

ARTICLE

The use of a formula-based ketogenic diet in children with refractory epilepsy

O uso da dieta cetogênica a base de fórmula em crianças com epilepsia refratária

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ABSTRACT

The ketogenic diet (KD) is a nonpharmacologic treatment that has been used for refractory epilepsy since 1921. The KD is a high-fat, low-carbohydrate, and restricted protein diet, which is calculated and weighed for each individual patient. Introducing and maintaining the diet for a long time remains a challenge. In this study, we evaluated the acceptability, tolerance, and efficacy of a formula-based KD in 10 children with refractory epilepsy. The ketogenic formula tested herein caused only mild KD-related adverse events and adequate adherence. Moreover, 60% of patients had more than 50% seizure frequency reduction and 10% were seizure-free.

Keywords: ketogenic diet; epilepsy; diet therapy

RESUMO

A dieta cetogênica (DC) é um tratamento não farmacológico utilizado para epilepsia refratária desde 1921. A DC possui um alto teor de gordura, sendo restrita em carboidratos e adequada em proteínas, calculada e pesada para cada paciente. A introdução e manutenção da DC por um tempo prolongado permanece um desafio. Neste estudo foi avaliada a aceitação, tolerância e eficácia da DC baseada em fórmula em 10 crianças com epilepsia refratária. A DC apresentou adequada aderência e efeitos adversos leves. Além disso, 60% dos pacientes apresentaram mais de 50 % de redução frequência das crises e 10% ficaram livres de crises.

Palavras-chave: dieta cetogênica; epilepsia; dietoterapia

Epilepsy is a devastating neurological disorder affecting approximately 50 million people of the world's population¹. Pharmacotherapy with anti-epileptic drugs is the main strategy adopted for treatment, but 20–40% of patients continue to struggle with recurrent seizures despite medications². Because of the physical, social, and psychological impact of even a single seizure, nonpharmacologic treatments such as dietary therapy have been considered to improve the quality of life of patients with medically-refractory epilepsy³.

Fasting has been used as a treatment for epilepsy since ancient times. The ketogenic diet (KD) is a high-fat, low-carbohydrate, and restricted protein diet created in 1921 at the Mayo Clinic by Dr. R.M. Wilder to mimic the fasting state, which has been found useful in patients with refractory epilepsy⁴. The mechanism by which the KD leads to a reduction in seizures in these patients is not yet clear. In response to this diet and in the absence of glucose, ketone bodies produced from fatty-acid metabolism are used as the main energy source in the brain, maintaining a ketosis status⁵. Further evidence includes carbohydrate reduction, activation

of adenosine triphosphate (ATP)-sensitive potassium channels by mitochondrial metabolism, inhibition of the mammalian target of rapamycin pathway, and inhibition of glutamatergic excitatory synaptic transmission^{5,6}.

Patients with epilepsy syndromes and conditions such as myoclonic-atonic epilepsy (Doose syndrome), severe myoclonic epilepsy of infancy (Dravet syndrome), Rett syndrome, infantile spasm, and tuberous sclerosis complex may particularly benefit from the KD. In addition, the KD is the treatment of choice for glucose transporter protein I deficiency and pyruvate dehydrogenase deficiency³.

The KD has been used worldwide⁷ and there are many alternative ketogenic diets such as the classical KD, medium chain triglyceride diet, modified Atkins diet, and low glyce-mic index treatment⁸. The classical KD is calculated based on the ketogenic ratio, which refers to the ratio of the amount of fat to the combined amounts of protein and carbohydrate and is typically a 3:1 or 4:1 ratio. The amount of carbohydrates is minimal and every meal is calculated based on the energy and protein requirements of the patient⁹.

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In Brazil, the KD is administered with solid foods and the most used ingredients are mayonnaise, bacon, eggs, heavy cream, meat, and some vegetables and fruits¹⁰. Since the KD is a highly restricted diet, one of the biggest challenges is to maintain patient adherence to the diet for at least two years. A formula-based KD can facilitate and improve the introduction of and adherence to the KD treatment for long periods in oral-fed children and can be especially practical and safe in tube-fed patients. The objective of this study was to evaluate the acceptability, tolerance, and efficacy of a formula-based KD in children with refractory epilepsy.

METHODS

Ten children with refractory epilepsy, who did not have remission of their seizures despite appropriate trials of two tolerated and appropriately chosen antiepileptic drugs, and who were referred to the KD program between October 2014 and June 2015 were included in the study. Children with disorders that contraindicated the use of the KD were excluded². This study was approved by the Research Ethics Committee at the Child Institute of the Clinical Hospital, University of São Paulo, Brazil. An informed consent was obtained from each parent or caregiver.

The KD was introduced in the outpatient setting. Before an initial screening visit, the patients' families were invited to a meeting to learn about the KD and the current trial. Next, they came for a visit, when the clinical history of the child was recorded and neurological and baseline exams were performed. Parents were instructed to record in a diary the frequency of seizures for one month from baseline and for the three months of treatment.

At the time of study entry, one child was taking one anti-epileptic medication, one was taking two anti-epileptic medications, six children were taking three anti-epileptic medications, one child was taking four anti-epileptic medications, and one child was taking five anti-epileptic medications. The medications were not changed during the three-month study period.

For orally fed patients, we introduced the KD at a ratio of fat to protein and carbohydrate of 2:1 in the first week with solid foods distributed over four meals during the day. In the second week, we introduced a 3:1 KD powdered formula at two meals plus two meals with solid foods, and after another two weeks we introduced a 4:1 KD formula at two meals plus two meals with solid foods.

For enterally fed patients, we introduced a modulated 3:1 KD formula exclusively and, after two weeks, a 4:1 KD formula.

After starting the 4:1 diet, all children were reviewed as outpatients once a month, for three months.

We evaluated the acceptability, tolerance, and efficacy of the formula-based KD by the frequency of seizures,

adverse events, level of ketosis, and intake of formula for the three-month period.

The frequency of seizures, adverse events, level of ketosis (whole blood β HB testing with a portable bedside machine or urine), and acceptability of the diet were recorded by the patient's parents. During the medical/dietitian visit, the records were checked and the parents were asked to rate the overall acceptability of the product and list any adverse events. Children received KetoCal[®] 4:1 (Nutricia North America Inc., Gaithersburg, MD, USA).

RESULTS

Ten children (five boys) participated in the study. The age at the KD onset ranged from nine months to 16 years (mean: 6.3 years). All patients completed the three months of treatment (Table 1).

Ketone levels were measured in blood in six patients and a level of 3–5 mmol/L was achieved in 7–10 days. In four patients, ketone urine levels were measured and rated ++/+++ on the 7th and 15th days in two children each. Two children did not have their ketosis level measured in the first three weeks. After three months, the responder rate (more than 50% seizure frequency reduction) was 6/10 (60%) and 10% (1/10) of patients were seizure-free.

The most frequently reported adverse effects were hunger, constipation, drowsiness, and hypoactivity, and one patient who received the formula exclusively presented with an intense perineal rash following the contact between the patient's feces and skin. Eight children reported improved attention and activity.

The formula was well accepted and tolerated by most patients and only one patient did not like its taste. Parents and clinicians considered that the formula was easy to use and facilitated the introduction of and adherence to the KD treatment. These results are shown in Table 2.

DISCUSSION

Due to the KD strictness, patient compliance depends on the type of diet and the patient population³. In Brazil, the KD was administered orally, or tube fed to children, using solid foods, and the most-used ingredients include mayonnaise, bacon, eggs, heavy cream, meat, and some vegetables and fruits. Despite the small number of patients in this study, the use of a formula-based KD was well accepted, tolerated and facilitated the compliance to the treatment.

The goal of the KD treatment is to bring the brain into a state of ketosis to control seizures. The traditional method of initiating the KD involves a period of fasting of 12–48 hours, depending on the urine ketone levels⁹. A prospective randomized study showed that fasting is not necessary for achieving

Table 1. Demographic and clinical features.

Case	Gender	Age at epilepsy onset	Etiology	Epilepsy type/Syndrome
1	M	1.5y	Unknown	Lennox Gastaut syndrome
2	M	9m	Unknown	Generalized and partial
3	F	4m	Unknown	Generalized
4	F	3y	Encephalitis	Lennox Gastaut syndrome
5	M	7m	Unknown	Lennox Gastaut syndrome
6	F	1y	Unknown	Generalized
7	M	4m	Asphyxia	West syndrome
8	F	3m	Lyssencephaly	Lennox Gastaut syndrome/Lissencephaly
9	M	2y	Unknown	Lennox Gastaut syndrome
10	M	4m	Asphyxia	Partial

M: male; F: female; y: year; m: month

Table 2. Results.

Case	Age of KD onset	Administration	Ketosis	Days to reach ketosis	Response	Acceptability	Adverse effects
1	6y	Oral feeding	4-5	10	Decreased < 50%	Good	Hungry, obstipation and hypoactivity
2	9y	Tube feeding	3-5	8	Decreased > 75%	Good	Perineal rash
3	3y	Oral feeding	3-5	7	Decreased < 50%	Good	Hungry, somnolence, obstipation, lack of energy and improved QoL
4	16y	Oral feeding	2-3	7	Decreased < 50%	Good	Drowsiness, hypoactivity and improved QoL
5	3y	Tube feeding	4-5	10	Decreased < 50%	Good	Constipation and improved QoL
6	2y	Oral feeding	4-5	8	Decreased 100%	Good	Improved QoL
7	9m	Tube feeding	+++	NA	Decreased > 75%	Good	Hypoactivity, obstipation and improved QoL
8	6y	Oral feeding	+++	NA	Decreased > 75%	Good	Improved QoL
9	5y	Oral feeding	++/+++	7	Decreased > 50%	Good	Hungry and obstipation and improved QoL
10	4y	Oral feeding	++/+++	15	Decreased > 50%	Didn't like	Hungry and improved QoL

KD: ketogenic diet; y: year; m: month QoL: quality of life.

ketosis. In that study, the fasting KD group became ketotic earlier, but after six days, no difference was found in the degree of ketosis between the two treatment groups, and gradual initiation protocols offered the same results at three months, with lower frequency and severity of early side effects¹¹. Fasting has the same effect as a “loading dose” of medication; however, acute adverse effects requiring patient hospitalization are more frequent¹¹. Gradual KD onset allows the diet to be followed with less adverse effects on an outpatient basis, which is especially welcome where the availability of hospital beds is restricted. In the current study, satisfactory ketone levels were achieved, on average, 10 days after gradual KD onset for patients who were receiving a 3:1 KD formula.

A major limitation of the current study is the small cohort of patients, due to the limited quantity of the formula available for testing.

Besides that, not all patients measured ketosis in the same way and two children did not have their ketosis level measured in the first three weeks. Ketosis measured in the blood or urine is a reliable parameter. The two patients who did not measure ketosis had more than 75% of their seizures improved, which leads us to infer that they reached a good ketosis level, although we cannot determine the onset.

A randomized controlled trial that tested the efficacy of the KD in children with intractable epilepsy found that 62% of patients in the KD group had less than 50% reduction in

seizures, 38% had more than 50% reduction in seizures, and 7% had more than 90% reduction in seizures at three months¹². In our sample, 60% of patients had more than 50% seizure frequency reduction and 10% were seizure-free, which is a high response rate despite the small number of patients studied. Our sample population included five patients (50%) with Lennox-Gastaut syndrome, who are more likely to experience a reduction in seizure frequency when receiving KD treatment¹³.

The KD powdered formula tested herein is nutritionally complete and has been successfully used in KDs, in Europe and in the United States of America, in patients with drug-resistant epilepsy, but in Brazil has only recently become available. Although we describe a small cohort of patients, this study was important to evaluate the acceptance of the formula in our population, facilitating the introduction of an already well-established, but not yet prescribed, treatment that is often misinterpreted by medical professionals, dieticians and the general population as laborious and difficult to adhere to.

We observed only mild KD-related adverse events and they were not responsible for diet discontinuation. Gradual KD initiation protocols are, in general, associated with fewer and milder adverse events^{14,15}. One patient had an intense perineal rash by contact that resolved with immediate hygiene after evacuation. This is the first report of this KD-related adverse event.

A well-balanced diet usually contains vitamins and minerals, but supplementation is essential for children receiving the KD due to the limited quantities of fruits and vegetables they can eat, making the use of a standard multivitamin

necessary. Nevertheless, ketogenic formulas are enriched with vitamins and minerals and supplementation may not be necessary, depending on the amount of formula prescribed per day. Formula-based KD can be used in enterally fed patients to facilitate KD management and reduces administration mistakes in preparation when administered orally. Indeed, using a formula-based KD is simpler for dieticians to calculate, requires less family teaching, ketosis is easily maintained, and preparation errors are less common³. However, children with epilepsy usually have several daily appointments, such as medical and nutritional consultations, tests, and therapies. Thus, homemade foods may not always be a practical solution since they are highly perishable and ketogenic formulas serve as a better dietary option for these patients. Moreover, introducing a successful KD in the outpatient setting can also reduce medical costs, as well as improving the quality of life of children with medically-refractory epilepsy as the number of seizures subsides. A barrier to the use of the formula in Brazil is the cost, making its use sporadic or limited to special situations.

In conclusion, epilepsy can have a high impact on the quality of life in children with intractable seizures and additional disabilities.

The ketogenic diet was effective in reducing the frequency of seizures and improving cognition and the quality of life of patients.

Homemade foods are normally used in the KD, but ketogenic formulas can be recommended to improve treatment acceptance and adherence.

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