Ketogenic Diet : An Alternative Treatment for Refractory Epilepsy in Children

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Abstract

Rationale : The aim of this study was to establish the first ketogenic diet treatment program for refractory epilepsy in Thailand and to assess its feasibility as well as its efficacy.

Method : Children with refractory epilepsy were enrolled in the study. This was a prospective open trial study with 35 children (16 boys and 19 girls). Not all patients started on the diet at the same time. Each patient was cumulatively enrolled in this study over the period of 4 years. The mean age on diet was 5.37 ± 3.57 years (2 months - 13 years), mean age of onset of seizures was 19.2 ± 27.47 months (1 days - 8 years), and an average duration on ketogenic diet was 7.67 months (6 days to 29 months). The classic "4:1" formula ketogenic diet was used with some modification. The patient's parents were allowed to improvise and use any fatty diets available in the market such as coconut milk if needed. Parents were closely supervised and instructed on how to prepare the patient's own meals while in the hospital and continued to attend neurology and nutrition clinics. The seizure outcome and side effects were monitored as well as a daily test for urine ketone.

Results : At 1 month, 3 months, 6 months, and 12 months duration on the diet, 90 per cent seizure reductions were achieved in 62.5 per cent, 68.18 per cent, 75 per cent, and 66.67 per cent of patients remaining on the diet, respectively. The number of antiepileptic drugs (AEDs) used by each patient also decreased as a result of better seizure control.

Conclusion : Ketogenic diet can be tried as a management option for refractory epilepsy. It is not difficult to implement even in a developing country like Thailand where resources are limited. It may also help reduce the cost of treatment especially in view of the high prices of the new AEDs.

Key word : Ketogenic Diet, Refractory Epilepsy, New Antiepileptic Drugs, Developing Country

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Epilepsy remains one of the most common neurological disorders in childhood. Around 20 per cent of patients with epilepsy are refractory to most conventional antiepileptic drugs (AEDs)[1]. Many new AEDs have recently been developed to control seizures in refractory patients[2].

The classical ketogenic diet, an alternative therapy for epilepsy has not been widely used in Thailand before. Its efficacy in controlling refractory epilepsy has been shown both *in vitro* and *in vivo* in previous studies[3-8]. Because the ketogenic diet has never been routinely implemented in refractory epilepsy in Thailand before, our goal in this study was to establish the first ketogenic diet treatment program for refractory epilepsy in Thailand. A prospective study was performed to assess its feasibility as well as its efficacy.

PATIENTS AND METHOD

All patients with epilepsy who had been followed-up at our hospital for more than 4 months and still had more than one seizure a week after adequate trials of conventional AEDs therapy at our hospital were asked to enroll in the study. The study design was a non-randomized prospective study. The parents of each child, who gave their consent to participate in the study, were asked to keep an accurate list of the number and nature of the child's seizures for a period of four weeks before starting the diet. During this period regular AEDs treatment was not altered. After this period the patients were admitted to the hospital for biochemical assessment with routine 32 channels digital EEG recording for 30 minutes as a baseline. Following this the patient fasted for 24-72 hours until urine ketone 4+ and serum ketones of more than 1.6 mmol/L developed. During this starvation period, the patient was closely monitored for signs and symptoms of hypoglycemia and dehydration. Following the fasting period, the ketogenic diet was started. There were three different ketogenic diet regimens in this study. Regimen 1 contained mainly whipped cream and regimen 2 comprised of coconut milk which replaced the whipped cream. Both regimens 1 and 2 were liquid forms and were used initially in small children who were still bottle-fed or in older children who required nasogastric tube feeding. Regimen 3 was a regular fatty diet comprised of common foods available in the market, such as bacon, fatty meat, eggs, cooking oil etc. A detailed constituent of each regimen is shown in Table 1.

After the fasting period, the ketogenic diet was started at one-fourth of the total calorie requirement. If the patient tolerated the diet, then it was slowly increased to the total calorie requirement in a few days. Every child received a sugar-free multivitamin supplement and additional calcium. The patients remained in the hospital until the parents or the caretakers were confident in preparing the patient's own ketogenic diet. After discharge, parents were asked to continue keeping a seizure calendar and to measure the patient's urine ketone every morning. Parents were advised to consult with our dietician periodically over the phone when making an appropriate adjustment to the diet. All adverse events related to the diet were recorded at each fol-

Table 1. A detailed constituent of each regimen of the ketogenic diet.

Regimen I			Regimen II			Regimen III		
1. Whipped cream	220	ml	1. Coconut milk	240	ml	1. Bacon	25	g
2. Egg	1	egg	2. Egg	1	egg	2. Egg	1	egg
3. Tab multivitamin + mineral	1	tab	3. Tab multivitamin + mineral	1	tab	3. Soy bean oil	10	tsp
4. NaCl	1/2	tsp	4. NaCl	1/2	tsp	4. Broccoli or collard green	50	g
5. Elixir KCl	1	tsp	5. Elixir KCl	1	tsp			
6. Water add up to	1,000	ml	6. Soy bean oil	8	ml			
			7. Calcium gluconate	10	tab			
			8. Water add up to	1,000	ml			
Total volume	1,000	ml		1,000	ml		-	
Total energy	825	kcal		800	kcal		570	kcal
Total fat	85	g		81	g		58	g
Total protein	11.5	g		18	g		11	g
Total carbohydrate	17.2	g		5	g		2.2	g

Table 2. Types of seizure.

Seizure types	Number of patients*
Generalized tonic clonic seizures	21
Generalized tonic seizures	9
Generalized clonic seizures	5
Atypical absence seizures	10
Atonic seizures	12
Myoclonic seizures	24
Partial seizures	19
Infantile spasms	3

* Most patients had more than one seizure type.

low-up visit. Other AEDs would be decreased or weaned off if the seizures decreased.

Because all patients were not started on the diet at the same time, frequency of seizures of each patient was tabulated from the baseline seizure calendar and from the collected seizure calendar at the time of follow-up at 1, 3, 6, and 12 months. Independent variables such as sex, age, type of seizures, and EEG were analyzed using Yates corrected and all P values are 2–tailed. Kaplan-Meier survival analysis was based on seizure reduction and the probability of remaining on the diet.

RESULTS

Thirty-five patients, 19 females and 16 males with a mean age of 5.37 ± 3.57 years (range, 2 months-12 years) were cumulatively enrolled in the study over a period of 4 years. The mean age of onset of seizures was 19.2 months (range, 1 day-8 years). All except 4 patients had more than one seizure type. Twenty-one had generalized tonic-clonic seizures, 9 had generalized tonic seizures, 5 had generalized clonic seizures, 10 had atypical absence seizures, 12 had atonic seizures, 24 had myoclonic seizures, 19 had partial seizures, and 3 had infantile spasms.

The average number of AEDs used by each patient was decreased from 3 medications prior to the study (mean = 3.8, mode = 3) to 2 medications (mean = 2.6, mode = 2) after taking the diet. Table 3 demonstrates the number of AEDs used by each patient.

Seven of 32 patients (21.88%) who were on the diet for 1 month were seizure free. An additional 13 patients (40.63%) had 90 per cent seizure reduction and 2 (6.25%) had 50-90 per cent seizure reduction. Ten patients (31.25%) had less than 50 per cent seizure reduction. Only 3 patients of 35 patients (8.57%) discontinued the diet. No one was lost to follow-up at 1 month on the diet.

Five of 22 patients (22.73%) who were on the diet for 3 months were seizure free, 10 of 22 (45.45%) had 90 per cent seizure reduction and 2 of 22 (9%) had 50-90 per cent seizure reduction. 5 of 22 (22.73%) had less than 50 per cent seizure reduction. Five patients had discontinued the diet and 4 were lost to follow-up.

Four of 16 patients (25%) who were on the diet for 6 months were seizure free, 8 of 16 (50%) had 90 per cent seizure reduction and 3 of 16 (18.75%) had 50-90 per cent seizure reduction. 1 of 16 (6.25%) had less than 50 per cent seizure reduction. Two patients had discontinued the diet and another 2 were lost to follow-up.

Three of 12 patients (35%) who were on the diet for 1 year were seizure free, 5 of 12 (41.67%) had 90 per cent seizure reduction and 2 of 12 (16.67%) had 50-90 per cent seizure reduction. 2 of 12 (16.67%) had less than 50 per cent seizure reduction. No patient had discontinued the diet or was lost to follow-up at one year. Table 4 demonstrates the summary of the outcomes of the ketogenic diet treatment.

Table 3. Number of antiepileptic drugs (AEDs) used before *vs* after on ketogenic diet therapy.

Number of AEDs	Number of patients on AED before ketogenic diet (Total N=35)	Number of patients on AED after ketogenic diet (Total N=35)
1	None	3
2	2	13
3	15	13
4	8	5
5	8	1
6	2	0

Table 4. Outcomes of ketogenic diet therapy.*

Duration on ketogenic diet	1 month	3 months	6 months	12 months
Seizure free	7 (21.88)	5 (22.73)	4 (25)	3 (35)
90% seizure reduction	13 (40.63)	10 (45.45)	8 (50)	5 (41.67)
50-90% seizure reduction	2 (6.25)	2 (9.09)	3 (18.75)	2 (16.67)
Less than 50% seizure reduction	10 (31.25)	5 (22.73)	1 (6.25)	2 (16.67)
Total number on diet	32	22	16	12
Discontinued diet	3	5	2	0
Lost to follow-up	0	4	2	0

*Not all patients started on the diet at the same time. This table depicts the results of seizure frequency of each patient who was cumulatively enrolled into the study.
( ) = % of patients remaining on diet

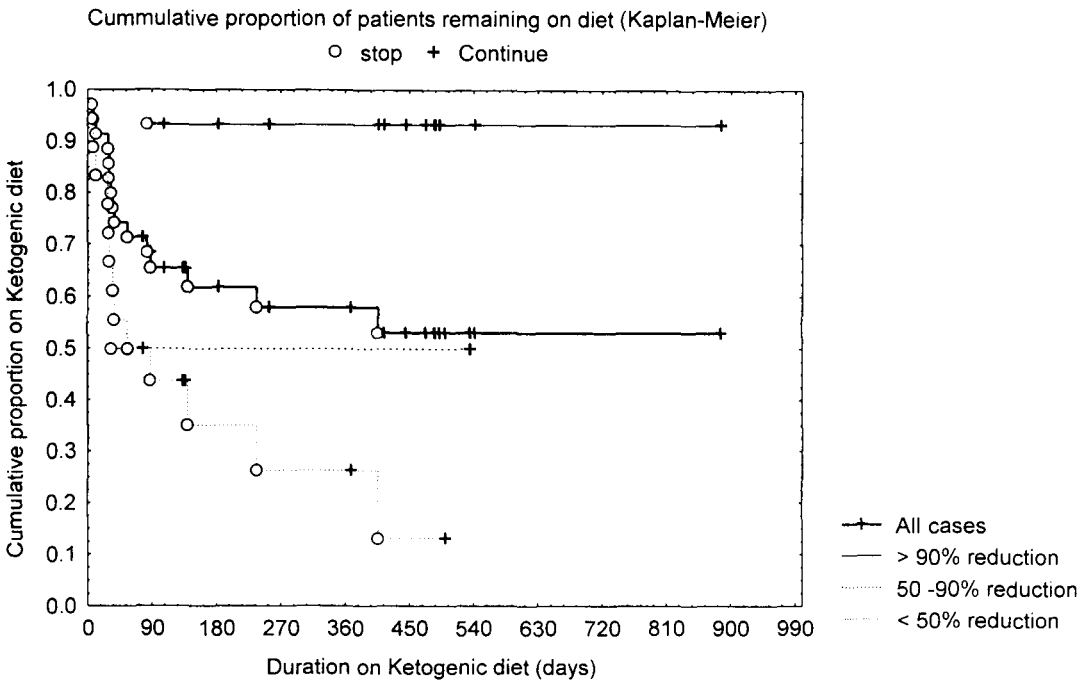

Fig. 1. Kaplan-Meier survival curves for the probability of remaining on the ketogenic diet in relation to seizure- reduction.

Between the group of patients who had more than 50 per cent seizure reduction and those who had less than 50 per cent seizure reduction, the probability of patients remaining on the diet was significantly greater in the group of patients who had more than 50 per cent seizure reduction (Gehan-Wilcoxon, P <0.001). Fig. 1 demonstrates Kaplan-Meier survival curves for the probability of remaining on the diet in relation to seizure control.

There was no statistically significant difference in outcome of seizure reduction (>50% *vs* <50%) among the independent variables: age, sex, type of seizures, and type of EEG abnormalities (focal *vs* non-focal abnormalities).

Adverse effects from the diets were diarrhea(3), vomiting and upper gastrointestinal bleeding(1), and renal tubular acidosis(1). No serious side effects were reported. A total of 10 patients discon-

tinued the diet during the treatment. Half of those who discontinued the diet were due to compliance, the other half were due to ineffectiveness of the diet.

DISCUSSION

The results of this study confirm that the ketogenic diet is beneficial for refractory epilepsy. The results of this study are essentially similar to previous studies[7-10]. Most of our patients who did not respond to the diet had stopped the diet therapy earlier in the course of therapy (usually within the first three months). They were usually not willing to be on the diet without good seizure control. There was only one patient that remained on the diet for 8 months without any significant seizure reduction. Most children responding to the diet therapy showed a substantial seizure reduction during the first 3 months of therapy. This resulted in only patients with high successful rates of seizure reduction remaining on the diet. From our study, there was no relationship between seizure types, types of EEG abnormality and seizure control of the ketogenic diet.

The side effects from the ketogenic diet treatment were usually mild and transient. Diarrhea and vomiting were the only common side effects in our study. The only serious side effect that we found in our study was renal tubular acidosis. After a thorough investigation, there was no explanation for this condition except the initiation of the diet. However, this problem was mild and responded to treatment. This side effect has also been reported in the previous study[11]. Most patients who responded to the diet continued to remain on the diet. The only complaints they all had were the lack of taste and variety in the diet. In terms of maintaining the ketosis, we found no difference among all 3 formula in our ketogenic diet formula. Patients could switch their diet from one formula to another formula which ever suited them best. From our experience, the key to success with the ketogenic diet is to let the patient and parents learn how to implement the diet little by little at their own pace and try not to be too restrictive from the beginning.

In summary, the ketogenic diet therapy is not difficult to implement even in a developing country with limited resources like Thailand. Although ketogenic diet therapy is not a solution for all refractory epilepsy but it may be a good alternative therapy for patients with refractory epilepsy [12]. It requires a team effort to set it up. First, the patient's parents must be dedicated in helping their own children and willing to follow all detailed instructions. Secondly, a good clinical dietician and a nutritionist who are good at improvising and making the diet from all the available common foods from the market are needed. Thirdly, a physician with compassion for their patients and who tries tirelessly to search all modalities of therapy to help them.

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อาหารคีโตจินิก : การรักษาทางเลือกสำหรับผู้ป่วยโรคลมชักที่รักษายากในเด็ก

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เหตุผล : จุดประสงค์ของการศึกษาครั้งนี้เพื่อจัดตั้งโครงการรักษาผู้ป่วยโรคลมชักด้วยอาหารคีโตจินิกเป็นแห่งแรกในประเทศไทย และพิจารณาประสิทธิภาพรวมทั้งความเป็นไปได้ในการรักษาผู้ป่วยโรคลมชักในประเทศไทยด้วยอาหารคีโตจินิก

วิธีการวิจัย : ได้ศึกษาวิจัยไปข้างหน้าแบบเปิดในผู้ป่วยเด็กโรคลมชักที่รักษาได้ยากที่โรงพยาบาลศิริราช ทั้งนี้ผู้ป่วยแต่ละคนที่ศึกษา มิได้เริ่มการรักษาด้วยอาหารคีโตจินิก ณ เวลาที่พร้อมกัน แต่เป็นการทยอยกันเข้ารับการรักษาและสะสมรวบรวมผู้ป่วยจำนวนทั้งสิ้น 35 คน (เพศหญิง 19 คน, เพศชาย 16 คน) ในช่วงเวลาที่ทำการศึกษา 4 ปี อายุเฉลี่ยผู้ป่วยมีอายุ 5.37 $\pm$ 3.57 ปี (พิสัย 2 เดือน ถึง 13 ปี), อายุที่เริ่มชักเฉลี่ย 19.2 $\pm$ 27.47 เดือน (พิสัย 1 วัน ถึง 8 ปี), ระยะเวลาเฉลี่ยที่ผู้ป่วยรับประทานอาหารคีโนจินิก 7.67 เดือน (พิสัย 6 วัน ถึง 29 เดือน) สูตรอาหารที่ใช้ในการศึกษาครั้งนี้ใช้สูตร 4 : 1 คือ ไขมัน 4 ส่วน ต่อ โปรตีนและคาร์โบไฮเดรท 1 ส่วน ทั้งนี้อนุโลมให้ผู้ปกครองของผู้ป่วยสามารถร่วมดัดแปลงรายการอาหารประจำวันที่ผู้ป่วยรับประทานได้ และสามารถใช้อาหารที่มีไขมันสูงที่มีจำหน่ายในตลาด อาทิเช่น น้ำมันกะทิ ในการปรุงอาหาร ผู้ป่วยทุกรายได้รับการเฝ้าระวังอย่าใกล้ชิดและผู้ปกครองของผู้ป่วยได้รับการฝึกสอนให้รู้จักวิธีการเตรียมอาหารของผู้ป่วยแต่ละมื้อในระหว่างที่อยู่ในโรงพยาบาล โดยมีการเฝ้าติดตามถึงผลข้างเคียง, ความถี่ของอาการชักในผู้ป่วยแต่ละราย และวัดปริมาณของคีโตนในปัสสาวะทุกวันอย่างต่อเนื่องภายหลังจากผู้ป่วยจำหน่ายออกจากโรงพยาบาล

ผลการวิจัย : พบว่าจำนวนผู้ป่วยที่ควบคุมอาหารชักได้และมีความถี่ของอาการชักลดลงถึงร้อยละ 90 มีจำนวนถึงร้อยละ 62.5 ในกลุ่มที่ได้รับการรักษาด้วยอาหารคีโตจินิก 1 เดือน, ร้อยละ 68.18 ในกลุ่มที่ได้รับการรักษาด้วยอาหารนาน 3 เดือน, ร้อยละ 75 ในกลุ่มที่ได้รับการรักษาด้วยอาหารนาน 6 เดือน, และร้อยละ 66.67 ในกลุ่มที่รับประทานอาหารคีโตจินิกอย่างต่อเนื่องนาน 1 ปีตามลำดับ นอกจากนั้นยังสามารถลดชนิดของยากันชักที่ผู้ป่วยแต่ละรายจำเป็นต้องใช้ลง แสดงให้เห็นว่าการรักษาผู้ป่วยโรคลมชักชนิดรักษาได้ยาก ด้วยอาหารคีโตจินิกสามารถช่วยให้ผู้ป่วยมีอาการดีขึ้น ความถี่ของการชักลดลง และมีความจำเป็นต้องใช้ยากันชักน้อยชนิดลง

สรุป : อาหารคีโตจินิกสามารถเป็นอีกทางเลือกทางหนึ่งในการรักษาผู้ป่วยโรคลมชักซึ่งสามารถปฏิบัติได้ในประเทศไทยซึ่งมีทรัพยากรอันจำกัด และเป็นหนทางเลือกอีกทางหนึ่งที่สามารถนำมาใช้ทดแทนยากันชักชนิดใหม่ที่มีราคาค่อนข้างแพงได้

คำสำคัญ : อาหารคีโตจินิก, โรคลมชักที่รักษาได้ยาก, ยากันชักชนิดใหม่, ประเทศที่กำลังพัฒนา

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