Brain & Development 41 (2019) 420–427

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

www.elsevier.com/locate/braindev

Original article

The ketogenic diet for super-refractory status epilepticus patients in intensive care units

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Received 26 April 2018; received in revised form 21 November 2018; accepted 25 December 2018

Abstract

Objectives: Super-refractory status epilepticus (SRSE) is one of the most challenging issues in intensive care units (ICUs) in that it is associated with high morbidity and mortality. Although the ketogenic diet (KD) has been reported to be effective in treating of SRSE, the use of the diet as therapy can be complicated by concomitant medical problems specific to critically ill patients. In this study, we aimed to describe our experience of the KD for SRSE patients in ICUs.

Methods: We retrospectively reviewed the medical records of 16 patients (10 males, 6 females) with SRSE who were treated with the KD in the ICUs at Samsung Medical Center from July 2005 to July 2017.

Results: The median age of seizure onset was 8 years (interquartile range 5–13.5). Prior to diet initiation, the patients were in convulsive or non-convulsive SRSE for a median of 23 days (range, 3–420). The median time to achieve ketosis was 3 days (range, 2–6). The KD was continued for a median of 2.1 months (range, 0.1–15.8). Of the 16 patients, nine (56.3%) achieved seizure freedom, six (37.5%) reported >50% seizure reduction, and one (6.2%) had <50% seizure improvement after the KD. There was no significant change in the number of antiepileptic drugs. The most commonly encountered complication during the KD was gastrointestinal disturbance.

Conclusions: Our experience indicates that the KD is an effective alternative therapeutic strategy for SRSE patients in ICUs with adequate efficacy and safety in reducing seizure frequency and weaning from prolonged mechanical ventilation, although functional outcome was not favorable for most patients. Close monitoring and preventive management of potential adverse effects are critical elements for success with the KD in patients with SRSE.

Keywords: Ketogenic diet; Super-refractory status epilepticus; Intensive care units; Epilepsy; Treatment

1. Introduction

Status epilepticus (SE) is a common neurological emergency that requires prompt evaluation and treatment. In some patients with SE, seizures do not respond to antiepileptic drugs (AEDs) and require anesthetic therapy. Shorvon et al. [1] defined super-refractory status epilepticus (SRSE) as SE that continues or recurs 24 h or more after the onset of anesthetic therapy, including cases in which SE recurs upon reduction or withdrawal of anesthesia.

One study demonstrated that 10–15% of the patients with SE progress to SRSE [2], and other study authors found that 5–17% of SE admissions became super-refractory [3–6]. SRSE is a serious, life-threatening neurological condition; the mortality rate is substantial,

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https://doi.org/10.1016/j.braindev.2018.12.007
0387-7604/

reported in various series to be between 30 and 50% [7,8]. Many therapies and treatments have been tried, including hypothermia, inhalational anesthetics, immunotherapy, epilepsy surgery, vagus nerve stimulation, electroconvulsive therapy, and the ketogenic diet (KD), all with varying levels of success [2,9]. However, limited information is available on the effectiveness, safety, or outcome of these therapeutic approaches [1].

The KD, a high-fat, low-carbohydrate, and low-protein diet that mimics the fasting state, has been proved to be effective for intractable epilepsy [2,10–12], and recent reports suggest that the KD can also be useful as an acute treatment for refractory SE in both adults and children [13–16]. However, despite its efficacy in controlling seizures, coexistent medical problems specific to critically ill patients in intensive care units (ICUs) may act as obstacles in initiating or maintaining the KD. Such challenges include decreased gastrointestinal (GI) motility due to prolonged coma therapy, increased susceptibility to infection, and preexisting acidosis [13,17]. Farias-Moeller et al. [17] noted that there were no sufficient data on how to manage these impediments and draw effectiveness from the KD when it is a treatment for SRSE in ICUs.

In this study, we aimed to describe our experience with SRSE patients who were on the KD in ICUs from the perspectives of efficacy and safety. We also suggest approaches for dealing with adverse effects related to the KD.

2. Material and methods

2.1. Patients

We performed a retrospective medical chart review on the patients who were diagnosed with SRSE and treated with the KD in the ICUs at Samsung Medical Center (Seoul, Korea). Subjects were recruited between July 2005 and July 2017, and we included in the study the 5 patients who were previously reported by Nam et al. [16]. All patients underwent continuous electroencephalography (EEG) monitoring for detection of seizures. We defined SRSE as SE continuing for at least 24 h after initiation of general anesthesia or recurring with anesthesia reduction or discontinuation.

2.2. KD initiation and monitoring

Initially, we attempted conventional treatment of SE with benzodiazepines, diphenylhydantoin, phenobarbital, or valproate. When these agents proved to be unsuccessful, the next step was coma therapy with midazolam, pentobarbital, or propofol [1]. We considered the KD an alternative treatment for patients with refractory seizures despite these anesthetic agents.

Before diet initiation, we screened patients for disorders of fatty acid transport and oxidation, which are contraindications to the KD, based on clinical features; these include developmental delay, cardiomyopathy, hypotonia, exercise intolerance, myoglobinuria, and easy fatigability [18]. After evaluating the nutritional status and requirement of energy, we designed feeding and hydration plans, and the KD was given by enteral formula or diet. Fourteen patients (87.5%) received a fat-to-protein and carbohydrate ratio of 4:1, and two patients (12.5%) received a ratio of 3:1. In all patients, the amount of the diet was increased from one third of the total amount and it escalated daily, reaching the full dose in three days. All dextrose was removed from fluids and medications, and gastric residue, bowel sounds, and stool passage were assessed before each meal. During the KD, parameters including serum glucose, blood gas analysis, and urine ketones were checked on a daily basis. The KD protocol is summarized in Table 1.

2.3. Clinical analysis

Data obtained included etiology of SRSE, duration prior to the KD, number of AEDs, number and duration of anesthetic agents, EEG at initiation of the KD, days to achieve ketosis (defined as >3+ ketones on urinalysis), KD duration, and complications of the KD. Additional data analyzed included resolution of SE, seizure burden at most recent follow-up as delineated by

Table 1
KD protocol at Samsung Medical Center.

I. Prior to diet initiation
• Screening patients for disorder of fatty acid transport and oxidation, which are contraindications for the KD, based on clinical features
• Estimate caloric and fluid needs
• Determine starting ratio and formula recipe
• Remove dextrose from intravenous fluids and change medications to low carbohydrate forms (tablets or capsules)
• Hold enteral feeds
• Monitor blood glucose levels every 6 h and measure urine ketones with every voids
II. Diet initiation and monitoring
• When the urine ketone level is >3+, initiate ketogenic formula at one third of goal calories over 24 h. Then escalate it daily, reaching the full calorie feeds in 3 days
• Check urine ketones daily
• Monitor for the occurrence of adverse effects, such as dehydration, hypoglycemia, and nausea/vomiting
III. During follow-up
• Measure urine ketones weekly using reagent sticks
• Regular outpatient visits at monthly intervals
• Blood tests are performed according to patients' status

KD, ketogenic diet.

number of seizures per week or month, and functional outcome at last follow-up.

The estimation of electrographic or electroclinical seizure frequency was used as a parameter determining seizure burden. We defined resolution of SRSE as the disappearance of electroencephalographic or electroclinical seizures after discontinuation of anesthesia.

We performed all statistical analyses using SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA), using the Fisher's exact and Mann-Whitney tests to compare the clinical outcomes by baseline demographics, which we considered statistically significant at $P < 0.05$.

Ethical approval for this retrospective study was given by the institutional review board of Samsung Medical Center (IRB 2017-02-042).

3. Results

3.1. Patient characteristics

We identified 16 patients (10 males, 6 females) with SRSE who were treated with the KD in ICUs. The median age of seizure onset was 8 years (interquartile range 5–13.5). Twelve patients (75%) showed multiple types of seizures, two had complex partial seizures or complex partial seizures with secondary generalization, and two had generalized tonic clonic seizures. Of the 16 patients, ten (62.5%) were diagnosed with febrile infection-related epilepsy syndrome (FIRES) based on the inclusion criteria [19] and two (12.5%) with proven viral encephalitis (1 herpes simplex encephalitis, 1 enteroviral encephalitis). Two of the 16 patients (12.5%) were 1-month-old infants who had acute hypoxic ischemic injury involving deep gray matter and multifocal cortical gray matter. The two remaining patients had hemimegalencephaly and cryptogenic frontal lobe epilepsy.

Prior to diet initiation, the patients were in convulsive or non-convulsive SRSE for a median of 23 days (range, 3–420). The median number of AEDs tried before the dietary therapy was five (range, 2–8). The patients had undergone coma therapy with a median of two anesthetic agents (range, 1–3). At the time of diet commencement, eight patients (50%) had persistent electrographic or electroclinical seizures despite coma therapy. Another six patients (37.5%) had recurrent seizures when anesthetics were tapered off, and the remaining two (12.5%) developed seizures after they were weaned off anesthetics (Table 2).

3.2. Efficacy of KD

The KD was maintained for a median of 2.1 months (range, 0.1–15.8). Fourteen of 16 patients (87.5%) achieved ketosis in a median of three days (range, 2–6), and the other two had 1+ ketone in their urine. Of the 14 patients who received continuous infusion of anesthetics at the time of diet initiation, ten were successfully weaned off anesthetic agents within a median of 6.5 days (range, 1–28). The remaining two had failed to achieve seizure control with anesthetics and were not given anesthetic agents at the time of diet commencement. With discontinuation of anesthetics after the KD, eight patients who were ventilator-dependent could be taken off ventilator support in a median of 6.5 days (range, 1–38). Four other patients received a tracheostomy before or during dietary therapy, and the remaining four were not ventilator-dependent because they had been given relatively small dosage of anesthetic agents.

Of 16 patients, nine (56.3%) achieved seizure freedom, six (37.5%) reported >50% seizure reduction, and one (6.2%) had <50% seizure improvement after the KD; to determine the factors related to favorable KD outcomes, we compared the characteristics of the patients in whom the KD led to successful seizure control with those in whom the diet did not work. Gender, age of seizure onset, etiologies of epilepsy, seizure types, number of previously tried AEDs or anesthetic agents, duration of SRSE before diet, time to ketosis, KD duration, and presence of adverse effects did not influence likelihood of good outcomes (Table 3).

There was no significant change in the number of AEDs during the diet ($p = .188$). However, six patients (37.5%) benefited from medicine reductions: Four patients who were receiving five to eight medications were reduced to four to six medications, and an additional two patients could have their medicine doses reduced.

In addition, we compared the characteristics of FIRES group (10/16 patients) with those of non-FIRES group (6/16 patients). The demographic and clinical characteristics of FIRES group did not differ from those of non-FIRES group. The number of patients who achieved >50% reduction in seizure frequency after the KD was significantly higher in FIRES group ($p < 0.05$) (Table 4).

Fifteen of 16 patients (93.8%) were followed for a median of 19 months (range, 3–85) after discharge. The remaining patient was 14-year-old female who had been hospitalized for long periods because of uncontrolled seizures. After she began KD, she experienced a 50% reduction in seizure frequency at three days and had 75% improvement by the end of the first month. She was bedridden with spontaneous eye opening but was unable to obey. She continued the KD for 16 months and had partial seizures every day before being transferred to a long-term care facility. Seizure outcomes and functional status at last follow-up are presented in Table 2. During follow-up, complete seizure control was achieved in 6 of 15 patients (40%), three of whom was performing well in school with no need for assistance with activities of daily living. The remain-

Table 2
Patient demographics and clinical characteristics.

Pt	Sex	Age (year)	SRSE etiology	Types of SRSE	Seizure type	Duration of SE before KD (days)	Duration of KD (months)	Seizure burden 1 week after initiation	Complications of KD	Seizure outcome at last follow-up	Functional outcome at last follow-up
1	F	14	FIRES	Recurrent*	GTC, CPS	420	15.8	>50% seizure reduction	Regurgitation, constipation, hypertriglyceridemia	1–5/day (partial seizures)	Bedridden, spontaneous eye open but unable to obey
2	M	8	FIRES	Recurrent*	GTC	30	0.7	Seizure free	Aspiration pneumonia	3–10/month (generalized or partial seizures)	Mild mental retardation, ADHD, need assistance with activities of daily living
3	M	10	FIRES	Persistent	GTC, CPS	38	6.5	>50% seizure reduction	Regurgitation, vomiting, constipation, aspiration pneumonia	Seizure-free for 1 month	Ambulatory, mild mental retardation
4	F	4	FIRES	Persistent	CPS	21	4.2	Seizure free	Aspiration pneumonia	2/week (partial seizures)	Moderate mental retardation
5	M	13	FIRES	Persistent	GTC, CPS	26	1	Seizure free	None	1–2/week (generalized or partial seizures)	Ambulatory, mild cognitive impairment
6	M	6	Enteroviral encephalitis	Persistent	CPS, myoclonic	237	2.2	<50% seizure reduction	Kidney stones, metabolic acidosis	7–8/day (partial seizures)	Bedridden, spontaneous eye open but unable to obey
7	M	7	FIRES	Persistent	GTC, CPS	12	1	>50% seizure reduction	Regurgitation, aspiration pneumonia, hypoproteinemia	Seizure-free for 39 months	Normal daily living
8	M	15	Hemimegalencephaly	Recurrent+	CPS with secondary generalization	10	1	Seizure free	None	2/month (generalized seizures)	Moderate mental retardation
9	F	21	FIRES	Recurrent+	GTC	37	2.5	>50% seizure reduction	Nausea, vomiting	1–2/week (partial seizures)	Ambulatory, mild cognitive impairment
10	M	0.1	HIE	Recurrent+	GTC, CPS	8	0.3	Seizure free	None	Seizure free for 24 months	Global developmental delay
11	M	12	FIRES	Persistent	GTC, CPS	30	2.1	>50% seizure reduction	Regurgitation, elevated liver enzymes, hypertriglyceridemia	1–2/month (partial seizures)	Bedridden, spontaneous eye open but unable to obey
12	M	0.1	HIE	Persistent	GTC, CPS	3	0.1	Seizure free	Regurgitation, aspiration pneumonia	Seizure-free for 25 months	Global developmental delay, mild mental retardation
13	M	40	FIRES	Persistent	GTC, CPS	12	1.2	Seizure free	None	1/2months (partial seizures)	Ambulatory, mild cognitive impairment
14	F	2	FIRES	Recurrent+	GTC, CPS	12	5	>50% seizure reduction	Regurgitation, hypoproteinemia	2–3/week (generalized or partial seizures)	Global developmental delay
15	F	8	Herpes simplex encephalitis	Recurrent+	GTC, CPS, myoclonic	25	2.3	Seizure free	Aspiration pneumonia	Seizure-free for 5 months	Normal daily living
16	F	6	Cryptogenic FLE	Recurrent+	GTC, CPS	12	3	Seizure free	None	Seizure-free for 17 months	Normal daily living

Pt, patient; SRSE, super-refractory status epilepticus; SE, status epilepticus; KD, ketogenic diet; FIRES, febrile infection-related epilepsy syndrome; GTC, generalized tonic clonic; CPS, complex partial seizure; ADHD, attention deficit hyperactivity disorder; HIE, hypoxic ischemic encephalopathy; FLE, frontal lobe epilepsy.

* Seizures recurred after weaning off continuous anesthetics.

+ Seizures recurred upon tapering continuous anesthetics.

Table 3
Comparison of response to the KD based on demographic features.

	Patients in whom the KD was proven to be effective (n = 9)	Patients in whom the KD had no profound effect (n = 7)	*p* value
Gender (Female)*	4	2	0.633
Median age (year)+	8	12	0.299
Seizure type*			
Multiple	6	6	0.585
Complex partial or complex partial with secondary generalization	2	0	0.475
Generalized tonic clonic	1	1	1.00
Median number of attempted AEDs+	6	5	0.408
Median number of attempted continuous anesthetic agents+	2	2	0.536
Timing of KD initiation*			
When seizures persisted during coma therapy	3	4	0.315
When seizures recurred upon tapering continuous anesthetics	4	3	0.633
When seizures recurred after weaning off continuous anesthetics	2	0	0.475
Median duration of SE before KD (days)+	21	26	0.536
Median time to ketosis (days)+	3	3	0.535
Median duration of KD (months)+	2.3	2.1	1.00
Presence of adverse effects*	6	5	1.00

KD, ketogenic diet; AEDs, antiepileptic drugs; SE, status epilepticus.
* Fisher's exact test was used.
+ Mann-Whitney test was used.

Table 4
Comparison of demographic and clinical characteristics between FIRES and non-FIRES groups.

	FIRES (n = 10)	Non-FIRES (n = 6)	*p* value
Gender (Female)*	4	2	1.00
Median age (year)+	11	6	0.118
Seizure type*			
Multiple	7	5	1.00
Complex partial or complex partial with secondary generalization	1	1	1.00
Generalized tonic clonic	2	0	0.500
Median number of attempted AEDs+	5	4.5	0.313
Median number of attempted continuous anesthetic agents+	2	1.5	0.118
Timing of KD initiation*			
When seizures persisted during coma therapy	6	2	0.608
When seizures recurred upon tapering continuous anesthetics	2	4	0.118
When seizures recurred after weaning off continuous anesthetics	2	0	0.500
Median duration of SE before KD (days)+	28	11	0.093
Median time to ketosis (days)+	3	4	0.839
Median duration of KD (months)+	2.3	1.6	0.220
Seizure reduction*			
Seizure-free	4	5	0.145
>50% seizure reduction	6	0	0.034
<50% seizure reduction	0	1	0.375
Presence of adverse effects*	8	3	0.299

FIRES, febrile infection-related epilepsy syndrome; AEDs, antiepileptic drugs; KD, ketogenic diet; SE, status epilepticus.
* Fisher's exact test was used.
+ Mann-Whitney test was used.

ing three patients had global developmental delays that required physiotherapy and speech and language therapy (n = 2) or mild mental retardation (n = 1). Of 15 patients, nine showed median seizure frequency of 8 times per month (range, 0.5–30). Functional status in these patients was as follows: bedridden and unable to care for themselves (n = 2), mild or moderate mental retardation requiring help with daily living (n = 3), mild

Table 5
Early- and late-onset complications of the KD.

	No. of patients (%)	
	Early-onset	Late-onset
Gastrointestinal disturbance[a]	6 (37.5)	3 (18.8)
Lipid aspiration pneumonia	5 (31.3)	2 (12.5)
Hypoproteinemia	2 (12.5)	
Hypercholesterolemia	1 (6.3)	1 (6.3)
Elevated liver enzyme	1 (6.3)	
Renal stone		1 (6.3)
Metabolic acidosis		1 (6.3)

KD, ketogenic diet.
[a] Nausea, vomiting, regurgitation, constipation.

cognitive impairment (n = 3), and global developmental delay (n = 1).

3.3. Tolerability of KD

Eleven of 16 patients (68.8%) reported adverse effects attributable to the KD. The complications were classified as either early or late onset depending on whether they were reported within four weeks of KD introduction until stabilization or thereafter [20]. As shown in Table 5, the most common early-onset adverse effect was GI disturbance such as regurgitation, nausea, vomiting, or constipation, which we observed in 6 of 16 patients (37.5%); of these adverse GI effects, regurgitation was noted in five patients (31.3%), vomiting in two (12.5%), constipation in two (12.5%), and nausea in one (6.2%). To manage GI problems, interventions such as upright position during feeding, more concentrated diet, frequent intake of small amounts or continuous feeding, and antiemetics or antacids were tried. In addition, signs and symptoms of respiratory infection such as fever, elevated C-reactive protein, chest radiograph showing haziness, and increased secretions were observed in 5 of 16 patients (31.2%). To reduce the risk of patients' developing pneumonia, temporary withholding the KD, reducing the amount of formula, and continuous slow feeding were attempted.

After the initial four weeks of the diet therapy, GI disturbance (3/16, 18.8%) and signs of respiratory infection (2/16, 12.5%) were still frequently encountered complications. Other established side effects such as hypoproteinemia, hypertriglyceridemia, elevated liver enzymes, metabolic acidosis, and kidney stones were also reported.

Except for one patient for whom data were not available, nine patients discontinued the KD for variable reasons; adverse effects (7/9, 77.8%), complete seizure control (1/9, 11.1%), and poor compliance (1/9, 11.1%). In two patients, respiratory symptoms and chest X-ray did not resolve in spite of changing body positions, adjusting feeding amount and medications, and chest physiotherapy; although the KD was successful for treating seizures, they had to discontinue the diet therapy. The remaining five patients had to withdraw from the diet therapy due to persistent regurgitation (n = 2), low serum albumin level that led to pleural effusion (n = 1), prolonged elevated liver enzymes (n = 1), and hydronephrosis associated with renal stones (n = 1). The two patients who had only 1+ ketone in their urine terminated the KD because of GI disturbances such as vomiting and regurgitation and no definite effects on seizure control.

4. Discussion

This study showed that KD was effective and tolerable in reducing seizure frequency and escaping from SRSE without any serious sequelae for SRSE patients in ICUs. When patients do not respond to benzodiazepines or intravenous AEDs, other treatments such as general anesthetics or hypothermia should be considered. However, those treatment could increase the risk of respiratory depression and require mechanical ventilation and cardiovascular monitoring, and thus they necessitate ICUs admission [1,9]. To date, 67 patients with refractory SE (RSE) or SRSE admitted to ICUs and treated by KD have been reported in literature [13,17,21,22]. This is a relatively large-scale study about the therapeutic roles of the KD in patients with SRSE in ICUs. In our experience, the clinical efficacy of the KD varied among individuals, but it was effective for weaning patients off continuous anesthetic agents or controlling seizures in more than half of our cases (9/16, 56.3%), which was consistent with findings from previous studies [21].

Although the diet therapy is typically used for patients with intractable epilepsy, there has been interest in its use as an emergent, acute therapy [16,23–25]. Retrospective case reports have demonstrated the therapeutic roles of the KD in SRSE. Bodenant et al. [26] first described 54-year-old man with RSE who exhibited a favorable outcome seven days after introduction of the KD, and the diet was shown to be effective for nine pediatric patients diagnosed with FIRES [15]. Also, the KD was used successfully to treat two adults with prolonged nonconvulsive SE [24].

Our study revealed that the KD played an essential role in cutting off continuous infusion of anesthetic agents or controlling seizures in more than half of patients (56.3%); the results were comparable with what has been described for the KD in RSE or SRSE patients [14–16,21]. The KD was also helpful for weaning from mechanical ventilation in six of eight patients (75%). Because prolonged coma therapy or ventilatory support, unremitting seizures, and use of a number of AEDs may increase the risk of serious infection or critical multiorgan dysfunction [27], the KD can serve as an alternative strategy to treat SRSE patients in ICUs. In addi-

tion, high responder rates of the KD were observed among patients diagnosed with FIRES in this study. These findings were consistent with previous studies by Nabbout et al. [15] that had demonstrated the alternative therapeutic role of the KD for FIRES patients. This favorable response to KD in patients with FIRES needs to be confirmed in prospective controlled studies. In our study, two of 16 patients (12.5%) were diagnosed with proven viral encephalitis and given antiviral agents in the early course of the disease, which were not effective in controlling seizures. Although acyclovir has reduced the mortality and long-term morbidity in herpes simplex encephalitis, patients treated with antiviral agents frequently have unfavorable neurological outcomes [28,29]. On that aspect, it is unlikely that therapeutic interventions such as antiviral agents had contributed greatly to seizure control in our study.

With regard to cognitive and functional outcome, 6 of 16 patients (37.5%) who were regularly followed-up returned to normal activities of daily living or had mild cognitive impairment, whereas the remaining patients had developmental delay or mental retardation, or they were bedridden. This relatively high rates of unfavorable functional outcome can be explained by clinical features of SRSE. In patients with SRSE, seizure intractability may be associated with more adverse effects leading to a negative impact on the brain and unfavorable functional outcome [30]. In addition, prolonged coma therapy or ventilatory support before starting the KD may lead to medical complications such as infection, which may be associated with longer hospital stay, lower return to baseline, and functional decline [31,32]. The patients who achieved favorable neurologic outcome had shorter median duration of SE, fewer adverse effects related to the KD, and fewer brain magnetic resonance imaging abnormalities, although the differences were not statistically significant.

The adverse effects related to the KD are usually transient, can be improved with conservative management, and only rarely require the diet to be discontinued [27]. However, given that serious complications can occur that necessitate interrupting the diet therapy, early recognition of adverse effects and proper intervention are crucial for maintaining the KD. In accordance with previous studies [16,20,27], our results revealed that the most frequently encountered early- and late-onset complication was GI disturbance; this could have been attributable to our early awareness of the adverse effect through close observation, which allowed us to prevent more serious adverse effect and helped us prolong the KD. GI complications are very important because they are directly associated with poor tolerance of the KD, involving significant resistance to the diet, and even affecting its efficacy [20]. In the ICUs setting, patients are prone to GI disorders due to low level of consciousness, immobility, decreased bowel movements, and prolonged ventilator therapy. Furthermore, a high-fat diet delays gastric emptying time and induces regurgitation or vomiting [20]. To prevent or reduce the degree of GI symptoms, interventions such as upright position during feeding, more concentrated diet, frequent feeding schedule with small volumes or continuous feeding, and antiemetics or antacids are helpful.

Because the KD is usually used as a last option after medical therapies have failed, by this time seizures may have progressed to a point at which no treatment is satisfactory [33]. Though questions regarding the proper timing of KD arise frequently in clinical practice, previous studies have not successfully determined the optimal timing for KD initiation. In our study, we attempted to resolve the timing question for KD commencement, but there were no associations between number of previously tried AEDs or anesthetic agents or duration of SRSE before the diet and successful control of seizures. Despite the mechanisms underlying its clinical efficacy remain unclear, there is increasing evidence that the KD has multiple mechanisms that confer anticonvulsant and neuroprotective properties [34]. Because the mechanisms of action by which the KD suppresses seizures are different from those of AEDs, the KD could be considered when seizures persist for at least 48 h after continuous anesthetic agents or seizures recur upon or after the anesthetics are tapered. In addition, active bowel movements and no evidence of active respiratory tract infection or profound systemic infection are decisive factors for starting the KD. For patients who are unable to absorb nutrients through intestinal tract, intravenous KD may act as a temporary bridge towards enteral KD [21,30,35].

Our study is limited by its retrospective nature. The small sample size and the heterogeneity of patients included likely influenced the lack of statistical significance. Clinical course and outcome of SRSE may be affected by underlying diseases. Thus, larger prospective studies or collaborative trials are warranted to elucidate definite therapeutic roles of the KD for SRSE patients and delineate the use of the KD early in the course of antiepileptic therapy.

In conclusion, SRSE is a life-threatening neurologic emergency in ICUs, and the KD may be a feasible and safe therapeutic approach for SRSE patients in that it plays a significant role in reducing the frequency of seizures and weaning patients off continuous infusions of anesthetic agents. Most of the patients tolerated the diet well without any serious side effects, although close monitoring and preventive management of potential adverse effects are critical elements for successful KD. However, relatively high rates of unfavorable functional outcome were noted, which can be explained in part by clinical features of SRSE. We suggest considering KD when seizures do not respond to continuous anesthetic agents within 48 h or recur during or after anesthetics

are tapered. Additionally, active bowel movements and no evidence of infection are prerequisites for initiating the KD.

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