis in 1 case (5.9%). This treatment did not lead to immediate seizure control but overall improvement was slowly seen in 4 cases with immune encephalopathy (case No. 3, 14, 16, 17).

3.2.3.2. Ketogenic diet. KD was used in totally 13 SRSE cases (76.5%) with various etiologies including pre-existing epilepsy, immune-mediated encephalitis (Anti NMDAR, SREAT, Rasmussen encephalitis), CNS infection (herpes simplex and rickettsial encephalitis), neurometabolic disorders (PLP dependent epilepsy), intracranial hemorrhage and FIRES. In our study, KD was done with medium chain triglyceride (MCT) protocol with ketogenic ratios ranging from 1.3 to 4.6 (median 2). This was given via enteral route in eight patients (61.5%) and parenteral route in five patients (38.5%). The average initial fasting time was 12 h before KD was started. In the enteral group, the diet was modularly formulated with MCT oil (45–55% of total energy). For parenteral ketosis induction, intravenous lipid emulsion of 30%MCT (SMOF®) or 50%MCT (Lipidem®) were used with the starting dose of 1 gm/kg/day, then increasing to the target of 24–40% of total energy. The ketogenic ratio was then up-titrated until reaching significant ketosis, and occasionally increased further in some cases that the seizure control was not achieved. The maximal ketogenic ratio was 4. The median time to target ketosis (serum ketone $\geq$2.0 mmol/L) was 2 days in parenteral route as opposed to 5 days in enteral KD.

KD was started for 2 main purposes. The first group was those still having repetitive clinical seizures despite multiple antiepileptic drugs and anesthetics infusion. This accounted for 9 cases (case 1, 2, 5, 6, 8, 11, 12, 13, 14), and 8 of them (88%) got seizure cessation and were able to wean off anesthetic infusion. However, 1 patient with FIRES (case 11) who was on very high dose of midazolam infusion did not get complete seizure control from ketogenic diet and shortly died from persistent hypotension with multiple-organ failure. Also, in the patient with Rasmussen encephalitis, the seizure control was good at first with KD, but later the seizures recurred and he required epilepsy surgery for complete SRSE control. The second group (case 9, 10, 16, 17) was those with complete seizure control initially by medications but anesthetic reduction after 24–48 h of seizure control failed at least twice. All cases in this group were able to stop continuous infusion of anesthesia eventually after KD.

3.2.3.3. Therapeutic hypothermia. Therapeutic hypothermia was done in a case of internal carotid artery occlusion and an infant with physical abuse and non-progressive subdural hematoma. None of these 2 cases achieved complete seizure control by this treatment.

3.2.3.4. Neurosurgical intervention. Left functional hemispherectomy achieved in SRSE control in a patient with Rasmussen encephalitis whose magnetic resonance imaging showed focal atrophy of left insular lobe, anterior limb of left internal capsule, and left caudate nucleus.

3.2.3.5. Neurometabolic treatment. Intravenous pyridoxine (100–300 mg) was given to 12 cases with SRSE but none showed positive response. Pyridoxal-5-phosphate (30 mg/kg/day) was then added in 6 patients, leading to complete seizure control in 2 cases (case No. 2, 5) with neonatal onset epilepsy who were proven later as having *PNPO* mutation.

3.3. Complication

Fourteen of the seventeen patients (82.4%) had medical complications related to SRSE treatment during hospitalization. Eight (47.1%) had cardiovascular compromised requiring vasopressor drugs, six (35.3%) had

antiepileptic drug hypersensitivity (half of which was caused by phenytoin), five (29.4%) had transaminitis. Adverse reaction from specific drugs included five cases out of nine patients receiving propofol infusion (55.5%) had propofol infusion syndrome, and 2 of 13 patients (1.4%) taking ketogenic diet had electrolyte imbalance (hyponatremia, hypokalemia and hypomagnesemia). Other complications were respiratory depression and cardiac arrhythmia. Three of the seventeen did not have any complications related to SRSE treatment. Treatment complications for individual case are described in Table 1.

3.4. Duration of treatment

Every patient got continuous EEG monitoring to ensure the control of subclinical seizure. The duration of SRSE which was counted from the seizure onset until ictal EEG termination and complete discontinuation of anesthetic infusion ranged from 4 to 16 days (median 9, mean 9) as shown on Table 1. All cases required PICU admission ranging from 4 to 57 days (median 23, mean 27.7) and the whole hospital stay ranged from 15 to 231 days (median 80, mean 80.8).

3.5. Outcome at discharge

Three patients (17.6%) deceased during the admission. Two of them had febrile SRSE of unknown etiology, categorized as having FIRES and did not achieve complete seizure control until death. In the other expired case, the cause of death was rickettsial encephalitis and he had been seizure free for 7 days before his death. All surviving patients were discharged from the hospital with complete seizure freedom on multiple oral antiepileptic drugs and, in most cases, were also on ketogenic diet.

4. Discussion

Pediatric SRSE cases in our study are caused by an acute condition rather than an escalation of the uncontrolled epilepsy. Most cases of new onset SRSE in this study have specific etiology. However, the cause of SRSE in our study is heterogeneous which means extensive investigations are required. In a recent retrospective study that includes large number of SE episodes in children, progressive encephalopathy was the most common etiology and risk of recurrent seizure [6]. Similar to this study, we found that immune mediated encephalitis and underlying epilepsy were two main etiologies in our patients. It is notable that among those with pre-existing intractable seizures, more than half of the case are genetic disorders who receive benefit from advance genetic test. On the other hand, immunological and microbiological tests focusing in central nervous system may have high diagnostic yield and lead to specific treatment in cases who present with their first seizure turning to SRSE.

Despite the extensive investigations, a few cases still had no identified cause. They were febrile related and could be classified as FIRES. Our treatment included steroid and KD similar to the suggestion from an evidence-based review [11], which shows the response rate of 17% and 54% respectively. In our study, 2 cases were started on KD. One child (50%) showed a good response in a few days when ketosis was achieved even though the seizure was previously very intractable despite continuous infusion of 4 drugs (case 1). The other patient (case 11) using KD did not get good seizure control. However, he has been treated with extremely high dose midazolam in another hospital before transferred to our PICU in a moribund state with multi-organ failure, and died in 4 days afterwards. This treatment duration may be too short to determine the response to either steroid or KD. Although the overall response of FIRES in this study was quite unsatisfactory and 2 of 3 cases died, KD was probably still a treatment option that should be offered early in FIRES as this condition is likely to be refractory to other medical treatment.

Regarding the anesthetic drugs for SRSE treatment, from the previous study of Kravljanac et al. which included 602 episodes of status epilepticus [6], midazolam was the primary infusion agent used in most SRSE patients. This is similar to our findings, but our patients were given higher average maximal dose (1.3 comparing to 0.4 mg/kg/h) and maximal dose (3.2 comparing to 1.2 mg/kg/h). Please note that the patient whose maximal dose of midazolam was 3.2 mg/kg/h (case No. 11) was already started on very high dose from another hospital before a referral to our center. After being admitted, the dose was titrated down continuously. This may affect the higher maximal and average maximal dose in our study. It is quite notable in this patient that extremely high dose of midazolam infusion resulted in severe systemic complication and the final mortality. The extremely high dose didn't get complete seizure control, but adding sodium valproate infusion and KD stopped the seizures resulting in midazolam reduction in this case. This was also similar in the other cases that increasing the dose of anesthetic infusion resulted in more adverse effect without better seizure control. We suggest from our observation that early combination of anesthesia or other therapeutic means will increase the chance of better seizure control.

Immunological therapies including IVIG, corticosteroid and plasmapheresis have been reported in many studies. Immunotherapy is mostly used in situations where paraneoplastic or autoimmune encephalitis is responsible for the development of seizure [13]. In clinical practice, this immune-mediated etiology cannot be

confirmed clinically and will take time for definite diagnosis. In our study, we started immunological therapies early in acute encephalopathy cases if the ongoing seizures became super-refractory and there was no definite cause found. After the investigations, we reported five patients with immune mediated encephalitis that were receiving IVIG and/or pulse methylprednisolone when antiepileptic drugs failed, and all these patients recovered with complete seizure control at discharge. This is accounted for 41.6% of the new-onset SRSE in our study. Therefore, we support that when antiepileptic drugs failed in new and acute cases, the use of immunotherapy might be of benefit even though the immunological results is still not known. Nevertheless, these cases will require other therapeutic means to control SRSE as immunological treatment did not bring immediate seizure control but targeting on the mechanism of the underlying conditions.

KD had been reported as an effective therapy in both adults and children [14–16]. Therapeutic success rates in adult were reported up to 70% at the 3rd International symposium on Dietary Therapies by several group using a ketogenic diet [17]. Study of Cobo et al. reported treatment of SRSE with enteral KD in children and supported early consideration of KD in SRSE as a safe and well-tolerated broad-spectrum agent [18]. In our study, we found KD was initiated in 13 patients, and 11 of these patients achieve good seizure control, and discontinuation of anesthetic infusion similar to the previous report. KD can be used in miscellaneous causes of SRSE, in either focal or generalized seizures, or even in electrographic seizures. However, we observed in 1 case with focal pathology like Rasmussen encephalitis that the effect of KD was initially helpful but not sustainable. Therefore, SRSE cases with focal pathology are not good candidates for KD unless proper epilepsy surgery cannot be done promptly.

We also proposed that KD should be considered early if more than 1 anesthetic drug infusion required and there is no other definite treatment like epilepsy surgery. This is from our data that 4 of 13 cases treated with KD (30.7%) were actually seizure-free but failed to reduce anesthetic drug before KD treatment. These cases ended up with prolonged and excessive use of anesthesia causing more side effects and prolonged ICU stay. KD will be a good option to avoid this morbidity. However, there is always a debate that these patients are critically ill, and cannot tolerate high fat diet enterally. Our study found the use of parenteral KD induction in 5 cases (38%) which had similar seizure control but faster ketosis than enteral KD by 3 days and had no significant adverse effect. This is similar to Lin et al. who also reported early intravenous KD initiation in children with SRSE as an effective and safe alternative treatment [19]. Our study suggests that either enteral or parenteral KD initiation can be an effective treatment in pediatric SRSE patients. However, the data regarding parenteral KD protocol is still limited and further study to minimize the biochemical adverse effects is required.

Shorvon and Fersili suggested that intravenous pyridoxine is an effective treatment in patients with an inborn error of metabolism of pyridoxine. It had also been claimed that intravenous pyridoxine therapy may be effective in SRSE when no clear deficit in pyridoxine metabolism was present. Pyridoxine is now routinely given in cases of SRSE in young children [9]. In our study, pyridoxine and pyridoxal-5-phosphate (PLP) were added in treatment protocol at high rate due to our study samples' age group that were at higher risk of pyridoxine metabolism deficiency than in adults. Surprisingly, we didn't find any pyridoxine dependent epilepsy in our SRSE study. This may be the result of early trial of pyridoxine for infants with intractable seizures or refractory status epilepticus so pyridoxine dependent epilepsy cases in our institute got a better control before going into SRSE. However, we found two patients proven of PLP deficiency got significant benefit from the treatment. These 2 cases share particular characteristics of intractable seizure of neonatal onset. Even though PLP dependent epilepsy is quite rare in normal population, it could be a relatively common in infants with SRSE like in our study, 2 in 17 cases (11%). From this finding, we propose the routine treatment with PLP in all infant with SRSE especially those with pre-existing seizure. Since PLP is effective in both pyridoxine-dependent and PLP-dependent epilepsy, it may be used alone without prior pyridoxine treatment.

Propofol infusion syndrome is a rare (reported incidence of 1.1–4.1%) but serious and life-threatening condition [20]. In this study, we reported five from nine patients (55.5%) receiving continuous propofol infusion had propofol infusion syndrome. The dose and duration of propofol in our study varied from usual to high dose, depending on the treating neurologist. All cases were closely monitored whilst on propofol and this syndrome was detected early in the course so propofol was discontinued without any permanent clinical morbidity. However, we found that the average maximal dose and duration of those with propofol infusion syndrome was higher than their counterpart. This observation is similar to the previous study which reviewed that this condition was appeared to be dose-dependent and strongly associated with propofol infusion at mean dose greater than 4 mg/kg/h for at least 48 h [20]. Prolonged and high dose of propofol infusion may be related to a higher incidence of propofol infusion syndrome in this study. Notably, propofol infusion was very effective in seizure control in all 9 cases refractory to midazolam infusion in our study, but none achieved a successful weaning in 48 h without electrographic seizure recurrence. Our observation suggests that propofol infusion can be initially useful for SRSE control but the adverse

effect should be closely monitored and other therapeutic means should be considered promptly to avoid the prolonged use of propofol.

Mortality rate of SRSE varies in adult and pediatric patients. The mortality rate ranged from 15.4 to 39.9% in adult patients, 5–20% in pediatric patients [5,6,15,21,22]. Comparing to previous studies, our study found similar mortality rate of 17.6%. From our observation, most occurs in unknown etiology whose seizures were much more difficult to control despite intensive treatment. On the contrary, those with specific cause had a good prognosis in seizure control at least in short term once SRSE is terminated.

Overall, the information from our study suggests that extensive investigations (genetic, metabolic, and immunological) should be done to guide specific treatment. If no cause is initially found, PLP and immunological therapy should be considered. Ketogenic diet should also be used early and the parenteral route is as safe and effective as enteral KD. Our study has limitation due to a small sample size of this rare condition. Also, the effectiveness of each treatment is also difficult to determine as several options are usually commenced in a relatively short period due to the urgent nature of this condition. On the other hand, this study includes various etiology of SRSE from extensive investigation, and explores broad spectrum of treatment modalities and determine the treatment effect by continuous EEG which ensure the complete termination of electrographic seizure. This should enhance the benefit of specific treatment like immunotherapy, KD, and PLP in the pediatric age group. However, further studies with larger sample size are needed to ascertain the significant effectiveness of each treatment option.

References

[1] Chin RFM, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006;368:222–9.

[2] Riviello JJ, Ashwal S, Hirtz D, Glauser T, Ballaban-Gil K, Kelley K, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review). Neurology 2006;67:1542–50.

[3] Smith DM, McGinnis EL, Walleigh DJ, Abend NS. Management of status epilepticus in children. J Clin Med 2016;5:47.

[4] Alford E, Wheless J, Phelps S. Treatment of generalized convulsive status epilepticus in pediatric patients. J Pediatr Pharmacol Ther 2015;20:260–89.

[5] Beg JM, Anderson TD, Francis K, Meckley LM, Fitzhenry D, Foster T, et al. Burden of illness for super-refractory status epilepticus patients. J Med Econ 2017;20:45–53.

[6] Kravljanac R, Djuric M, Jankovic B, Pekmezovic T. Etiology, clinical course and response to the treatment of status epilepticus in children: A 16-year single-center experience based on 602 episodes of status epilepticus. Eur J Paediatr Neurol 2015;19:584–90.

[7] Sahin M, Menache CC, Holmes GL, Riviello JJ. Prolonged treatment for acute symptomatic refractory status epilepticus. Neurology 2003;61:398.

[8] Shorvon S. Super-refractory status epilepticus: An approach to therapy in this difficult clinical situation. Epilepsia 2011;52:53–6.

[9] Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135:2314–28.

[10] Venkatesan A, Geocadin RG. Diagnosis and management of acute encephalitis: a practical approach. Neurol Clin Pract 2014;4:206–15.

[11] Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, Lancrenon J, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. Epilepsia 2018;59:745–52.

[12] Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Curr 2016;16:48–61.

[13] Bayrlee A, Ganeshalingam N, Kurczewski L, Brophy GM. Treatment of super-refractory status epilepticus. Curr Neurol Neurosci Rep 2015;15:66.

[14] Farias-Moeller R, Bartolini L, Pasupuleti A, Brittany Cines RD, Kao A, Carpenter JL. A practical approach to ketogenic diet in the pediatric intensive care unit for super-refractory status epilepticus. Neurocrit Care 2017;26:267–72.

[15] Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. Seizure 2016;41:62–5.

[16] Thakur KT, Probasco JC, Hocker SE, Roehl K, Henry B, Kossoff EH, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology 2014;82:665–70.

[17] Mackenzie CC, Bobbie H, Janak N, Susan W, Jeff SV. Worldwide dietary therapies for adults with epilepsy and other disorders. J Child Neurol 2013;28:1034–40.

[18] Nicole HC, Raman S, Kristina KM, Sarika LS, Michele AK, Joyce HM. The ketogenic diet as broad-spectrum treatment for super-refractory pediatric status epilepticus: challenges in implementation in the pediatric and neonatal intensive care units. J Child Neurol 2014;30:259–66.

[19] Lin JJ, Lin KL, Chan OW, Hsia SH, Wang HS. Intravenous ketogenic diet therapy for treatment of the acute stage of super-refractory status epilepticus in a pediatric patient. Pediatr Neurol 2015;52:442–5.

[20] Chidambaran V, Costandi A, D'Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. CNS Drugs 2015;29:543–63.

[21] Li Y, Tian L, Zeng T, Chen J, Chen L, Zhou D. Clinical features and outcome of super-refractory status epilepticus: a retrospective analysis in West China. Seizure 2014;23:722–7.

[22] Strzelczyk A, Ansorge S, Hapfelmeier J, Bonthapally V, Erder MH, Rosenow F. Costs, length of stay, and mortality of super-refractory status epilepticus: a population-based study from Germany. Epilepsia 2017;58:1533–41.