

ORIGINAL RESEARCH

CE Modified low ratio ketogenic therapy in the treatment of adults with super-refractory status epilepticus

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Abstract

Background: Induction of ketosis by manipulation of nutrition intake has been proposed as an adjunctive treatment for super-refractory status epilepticus (SRSE). However, the classical 4:1 ketogenic ratio may not meet the nutrition needs, specifically protein for critically ill adults. The aim of this study was to analyze the outcomes of adults with SRSE who received a lower ketogenic ratio of 2:1 grams of fat to non-fat grams, including 20%–30% of energy from medium chain triglycerides.

Methods: We reviewed patients aged ≥ 18 years with SRSE treated with ketogenic therapy between July 2015 and December 2020 at two quaternary teaching hospitals in Melbourne, Australia. Data collected from medical records included patient demographics, nutrition prescription, clinical outcomes, and ketogenic therapy-related complications. The primary outcome of the study was to assess tolerability of ketogenic therapy.

Results: Twelve patients (female = 7) were treated with ketogenic therapy for SRSE. Patients received between 4 and 8 antiseizure medications and 1–5 anesthetic agents prior to commencement of ketogenic therapy. Blood beta-hydroxybutyrate concentrations were variable (median = 0.5 mmol/L, range: 0.0–6.1 mmol/L).

SRSE resolved in 10 cases (83%) after a median of 9 days (range: 2–21 days) following commencement of ketogenic therapy. Ketogenic therapy-associated complications were reported in five patients, leading to cessation in two patients.

Conclusion: Despite the challenge in maintaining ketosis during critical illness, low ratio 2:1 ketogenic therapy incorporating medium chain triglycerides is tolerable for adults with SRSE. Further studies are required to determine the optimal timing, nutrition prescription and duration of ketogenic therapy for SRSE treatment.

KEYWORDS

beta hydroxybutyrate, critical care, intensive care unit, ketogenic diet, ketosis, neurocritical care, status epilepticus

CLINICAL RELEVANCY STATEMENT

Ketogenic therapy has been proposed as a potential adjunctive treatment for super-refractory status epilepticus, a life-threatening condition associated with poor neurological and functional outcomes for patients. In this study, we describe the clinical outcomes and ketogenic-related complications of 12 patients who received a lower-ratio ketogenic therapy of 2:1 grams of fat to non-fat grams including 20%–30% energy from medium chain triglycerides for treatment of super-refractory status epilepticus. This lower ratio ketogenic therapy may better align with current critical care nutrition guidelines and potentially result in fewer complications.

INTRODUCTION

Status epilepticus is defined as the failure of seizure cessation, causing abnormally prolonged seizures, the long-term consequences of which, can lead to neuronal injury or death, and alteration of neuronal network function.¹ Status epilepticus has an estimated prevalence of 10–41 per 100,000 population; 26%–50% of cases are fatal.²

Initial treatment includes administration of a benzodiazepine followed by an antiseizure medication.³ Status epilepticus, which fails to respond to initial treatment, is considered refractory.⁴ Refractory status epilepticus that continues for >24 h following initiation of anesthesia, or seizures recurring after anesthesia is weaned is considered super-refractory status epilepticus (SRSE), which carries an in-hospital mortality rate of >40%.^{5,6} Prolonged SRSE can result in cardiorespiratory and metabolic complications, leading to long-term neurological deficits or death.⁷ It is estimated that only 20%–33% of patients who survive SRSE will return to their functional baseline.

Currently, there is a lack of high-quality evidence to support the treatment of SRSE, relying on clinical experience and expert opinion.⁸ Several case reports and case series have examined potential treatments such as additional antiseizure medications, therapeutic hypothermia, ketamine, and electroconvulsive therapy, among others, to treat SRSE.⁷ Barbiturate coma is an effective treatment for suppressing seizures but causes significant hemodynamic instability and prolongs ventilation even after the drug is ceased because of the long half-life. An emerging treatment modality for SRSE is ketogenic therapy.⁹ In contrast to issues with drug interventions, ketogenic therapy, via manipulation of enteral or parenteral nutrition, can be rapidly commenced and ceased without the same sedating effects or drug-drug interactions.

Ketogenic therapy involves a high fat, very low carbohydrate diet in patients receiving ambulatory care, with use widely reported to treat children with drug-resistant epilepsy and growing evidence for use in adults.¹⁰ The classical ketogenic diet is provided as a 4:1 ratio of grams of fat to non-fat grams. Adults with drug-resistant epilepsy receiving dietary therapy are usually treated with diets adapted from the classical ketogenic diet, such as the medium chain triglyceride ketogenic, modified Atkin's,

modified ketogenic, and low glycemic index diets.^{11,12} These diet variations are prescribed based on specified daily carbohydrate restriction, or macronutrient distribution, resulting in a lower ratio of grams of fat to non-fat grams compared with the 4:1 classical ketogenic diet.

The role of ketogenic therapy in adult patients admitted to the intensive care unit (ICU) for SRSE is uncertain. There have been case reports and series, the vast majority of which reported utilizing the 4:1 ketogenic ratio.¹³ This is similar to studies in children with SRSE treated with ketogenic therapy; however, other ketogenic ratios ranging from 1:1 up to 6:1 have also been reported.¹⁴ In a recent systematic review of studies involving children with SRSE who received ketogenic therapy, 96% achieved ketosis and SRSE resolved in 60% of cases after a mean of 6.3 days (range: 0–19 days). Adverse effects, predominately gastrointestinal, occurred in approximately one-third of children.¹⁴

The 4:1 ketogenic prescription substantially diverges from standard adult critical care nutrition guidelines.^{15,16} Nutrition requirements may vary based on body composition, etiology, and severity of illness and may change over the course of critical illness.¹⁷ A 4:1 ketogenic prescription provides protein at approximately 0.5 g/kg body weight, per day, well below the daily protein load of 1.2–2.0 g/kg that is recommended in international guidelines for critically ill patients.¹⁸

The use of ketogenic therapy in the critical care setting also poses a practical challenge because of unavoidable or incidental carbohydrate administration, enteral feeding intolerance, hypoglycemia, and metabolic acidosis.¹⁹ Additionally, increasing the fat content of enteral nutrition may further slow gastric emptying, worsen enteral feed intolerance, and reduce nutrient absorption.²⁰

Given that ketogenic therapy is a potential therapeutic intervention for SRSE, yet it may be poorly tolerated in adult patients who are critically ill, and its use in this cohort has been rarely reported, we conducted a retrospective cohort study at two large volume quaternary hospital ICUs to explore tolerability of ketogenic therapy and adverse events associated with its use.

MATERIALS AND METHODS

A retrospective cohort study was conducted at two metropolitan, quaternary hospitals in Melbourne, Australia: The Alfred Hospital and Royal Melbourne Hospital. Patients included were aged >18 years, admitted to the ICU between July 2015 and December 2020 with SRSE diagnosed by a neurologist with continuous video electroencephalography, and received ketogenic therapy.

The study received approval by the Human Research Ethics Committee at The Alfred Hospital and Royal Melbourne Hospital.

Data collected from medical records included demographics, diagnosis, epilepsy history, and hospital and ICU length of stays. Clinical information including antiseizure medications, anesthesia agents, continuation or cessation of status epilepticus, blood glucose levels, blood beta-hydroxybutyrate levels, serum triglycerides, weight, nutrition

requirements and ketogenic prescription, duration and adverse effects were also collected. Volume of enteral and parenteral nutrition was collected from documentation on the daily fluid balance and medication charts. Nutrition adequacy was assessed by percentage of goal volume met (delivered volume divided by prescribed volume multiplied by 100).²¹

The primary outcome of the study was to assess tolerability of ketogenic therapy. Secondary outcomes included nutrition adequacy, blood beta-hydroxybutyrate levels, ketogenic therapy-related adverse events, resolution of SRSE, duration of hospital and ICU length of stays, and discharge destination.

Proportions were calculated for categorical variables. For continuous variables, mean, standard deviation, median, and inter-quartile range were calculated as appropriate.

Nutrition prescription

Neither site had a formalized protocol for initiating ketogenic therapy but the approach at both sites was similar. Propofol infusions were ceased prior to commencement of ketogenic therapy, due to risk of propofol infusion syndrome.²² The nutrition prescription was calculated individually for each patient by a dietitian. The daily energy prescription was set at 25 kcal/kg/day. Daily protein prescription was set at a minimum of 1 g/kg/day.²³

Instead of the classical 4:1 ratio, the ketogenic ratio for all patients was 2:1 grams of fat to non-fat grams. Medium chain triglycerides provided 20%–30% of total energy intake. All patients received a multivitamin supplement once daily. Patients receiving valproic acid were also supplemented with levocarnitine at a minimum dose of 10 mg/kg/day. Target ranges for blood glucose levels were ≥ 4 and < 10 mmol/L, with hypoglycemia defined as a blood glucose < 4 mmol/L²⁴ and blood beta-hydroxybutyrate concentration ≥ 2 and ≤ 5 mmol/L²⁵ (see Table 1 for frequency of monitoring parameters).

Ketogenic therapy administration

Ketogenic therapy was provided predominately by an enteral feeding tube using a combination of commercial ketogenic formula (Ketocal® 4:1 powder or Ketocal® 4:1 LQ; Nutricia),

protein powder (Beneprotein®; Nestlé Health Science) and medium chain triglyceride supplements (Liquigen®; Nutricia, MCT Oil; Nutricia or Betaquik®; Vitaflo) to meet the patient's individual ketogenic prescription (see Table S1). Three patients received intravenous amino acid solution (Synthamin® 17 without electrolytes; Baxter). For two patients, where enteral fat malabsorption was suspected, enteral nutrition formula was supplemented with intravenous lipid emulsion (Intralipid® 20%, Baxter).

RESULTS

Baseline characteristics

Over the 4.5-year audit period, 12 patients (females = 7), aged between 23 and 74 years, were identified that met the study inclusion criteria (Table 2). Five patients (42%) had preexisting epilepsy. The main precipitants of SRSE were traumatic brain injury ($n = 4$), antiseizure medication withdrawal or non-compliance ($n = 3$) and autoimmune causes ($n = 2$). Prior to commencing ketogenic therapy, patients received between 4 and 8 antiseizure medications and 1–5 anesthetic agents; five patients received immunotherapy and/or steroids (Table 3). The time to commencement of ketogenic therapy ranged from 4 to 29 days (median, 11.0 days; IQR, 6.8–11.5 days) following diagnosis of status epilepticus.

Ketogenic therapy delivery

Duration of ketogenic therapy during ICU admission ranged from 4 to 26 days (Table 3). Three patients continued on enteral ketogenic feeds following discharge from the ICU to the ward, two ceased ketogenic therapy on commencement of oral diet. One patient, transitioned from enteral to oral ketogenic diet.

The daily mean $\pm$ SD estimated energy and protein targets during ICU admission were 1669 ± 274 kcal and 71 ± 22 g,

TABLE 1 Monitoring parameters during ketogenic therapy.

Parameter	Method	Frequency
Blood glucose level	Arterial blood gas or capillary blood	Every 4–6 h
Blood ketone level	Capillary blood	Every 12 h
pH	Arterial blood gas	Every 4–6 h
Urea and electrolytes	Serum blood	Daily
Triglycerides	Serum blood	Baseline and twice weekly

TABLE 2 Baseline nutrition information of patients receiving ketogenic therapy.

Demographic	Result
No. of patients, n	12
Sex	
Female, n (%)	7 (58%)
Male, n (%)	5 (42%)
Age, years, median (range)	58 (23–75)
BMI, kg/m ² , median (range)	24.5 (19.6–29.4)
Daily prescribed energy, kcal, median (range)	1679 (1230–2190)
Daily prescribed protein, g, median (range)	69 (40–120)

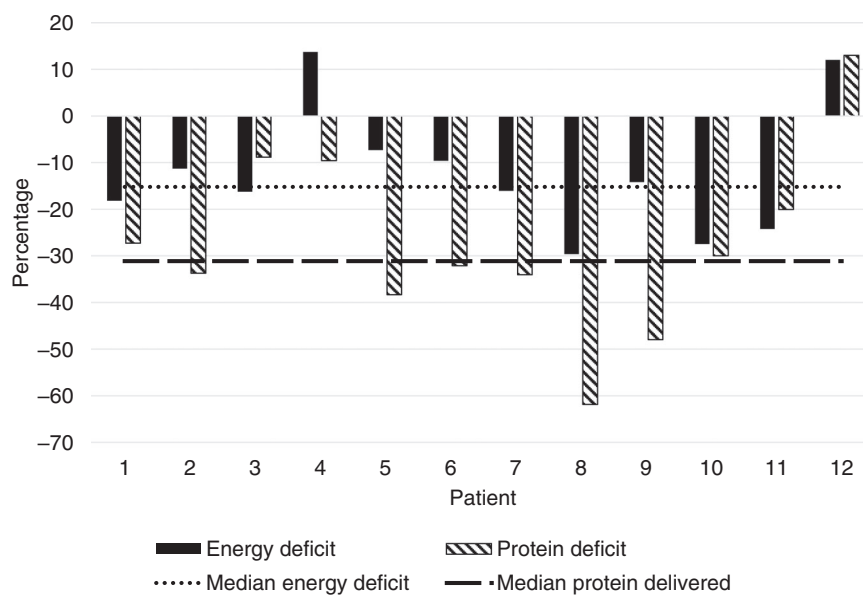
Abbreviation: BMI, body mass index.

TABLE 3 Duration of ketogenic therapy and patient outcomes.

No.	Days in SE prior to KT	No. of ASMs prior to KT	No. of anesthesia agents prior to KT	Duration of KT in ICU, days	Time to resolution of SRSE after KT started, days	Additional treatments commenced after KT	KT-related complications	ICU LOS, days	Hospital LOS, days	Discharge destination
1	12	6	2	7	4	Nil	Nil	47	49	Deceased
2	10	5	2	12	2	Nil	Nil	36	61	IRF
3	5	6	4	16	21	Nil	Diarrhea; hyper-TG	42	55	IRF
4	4	4	4	8	10	CLN	Nil	25	41	IRF
5	11	4	3	23	14	CLN, PER, KET	Nil	39	68	IRF
6	29	8	4	7	15	Nil	Nil	36	86	IRF
7	6	4	2	14	2	LCM	Hyper-TG ^a	20	42	IRF
8	14	4	1	8	NA	Nil	Diarrhea and vomiting	21	23	Deceased
9	11	5	3	8	NA	KET, TPM	Nil	24	24	Deceased
10	11	5	4	6	2	Nil	Nil	16	106	IRF
11	7	4	3	26	13	CLN	Diarrhea	39	40	Deceased
12	13	5	5	4	8	Nil	Tongue swelling; hypoglycemia	33	47	IRF

Abbreviations: ASM, antiseizure medication; CLN, clonazepam; hyper-TG, hypertriglyceridemia; ICU, intensive care unit; IRF, inpatient rehabilitation facility; KET, ketamine; KT, ketogenic therapy; LCM, lacosamide; LOS, length of stay; NA, not applicable; Nil, zero; PER, perampanel; SE, status epilepticus; SRSE, super-refractory status epilepticus; TPM, topiramate.

^aOccurred on the ward, following discharge from the ICU.

**FIGURE 1** Percentage of estimated energy and protein requirements delivered per patient during ketogenic therapy.

respectively. Median energy delivered compared with prescribed during ketogenic therapy was 85% (range: 70%–114%). Median protein delivered compared with prescribed was 69% (range: 39%–113%) (Figure 1).

Clinical outcomes

We measured blood beta-hydroxybutyrate concentrations on 416 occasions. Of these, 72 (17%) were in the recommended therapeutic

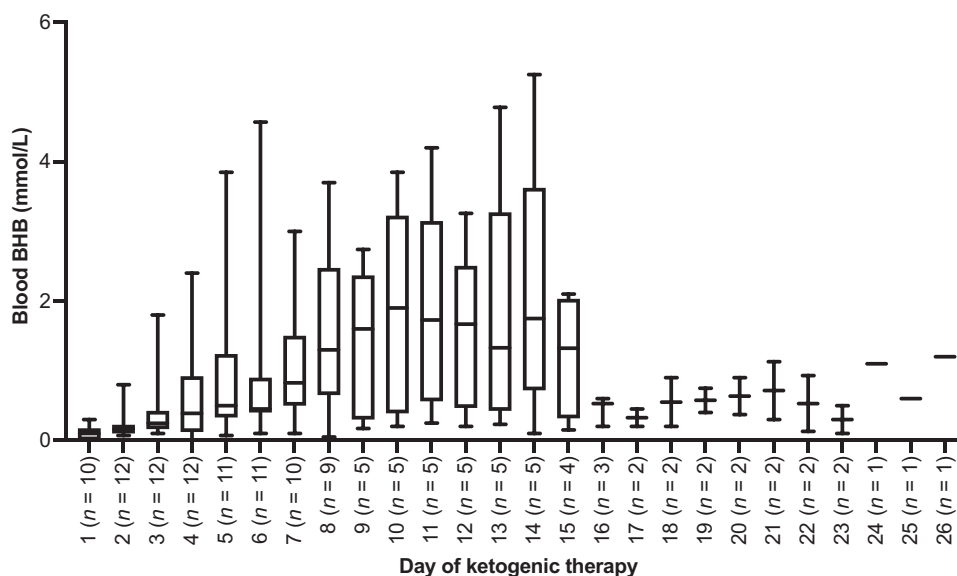


FIGURE 2 Median and range of average blood beta-hydroxy butyrate concentration by day of ketogenic therapy.

range, with 335 (81%) below and 9 (2%) above the suggested range. Over time and between patients, blood beta-hydroxybutyrate levels during ketogenic therapy were highly variable (median = 0.5 mmol/L; range, 0.0–6.1 mmol/L) (Figure 2). Low ketone levels (eg, <2 mmol/L) were frequently documented to be related to suspected carbohydrate administration, steroid use or incomplete administration of prescribed nutrition.

Five patients received additional antiseizure medications and/or anesthesia agents following commencement of ketogenic therapy (Table 3). SRSE resolved in 83% of cases ($n = 10$) in a median of 9.0 days (range: 2–21 days) following commencement of ketogenic therapy (Figure 3). In the two cases where SRSE continued, and an additional two cases where the patients' condition did not improve despite seizures being controlled, active medical treatment was withdrawn and subsequently these patients died in the hospital. The remaining eight (67%) patients were transferred to an inpatient rehabilitation facility on discharge from acute care.

Adverse effects

One episode of hypoglycemia with a blood glucose level of 2.9 mmol/L was recorded for one patient on day 3 of ketogenic treatment (Figure 4). There were no instances of metabolic acidosis (Figure S1). Two patients developed hypertriglyceridemia, leading to cessation of ketogenic therapy in one patient (Figure S2). Gastrointestinal side effects, including vomiting and diarrhea were documented in three patients. One patient had suspected allergy to the protein powder supplement causing tongue swelling. One patient developed drug-induced fever associated with thiopentone and required administration of propofol and therefore ketogenic therapy was ceased because of the risk of propofol infusion syndrome with coadministration.

DISCUSSION

In our study, utilizing a 2:1 ratio ketogenic therapy, resolution of SRSE occurred in 10 of the 12 patients (87%). This is a similar response rate, with fewer complications compared with previously published studies that have used higher ratio ketogenic prescriptions.¹³ We observed seven instances of complications associated with ketogenic therapy over a total of 139 ketogenic therapy days in the ICU. In pooled analysis of four observational studies, SRSE resolved in 31 of 38 (82%) patients following treatment with 3:1 or 4:1 ketogenic therapy. The most commonly reported adverse effects were metabolic acidosis (34%), followed by hyperlipidemia (11%) and hypoglycemia (8%).^{9,26–28} Inpatient mortality in our study was 33%, which is comparable to other studies of SRSE, where mortality has been reported between 36% and 50%.^{29,30}

SRSE is a life-threatening condition, that requires emergency treatment to prevent long-term neurological complications and death. Treatment with additional antiseizure medications may cause drug-drug interactions, liver toxicity, drowsiness, and/or behavioral disturbance.³¹ Additional anesthesia medications and barbiturates are effective in controlling seizures, but may cause hemodynamic instability, prolong impaired consciousness and delay extubation. Ketogenic therapy in contrast, does not have these same treatment interactions and can be provided as part of standard nutrition support. It may also directly address the metabolic crisis that occurs during SRSE.³² In our study, we observed that ketogenic therapy was commenced after multiple drug trials had failed and late in the treatment course.³³ Francis et al²⁸ published a single-center, retrospective study that reported the feasibility of initiation of ketogenic therapy within 1 day of diagnosis of refractory status epilepticus, prior to progression to SRSE.

However, a challenge of utilizing a nutrition-based therapy for SRSE treatment, is incomplete delivery of prescribed nutrition.

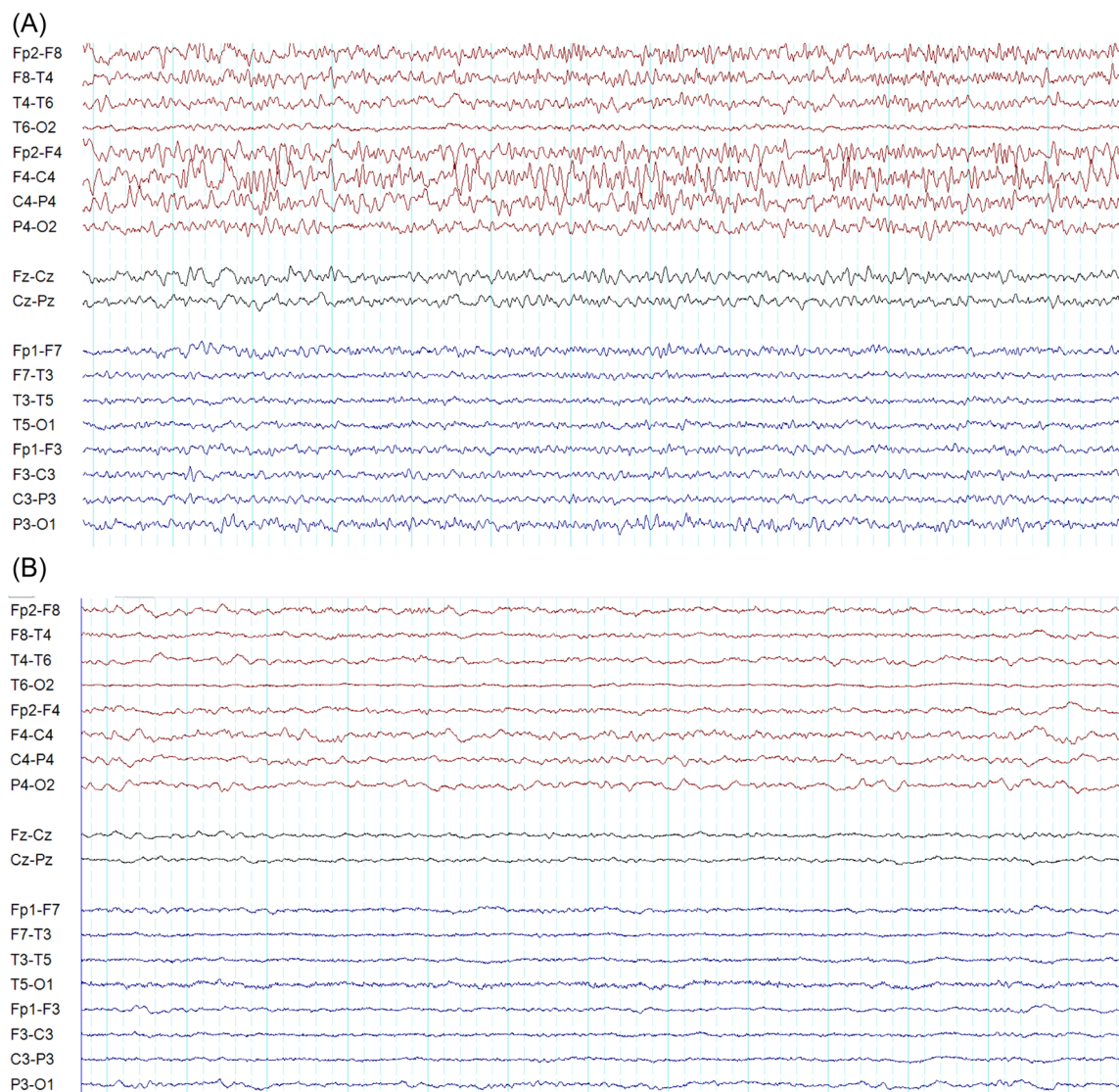


FIGURE 3 (A) Patient 7– Electroencephalogram (EEG) on day 6 of intensive care unit (ICU) admission, demonstrating status epilepticus with seizure activity arising from the right hemisphere. The patient was receiving a midazolam infusion, propofol (ceased prior to commencement of ketogenic therapy), levetiracetam, valproic acid, and phenytoin. (B) Patient 7–comparison EEG on day 8 of ICU admission, 48 h following commencement of ketogenic therapy demonstrating resolution of status epilepticus. Other treatments remained stable.

As observed in our study, compared with the nutrition prescribed, incomplete provision of total energy occurred in 10 out of 12 patients and incomplete protein provision occurred in 11 out of 12 patients. Observational studies report that critically ill patients typically only receive 50%–60% of estimated energy and protein requirements over the ICU admission.³⁴ Inadequate provision of ketogenic enteral or parenteral formula may reduce the effectiveness of this therapy, in particular ketogenesis. Strategies to ensure adequate nutrition delivery, such as limitations on periods of fasting and interruptions to nutrition provision or daily volume-based feeding regimens may be utilized.^{35,36} Provision of parenteral nutrition may be considered during periods of interruptions to enteral nutrition; however, further safety data on the use of ketogenic parenteral nutrition is required.

One of the main modes of action of ketogenic therapy is thought to be due to induction of ketosis. Blood beta-hydroxybutyrate levels ≥ 2 mmol/L have been associated with seizure reduction.³⁷ As observed in our cohort and previous studies, achieving and maintaining ketosis in the critical care setting may be challenging, due to incidental or unavoidable carbohydrate-containing medications and infusions, immunotherapy, fasting and feeding intolerance.³⁸

The underlying mechanism of ketogenic therapy is likely due to a combination of factors and not ketogenesis alone, including increased fatty acid oxidation, metabolic shift, hormonal changes, and modulation of gut microbiota.³⁹ Further research into the optimal range for blood beta-hydroxybutyrate levels is required. However, continuing ketogenic therapy despite blood beta-hydroxybutyrate levels of <2 mmol/L may still be of some clinical benefit.

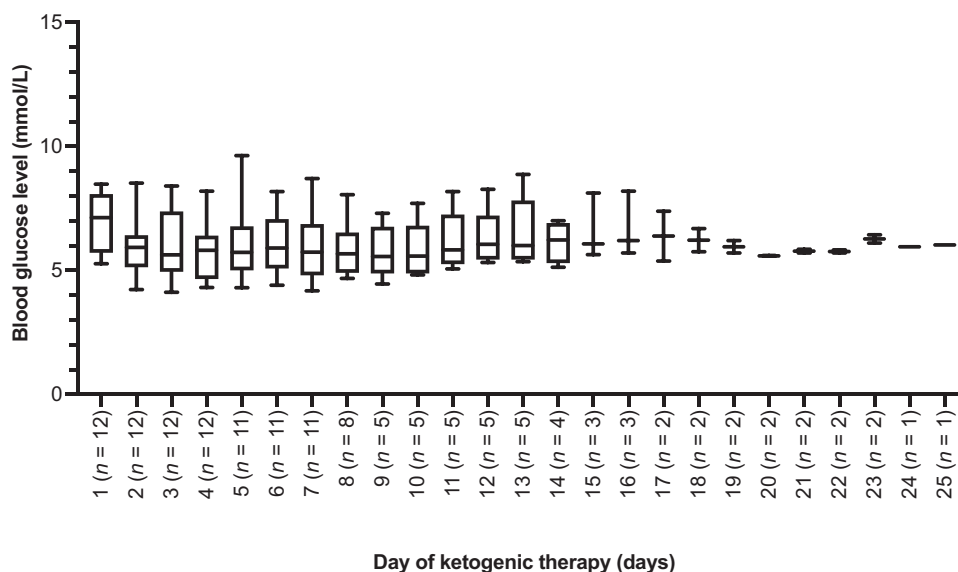


FIGURE 4 Median and range of daily average blood glucose levels.

The addition of 20%–30% of total energy from medium chain triglycerides into the ketogenic prescription may assist in increasing ketone levels. Medium chain triglycerides are readily metabolized to ketone bodies, thereby increasing ketosis.⁴⁰ In addition, the anticonvulsant properties of caprylic (C8) and capric (C10) fatty acids may also be beneficial when treating SRSE.⁴¹ However, medium chain triglycerides are known to cause gastrointestinal disturbances, which may have contributed to adverse events observed in our cohort. Reducing the proportion of medium chain triglycerides in the nutrition prescription, may reduce gastrointestinal side effects.

This study provides insights into a novel ketogenic therapy prescription, utilizing a 2:1 ketogenic ratio, incorporating medium chain triglycerides, for the treatment of SRSE. This is the first study to report nutrition adequacy of ketogenic therapy delivered compared with prescribed energy and protein targets.

Our study is limited by the retrospective nature, small sample size, lack of control arm and uncontrolled for adjuvant treatments. Suitability and duration of ketogenic therapy was determined by the treating clinicians. There was no standardized protocol for commencing ketogenic therapy at either site. As a result, ketogenic therapy initiation, delivery method, and monitoring varied between patients. Therefore, it remains uncertain that ketogenic therapy alone was responsible for improvement in the patients' condition.

Centers treating patients with SRSE may benefit from the implementation of a standardized protocol, to reduce variation in nutrition regimens and optimize provision of ketogenic therapy. The effect of ketogenic therapy on patient functional status and body composition in critical illness remains unknown. Future trials comparing ketogenic therapy to usual enteral nutrition are of merit and should report these outcomes as well as time to cessation of seizures.

CONCLUSION

Our study suggests a 2:1 ratio ketogenic prescription, incorporating 20%–30% of total energy as medium chain triglycerides, may be tolerable as an adjunct therapy for SRSE in the critical care setting. Although this approach only resulted in 17% of blood beta-hydroxybutyrate concentrations in the recommended therapeutic range, a lower ratio ketogenic prescription may be better tolerated and align with standard critical care nutrition guidelines and practice. Further prospective clinical trials are required to understand the optimal timing, ratio, and duration of ketogenic therapy for adults with SRSE.

AUTHOR CONTRIBUTIONS

Neha Kaul contributed to the conception and design of the research; Neha Kaul, Joshua Laing, and John-Paul Nicolo contributed to the acquisition of the data; Neha Kaul and Adam M. Deane contributed to the analysis of the data. Neha Kaul, Judy Nation, Andrew A. Udy, Adam M. Deane, Patrick Kwan, and Terence J. O'Brien contributed to the interpretation of the data and Neha Kaul drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approve the final manuscript.

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CONFLICTS OF INTEREST

Neha Kaul has received a postgraduate research scholarship from the Australian Government National Health and Medical Research Council (NHMRC). Judy Nation is an employee of VitaFlo Australia Pty Ltd. Joshua Laing has received a postgraduate research

scholarship from the Australian Government NHMRC and he/his institution have received support from UCB. John-Paul Nicolo's institution has received speaker fees from Eisai. Adam M. Deane has no conflicts of interest to declare. Andrew A. Udy/his institution have received in-kind support from Integra Lifesciences. Patrick Kwan is supported by a Medical Research Future Fund Practitioner Fellowship (MRF1136427). He/his institution has received speaker or consultancy fees and/or research grants from Biscayne, Eisai, GW Pharmaceuticals, LivaNova, Novartis, UCB Pharma, and Zynerva. Terence J. O'Brien has received research grant funding from the Australian Government NHMRC and the US Government NINDS. He has also received commercial clinical trial funding from Eisai, UCB, Zynerva, Anavex, and Biogen Pharma.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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