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BRIEF COMMUNICATION

Ketogenic Diet as a Therapeutic Option in Super-refractory Status Epilepticus

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Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) that continues or recurs 24 hours or more after the onset of anesthetic therapy and constitutes up to 15% of all SE admissions. One underpowered randomized controlled study has compared barbiturate treatment and propofol treatment for SRSE.[1] Limited additional information on potential treatments for SRSE comes from single case reports and small case series.[1,2]

A ketogenic diet (KD) has an antiepileptic effect and is suggested as a treatment option for refractory epilepsy in children and young adults.[3] KD is generally well tolerated and side effects are relatively mild.[4] However, the lack of robust data, together with limited clinical experience, has limited the use of KD in SRSE. In addition, SRSE is a heterogeneous group of conditions with variable etiology, course, and prognosis. It is recognized that conducting adequate trials to support the efficacy of KD in SRSE will be difficult.[2] Shorvon and Ferlisi[1] reviewed available therapies for SRSE and suggested that KD should probably be tried in all severe cases. Successful implementation of KD requires the collaboration and communication between neurologists, intensivists, dietitians, and nursing staff. Health care professionals using KD need to know the principles and potential uses of the diet and the importance of meticulously calculating the carbohydrate load of infusions.

Here we report the clinical characteristics, treatment, and outcome of four patients with SRSE treated with KD in our intensive care unit (ICU) from January 2011 to August 2014 (Table 1). However, possible efficacy of KD was observed in only one patient (Patient 4), whose seizures were fully controlled after achieving ketosis for 3 days. At that stage we could successfully wean the patient off the anesthetic agents. One patient failed to achieve ketosis while the other two patients had ongoing seizures despite ketosis. Our review of these patients identified some practical points regarding the use of KD in an ICU setting.

(1) *Optimal timing to start KD*

Nam et al[5] suggest starting KD when the patients have active bowel movements and in the absence of infection, sepsis, or disseminated intravascular coagulation. Other reports indicate that the interval between the onset of SE and the use KD have ranged from 2 days to 14 months. We started KD at a median time of 17.5 days after the development of SE (range, 12–21 days).

(2) *Optimal mode and rate of initiation*

Ready-made enteral formula was used in most reported series. O'Connor et al[6] suggested that continuous feeding could improve tolerability. Gradually stepping up the

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Table 1 Use of Ketogenic Diet (KD) in four patients admitted to the Pediatric Intensive Care Unit, Prince of Wales Hospital, Hong Kong with super-refractory status epilepticus from January 2011 to August 2014.

	Patient 1	Patient 2	Patient 3	Patient 4
Demographic & medical background				
Age (y)	16	16	6	8
Sex	Female	Male	Male	Female
Pre-existing epilepsy	Nil	Nil	Nil	Nil
Neurodevelopment	Normal	Normal	Normal	Normal
Fever	Yes	Yes	Yes	Yes
MRI brain	Normal	Basal ganglia T2 hyperintensities	Normal	Limbic encephalitis
CSF Studies	Normal	Normal	Normal	Normal
Immunological	Negative	Anti-Caspr2 Antibody positive	Not done	Anti-GAD antibody low positive
Presumptive diagnosis	NORSE	VGKC antibody associated encephalitis	FIRES	Encephalitis of possible autoimmune origin
Treatment history				
Thiopentone use	Yes	Yes	Yes	Yes
Midazolam use	Yes	Yes	Yes	Yes
Propofol use	Yes	Yes	No	No
Number of anticonvulsants tried before KD	3	4	4	5
Duration of status epilepticus before KD use (d)	18	17	12	21
KD usage				
Regime	Fat to protein/ carbohydrate ratio 3:1 on Day 1 & then step up to 4:1 in next 2 days	Fat to protein/ carbohydrate ratio 4:1 with 1/3 of total calories on Day 1 & then step up to full calories in next 2 days	Fat to protein/ carbohydrate ratio 4:1 with 1/3 of total calories on Day 1 & then step up to full calories in next 2 days	Fat to protein/ carbohydrate ratio 4:1 with 1/3 of total calories on Day 1 & then step up to full calories in next 2 days
Formula used	Ketocal - Nutricia Advanced Medical Nutrition			
Total duration of KD use (d)	10	9	10	11
Ketosis achieved	No	Yes	Yes	Yes
Concomitant treatment adjustment	Plasmapharesis	Plasmapharesis phenyotin	B6/folinic acid/ midazolam infusion	Clobazam & midazolam infusion
Perceived efficacy of KD	No	No	No	Yes Seizures stopped 5 days after ketosis established
Difficulties/ problems encountered	Falling plasma protein	Vomiting, suspected sepsis	Increase breakthrough seizures	Refuse KD upon recovery
Reasons for stopping KD	Not useful	Not useful	Not useful	Compliance problems
Final Outcome				
ICU stay	3 months	6 months	4 weeks	32 days
Outcome	Refractory epilepsy Mild cognitive impairment Critical illness polyneuropathies	Refractory dystonia Severe physical handicap	Refractory epilepsy Behavior problems	Seizure free Return to "baseline" without significant deficit

CSF = cerebral spinal fluid; FIRES = fever induced refractory epileptic encephalopathy in school-age children; GAD: glutamic acid decarboxylase; ICU = intensive care unit; KD = ketogenic diet; MRI = magnetic resonance imaging; NORSE = new onset refractory status epilepticus syndrome; VGKC = voltage gated potassium channel.

formula as tolerated may be a good option since gastroesophageal reflux is commonly encountered in these patients. However, this carries a disadvantage since it may take longer to achieve ketosis.

(3) *Expected course of treatment*

Other reports note that apparent clinical response to KD occurs after a mean/median of 3 days[5] to 10 days.[7] In our series, we continued KD for at least 5 days after achieving ketosis before concluding that there was a lack of response. O'Connor et al[6] has suggested that KD should be continued for at least 2 weeks to observe any effect.

(4) *Monitoring treatment response*

Since patients with SRSE are usually critically ill, it may take several days for ketosis to be established. In addition it is often necessary to add other treatments while stepping up KD, making it difficult to be certain whether patients who stop seizing do so because of KD or because of concomitant treatment changes or a combination of both treatments. These difficulties emphasize the importance of careful qualitative documentation of the use of KD and other concomitant treatments for SRSE.

(5) *Duration of treatment after seizure control*

In the literature, many SRSE patients showing an apparent response to KD will continue this diet, or change to a modified Atkin's diet, for weeks to months. The optimal duration of continuing KD is uncertain. We found some difficulties in keeping patients on KD once full oral feeding was resumed. Patients and their families need to be fully counseled about the practical issues of KD to help them accept the limitations and difficulties of taking KD, especially when there is clinical improvement.

In summary our experience suggests that KD is a safe and feasible option in an ICU setting and can be considered as a treatment option for SRSE. Standardized guidelines for the implementation and monitoring of KD in ICU settings for SRSE may help to improve our understanding of its role and efficacy in status epilepticus.

Conflicts of interest

The authors declare that there is no conflict of interest with reference to the search or publication of this article.

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