

Medium-chain triglyceride ketogenic diet for drug-resistant epilepsy in Taiwan: A prospective study in a single center

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Abstract

Objective: This study aimed to determine the efficacy of a medium-chain triglyceride ketogenic diet on patients with drug-resistant epilepsy over a period of 1 year and 8 months. **Methods:** Patients with refractory epilepsy on a medium-chain triglyceride ketogenic diet were prospectively enrolled. Their clinical condition and the effectiveness of the ketogenic diet were followed-up every month for 1 year. Adverse events and the reasons for discontinuing the diet were recorded. **Results:** Fifty-three patients (27 males and 26 females) were enrolled. At the end of the study, 21 patients remained on the diet, 14 of whom were followed-up for 1 year. Among the 53 patients, 22.6% had a more than 50% reduction in seizure frequency, and 16.9% became seizure-free.

Conclusions: After a 1-year follow-up, the use of a medium-chain triglyceride ketogenic diet for patients with drug-resistant epilepsy was found to be a safe and effective therapy, and may be considered to be an alternative for patients with difficult-to-control seizures in children as well as young adults.

INTRODUCTION

The ketogenic diet is a high-fat, low-carbohydrate, adequate-protein diet developed in the 1920s for the management of drug-resistant epilepsy.¹ The classic ketogenic diet severely restricts calories to 85-90% of the estimated daily requirement with reduced fluid intake.² The prescription of the classic diet includes a typical 4:1 ratio of fat to carbohydrates and protein combined, which can be lowered to 3:1 or 2:1 for infants, adolescents, and/or patients who require higher protein and carbohydrate content. In this diet, fat is provided by long-chain triglycerides and protein is kept to the minimum requirement for growth, with carbohydrates being very restricted. However, under such conditions, children frequently feel hungry and thus may not accept the diet. Difficulties in changing their lifestyle to adapt to the diet have been reported, especially for children

and parents in Asia because rice is often the major component of the daily diet, and sharing dishes is a common practice when having meals.

The medium-chain triglyceride (MCT) ketogenic diet was introduced by Huttenlocher in 1971.³ A MCT ketogenic diet yields more ketones per kilocalorie of energy than long-chain fatty acids, which are absorbed more efficiently and are carried directly to the liver in the portal blood.⁴ Therefore, the increased ketogenic potential yield means that less total fat is needed in the MCT ketogenic diet, allowing for more carbohydrate and protein components. Thus, a MCT ketogenic diet can provide more dietary options than the classic diet, making it more palatable and more suitable for Asian children. As patients are able to consume a wider variety and greater quantity of food with a MCT ketogenic diet, children have better growth and require fewer micronutrient supplements compared to the classic ketogenic

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diet.⁵ In addition, the efficacy of seizure control with a MCT ketogenic diet is generally equivalent to a classic ketogenic diet, and is used in the United Kingdom and Canada.⁵⁻⁷

One randomized trial on classic and MCT ketogenic diet treatment involving 145 children with drug-resistant epilepsy reported no significant differences between the diets in the number achieving a >50% and >90% reduction in seizures, or a reduction in the dose of antiepileptic drugs after 3 months.⁴ The aim of this study was to evaluate the efficacy and tolerability of a MCT ketogenic diet in patients with drug-resistant epilepsy in Taiwan.

METHODS

Patients

Patients with the diagnosis of drug-resistant epilepsy who were followed-up at the Division of Pediatric Neurology of Chang Gung Memorial Hospital and those referred from other institutions were prospectively enrolled from February 2012 to October 2013. Drug-resistant epilepsy was defined as failure of adequate trials of two (or more) tolerated, appropriately chosen and used antiepileptic drugs to achieve a seizure-free status, as previously described.⁸ Patients with known metabolic disorders, severe systemic illnesses, or contraindications were excluded.

The hospital's Institutional Review Board approved the study protocol, and the patients or their parents or guardians provided informed consent.

Methods

All of the participants were admitted to the hospital and treated with a MCT ketogenic diet after 12-36 hours of fasting (modified protocol for infants with 12-24 hours of fasting). Baseline chemical, lipid, and metabolic profiles were recorded before the start of the diet to exclude inborn errors of metabolism or other contraindications for the ketogenic diet.

The MCT ketogenic diet was gradually titrated to a full dose of MCT oil within 1 week and closely monitored by a dietician. It was designed on a full prescription for carbohydrates providing 19% and protein 10% of the total energy, with long-chain triglycerides (LCTs) typically providing 21% of total energy to keep the total fat percentage (MCTs + LCTs) not exceeding 71% of total energy. The MCTs in the diet were gradually increased up to 40-60% of total energy according to clinical

tolerance. Ongoing evaluation of ketosis was assessed by twice-daily home urine testing, and by measuring blood ketone concentrations during clinic appointments.

The patients' clinical condition and the effectiveness of the treatment were assessed in the follow-up every month at our out-patient clinics. Seizure frequencies were recorded on the patients' daily seizure calendars before and after the diet. Changes in seizure frequency were calculated as the difference in frequency before and after receiving the diet. The classification of the etiologies of epilepsy and epileptic syndrome was based on the 2010 International League against Epilepsy report.⁹ Any adverse events after introduction of the diet and the reasons for discontinuation were recorded. The patients' height and weight were recorded at each follow-up visit to monitor growth. Cardiac and abdominal sonography, bone densitometry, and electroencephalography were assessed at 6-month intervals.

The efficacy of treatment was assessed at 1, 3, 6 and 12 months after the start of the MCT ketogenic diet based on the decrease in seizure frequency, as assessed through parental reports and seizure diaries. The efficacy of seizure control was categorized as <50% seizure reduction (including no change in seizure frequency), 50-99% seizure reduction, or seizure-free. Patients remaining on the diet during the follow-up period were classified as the diet continuation group (Group 1). Those who withdrew from the study as the diet discontinuation group (Group 2).

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences for Mac OS X (version 20.0.0; IBM SPSS Statistics). The Student's t-test was used to compare continuous parametric data. The χ^2 test and two-tailed Fisher's exact test were used to compare categorical data. Statistical significance was set at $p < 0.05$.

RESULTS

Clinical data

From February 2012 to October 2013, 53 patients with drug-resistant epilepsy were prospectively enrolled in this study, including 27 males and 26 females; 42 children and 11 adults (age >18 years). The mean age at the start of the MCT ketogenic diet was 11.3 years (range, 0.3-29.8 years). Before the diet, the patients had an average of 47.62

Table 1: Demographic data of the patients with drug-resistant epilepsy receiving a medium-chain triglyceride ketogenic diet (n=53)

	Total	Group 1	Group 2	p*
No.	53	21	32	
Sex (M/F)	27/26	12/10	15/16	
Mean age at diet Initiation (years)	11.35 (0.3-29.8)	11.75±7.46 (0.4-27.2)	11.05±9.17 (0.3-29.8)	0.097
Age <18 years	42	18	24	0.494 [¶]
≥18 years	11	3	8	
Mean diet duration (days)	202±188.27	388.29±152.99	80.88±75.5	<0.01
Mean seizure frequency (daily)	47.62(0-525)	42.37 (0-175)	53.21 (0-525)	0.883
Mean number of AEDs prior to diet	3 (1-5)	3.27 (1-5)	2.8 (1-5)	

*t-test, [¶]Fisher's exact test

Group 1, Diet-continuation; Group 2, Diet-discontinuation; AEDs, antiepileptic drugs

seizures per day of multiple seizure types, and took a mean of three antiepileptic drugs (range, 1-5) (Table 1). The mean duration of diet maintenance was 202±188.27 days. At the end of the study, 21 patients remained on the diet (Group 1), while the other 32 had discontinued the diet (Group 2). There were no significant differences in age and sex between the two groups (Table 1). At the end of the follow-up period, none of the patients had died, and two were lost to follow-up.

Diet duration

At the end of this study, 21 of the 53 patients (39.6%) remained on the diet, including 14 who continued for 12 months. The mean diet maintenance duration in Groups 1 and 2 were 388.29±152.99 and 80.88±75.5 days, respectively (Table 1).

Seizure classification and etiology

Twenty-seven (50.9%) patients were classified as having a structural/metabolic etiology, 10 (18.9%) with an unknown etiology (risk factors according to medical history and/or abnormal neuro-development examinations, but negative in imaging or specific investigation), and 16 (30.2%) with a genetic etiology (Table 2).

Diet efficacy in seizure-control

Evaluation of the efficacy of the diet over 12 months

(Figure 1) revealed that 12 (22.6%) patients had a >50% reduction in seizure frequency, including 9 (17%) who were seizure-free, and 3 (5.6%) who had a 50-99% decrease in seizure frequency. The number of patients who remained on the diet during the follow-up period and the levels of seizure control are shown in Figure 1.

The number of patients in the two groups and the percentage of those who achieved various levels of seizure control (Figure 1) demonstrated that more than 50% of the patients achieved a >50% reduction in seizures within 1 month of starting the diet. The patients in Group 1 achieved better seizure control than those in Group 2.

Seizure control by age and seizure type

There were no significant differences in seizure control between age groups. In addition, there were no significant differences between the children (age <18 years) and adults (age ≥18 years) in seizure control at 1, 3, 6 and 12 months of follow-up. There was also no significant difference in age for earlier discontinuance of the diet. A higher percentage of the patients who were younger than 2 years achieved a >50% improvement in seizure control than the older age groups, but the difference was not statistically significant.

Twenty-three of the patients had focal seizures (8 with secondary generalization), 12 had generalized tonic-clonic seizures, 7 had

Table 2: Etiologic classification of epilepsy in the patients with drug-resistant epilepsy receiving a medium-chain triglyceride ketogenic diet (n=53)

	Group 1 No. (%)	Group2 No. (%)	Total No. (%)
Genetic	5 (23.8)	11 (34.4)	16 (30.2)
Unknown	6 (28.6)	4 (12.5)	10 (18.9)
Structural/Metabolic	10 (47.6)	17 (53.1)	27 (50.9)
Tuberous sclerosis	2	0	2
Complications of prematurity (PVL, CP)	2	5	7
Cerebral malformation			
Cortical dysplasia	1	0	1
Heterotopia	0	1	1
Pachygyria	0	2	2
Mesial temporal sclerosis	1	1	2
Brain insult			
Subdural hemorrhage	1	0	1
Hypoxic-ischemic encephalopathy	1	3	4
Hypertensive encephalopathy	1	0	1
Encephalitis	1	4	5
GLUT-1 deficiency syndrome	0	1	1

Group 1, diet-continuation; Group 2, diet-discontinuation; PVL, peri-ventricular leukomalacia; CP, cerebral palsy; GLUT-1 deficiency syndrome, glucose transporter type 1 deficiency syndrome

infantile spasms, 5 had myoclonic seizures, 1 had tonic seizures, 1 had atonic seizures, and 4 had unclassified seizure type. There were no differences in diet continuation based on the seizure type or underlying etiology.

Adverse events and tolerability of the diet

Out of 32 patients who discontinued the diet, 6 patients (18.8%) discontinued before the first month, 16 (50%) between first and third month, 6 (18.8%) between fourth and sixth month, and 4 (12.5%) between seventh and twelfth month (Figure 1).

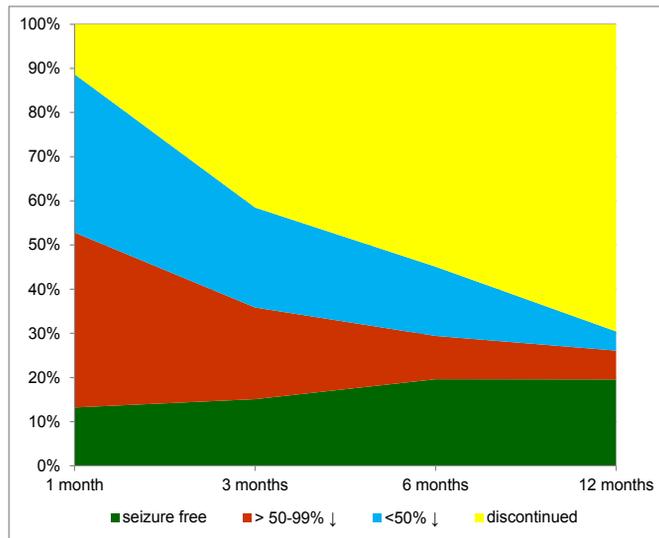
The three most common reasons for discontinuing the diet were food refusal, ineffectiveness, and diarrhea (Table 3). The most common adverse effect was dyslipidemia (n=39, 73.6%), followed by diarrhea (n=6, 11.3%), infections (n=3, 5.7%), constipation (n=2, 3.8%), vomiting (n=1, 1.9%), and renal stones (n=1, 1.9%). None of those who continued the diet died.

DISCUSSION

Studies on the efficacy of a ketogenic diet in patients with epilepsy have shown remarkable

effectiveness over the past decade.¹⁰⁻¹² However, most of the patients in these studies were treated with a classic ketogenic diet, and few studies have reported the use of a MCT ketogenic diet, especially in Asian patients.^{3-5,13,14} These studies have shown that >50% of the children achieved a >50% reduction in seizures using both a MCT ketogenic diet and classic ketogenic diet. Furthermore, in several animal studies^{15,16}, both a classical ketogenic diet and MCT ketogenic diet have been reported to have positive effects in decreasing brain cerebral excitability in young animals.¹⁵ In addition, the acute anticonvulsant property of caprylic acid, the main constituent of a MCT ketogenic diet, may also add to its overall clinical efficacy.¹⁶ Therefore, the MCT ketogenic diet provides the same improvement as the classic ketogenic diet while also providing more carbohydrates and calories, resulting in increased palatability that is more suitable for Asian patients who find a classic ketogenic diet more challenging.

In our patients, 7 (13.2%) became seizure-free after 1 month of the MCT ketogenic diet, and 28 (52.8%) achieved a >50% improvement in seizure control. This is promising and indicates that the



Responder rate*	1 months	3 months	6 months	12 months
Group 1	17(77.3%)	16(76.2%)	14(73.77%)	12(85.7%)
Group 2	11(44%)	3(30%)	1(30%)	0
Total	28(52.8%)	18(34%)	15(28.3%)	12(22.6%)

*denotes proportion of patients with reduction of seizure frequency by >50%
Group 1, Diet-continuation; Group 2, Diet-discontinuation

Figure 1: Figure showing the responder rates at 1, 3, 6, and 12 months after starting a medium-chain triglyceride ketogenic diet

clinical efficacy of a MCT ketogenic diet can be seen early. At 12 months, 14 patients (14/53, 26.4%) remained on the diet, 12 (12/53, 22.6%) achieved a >50% reduction in seizures, and 9 (9/53, 16.9%) were seizure-free. Among those who continued the diet, more than half (9/14, 64%) became seizure-free, indicating a high seizure control rate in the patients who remaining on

the MCT ketogenic diet for a long period. Other studies have reported a range between 18-50% of patients with a >50% reduction in seizures, and 4.8-25% becoming seizure-free. Our results are similar to those of other Asian studies, albeit at the lower end of the range.^{4,17-20} This suggests that a MCT ketogenic diet is effective for seizure control in Asian epilepsy patients.

Table 3: Reasons for discontinuing the medium-chain triglyceride ketogenic diet

No. (%) (n=32)*Reasons for discontinuation

12 (37.5%)	food refusal
9 (28.1%)	no improvement
8 (25%)	diarrhea
3 (9.4%)	infection
2 (6.3%)	transfer to other hospital
1 (3.1%)	economic reason
1 (3.1%)	shift to other diet (MAD)
1 (3.1%)	VNS

MAD, modified Atkins diet; VNS, Vagus nerve stimulation

*One patient may have more than one reason for discontinuation of diet.

There were several reasons for withdrawal from the diet, of which food refusal was the most common. Most types of Asian food are starch-based with carbohydrates playing a major role. Thus Asian patients find it difficult to accept a classic ketogenic diet. In a MCT ketogenic diet, the total fat content is less and the total carbohydrate and protein components are higher compared to the classic ketogenic diet. Nonetheless, the percentage of carbohydrate is still lower than in a normal Asian diet, which is still intolerable for some patients. Other patients reported feeling hungry easily because of the restricted daily calorie intake, making them give up on the diet. Other patients stopped the MCT ketogenic diet because both of their parents had to work and had less time for food preparation.

In our patients, the age at diet initiation was not statistically different between the responders and non-responders. However, those of adolescent age showed worse efficacy than the other age groups, which may be related to poor compliance with the MCT ketogenic diet due to the rebellious tendency at this age. In addition, it is harder to dramatically change the diet of a functioning patient who has never had food restriction before. More patients younger than 2 years achieved a >50% improvement in seizure control than the other age groups. However, this was not statistically significant. This may suggest that a ketogenic diet should be used at an earlier age.^{10,21} Furthermore, we also showed that a MCT ketogenic diet can be used in young adults (>18 years) with good results. This indicates that a MCT ketogenic diet can be used as an alternative treatment for young adults with drug-resistant epilepsy.

With regards to long-term adverse effects after taking the diet, hypercholesterolemia was the most common. Although the level of cholesterol was high, none of the patients had a level higher than 6.46 mmol/L and there were no clinical symptoms of cardiovascular problems. Further studies with a longer follow-up period are necessary to clarify the effects of hypercholesterolemia.

Gastrointestinal symptoms causing discomfort such as constipation, abdominal pain, vomiting and diarrhea are the major adverse effects reported in patients treated with a MCT ketogenic diet.¹⁰ Comparing the diet-continuation and diet-discontinuation groups, the incidence rates of gastrointestinal problems were higher in the diet-discontinuation group. In addition, diarrhea was more commonly reported than constipation, which is similar to previous studies.^{13,14} To decrease the adverse effect of diarrhea in patients receiving a

MCT ketogenic diet and maintain good ketosis to achieve optimal seizure control, the percentage of MCT oil in the diet was kept within 40-60% of total energy, according to the clinical response of the patients. The goal was to provide the best balance between good seizure control and acceptable tolerability with the slow titration of the daily amount of MCT oil and methods of preparation.

In conclusion, a MCT ketogenic diet provides more carbohydrates and calories than a classic ketogenic diet, resulting in increased palatability that is more suitable for Asian patients. Treatment with a MCT ketogenic diet was associated with a substantial decrease in seizure frequency in the patients with difficult-to-control seizures. The diet was generally tolerable and may be considered an alternative therapy for children and young adults with drug-resistant epilepsy.

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DISCLOSURE

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Conflicts of interest: None

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