RESEARCH PAPER

Ketogenic Diet in Indian Children with Uncontrolled Epilepsy

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Objective: To evaluate the efficacy of the ketogenic diet in Indian children with uncontrolled epilepsy.

Study Design: Prospective observational study.

Setting: Hospital based.

Patients: 105 children (age 4 months to 18 years) with uncontrolled epilepsy enrolled in the ketogenic diet program over a period of 9 years and followed up for 25.7 ± 20.3 months (median:17 months) on the ketogenic diet.

Main outcome measures: Reduction in seizure frequency and comparison of improvement in two main groups of epilepsies, namely epileptic encephalopathies and localization related epilepsies.

Results: Thirty seven (35%) out of 105 children dropped out of the study and 68 remained on the diet. Thirty nine (37%) achieved 100% control, 23 (22%) achieved between 90 and 99% control, 7 (6.8%) achieved between 75 and 90% control, and 16 (15.2%) achieved between 50 and 75% control. Twenty (19%) achieved less than 50% control. Epileptic encephalopathies had a better response than localization related epilepsies.

Conclusion: The Indian version of ketogenic diet used is well tolerated and efficacious in controlling difficult-to-control epilepsy in children. Epileptic encephalopathies respond better than localization related epilepsies

Key Words: *Children, Ketogenic diet, India, Treatment, Uncontrolled Epilepsy.*

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The ketogenic diet has been used in difficult-to-control epilepsy since the 1920s. The diet is used in several countries(1). We present the first Indian version of the classic ketogenic diet. The objective was to fashion a culturally acceptable diet with regional food changes and to determine whether this 'Indianization' would be as successful as the original diet. We also looked at whether a particular type of epilepsy responded better.

METHODS

This was an open, non-blinded, prospective study of 105 consecutive patients (≤18 year age) who had entered the program between 1996-2005. Inclusion criteria were children with difficult-to-control epilepsy as per ILAE guidelines, namely those who had tried a minimum of 2 appropriate first-line anti-epileptic drugs (AEDs) in a maximally tolerated dose and still had a minimum of 2-3 seizures per month(2), and children who had a follow-up of atleast 6 months. Exclusion criteria were inappropriate or ineffective dosage of AEDs, any other serious systemic disease and those living in distant places, thus making regular follow-up difficult. Informed consent was taken from caregivers of all patients. Approval of the Ethics Committee of the Shushrusha Hospital was obtained for the above intervention and the study.

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Patients were enrolled from the Shushrusha Hospital clinic and a private clinic. Total patients assessed for eligibility were 174, of whom 69 were

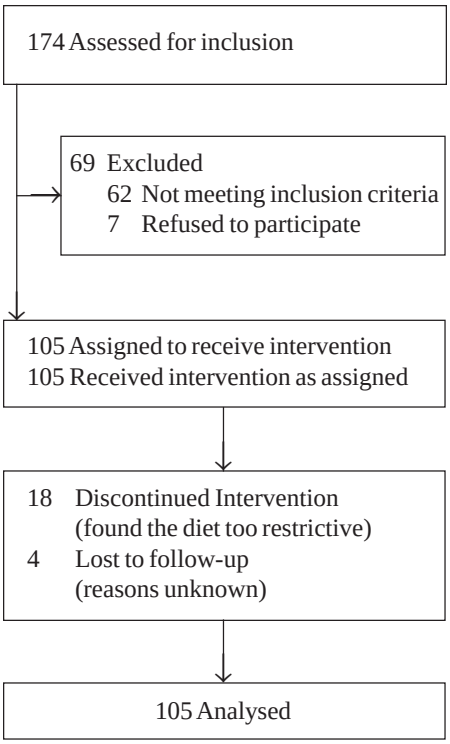

FIG. 1 *Flow of patients in the study.*

excluded. A total of 105 patients were thus included in the study (***Fig.*1**). Duration of follow-up ranged from 6 months to 60 months with an average follow-up of 25.7+20.3 months (median, 17 mo).

We followed the Johns Hopkins Hospital protocol with few changes(3). Detailed counseling was given including a recipe demonstration. The counseling included the scientific basis of the diet, the rigid nature of the diet (only prescribed food could be taken), demonstration of the urine ketone testing and the possible side effects. Sugar-containing medi-cations for any other incidental illness were not allowed. Sugar-free toothpaste was used. Caregivers were taught how to weigh different foods using digital weighing scales. The scales were either bought by parents or provided on loan. Before starting the diet, complete blood count, blood sugar, renal and liver function tests, lipid profile, serum electrolytes, uric acid and urine (routine and microscopic) examination were done. These were repeated every three months in the first year and every six months thereafter. EEG was recorded prior to commencing the diet using the standard 10-20 protocol and repeated at the above intervals. All patients had a prior computed tomography (CT) or Magnetic Resonance Imaging (MRI) of head.

Initially, patients (42 in all) were admitted for four to six days and during the fasting phase of between 2 to 3 days (only water being allowed), blood sugar, vital parameters and urine ketones were checked every four hours. Once urine ketone level reached four plus (4+) (160 mg/dL), they were started on the ketogenic diet. One-third of the calculated calories were given on the first day, two-third on the second and full calories on the third usually on a 4:1 to 3:1 ketogenic ratio. Later, patients (63 in all) were not admitted or fasted due to parental resistance. After a carbohydrate washout (food with only up to 10 grams carbohydrate) and on achieving urine ketone level of 4+, full calories were started at lower ratios.

The ketogenic diet was calculated for each patient individually with 75% of the RDA (Recommended Daily Allowance) calories being given(4). The ketogenic ratio refers to the ratio of the fat amount in grams to the combined protein and carbohydrate amount in grams and initial ratio ranged from 2:1 to 4:1. Protein is given as per the World Health Organization recommendation for the age of the person. To Indianize the diet, we developed a recipe book of 100 Indian meals of different communities. For vegetarians, protein substitutes like soy and whey powder were included. A list of food ingredients was developed with typical Indian foods and their local names. The basic food products like cream, butter and milk and commercial products were sent for macronutrient analysis. An extensive dietetic history was taken including family food habits, taboos and food preferences. Water quota was calculated at approximately 1 mL/calorie. The caregivers maintained a daily urine ketone level chart, the urine being checked 3-4 times a day. A daily seizure chart was maintained. Initially follow-ups were at intervals of two weeks and the calorie and ketogenic ratio fine-tuned to achieve a stable urine ketone level of four plus (4+) throughout the day. At every follow-up the seizure frequency was recorded. Also, the height, weight, urine ketone level and a routine urine examination was noted. After the initial fine tuning, follow-ups were less frequent. Caloric adjustments were made to bring the person

as close to the ideal height and weight as possible (as per Indian Council for Medical Research standards). Water was adjusted to ensure patient passes urine at least 5-6 times per day. If crystals were found in the urine or the patient passed urine infrequently, the water quota was increased.

Statistical analysis

For the purposes of data analysis, the patient data was primarily grouped based on the type of seizure and epilepsy syndrome. The data was classified based on the extent of seizure control in to 5 groups: 100%, 90 to 99%, 75 to 90%, 50 to 75%, and 50% or less seizure control, respectively. The χ^2 test was used to determine whether the differences in the frequency of patients in each of the groups for seizure control were statistically significant. A Pearson's χ^2 test was performed to determine whether the differences in frequency of seizure control were significant across the two largest syndrome groups, namely, Epileptic encephalopathies and Localization related epilepsies. The data on number of antiepileptic drugs (AEDs) received by patients prior to starting the ketogenic diet and post-diet was also analyzed. A paired samples *t* test was performed to compare the difference between the number of medicines pre and post-diet. The data on AEDs was further analyzed to determine the number of patients for whom the AEDs were stopped, reduced or remained the same. A χ^2 test was used to determine if the differences between these numbers were significant. The data was analyzed with the Statistical Package for Social Sciences program (version 12.0) (SPSS, Chicago, IL, USA).

RESULTS

Of the 105 patients, 40 were below 3 years age, 50 were between 3 and 15 years age and, 15 were between 12 and 18 years age. Twelve children had simple partial seizures, 11 had complex partial seizures, 44 had primary generalized seizures, 7 had secondary generalized seizures, 46 had myoclonic seizures and 17 had atonic seizures. Of these, 82 (78%) had mixed types of seizures. Seizure frequency ranged from 2 to 3 per day to 300 per day. Thirty three patients (31%) had tried two AEDs, 35 (33%) had tried three AEDs, 20 (19%) had tried four AEDs and 17(16%) had tried more than four AEDs. Mean number of AEDs tried was 3.67 (±2.94). Twenty-two discontinued the diet after following the protocol for periods from 2 to 10 months and one child after 2 years and 6 months. Those who dropped out after informing us (18) were taken off the diet in a graded manner similar to those who were successfully withdrawn from the diet. Four were lost to follow-up.

Thirty seven (34%) achieved 100% control, 18 (17%) achieved 90 to 99% seizure control, 13 (12%) achieved 75 to 90% seizure control, 10 (9%) had 50 to 75% seizure control, and 31 (28%) achieved seizure control of 50% or less ($P<0.05$). Comparison of the two largest syndrome groups indicated that the differences in frequency of seizure control were significant ($P<0.05$) implying that 100% seizure control was achieved more frequently in epileptic encephalopathies than localization related epilepsies. In contrast, localization related epilepsies showed more frequency of patients with up to 99%, 90%, and 50% seizure control compared to epileptic encephalopathies **(*Table* I)**. The results indicate that patients were on an average of 3.67 (SD, 1.47) medicines prior to beginning of the diet. At the end of the study, the number of medicines reduced to an average of 1.95 (SD, 0.96). The results of the paired samples *t* test indicated that these differences are significant ($P<0.005$). AEDs were stopped for 11 of the patients, while the number was reduced for 70 and remained the same for 23 patients. These differences were found to be statistically significant ($P<0.005$).

TABLE I SEIZURE CONTROL BASED ON EPILEPSY SYNDROME

	Seizure control				
	≤ 50%	50-75%	75-90%	90-99%	100%
Epileptic encephalopathies (*n* = 46)	9	6	5	4	22
Localization related epilepsies (*n* = 53)	16	3	8	13	13

Side effects of the diet were minor and temporary. Seven (7%) had nausea at the onset, 8 (7%) had diarrhea, 41(39%) had temporary constipation, 33(31%) had temporary vomiting, and 2 had steatorrhea. Many had transient trace albuminuria (71%). None had low glucose levels during the fasting phase. Those who achieved 100% control were tapered off the diet over few months; the ratio being slowly reduced by 0.5, every month till they reached 1:1.

DISCUSSION

The ketogenic diet is an alternative therapy useful in difficult-to-control epilepsy. Alhough there has been no double-blind controlled study, numerous studies have prospectively documented the efficacy of this diet. A recent review came to the following conclusion, "The diet's effectiveness in providing seizure control for children with difficult-to-control seizures has remained as good as or better than any of the newer medications"(5).

The responder rate (those with more than 50% decrease in seizure frequency) was 72%. Of these a large proportion had over 90% control (57%) with a significant number becoming seizure free (34%). Our results of seizure reduction are comparable to those achieved in other centers around the world **(*Table* II).** Similar to our results, other studies have also noted that the generalized epilepsies respond better than the focal epilepsies(13).

Side effects in our series were mild and reversible. Nausea seen at the onset was probably due to the high content of fat. Eight had diarrhea and 41 had temporary constipation, which was corrected by increasing the intake of insoluble fiber and the daily water allowance. Thirty-three had temporary vomiting due to either gastroenteritis (usually due to inadequate boiling of water) or deep ketosis. The latter was easily resolved by immediately giving 30-100 mL plain orange juice before each meal and then reducing the ratio. Two had steatorrhea which was resolved by reducing the ratio. Many had transient trace albuminuria. Forty one (39%) had mild crystalluria, usually during the summer season, which was overcome by increasing the water quota.

Problems during the Indianization of the diet included; large percentage of vegetarians; religious taboos with consequential ban on several foods; non-availability of packaged foods; absence or rare labeling of basic foods like milk, butter and cream; wide variety of foods used by Indians in various ethnic and religious categories; frequent non-availability of basic foods like cream, cheese, etc.; over-protection of children with epilepsy; and, interference in diet instructions by relatives. There was difficulty in changing to high fat diet as routine Indian food has higher proportion of carbohydrate (65-70%) and less fat (12%) as compared to American food (40% carbohydrates and 18-20% fat)(14).

TABLE II COMPARISON OF SEIZURE CONTROL IN THE PRESENT STUDY WITH PUBLISHED DATA FROM OTHER CENTERS

Study	Country	No. of Patients	Seizure control				
			<50%	50-75%	75-90%	90-99%	100%
Freeman, *et al*.(6)	USA	150	22%	34%		43%(>90%)	
Batchelor, *et al*.(7)	USA	27	35%	40%	–	–	25%
Hassan(8)	Canada	49	–	67.3%	–	–	12.2%
Francois(9)	France	29	–	41.3%	–	–	–
Kang, *et al*.(10)	Korea	129	27.9%	44.2%	–	–	27.9%
Mak, *et al*.(11)	Taiwan	13	23.1%	23.1%	53.8%	–	–
Kankirawatana(12)	Thailand	32	–	–	–	66.07%	–
Present study	India	105	19%	15.2%	6.8%	22%	37%

WHAT IS ALREADY KNOWN?

- The ketogenic diet is effective in uncontrolled epilepsy.

WHAT THIS STUDY ADDS?

- An Indian adaptation of the ketogenic diet is safe and efficacious in uncontrolled epilepsy.

This study shows that the use of the ketogenic diet is feasible in India and is effective in reducing seizures in those with difficult to control seizures.

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