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Original Article

The Ketogenic Diet: Initiation at Goal Calories Versus Gradual Caloric Advancement

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ABSTRACT

BACKGROUND: Inpatient initiation of the ketogenic diet has historically involved fasting followed by gradual advancement of calories and/or diet ratio. Complications during this initiation period are common. We sought to determine if the initiation of the diet at goal calories would reduce these complications while maintaining efficacy. **METHODS:** Sixty patients were admitted to a tertiary care hospital for elective initiation of the ketogenic diet between October 2007 and January 2013. All patients were placed on a ketogenic diet initiation pathway. In 2010, the pathway was modified from gradual caloric advancement to initiation at goal calories. We selected 30 consecutive patients before and after the change for comparison. Each child's record was reviewed for the occurrence of hypoglycemia, number of days to reach full ketosis (defined as 4 + urine ketones), acidosis requiring commencement of sodium citrate, length of admission, and long-term efficacy. **RESULTS:** Both methods of initiation had similar rates of dehydration, vomiting, lethargy, and irritability. More patients initiated at goal received sodium citrate ($P = 0.005$); however, mean daily values of carbon dioxide were not significantly different. Onset of ketosis was slightly delayed ($P = 0.009$) in patients initiated at goal, but length of stay was not affected ($P > 0.1$). Hypoglycemia was uncommon and rates were similar between the groups. Efficacy at 3 months was better in patients initiated at full calories ($P < 0.05$). **CONCLUSION:** Initiation of the ketogenic diet full calories is a reasonable alternative to the current standard practice of gradual advancement of calories and/or diet ratio.

Keywords: ketogenic diet, epilepsy, initiation, children, nonfasting

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Introduction

Since the third century BC when Hippocrates noted that fasting reduced the incidence of convulsions in people prone to "epileptic fits," ketosis has been recognized as a treatment for seizures. In the 1920s, Keith and Helmholz at the Mayo Clinic reported a series of epilepsy patients who had been successfully treated with a high-fat, low-carbohydrate diet.[1] Subsequent studies demonstrated the benefits of the diet on behavior and cognition as well.[2] With the development of phenytoin in the 1930s and successive other anticonvulsants, the diet's popularity diminished. In recent years, however, the ketogenic diet has again become a valued therapeutic option.

Both fasting and a high-fat, low-carbohydrate diet will increase production of ketone bodies, specifically acetone, acetoacetate, and beta-hydroxybutyrate. During ketosis the brain shifts its primary energy source from glucose to ketone bodies. With the ketogenic diet, approximately 90% of the daily caloric intake is in the form of fat. Alternative dietary treatments for epilepsy such as the modified Atkins diet and low glycemic index diet provide 60-65% of daily calories in the form of fat. Although the exact mechanism by which the diet decreases seizures is not known,[3] several diseases, such as Dravet syndrome, respond particularly well.[4]

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TABLE 1.
Comparison of protocols for initiation of the ketogenic diet

	HD 1 (Ratio/Calories)	HD 2	HD 3	HD 4	HD 5	HD 6
Bergqvist, 2005						
FAST-KD	Regular dinner/100%	0/0%	4:1/33%	4:1/67%	4:1/100%	Discharge
GRAD-KD	Regular dinner/100%	1:1/100%	2:1/100%	3:1/100%	4:1/100%	Discharge
Kim, 2004						
IFKD	0/0%	0/0%	4:1/33%	4:1/67%	4:1/100%	Discharge
NFKD	4:1/33%	4:1/67%	4:1/100%	Continue until discharge		
Our series						
GRAD	4:1/33%	4:1/67%	4:1/100%	Continue until discharge		
GOAL	4:1/100%	4:1/100%	4:1/100%	Continue until discharge		

Abbreviations:
FAST-KD = Fasting ketogenic diet initiation protocol
GOAL = Goal calories initiation protocol
GRAD = Gradual caloric initiation protocol
GRAD-KD = Gradual ketogenic diet initiation protocol
HD = Hospital day
IFKD = Initial fasting ketogenic diet
NFKD = Nonfasting ketogenic diet

Initiation of the ketogenic diet is typically done in a tertiary care center with the expertise of a pediatric neurologist and a specialized dietitian, but exact protocols for initiation vary greatly from one institution to the next (Table 1). Little data regarding optimal regimens for initiation have been published. Three groups have compared different methods of initiating the diet. Kim et al. compared nonfasting with fasting initiation and found that there was less dehydration in nonfasting initiation without a significant delay in the onset of ketosis.[5] Vaisleib et al. found no significant differences in effect on seizure control, school performance, and level of alertness in patients who underwent outpatient initiation compared with those initiated as inpatients.[6] Finally, Bergqvist et al. compared fasting versus gradual advancement of diet ratio and found that gradual initiation improved tolerability while maintaining efficacy.[7] Ultimately, the 2009 International Ketogenic Diet Study Group failed to reach a consensus as to whether fasting is recommended.[8]

At our institution, a nonfasting, gradual initiation protocol was initially used in which daily caloric intake was increased over 3 days (Table 1). We observed frequent instances of hypoglycemia and extreme patient discomfort during this initiation phase. Therefore, in 2010, we began initiating full calories on admission. In this study, we compare patients before and after the change in protocol to determine whether there were significant differences in tolerability and efficacy.

Methods

This study was approved by the institutional review board at the Children's National Medical Center. Patients were identified from an institutional ketogenic diet database. Sixty patients were admitted for elective initiation of the diet between October 2007 and January 2013. Before admission, patients met with a registered dietitian specializing in the ketogenic diet as well as a pediatric epileptologist in the outpatient clinic for screening, education, and counseling. Patients suspected to have underlying metabolic disorders were first cleared by a metabolic specialist.

On admission, all patients were placed on a ketogenic diet initiation protocol. A gradual initiation protocol (GRAD) was used before September 2010. Under this protocol, patients were fed one third of their total daily caloric requirement on the day of admission, two thirds of the daily calorie total on hospital day 2, and full calories on hospital day 3. A 3:1 diet ratio is typically used in children younger than 18 months and children older than 12 years. A 4:1 diet ratio is used in all other patients. In September 2010, the protocol was modified to initiation at goal calories (GOAL). Patients did not undergo a prolonged fast before admission in either group. We selected 30 consecutive patients before and after the change in protocol for this study. Patients who were already on a modified Atkins diet and those who were initiated on an urgent basis were excluded.

Complete medical records of all patients were reviewed for demographic information and clinical course. Per protocol, a complete metabolic panel was sent daily, with additional electrolytes as needed. Hypoglycemia was defined as blood glucose <45 mg/dL that was confirmed by a second measurement and/or was symptomatic, thus requiring intervention. Acidosis was defined as carbon dioxide ≤ 16 mmol/L necessitating intravenous rehydration or commencement of sodium citrate. Carbonic anhydrase inhibitors were adjusted based on physician discretion. Development of ketosis was assessed via urine ketones. Urinalysis was done every 8 hours until onset of 4 + ketosis and then monitored every 12 hours. Efficacy of the diet was assessed at 1-month and 3-month follow-up visits. Seizure reduction was classified as 50-90%, $>90\%$, or seizure-free. Those who reported improvement but failed to report a specific percentage were considered to have a $<50\%$ response. In the case of two patients who were seizure-free at baseline and were treated for primary metabolic indications for the ketogenic diet, efficacy was measured as subjective improvement in mental status per parental report.

Primary outcomes analyzed were tolerability, onset of ketosis, length of hospital stay, and efficacy. A χ^2 test was used to compare categorical variables and a two-tailed t test was used for continuous variables. A two-sided P value <0.05 was used to denote significance.

Results

The two groups were similar at baseline (see Table 2 for details). The mean age at the time of initiation of the ketogenic diet amongst all patients was 4.29 ± 3.88 years. Fifteen patients in either group were on the carbonic anhydrase inhibitors topiramate or zonisamide. The severity of epilepsy appeared similar between the groups. Sixty-three percent of patients had a known diagnosis, whereas the remaining had cryptogenic epilepsy; this was similar between groups. Most patients (66.7%) had failed at least two antiepileptic drugs before initiation of the diet (not including antiepileptic drugs given concurrently with the diet) and 86.7% of patients were on two or more