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Seizure control and biochemical profile on the ketogenic diet in young children with refractory epilepsy—Indian experience

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ABSTRACT

Aim: This study evaluated the efficacy and tolerability of the ketogenic diet (KD) in young Indian children with refractory epilepsy. The changes in biochemical and lipid profile with KD were also assessed.
Methods: Children aged 6 months to 5 years who had daily seizures (or at least 7 seizures/week) despite the appropriate use of at least three antiepileptic drugs were enrolled. KD was introduced using a non-fasting gradual initiation protocol. Seizure frequency, biochemical profile (liver and kidney function tests, fasting lipid profile, and spot urinary calcium–creatinine ratio) and adverse effects were recorded. Patients continuing KD were followed up for a minimum period of 12 months.
Results: Twenty-seven children were enrolled. Non-fasting gradual KD initiation was well tolerated. Eighty-eight percent remained on KD at 3 months, 55% remained on KD at 6 months, and 37% remained on it at 1 year. Intention-to-treat analysis revealed that 48% (13 of 27) had >50% reduction in seizures, and four children (15 %) were seizure free at 6 months. At 1 year, 37% had >50% reduction in seizures and five children (18.5%) were seizure free. Adverse effects included constipation (74%), weight loss (14.8%), edema due to hypo-albuminemia (7.4%) and renal stones (3.7%). Biochemical profile did not reveal significant changes over time, except for reduced serum albumin and increased spot urinary calcium–creatinine ratio.
Conclusion: KD is an effective and well-tolerated treatment option in young Indian children with refractory epilepsy. However, careful ongoing medical supervision is needed.

1. Introduction

Several severe catastrophic epilepsies such as West syndrome, Lennox-Gastaut syndrome and myoclonic-astatic epilepsy present in infants and young children. Seizures in these disorders are difficult to control; sometimes only at the expense of multiple and toxic levels of antiepileptic medications. Epilepsy surgery is not a very beneficial option in this group. The shortcomings of antiepileptic drug therapy and epilepsy surgery have led to the need for alternative treatments. Ketogenic diet (KD) is a medically supervised high fat, low carbohydrate diet that maintains a chronic state of ketosis while providing proteins and calories for adequate growth.[1] The reported effectiveness of KD matches or exceeds that of antiepileptic drugs (AED) in many cases. Past studies have shown that at least 40–50% of children with epilepsy have more than a 50% reduction in seizures when on KD.[1–8]

There is paucity of data on the usefulness of KD in Indian children with epilepsy. Perceived difficulties include doubtful acceptability in a predominantly vegetarian population, unavailability of labelled foods, and unfamiliarity of dieticians with KD. Therefore, this study was planned to assess the feasibility, efficacy, and tolerability of KD in young Indian children with refractory epilepsy. We also assessed the changes in biochemical and lipid profile with KD.

2. Methods

2.1. Patient selection

This prospective open label, uncontrolled, study was conducted in the Pediatric Department of a tertiary care hospital between September 2006 and April 2008. Ethical approval by the institutional ethics committee was obtained. Written informed consent was obtained from the parents. Children aged 6 months to 5 years who had at least 1 seizure/day or 7 seizures/week despite the appropriate use of at least three antiepileptic drugs (AED) including one newer AED were enrolled. Children with known or suspected inborn errors of metabolism, systemic illness, or surgically remediable causes of epilepsy were excluded.

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2.2. Pre-diet preparation

Each child underwent detailed history and examination. Seizure type, frequency, age at onset, perinatal details, family history, developmental status and treatment history were noted. Medications were changed to carbohydrate free preparations, wherever available. Corticosteroids or ACTH were tapered off 2 weeks before starting the diet. The following investigations were obtained at baseline: electroencephalography (EEG), blood urea, serum creatinine, liver function tests (serum bilirubin, serum glutamate oxaloacetate transaminase [SGOT], serum glutamate pyruvate transaminase [SGPT] and serum albumin), fasting lipid profile including total cholesterol, serum triglycerides, low density lipoprotein [LDL], high density lipoprotein [HDL], and very low density lipoprotein [VLDL] and urinary spot calcium–creatinine ratios.

2.3. KD initiation

The children were admitted to the hospital for KD initiation using the non-fasting gradual initiation protocol described by Bergqvist et al.[9] KD was started with a full calorie, ketogenic ratio (ratio of fat:protein + carbohydrate) by weight of 1:1. This was built up over a period of 4 days to 3:1 in children younger than 18 months, and 4:1 in children older than 18 months. The recipes were planned in-house and calculated considering the families and the child's preferences and cultural taboos. Diets were based on Indian recipes and prepared with common locally available foods. Blood sugar was monitored 8 hourly, and urine ketones were checked by Dipstick at every void. The child was discharged by the fourth or fifth day. The AED were continued unchanged.

While the child was hospitalized, training about the calculation of meals, weighing of foods, and the rationale behind the diet was re-inforced. Parents were given diet plans and recipes to be made at home. Each child also received a sugar-free, fat soluble vitamin supplement and calcium supplementation.

2.4. Follow up

Patients were followed up at 1, 2, 3, 6 months and 1 year after KD initiation. Seizure frequency was checked according to parental reports and seizure diaries. The seizure control was categorized as seizure free, >90% seizure reduction, 50–90% seizure reduction, <50% seizure reduction or increase in seizures. Compliance with the diet was checked by parental records of daily urine ketones chart. Adverse effects were noted. The biochemical profile including a fasting lipid profile, and urinary spot calcium–creatinine ratios were tested at each follow up visit. Oral potassium citrate supplementation was started in children with urinary spot calcium creatinine ratio more than 0.2. EEG was obtained at 3 months, 6 months and 12 months after diet initiation.

2.5. Statistical analysis

Data was analysed using SPSS software version 15. The non-parametric two way analysis of variance, i.e. Friedman test was applied to see any change over time for continuous variables. For categorical tests, Chi square test was applied. The level of significance was taken as 0.05.

3. Results

During the study period, parents of 27 of the 41 children found eligible for inclusion were willing for trial (Fig. 1). In 14 patients; the parents were not willing for KD trial. The reasons cited were: feeling that child would find diet too restrictive (6), financial constraints (2), unwilling for hospital admission (2), mother having too much work at home, and unable to spare time for weighing and preparation of meals (2), staying far-off and unwilling for regular follow up (2). Out of the 27 patients included in the trial, 18 were vegetarian. Apart from those with infantile spasms, seizure frequency ranged from 5 to 100/day. Most patients suffered from mixed seizure types (Table 1). All the patients suffered from generalized epilepsy syndromes: the most frequently encountered types being Lennox-Gastaut syndrome (14), West syndrome (6) and myoclonic astatic epilepsy (4). In three patients, the epilepsy syndrome could not be classified, but the predominant seizure type was myoclonic. Multiple AED had been tried (median 5 AED, range 3–11).

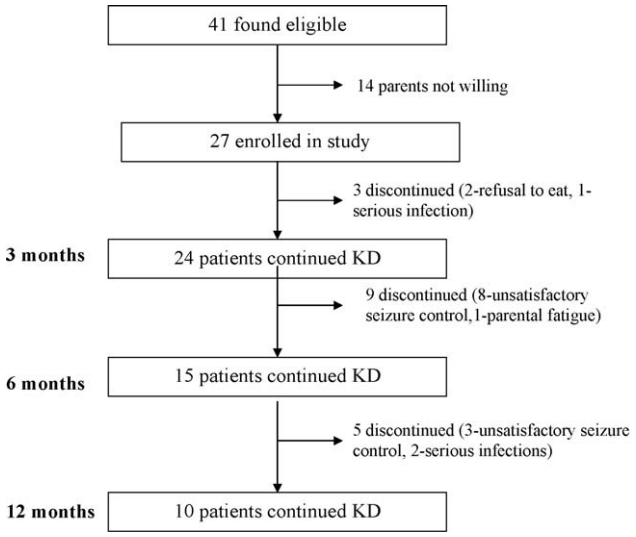

Fig. 1. Flow of patients in the study.

KD initiation was well tolerated. The most common side effect was vomiting, noted in 75% of the patients. No patient developed

Table 1
Demographic and clinical characteristics of the study population ($n = 27$).

Characteristic	Median (range)
Age at first seizure	4 months (15 days to 36 months)
Age at start of diet	2.5 years (9 months to 5 years)
AED tried (no.) before KD institution	5 (3–11)
Characteristic	**Number (%)**
Seizure type[a]	
Myoclonic	17 (62.9%)
Atypical absence	15 (55.5%)
Atonic	7 (25.9%)
Generalized tonic	18 (66.6%)
Infantile spasms	6 (22.2%)
Partial	2 (7.4%)
Generalized tonic clonic	3 (11.1%)
Epilepsy syndrome	
Lennox Gastaut syndrome	14 (51.8%)
West syndrome	6 (22.2%)
Myoclonic astatic epilepsy	4 (14.8%)
Symptomatic generalized epilepsy (unclassified)	3 (11.1%)
Co-morbidity	
Development delay	27 (100%)
Cerebral palsy	17 (62.9%)
Vision impairment	5 (18.5%)
Hearing impairment	4 (14.8%)
Feeding difficulties	9 (33.3%)
Hyperactivity	6 (22.2%)

[a] Most children had mixed seizure types.