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ORIGINAL ARTICLE

A Practical Approach to Ketogenic Diet in the Pediatric Intensive Care Unit for Super-Refractory Status Epilepticus

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Abstract
Background Super-refractory status epilepticus (SRSE) ensues when there is no improvement of seizure control in response to anesthetic therapy or seizure recurrence after reduction of anesthetic agents. There is no consensus on standard of care for SRSE. Ketogenic diet (KD) has reported success, but technical challenges exist including inability to feed patients, concomitant steroid use, acidotic states, and lack of dieticians with experience. The optimal protocol for KD is yet to be determined. We describe our approach to initiation of KD in the pediatric intensive care unit (PICU).
Methods Patients with SRSE who had KD initiation in the PICU were identified. Data from the hospital course were supplemented by review of the electronic medical record.
Results Nine children with SRSE who had KD initiated in the PICU were identified. Descriptive analysis was performed. Mean age was 5.4 years (SD 2.24). Median number of days to start KD from detection of seizures was 13 [interquartile range (IQR) 10–16]. Mean time to achieve ketosis was 4.2 days (SD 3.4). The median number of antiepileptic drugs (AEDs) trialed before KD was started was 4 [IQR 3–4], and the median number of continuous infusions was 2 [IQR 2–3]. After initiation of KD, most patients were weaned off anesthetic infusions by 1 week. Outcomes were variable.
Conclusions We demonstrated the feasibility of a practical approach to initiation of KD for children with SRSE. These children were successfully weaned off continuous anesthetic infusions. Larger studies are needed to determine effectiveness, safety, and tolerability of KD in the management of SRSE as well as ease of implementation.

Keywords Ketogenic diet · Super-refractory status epilepticus · FIRES

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Introduction

According to the Neurocritical Care guidelines, status epilepticus (SE) is defined as 5 min or more of seizure activity or recurrent seizure activity without a return to baseline between seizures [1]. SE is a neurological emergency and must be treated aggressively to prevent permanent neurological damage. Refractory status epilepticus (RSE) occurs when SE does not respond to standard first-line treatment with at least 1 first-line antiepileptic drug (AED) (i.e., benzodiazepine) and 1 second-line AED (i.e., phenytoin, phenobarbital, or valproate) [1, 2]. Once first- and second-line therapies have failed to control SE, physicians typically resort to therapies such as continuous infusion of benzodiazepines and barbiturates. When these infusions fail, additional therapies may be employed such as ketamine, corticosteroids, hypothermia, inhaled anesthetic agents, or ketogenic diet (KD) [2]. Super-refractory status epilepticus (SRSE) ensues when there is no response to anesthetic therapy or seizures recur after reduction of anesthetic agents [3].

There is no current consensus on how to care for patients whose seizures continue despite aggressive treatment. There is reported success in treating children in RSE with KD [4–7], but use of the diet can be complicated by

logistical considerations specific to critically ill patients. Such technical challenges include the inability to feed a patient enterally, the concomitant use of steroids, preexisting acidotic states, and a lack of dieticians with expertise in ketogenic formulations. There is little guidance available to neurologists and intensivists working in the pediatric intensive care unit (PICU) to manage these obstacles when KD is being considered as a therapy for SRSE.

KD is a high-fat, low-carbohydrate diet considered to be an effective and safe therapy for patients with intractable epilepsy [8, 9]. It alters the primary cerebral energy metabolism from glucose to ketone bodies and is thought to have anti-epileptogenic properties, anti-oxidant and anti-inflammatory effects [10, 11]. The use of KD for the treatment of SE has been reported on multiple occasions since 2008 [12], including several studies in children [6, 10, 13].

Initiation of the KD is typically done with a skilled team and thoughtful preparation. Though the KD has a low rate of adverse effects, it requires surveillance of several blood parameters prior to its initiation. Adequate caloric and fluid needs are calculated for each patient, nondietary sources of dextrose are considered (e.g., medications), a plan to monitor for ketosis is established, and education is provided to the family. When the KD is used for patients with RSE, many of these parameters need to be adjusted to consider variables specific to critical illness. Screening labs may be abnormal and thus raise concern about safety of the diet in the context of organ dysfunction. Fluid management may change over short intervals. Dextrose must be removed from all infusions and bolus dose medications and all members of the care team alerted to the dextrose restrictions. Monitoring of ketosis and complications requires multidisciplinary education of bedside caregivers. Successful implementation of the KD for RSE is labor intensive and requires a collaborative effort from dieticians trained in the ketogenic diet, pharmacists, neurologists, and intensivists that may not be available in every PICU.

Since 2005, our pediatric neurocritical care team has worked to create a step-by-step algorithm to initiate KD in the PICU. The purpose of this manuscript is to describe our experience with nine children who were successfully started on the KD in the PICU for treatment of SRSE, including our approach to its initiation in the PICU and continuation in the outpatient setting.

Methods

Patients

Patients with SRSE who had KD initiation in the PICU were identified from Children's National Health System prospective Neurocritical Care database with IRB approval. Data from the hospital course were supplemented by retrospective review of the electronic medical record. Patients met inclusion criteria if they had SRSE and KD was initiated in the PICU. A descriptive analysis was performed (Table 1). Demographic characteristics were investigated for comparison.

Clinical variables studied included etiology of SRSE, time from diagnosis of SRSE to initiation of KD, days to achieve ketosis (defined as $>3+$ ketones on urinalysis), duration of KD therapy, and concomitant use of steroids. Complications of the KD were investigated including acidosis and severe hypoglycemia. Bicarbonate level below 16 measured in a basic metabolic panel was used as a measure of acidosis given that not all patients had sufficient blood gases to assess pH. Severe hypoglycemia was defined as glucose less than 40 as per convention in the pediatric literature [14]. All patients had screening laboratories (Fig. 1), including bicarbonate level and glucose, performed prior to initiation of the KD.

Additional variables analyzed included the number of AEDs and anesthetic agents used to treat SRSE. These parameters were followed for the duration of the hospitalization for SRSE. After discharge, patients were monitored for adherence to KD, number of AEDs prescribed, and seizure control as defined by number of seizures per week. Functional outcome was assessed at 3 months for all nine patients.

Diet Initiation and Monitoring

All patients started on the KD were treated by a collaborative team including neurology, critical care medicine, and nutrition. Figure 1 describes our step-by-step approach to initiation of KD diet. All patients underwent routine laboratory screening prior to KD initiation. Individualized feeding and hydration plans were developed, taking into consideration caloric and fluid needs using the Holliday–Segar method [15]. All dextrose was removed from fluids and medications with assistance of the intensive care unit pharmacists. Dextrose was entered in the electronic medical record as an allergy to avoid inadvertent administration of dextrose-containing medications.

Once the KD was initiated, monitoring parameters were followed as per institutional KD pathway including a daily metabolic panel, urine dipsticks for ketones, and serum glucose checks. Complications requiring intervention included metabolic acidosis defined as serum CO_2 below 16 and severe hypoglycemia defined as blood sugar below 40. Interventions included initiation of bicarbonate and sugar supplementation.

Table 1 Patient demographics and clinical characteristics

Patient ID	Age (years)/sex	SRSE etiology	Days to KD	Days to ketosis	Ratio/ route	Seizure burden 1 week after initiation	Duration on KD (months)	Steroids	Complications of diet	Seizure burden and functional outcome 3 months after KD
1	8/F	Encephalitis/ FIRES	13	2	4:1/ Enteral	Seizure free	1	Y	None	One seizure per month/mild cognitive impairment, independent in all ADLs
2	8/M	FIRES	11	2	4:1/ Enteral	10 % decrease in seizure burden	2	Y	None	Multiple seizures daily/severe encephalopathy, dependent for all ADLs* Death at 4 months
3	6/F	Encephalitis/ FIRES	15	3	4:1/ Enteral	50 % decrease in seizure burden	3	Y	None	No seizures/moderate cognitive impairment, required some assistance with ADLs
4	3/F	FIRES	36	3	4:1/ Enteral	Seizure free	3	Y	None	No seizures/severe encephalopathy, dependent for all ADLs
5	2/F	Epileptic encephalopathy (preexisting)	7	3	4:1/ Enteral	Seizure free*	4	N	None	Multiple seizures per day/severe encephalopathy, dependent for all ADLs (pre-morbid baseline)
6	5/M	Encephalitis/ FIRES	9	3	4:1/ Enteral	10 % decrease in seizure burden	>6	Y	None	Multiple seizures per day/severe encephalopathy, dependent for all ADLs
7	8/F	Encephalitis/ FIRES	41	13	4:1/ Enteral	No EEG data available	>6	Y	None	Multiple seizures per day/severe encephalopathy, dependent for all ADLs
8	5/F	CNS HLH	16	4	3:1/IV	Seizure free	0.5	Y	Hypertriglyceridemia in the setting of HLH	No seizures/moderate cognitive impairment
9	5/M**	Encephalitis/ FIRES	10	5	2.75:1/ IV	No improvement	0.25	Y	Hypertriglyceridemia, pancreatitis while on Valproate	No seizures/moderate encephalopathy, dependent for most ADLs
			39	8	1:1/ Enteral	Seizure free	4		None	

SRSE super-refractory status epilepticus, *KD* ketogenic diet, *FIRES* febrile infection-related epilepsy syndrome, *CNS* central nervous system, *HLH* hemophagocytic lymphohistiocytosis, *ADLs* Activities of daily living

* EEG was available after 10 days of KD start

** Patient had KD initiated twice during same SRSE course

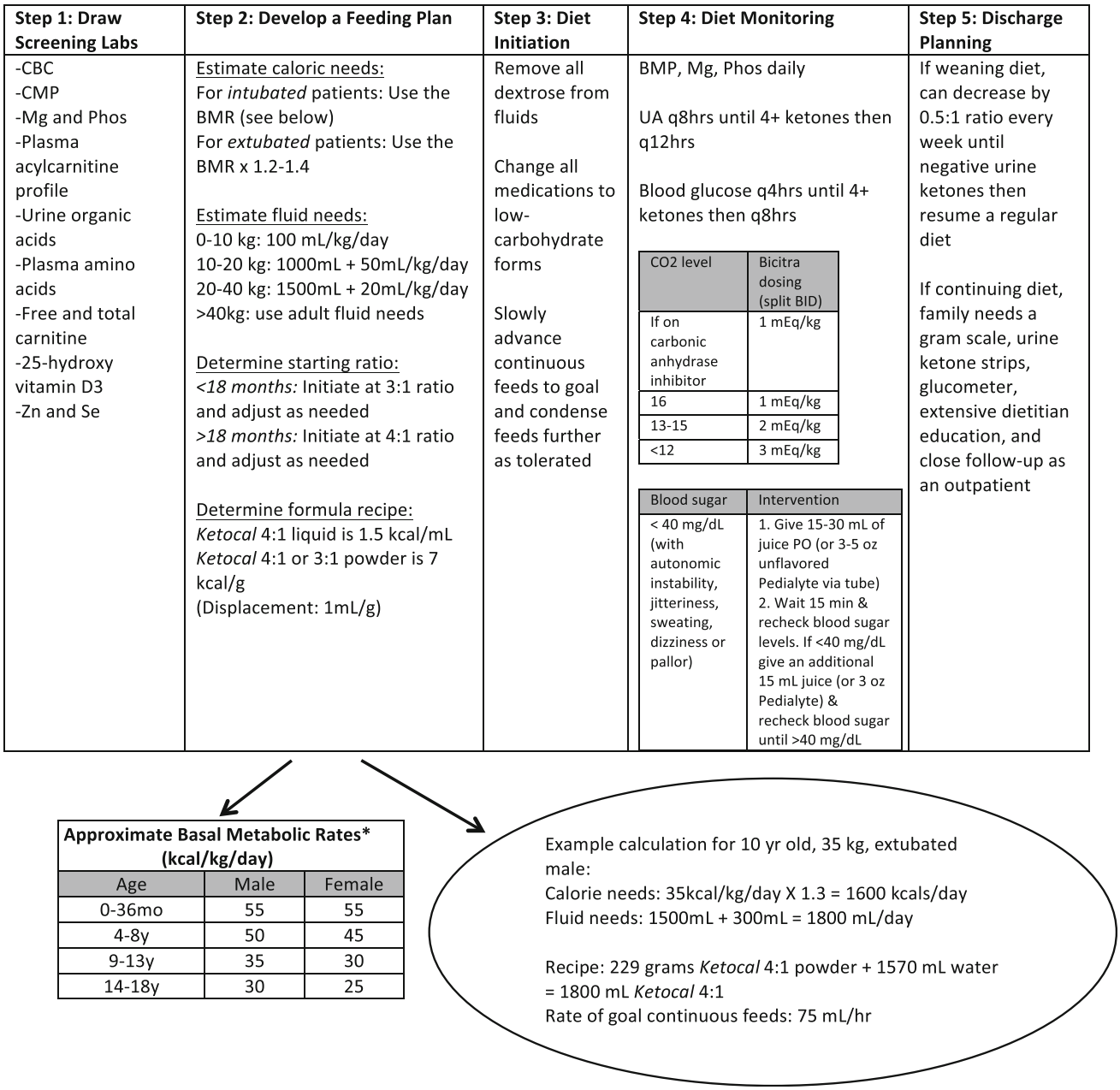

Fig. 1 Step-by-step guidelines. *CBC* complete blood count, *CMP* complete metabolic panel, *Mg* magnesium, *Phos* phosphorus, *Zn* zinc, *Se* selenium, *BMR* basic metabolic rate, *UA* urinalysis

Results

From 2005 to 2016, we identified 9 patients (6 female and 3 male) with SRSE with KD initiated in the PICU. Demographic data are described in Table 1. The mean age was 5.4 years (SD 2.24). Median number of days to start KD from detection of seizures was 13 [interquartile range (IQR) 10–16]. Mean time to achieve ketosis was 4.2 days (SD 3.4). Six of the nine children remained on the KD for 3 months or longer. Only one patient (#6) fasted for 8 h in order to achieve ketosis more rapidly. All patients except two (Patients #8 and #9) were started on enteral KD.

The median number of AEDs trialed before KD was started was 4 [IQR 3–4], and the median number of continuous anesthetic agents was 2 [IQR 2–3]. Seizure control 1 week after KD initiation was variable (Table 1). After initiation of KD, the number of AEDs did not change significantly; but most patients were weaned off continuous anesthetic infusions by 1 week after KD initiation.

The average bicarbonate level during the week prior to KD initiation was 28 (SD 7.1) and decreased in all patients

after 1 week of KD, with a mean of 22.7 (SD 3.5). No patient was started on bicarbonate supplementation in the setting of KD initiation. Events of severe hypoglycemia were analyzed. During the first week of KD therapy, two children (Patients #2 and #5) had 5 or more hypoglycemic events, and one child (Patient #1) had one event. After the second week of KD, no patient had events of severe hypoglycemia. None of the hypoglycemia events were clinically apparent, and all were successfully treated with enteral glucose.

Two patients (Patients #8 and #9) developed severe hypertriglyceridemia, and KD was discontinued. Patient #8 had KD discontinued after 15 days, when central nervous system (CNS) hemophagocytic lymphohistiocytosis (HLH) was diagnosed. Patient #9 developed severe hypertriglyceridemia and pancreatitis while receiving parenteral KD, causing it to be discontinued at 8 days. However, KD was successfully restarted 3 weeks later in the enteral form with marked improvement of seizure control once ketosis was achieved. One patient died (Patient #2) 3 months after initiation of the diet. All patients were evaluated 3 months after KD start. Outcomes were variable (Table 1). Three months after KD initiation, 6 patients remained on KD with a median number of AEDs of 3.

Discussion

Our study describes Children's National Health System's approach to initiation of KD in the PICU for 9 patients with SRSE. We demonstrate that initiation of the KD for SRSE in PICU patients is feasible. We observed a relatively low rate of complications despite concomitant critical illness. Seizure control after initiation of the KD was variable. Given the retrospective nature of this study, exact effectiveness of the KD for SRSE cannot be determined; but it is worth noting that all patients were successfully weaned off continuous infusions of anesthetic agents within a few days after initiation, coinciding to when ketosis was achieved. Further investigation of KD for treatment of SRSE is warranted.

There are reports of emergency initiation of KD for SRSE dating back to 2008 [12]. Studies with pediatric and adult patients describe a low complication rate. Initiation of the diet in the ICU setting requires thoughtful consideration of several potential complicating factors. Patients receiving high-dose corticosteroids may struggle to achieve ketosis. Though propofol is seldom used in children for treatment of RSE, it is worth noting that its use with KD is likely contraindicated due to its association with propofol infusion syndrome [16]. In the ICU, patients receive multiple scheduled and unscheduled medications per day and are at risk for accidental administration of dextrose-containing medications. We did not observe this in our cohort, but our institution has worked closely with our pharmacists and nurses to refine our process for identifying patients on the KD and avoiding inadvertent administration of glucose-containing products.

As reported by Kossof and Nabbout in 2013 [17], the optimal KD protocol is yet to be described. Perhaps the most important considerations are the indication for and timing of initiation of KD for SRSE. Upon review of the literature, we found that the mean number of days to start the KD varied between 12.8 and 35 days [5, 7, 18, 19]. In our series, the KD was started on average 17 days after SRSE was recognized, just slightly sooner than previous reports. In recent years, we have trended toward earlier initiation. Between 2005 and 2010, the average KD start time in our center was 28 days after SRSE was identified. From 2011 to 2016, the number of days to initiate KD decreased by half to an average of 14.8 days. The evolution of our practice coincides with an increase in the number of reports of emergent KD initiation in the literature and growth of our clinical experience under a KD initiation pathway. The impact of earlier initiation of the diet is not defined at this time.

Another consideration is whether fasting prior to diet initiation is indicated. In a study by Bansal et al. [20], two protocols used at our center were compared. One involved a gradual initiation of the diet via caloric restriction, while the other involved immediate administration of goal calories upon initiation of the diet. This study demonstrated similar tolerability between the 2 approaches and number of episodes of severe hypoglycemia. The calorie-restricted protocol was associated with a faster achievement of ketosis, but the finding was not deemed to be clinically significant. In our series, the two patients who had intravenous KD had a gradual approach to initiation, whereas the seven patients with enteral KD received goal calories from the start. There were no clear differences in tolerability or days to achieve ketosis between these groups.

In patients with SRSE receiving multiple medical therapies including anesthetic agents, it is sometimes impossible to start the KD enterally. These critically ill patients often suffer from intestinal dysmotility, malabsorptive states, and/or perfusion abnormalities. To overcome this barrier, parenteral initiation of KD has recently gained attention.

Intravenous KD may increase the risk of transient elevation of liver enzymes, lipid profiles, and pancreatic enzyme concentrations [10]. Additionally, patients with SRSE are often receiving multiple medications metabolized in the liver; intravenous KD may enhance cholestasis and hepatotoxicity [6]. Close monitoring of drug levels and interactions may be warranted. Of particular concern is the combination of valproic acid and KD and the potential

increased risk of hepatic dysfunction [20]. It may be helpful to adjust guidelines for IV KD patients to include more rigorous monitoring of lipids and pancreatic enzymes. For many patients, the goal ratio for the KD is 4:1; but this ratio may be difficult to deliver in the IV KD given restrictions on lipid infusions. In our institution, we initiated intravenous KD in two patients (Patients #8 and #9) using a 3:1 and 2.75:1 ratio with ketosis. Patient #9 experienced severe pancreatitis while on the combination of valproic acid and intravenous KD. The KD was aborted but later successfully restarted in the enteral form once the valproic acid was discontinued and the pancreatitis resolved.

Our study has several limitations including the small number of patients, the retrospective design, the heterogeneity of patients included, and lack of standardization of care received. Because of the retrospective design and small sample size, we could not assess the exact efficacy of the KD on seizures specifically. We demonstrated a significant decrease in number of continuous infusions after 1 week of KD and a tendency toward improved seizure control. However, there was no observed decrease in number of AEDs after 2 weeks of KD. In our patients, functional outcomes and seizure frequency at 3 months were variable, likely due to the heterogeneity of our cohort, which was contributed to by differences in etiology of the SRSE, timing of KD initiation, and concomitant therapies.

In conclusion, we demonstrated the feasibility of initiation of the KD in the ICU for children with SRSE. The diet was relatively well tolerated, and children with complications were identified early through a standardized monitoring protocol. Larger studies are needed to determine the effectiveness, safety, and tolerability of KD in the management of SRSE.

Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest to disclose.

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