Original Article

The efficacy and safety of a ketogenic diet for children with refractory epilepsy in China: a retrospective single-center cohort study

Hua Li, Mei Ouyang, Peiqi Zhang, Lingxia Fei, Xiangshu Hu

Department of Epilepsy, Guangdong 999 Brain Hospital, Guangzhou, China

Contributions: (I) Conception and design: H Li; (II) Administrative support: M Ouyang; (III) Provision of study materials or patients: M Ouyang, P Zhang; (IV) Collection and assembly of data: H Li, P Zhang, L Fei ; (V) Data analysis and interpretation: H Li, L Fei, X Hu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hua Li. Department of Epilepsy, Guangdong 999 Brain Hospital, No. 578 Shatai South Road, Guangzhou 510510, China.
Email: lihua1051@163.com.

Background: The ketogenic diet (KD) has been implemented in many different counties. However, in China, study concerning the efficacy of the KD is still at an early-stage of evaluation. Furthermore, the KD is thought to be incompatible with Chinese children because of its lack of palatability, especially for the Asian population. In addition, its substantial antiepileptic effect remains to be confirmed.

Methods: To evaluate the efficacy and safety of the KD treatment of refractory childhood epilepsy in China, we prospectively enrolled 147 children with refractory epilepsy for KD treatment in Guangdong 999 Brain Hospital and followed up the children for 6 months. Outcome was measured by seizure frequencies before and after the KD diet and adverse effects. We also evaluated influences of different variables (starting age, duration of epilepsy, and others) on the outcome.

Results: We found after 1 month, 3 months, and 6 months of KD treatment, 28.0%, 55%, and 67.9% of the subjects remained on diet with a >50% seizure reduction and seizure-free rates of 6.5%, 13.2%, and 23.3%, respectively. Gender, starting age, duration, etiology, classification, and seizure type of epilepsy showed no significant influence on efficacy. Anorexia, diarrhea, and gravel were the main side-effects of the KD treatment.

Conclusions: In conclusion, the KD is a safe and efficacious method for childhood refractory epilepsy treatment.

Keywords: Ketogenic diet (KD); refractory epilepsy; effect; safety

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Introduction

Epilepsy is one of the most common chronic neurological disorders in children, and is estimated to affect more than 2 million people in China (1). Although the recent effective treatment of anticonvulsants include drug therapy or surgical treatment, 20–30% of childhood epilepsies are not fully controlled and become medically refractory (2). Furthermore, the continued use of antiepileptic drugs for refractory epilepsy was found to not significantly reduce seizures (3), but rather increase adverse reactions including cognitive impairment, kidney injury, allergy, etc. (4). Left uncontrolled, these seizures pose a significant risk to the patient's quality of life.

For the reasons outlined above, dietary therapy has become an important way to improve the quality of life of patients with refractory epilepsy, especially for children. Ketogenic diet (KD) therapy is an effective and well-tolerated diet therapy for child with refractory epilepsy, and

has been widely used since the first reports of its beneficial action in seizure control were published (5). KD treatment has no adverse effects on the cognition and behavior of children and has been linked to the improvement of neurobehavioral development in children with refractory epilepsy (6).

The KD has a high-fat, adequate-protein, and low-carbohydrate composition that causes metabolic changes which mimic a state of fasting. Often initiated with a brief fasting period and an in-hospital stay, changes in plasma ketones, insulin, glucose, glucagon, and free fatty acids occur within hours of starting the diet (7). Thus far, the KD has been implemented in many different counties. However, studies concerning its efficacy in China are still at an early stage of evaluation. Moreover, the KD is thought to have low toleration in children due to its unpalatable nature, especially for the Asia population, while its substantial antiepileptic effect remains to be confirmed (8).

Our study was conducted to carefully evaluate the efficacy and safety of the KD for children with refractory epilepsy in China and to provide detailed data on the potential factors influencing the therapeutic effect of KD therapy including age, etiology, and class of epilepsy.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-20-219).

Methods

Subject enrollment

From May 2016 to February 2019, 147 children and adolescents of ages ranging from 4 months to 22 years with refractory epilepsy at Guangdong 999 Brain Hospital were included in this study. The inclusion criteria were subjects (2) diagnosed as refractory epilepsy according to the national guidelines developed by the China Association Against Epilepsy (CAAE) and (2) age >4 months. The subjects with known metabolic diseases or severe systemic illnesses were excluded. The study protocol was approved by the ethics committees of Guangdong 999 Brain Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As the study was retrospective, written informed consent from subjects was not required.

KD treatment for children with refractory epilepsy

Before KD treatment, blood routine; urine routine; blood glucose; blood lipid; liver and kidney function; electrolyte; B-ultrasound of the liver, gallbladder, and spleen; electroencephalogram (EEG); and genetic metabolic screening of all subjects were acquired. Those with contraindications as discussed in subject enrollment were excluded.

KD treatment of subjects was initiated at hospital for 5 to 7 days. The initial ketogenic ratio (fat: carbohydrates plus protein) of most subjects was 2 to 1, while the others was 1 to 1 or 3 to 1. The recommended caloric intake was calculated according to the patient's height, weight, and age by a dietitian. The calorie of the KD was 75% and 80% of the recommended caloric intake. The doctors and nurses detected the concentration of blood glucose and ketone, and closely monitored the patients for any acute adverse effects. At the same time, the dietitian explained to parents their critical role in the administration of KD and taught them how to prepare the KD for children and how to detect the concentration of blood glucose and ketone. The ketogenic nutritional powder of the KD was provided by Jiantong, Guangzhou Kinton FSMP Co., Ltd (Guangzhou City, Guangdong province, China).

When blood ketone achieved a stable level, subjects would continue to receive KD treatment at home and were brought back to hospital for disease assessment and laboratory tests such as blood routine, urine routine, liver and kidney function, blood lipids, urinary ultrasound, and EEG every 3 months until KD treatment was over. The antiepileptic drugs were unchanged for the first 3 months of the KD and adjusted according to children's conditions afterwards.

Data collection

The following data were collected: gender, age, duration of epilepsy, weight, etiology of epilepsy, epilepsy seizure type, and epilepsy type at the beginning of the KD.

To assess the clinical effectiveness, data on seizure frequency at baseline and after 1, 3, and 6 months were collected by parental report. Seizure reduction rate was defined as average seizure frequency per month of all seizure types after the KD compared to the baseline seizure frequency. The seizure reduction rate was categorized into 5 groups: (I) seizure free; (II) >75% seizure reduction; (III) 50–75% seizure reduction; (IV) <50% seizure reduction; (V) no change or increase in seizure frequency. Patient with a seizure reduction >50% were defined as responders, and the rest were defined as non-responders.

Table 1 Patients' characteristics

Characteristics	Numbers (%)
Gender, male:female	102:37
Subjects performed gene test, n (%)	58 (41.7)
Epilepsy etiology, n (%)	
Genetic	40 (28.8)
Structural/metabolic	42 (30.2)
Unknown	57 (41.07)
Classification of epilepsy: syndrome and non-syndrome, n (%)	
Syndromes	25 (18.0)
Non-syndrome	114 (82.0)
Classification of epilepsy: infantile spastic and non-infantile spastic, n (%)	
infantile spastic	39 (28.2)
non-infantile spastic	100 (71.9)
Seizure type, n (%)	
Myoclonic	9 (6.5)
Tonic-clonic	16 (11.5)
Spasm	47 (33.8)
Tonic	52 (37.4)
Absence	5 (3.6)
Others	10 (7.2)
At the beginning of the KD	
Age, medium (range, yr)	5 (4/12–22)
Weight, medium (range, Kg)	12.5 (5–65)
Duration of epilepsy, medium (range, mo)	17 (1–145)
Duration of KD, medium (range, mo)	9 (1–55)
Number AEDs, medium (range)	3 (0–5)

KD, ketogenic diet; yr, year.

We also collected data on weight at 6 months after the KD and side-effects in the treatment of KD.

Statistical analyses

Statistical analyses were conducted using SPSS 17.0 software for Windows. To evaluate the effect of age, duration of epilepsy, etiology, classification of epilepsy, and seizure syndromes on the efficacy of treatment, we divided the cohort according these variables and analyzed the efficacy of the KD for each group. Statistical evaluation was performed using Pearson's Chi-square analysis. In all analyses, a P value less than 0.05 was considered statistically significant.

Results

Patients characteristics

There were 139 patients included in this study, with 1 child dying of heart disease, 3 lost to follow-up, and 4 abandoning treatment of KD. Etiologies of epilepsy included heredity, structural/metabolic (including brain dysplasia, congenital perinatal injury, encephalitis, cerebral hemorrhage, brain trauma), and unknown causes; epilepsy seizure types were classified as myoclonic, tonic-clonic, tonic, absence, spasm, and others (including atonic, tonic-ationic, myoclonic-atonic, and uncertain seizure type). Epilepsy types were classified as syndrome (including Ohtahara syndrome, Dravet syndrome, DOSSE, Lennox-Gastaut syndrome, and infantile spastic epilepsy) and non-syndrome (including epilepsy, RETT syndrome, glucose transporter 1 deficiency syndrome, cerebral palsy, tuberous sclerosis, epileptic encephalopathy, encephalitis sequela, hypoxia-ischemia encephalopathy, and mitochondrial encephalomyopathy) or as infantile spastic and non-infantile spastic epilepsy (including all other epileptic types excluded infantile spastic epilepsy). Baseline demographic characteristics of all subjects are given in *Table 1*.

Treatment efficacy

The clinical effectiveness of the KD after 1, 3, 6 months is shown in *Table 2*. At 1 month' follow-up, 39 of 139 (28.0%) subjects were responders: 9 (6.5%) were seizure-free, 12 (8.6%) had a seizure reduction of >75%, and 18 (12.8%) had a seizure reduction of 50–75%. At 3 months' follow-up, 71 of 129 (55%) subjects were responders: 17 (13.2%) were seizure-free, 23 (17.8%) had a seizure reduction of >75%, and 31 (24.0%) had a seizure reduction of 50–75%. At 6 months' follow-up, 70 of 103 (67.9%) subjects were responders: 24 (23.3%) were seizure-free, 16 (15.5%) had a seizure reduction of >75%, and 30 (29.0%) had a seizure reduction of 50–75% as shown in *Table 2*. By Pearson's Chi-square analysis, we found there was a significant difference concerning the efficacy between 1 month and 3 months (P=0.000), 6 months (P=0.000), but there was no significant difference between that of 3 months and that

Table 2 Clinical outcome of KD after 1, 3, and 6 months

Clinical outcome	1 month[a] (n=139)	3 months[b] (n=129)	6 months[c] (n=103)
Seizure reduction-responder, n (%)	39 (28.0)	71 (55.0)*	70 (67.9)*
Seizure free	9 (6.5)	17 (13.2)*	24 (23.3)*
>75% reduction	12 (8.6)	23 (17.8)*	16 (15.5)*
50–75% reduction	18 (12.9)	31 (24.0)*	30 (29.1)*
Seizure reduction non-responder, n (%)	100 (72.0)	58 (45.0)*	33 (32.0)*
<50% reduction	49 (35.3)	35 (27.1)*	22 (21.4)*
No change	51 (36.7)	23 (17.9)*	11 (10.6)*
Other clinical outcome			
Weight, medium (range, Kg)	–	–	14.0 (1.5–59.7)
Neurobehavioral improvement, n (%)	67 (48.2)	–	–
EEG improvement, n (%)	59 (42.4)	–	–

[a], lost to follow-up: 7 patients; [b], lost to follow-up: 10 patients; [c], lost to follow-up: 36 patients. *, compared with efficacy at 1 month; P value <0.05. KD, ketogenic diet.

Table 3 Comparison of efficacy after 3 months of KD by different gender, age, or duration of epilepsy at the beginning of the KD (n, %)

Efficacy	Gender			Age starting the KD			Duration of epilepsy		
	Male	Female	P value	≤5 years	>5 years	P value	≤17 mo	>17 mo	P value
Responder	53 (58.9)	18 (50.0)	0.555	40 (43.7)	30 (47.4)	0.723	41 (48.2)	17 (38.6)	0.352
Non-responder	40 (41.1)	18 (50.0)		32 (56.3)	27 (52.6)		44 (51.8)	27 (61.4)	

KD, ketogenic diet.

of 6 months (P=0.058), as shown in *Table 2*. There was no significant difference between the weight at the beginning of the KD and that at 6 months after the KD (P=0.1167). At 1 month after KD, 67 of 139 (48.2%) subjects showed neurobehavioral improvement, while 59 of 139 (42.4%) subjects showed EEG improvement (*Table 2*).

Effect factors on KD treatment efficacy

As there was no significant difference in the efficacy between 3 months' KD and 6 months' KD, we only chose the subjects with 3 months' KD treatment for factor effect evaluation. To investigate the factor effect on the treatment efficacy, we divided the subjects into two groups by gender, medium value of the age, and duration of epilepsy at the start of the KD. By Pearson's Chi-square analysis, we found no differences in gender, age, and duration of epilepsy (*Table 3*). There was also no difference in the efficacy of KD due to variable etiology, classification of epilepsy syndrome (*Table 4*), or seizure type of epilepsy (*Table 5*).

Side-effects of KD treatment

A total of 31 subjects experienced side-effects, which included nausea, diarrhea, constipation, hypoglycemia, ketoacidosis, dyslipidemia, and gravel. We observed that the most common side-effect was anorexia with 17 subjects (12.2%), followed by diarrhea with 5 subjects (3.6%), and renal stones with 4 subjects (2.9%); other side-effects accounted for just 0.7% of total occurrences.

Discussion

Since it was first adopted by Wilder in 1921, the KD has been used to treat refractory epilepsy for nearly 100 years (9), and has attracted widespread attention during this time. Retrospective, multicenter studies and randomized controlled trials have confirmed the effectiveness of the

Table 4 Comparison of efficacy of the KD by different etiology or classification of epilepsy (n, %)

Efficacy	Etiology of epilepsy				Classification of epilepsy					
	Genetic	Structural/ metabolic	Unknown	P value	Syndrome	Non-syndrome	P value	Infantile spastic	Non-infantile spastic	P value
Responder	20 (51.3)	19 (47.5)	32 (64.0)	0.251	16 (64.0)	55 (52.9)	0.375	19 (52.8)	52 (55.9)	0.844
Non-responder	19 (48.7)	21 (52.5)	18 (36.0)		9 (36.0)	49 (47.1)		17 (47.2)	41 (44.1)	

KD, ketogenic diet.

Table 5 Comparison of efficacy of the KD by different seizure type of epilepsy (n, %)

Efficacy	Seizure type						
	Myoclonic	Tonic-clonic	Spasm	Tonic	Absence	Others	P value
Responder	5 (55.6)	6 (40.0)	22 (52.4)	34 (66.7)	0 (0.0)	4 (50.0)	0.091
Non-responder	4 (44.4)	9 (60.0)	20 (47.6)	17 (33.3)	4 (100.0)	4 (50.0)	

KD, ketogenic diet.

KD in the treatment of refractory epilepsy (10,11). During KD therapy, the main energy for the body comes from fat metabolism, and fatty acid β-oxidation becomes the main metabolic pathway of the body, causing systemic changes in metabolic products such as ketone bodies (12). However, the related factors affecting the efficacy of KD have not been determined in China. For this reason, this study evaluated the efficacy of KD in the treatment of refractory epilepsy and analyzed the effects of sex, treatment time, age, epileptic syndrome, and types of seizures on the efficacy, in order to guide the screening of children with KD and achieve accurate individualized treatment.

We found that after 1, 3, and 6 months of treatment, the complete control rate increased from 6.5% to 13.2% to 23.3%, respectively; the proportion of 75%-reduction patients was 8.6%, 17.8%, and 15.5%, respectively, while the proportion of 50%-reduction patients was 12.8%, 24.0%, and 29.1%, respectively, but there was no significant difference between the 3 months' and 6 months' KD. Overall, the efficacy of KD therapy after 3 months and 6 months was significantly higher than that after 1 month, (55.0%, 67.9%, and 27.8%, respectively) but there was no significant difference between efficacy after 3 months and 6 months. Therefore, we believe that in clinical practice, the longer the duration of the KD, the better the curative effect. Unfortunately, however, we did not have a longer follow-up to fully confirm this.

Furthermore, age, gender, and duration of epilepsy at the beginning of KD had no significant impact on KD efficacy, which was consistent with the results of most of the relevant studies. We also did not find a difference in KD efficacy between different etiologies or classifications of epilepsy or different seizure types of epilepsy. This may be due to the small sample size in each group. In our study, we also found that inappetence was the most common side-effect, following by diarrhea, and renal stones. We speculate that the adverse reactions of kidney stones may be caused by the absence of potassium citrate in the CK diet. Therefore, we should pay more attention to these side-effects in the course of treatment with KD. Other studies (13), however, reported no weight loss after KD treatment.

In conclusion, KD is effective in the treatment of refractory epilepsy. However, after 3 months of treatment, the effect will not significantly increase with the extension of treatment time. We further found that age, sex, etiology, type of epilepsy, and type of seizure had no significant effect on the efficacy. However, our study also has some limitations, such as its small sample size and its single-center, regression study design; thus, further large-sample–size, multicenter prospective studies are warranted.

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Footnote

Reporting Checklist: The authors have completed the

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