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Original article

Low glycemic index treatment in patients with drug-resistant epilepsy

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Abstract

Objective: Low glycemic index treatment (LGIT) is a newly developed dietary therapeutic option for epilepsy that is less restrictive than the ketogenic diet (KD). Our objective was to determine the efficacy and tolerability of LGIT.

Methods: From March 2014 to February 2015, 36 patients received LGIT at Severance Children's Hospital. One-year seizure outcomes and side effects were evaluated.

Results: A total of 36 patients were assessed. Fourteen were female. Common diagnoses were Lennox-Gastaut syndrome (33%, 12/36) and Dravet syndrome (14%, 5/36). The median age at the initiation of the LGIT was 12.6 years (min. = 1.5, max. = 28, interquartile range (IQR) 8–17). After 3 months of therapy, 20 (56%) patients experienced a 50% or greater reduction in seizure frequency, which was maintained in 19 (53%) patients for 1 year. Two (6%) patients became seizure-free after 3 months of LGIT; they remained seizure-free for 1 year. These two had Dravet syndrome and generalized epilepsy. Only three (8%) patients discontinued treatment within 1 year. Adverse events were rare, and two patients (6%) reported transient diarrhea.

Conclusions: LGIT effectively reduced seizure frequency in the present study, although seizure freedom was infrequently achieved. LGIT may be considered as a therapeutic option for patients with drug-resistant epilepsy, particularly those who find KD effective but intolerable.

Keywords: Low glycemic index treatment; Ketogenic diet; Epilepsy; Children

1. Introduction

The ketogenic diet (KD) is a high-fat, low carbohydrate diet that is an effective treatment option for patients with drug-resistant epilepsy [1–5]. A randomized clinical study showed that 38% of patients had a greater than 50% seizure reduction with three months of KD, while only 6% of patients did with placebo [1]. Therefore, experts have recommended early use of KD for patients with drug-resistant epilepsy [6]. KD is also generally well-tolerated in children of young age, even infants [7]. However, in older children and adults, KD is often poorly tolerated, and KD is rarely considered as a therapeutic option, mostly due to low palatability [8,9]. Recent data suggest that more liberal diets, such as a modified Atkins diet (MAD), may have higher tolerability than KD with comparable efficacy [10,11]. These liberalized KD-resembling diets may be good treatment options and worthy of consideration in older children and adults who cannot tolerate KD [9].

Low glycemic index treatment (LGIT) is the most liberal dietary treatment option developed for epilepsy. LGIT is similar to KD in that it encourages intake of

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fat; it is different from KD in that it allows higher daily intake of carbohydrates and protein. LGIT particularly focuses on stabilizing blood glucose levels by only allowing the consumption of carbohydrates that increase postprandial blood glucose slowly with small fluctuations [12]. Abrupt changes in blood glucose levels are known to reduce seizure threshold [13].

Our goal in this study was to assess whether LGIT shows tolerability and efficacy against epilepsy. We also evaluated which patient groups experience the optimum benefits from LGIT.

2. Materials and methods

Patients who were treated with LGIT at Severance Children's Hospital between March 1, 2014 and February 28, 2015 were included. All patients had drug-resistant epilepsy. Drug-resistant epilepsy was defined as failure of adequate trials with two tolerated, appropriately chosen, antiepileptic drug schedules to achieve sustained seizure freedom [14]. For inclusion, patients had to have drug resistant epilepsy, with seizures occurring more frequently than once per month, and no prior treatment with LGIT. Exclusion criteria included (1) patients who were directly transitioned from KD to LGIT, (2) patients who did not have any seizures for three months prior to LGIT initiation, (3) patients who never started LGIT, despite it being recommended, and (4) patients lost to follow-up. Age was not an exclusion criterion. Patients with previous uses of KD, modified Atkins diet, or a history of epilepsy surgery were not excluded.

Data were obtained by medical chart review. Antiepileptic drug adjustments were allowed, at the physician's discretion, during the diet therapy at 3 months from the day LGIT was initiated. This study was approved by the Institutional Review Board of Severance Children's Hospital (4-2015-0778).

2.1. Dietary protocols

To administer LGIT, we followed the Massachusetts General Hospital protocol that was proposed in 2005 [15]. LGIT was initiated without a fast in the outpatient clinic [16]. Patients were instructed to consume 10% of their caloric intake from carbohydrates, 30% from protein, and 60% from fat. For carbohydrates, patients were instructed to only consume foods with a low glycemic index (GI) of 50 or less. The approved low GI foods ($GI \leq 50$) were selected based on the International Table of Glycemic Index [12]. GI was defined as the incremental area under a blood glucose response curve after consumption of 50 g of carbohydrate, expressed as a percent of the comparative response to the consumption of 50 g of glucose. GI represents the postprandial glucose peak that occurs two hours after consumption of 50 g of carbohydrate, compared with that after consumption of 50 g of glucose [12]. Foods with GI values higher than 50 were restricted. Water intake was not restricted. Individual dietary plans were designed by our dietician [17]. Diets were supplemented with vitamins and minerals. The total caloric intake was determined based on the patient's daily activity, height, weight, and their habitual meal size. Patients received supplemental multivitamins and calcium.

2.2. Efficacy and related factors

The primary endpoint was the number of patients who had a 50% or greater seizure reduction after three months of therapy. Seizure outcomes after 3 months of treatment were assessed. Seizure frequency was compared with the mean seizure frequency that was reported by the children's parents or the patients themselves during the three-month baseline period prior to initiating LGIT. Efficacy was evaluated with respect to reductions in seizures, and patients were assigned to one of the following three groups: (1) seizure freedom, (2) seizure reduction of $\leq$50–99%, and (3) seizure reduction of $<$50%. The number of patients who showed urine ketosis was recorded.

To evaluate factors related to diet efficacy, patients who received LGIT were categorized as (1) good responders or (2) poor responders. Good responders included patients who experienced a 50% or greater reduction in seizures with the diet. Poor responders included patients who experienced a $<$50% reduction in seizures and patients who discontinued the diet before three months due to poor tolerability or side effects. The two groups were compared with respect to the following characteristics: age of seizure onset, age at initiation of the diet, epilepsy duration, epilepsy syndrome, etiology, epilepsy surgery, previous use of KD, and previous use of anti-epileptic drugs.

2.3. Diet tolerability and side effects

Diet tolerability, compliance, and side effects were closely monitored with regularly scheduled assessments according to our epilepsy center diet protocol [18]. The following side effects were assessed: hematuria, acidosis, diarrhea, vomiting, pancreatitis, hypercholesterolemia, hypertriglyceridemia, aspiration tendency, and seizure aggravation. Tolerability was assessed by recording early withdrawal, which was defined as discontinuation of the diet before 3 months.

For laboratory evaluation, complete blood count with platelets, liver function test, renal function test, electrolytes, serum bicarbonate, calcium, and phosphate were collected. Additionally, lipid profiles, urine calcium, creatinine, and urine ketone were assessed. Values obtained at 3 months after the LGIT was initiated were