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ORIGINAL ARTICLE

Efficacy and safety of the ketogenic diet therapy in Pakistani children with refractory epilepsy

Naveed Anjum[1✉], Faisal Zafar[1], Muhammad Yousuf[1,2], Zia-ur-Rehman[1]

1. Department of Paediatric Neurology, The Children's Hospital & Institute of Child Health, Multan, Pakistan
2. Department of Paediatric Medicine, Nishtar Hospital, Multan, Pakistan

Cell # : +92-301-7420615
Email✉ : drnaveedanjum284@gmail.com

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ABSTRACT

OBJECTIVE: To find the effectiveness and tolerability of the ketogenic diet (KD) for Pakistani children with refractory epilepsy.

METHODS: This study was conducted at Child Neurology Department, Children's Hospital & Institute of Child Health Multan, Pakistan. Data of diagnosed patients of refractory epilepsy, not responding to ≥2 antiepileptic drugs (AEDs), were well-tolerated, adequately utilized and received KD treatment from 2017 to 2020 was retrieved and analyzed. Data was analyzed through SPSS-23.

RESULTS: Fifty-five children, including 18 (32.7%) girls and 37 (67.3%) boys, underwent KD initiation phase. Forty (72.7%) children received >2 AEDs. Fifteen (27.3%) children had >17 months' duration of epilepsy. Type of epilepsy was undetermined in 25 (45.5%) cases, 14 (25.5%) had epileptic syndrome & 8 (14.5%) had progressive myoclonic epilepsy. Spasm (n=19, (34.5%), tonic (n=14; 25.5%) and tonic-clonic (n=7; 12.7%) were the commonest types of seizures. Out of 55 patients, 51 (92.7%), 39 (70.9%) & 24 (43.6%) patients continued CD for three, six and twelve months respectively. Seizure-free status at three, six and twelve months was achieved in 29.4% (n=15/51), 28.2% (n=11/39) and 25% (n=6/24) cases respectively. While >75% reduction in seizures at three, six and twelve months was observed in 31.4% (n=16 /51), 33.4% (n=13/39) and 29.1% (n=7/24) cases respectively. Common side effects included anorexia (n=30/55; 54.55%), diarrhea (n=12; 21.82%), kidney stones (n=7; 12.73%), and other side effects like constipation, hypoglycemia, ketoacidosis and gravel (n=6, 10.91%).

CONCLUSION: KD combined with gradual commencement approaches is safe and effective therapy for Pakistani children with refractory epilepsy.

KEYWORDS: Seizures (MeSH); Diet, Ketogenic (MeSH); Children (MeSH), Drug Resistant Epilepsy (MeSH)

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INTRODUCTION

Epilepsy is one of the most prevalent children's neurological disorders.[1] The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as "failure of adequate trials of two tolerated, appropriately chosen antiepileptic drugs (AEDs), whether as mono-therapies or in combination, to achieve sustained seizure freedom".[2] Although drug therapy is currently effective, but 20–30% of childhood epilepsies are not fully recovered or controlled. These uncontrolled epilepsies eventually develop into medically refractory cases.[3] Additionally, revealed that the continuing use of AEDs for refractory epilepsy increased unfavorable responses, such as drug interaction and body-organ damage,[4] rather than considerably reducing convulsions.[5] Due to these factors, special nutritional therapy has emerged as a critical strategy for improving the standard of living of refractory epilepsy patients, particularly in children. Since the initial reports of its therapeutic activity in symptom control were revealed, for children with refractory epilepsy, the ketogenic diet (KD) therapy has regularly been used as an effective and well-tolerated diet therapy.[6] KD therapy has also a positive impact on children's cognition or behavior.[7] The KD composition includes high fat, moderate protein, and low carbohydrates, which leads to metabolic alterations that resemble fasting.[8] The KD has been put into effect in numerous countries so far. Additionally, the KD is believed to have limited toleration in youngsters since it is unpleasant, and its significant antiepileptic impact is still under investigation.[9] Patients with GLUT-1 and pyruvate dehydrogenase complex deficiencies were first treated with KD.[10] Gastrointestinal discomfort, hyperlipidemia, hyperuricemia, hypoglycemia, hypomagnesemia, and hyponatremia are the early-onset adverse effects of KD therapy. Growth failure, iron deficiency anemia, kidney stones, and cardiomyopathy are side effects that can appear later in life.[11] Due to a lack of local data on the KD therapy in refractory epilepsy from Pakistan, this retrospective study was planned to evaluate the efficacy and tolerability of the KD in children with refractory epilepsy, who were previously treated at Neurology Department of Children's Hospital Multan in the Punjab region of Pakistan.

METHODS

This study was conducted at Children's Hospital & Institute of Child Health Multan Child Neurology Department Multan, Pakistan. Data of 55 children with refractory epilepsy, who received KD from January 2017 to December 2020, was retrieved from record of the

Table I: Patient's baseline characteristics

Variables	Characteristics	Numbers (%) (n=55)
Gender	Male	37 (67.3)
	Female	18 (32.7)
Age (years)	> 5	34 (61.8)
	≤ 5	21 (38.2)
Number of antiepileptic drugs	2	15 (27.3)
	> 2	40 (72.7)
Epilepsy etiology	Undetermined cause	25 (45.5)
	Epileptic syndrome	14 (25.5)
	Progressive myoclonic epilepsy	8 (14.5)
	Complex partial seizures	4 (7.3)
	Metabolic disorders	4 (7.3)
Seizure type	Spasm	19 (34.5)
	Tonic	14 (25.5)
	Tonic-clonic	7 (12.7)
	Myoclonic	6 (10.9)
	Absence	4 (7.3)
	Others	5 (9.1)
Duration of epilepsy (At the beginning of KD)	≤ 17 months	40 (72.7)
	> 17 months	15 (27.3)

KD: Ketogenic diet

Table II: Efficacy: a response rate of patients during ketogenic diet

KD Continued		At 1 month (n = 55)	At 3 months (n = 51)	At 6 months (n= 39)	At 12 months (n = 24)
Seizure reduction-responder	Seizure free	16/55 (29.1%)	15/51 (29.4%)	11/39 (28.2%)	6/24 (25%)
	>75% reduction	18/55 (32.8%)	16/51 (31.4%)	13/39 (33.4%)	7/24 (29.1%)
	50–75% reduction	21/55 (38.1%)	20/51 (39.2%)	15/39 (38.4%)	11/24 (45.9%)

Table III: Univariate analysis of factors affecting the response rate of ketogenic diet

KD Continued		Outcome		Test Statistics (X2)	P-value
		Favorable	Unfavorable		
Gender	Male	21	16	3.282	0.02
	Female	11	7		
Age	> 5 Years	25	9	0.016	0.00
	≤ 5 Years	13	8		
Number of AED at KD initiation	≤2	10	5	0.610	0.04
	> 2	22	18		
Duration of KD retention (months)	≤ 6	6	12	6.79	0.00
	> 6	26	11		
Seizure type	Myoclonic	5	1	0.673	0.00
	Tonic-clonic	4	3		
	Spasm	12	7		
	Tonic	8	6		
	Absence	4	0		
	Others	4	1		
Duration of seizure onset to KD initiation ≤ 6 (months)	Yes	19	5	7.707	0.00
	No	13	18		
Duration of seizure onset to KD initiation ≤ 12 (months)	Yes	24	10	5.633	0.01
	No	8	13		

AED: Antiepileptic drugs; KD: Ketogenic diet

hospital. The study was approved by the institutional ethical approval and administrative review committee. Patients did not need to provide explicit consent because the study was retrospective. The Epilepsy Association of Pakistan's guideline[12] recommendations for refractory epilepsy diagnosis and age categories of >5 years and 5 years served as the criteria for inclusion. Patients who stopped responding to at least two AEDs that were well-tolerated, wisely prescribed, and adequately utilized were included. Before starting KD therapy, all patients received these investigations: Electroencephalogram (EEG), urine examination, blood sugar levels, lipid profile, LFT, RFT, electrolytes, and ultrasound of the liver, gallbladder, and spleen. Those who had contraindications were disqualified, as discussed during subject enrolment. At 3 months, a multidisciplinary KD team evaluated the participants. Each patient received a written diet plan from the nutritionist, who also showed the family how to make KD and recorded the patient's blood sugar and ketone values in a diary. We examined each child's clinical file who received KD treatment. The type of seizures, gender, age, and length of epilepsy, the cause of epilepsy, the time between the onset of the first seizure and the start of the KD, and the number of AEDs that failed at the start of the KD were all collected from the health records. We evaluated the clinical efficacy of the diet. As per protocol of the hospital, KD was started at a 1:1 ratio without a fast for inpatients. The diet ratio was gradually increased daily until the patients were given complete calories and a 3:1 diet when sent them home. Parents had the opportunity to ask questions and receive guidance regarding KD through a WhatsApp group created for communication with the attending physicians. Multivitamins, calcium, and vitamin D supplementation were suggested. AED were maintained for the first three months before being changed to accommodate the requirements of the children. Information on the timing of the patient's response to KD treatment and the response rate after one, three, six, and twelve months were gathered via a parental report to evaluate the clinical effectiveness. KD-related symptoms experienced by participants were recorded. Respondents identified as patients with greater than 50% seizure reduction. Statistical analysis was performed via SPSS 23. Frequencies and

percentages were calculated for categorical variables and mean±standard deviation for continuous variables. Pearson Chi-square tests were applied to look at possible influences on the KD's efficacy. At a 0.05 p-value, statistics were declared significant (two-sided).

RESULTS

Fifty-five children, including 37 (67.3%) boys and 18 (32.7%) girls, underwent the ketogenic diet initiation phase. More than two AEDs were given to 40 (72.7%) of children during KD commencement (Table I). Majority (n=25; 45.5%) of patients had idiopathic epilepsy, followed by epileptic syndrome (n=14; 25.5%) and progressive myoclonic epilepsy (n=8; 14.5%). Spasm (n=19; 34.5%), tonic (n=14; 25.5%) and tonic-clonic (n=7; 12.7%) were common types of seizures. More than one type of seizure was observed in 19 (34.5%) patients. Mean duration of the seizure from onset to KD initiation was 14.4 ±11.2 months.

Table II shows the patients' various seizure outcomes. Patients who experienced a reduction in seizures of more than 50% to 75%, continued KD for extended durations of time. At one month, three months, six months, and twelve months, the rates of participants were 100% (55/55), 92.7% (51/55), 70.9% (39/55), and 43.6% (24/55), respectively. At one month, out of 55 participants 29.1% were seizure free, 32.8% had >75% reduction in seizure, and 38.1% shown 50-75% reduction in seizure. When the KD continued, in third months, seizure reduction response rate was fluctuated such as total respondents were 51 and 29.4% were seizure free while 31.4% shown response >75% seizure reduction. At 12 months, only 24 participants continued KD and 25% were seizure free, 29.1% shown response >75% seizure reduction and 45.9% shown 50-75% reduction in seizure.

When all other characteristics were controlled for, univariate analysis showed a significant relationship between the length of KD and the severity of the seizures and a strong relationship between the size of KD and covariates (Table III).

Common side effects included anorexia (n=30/55; 54.55%), diarrhea (n=12; 21.82%), kidney stones (n=7; 12.73%), and other side-effects like constipation, hypoglycemia, ketoacidosis & gravel (n=6, 10.91%).

DISCUSSION

In this study, 55 Pakistani children with refractory epilepsy were evaluated for their response and safety with a ketogenic diet. We researched that 25% of patients on KD at the last contact experienced seizure-free periods, whereas 45.9% experienced seizure reductions of >50%. This is in line with studies done by Baby et al., who reported that the responder rate is 59.4% on KD in kids in South India.[13] The study has done by Lambrechts et al., who reported 50% in the Netherlands in a randomized clinical trial (RCT).[14] A systematic evaluation of eleven studies on seizures showed that 16% of children claimed seizure independence, and 56% reported a seizure decrease of more than 50%.[15] According to another RCT conducted in the UK, 38% of patients experienced a reduction in seizures, more than 50% after three months.[16] Our study's findings are consistent with earlier research, as indicated by responder rates of 39.2% (n=20/51), 38.4% (n=15/39), and 45.9% (n=11/24) respectively, at three, six, and twelve months. Overall 24/55 (43.6%) patients continued KD for minimum one year's duration. According to a comprehensive longitudinal study[17] the retention rate at six and twelve months was 44.8% and 26.4%, respectively. At 6 and 12 months, a further single-center study[18] with 389 Turkish patients revealed a retention rate of 69% and 64%. At six and twelve months, respectively, 70.9 and 43.06% retention rates were reported, which were comparable to other data.[13,19,20] However, the precise moment of KD's beginning has not been advised. Contrary to earlier investigations, the current study demonstrated a strong correlation between epileptic duration and the effectiveness of the KD. Another reason could be that, following earlier research,[21] KD therapy was showing the best results in kids who have the problem of seizures for a short period. Therefore, the early and effective implementation of KD therapy may be a key component of KD effectiveness. In line with the findings of the earlier study,[22] we also discovered that maintaining the diet for longer than six months was related to the seizure control. Additionally, we discovered that 23 cases, or 71.9% of the studied responders, responded to the KD within six months. Only 7 cases, or 21.9%, responded at one year. Similarly, research conducted in Turkey found that 26 individuals (8.2%) unable to respond at 3 months turned out to be responders after twelve months.[23] Parental patience and effort are the most significant factors influencing the continuation of KD. All 55, including patients, completed the starting step and did not show any serious side effects. This is only due to a steadily increased diet ratio. Baby et al., conducted research, and in their case study, KD was started after following a fasting protocol. These patients did not finish the starting phase because of side effects.[13] Additionally, our study's responder rate at the most recent follow-up, 58.2%, was close to that of Baby et al.[13] These findings suggested that gradual initiation techniques may help increase patients' tolerance during the initiation phase. It was helpful to maintain the same efficacy throughout the phase of maintenance. Like earlier research,[24-26] our analysis found evidence of a significant relationship between age, sex, the variety and the types of seizure, and AEDs (Antiepileptic drugs) usage before the onset of the ketogenic diet. Epileptic syndrome and the outcome of seizure also have a relationship. With a few unfavorable outcomes, the diet resulted to be safe to use in the first current trial. Additionally, we discovered in our study that appetite was the most frequent adverse effect, followed by diarrhea and kidney stones. We hypothesized that the CK diet's lack of potassium citrate might be to blame for the negative effects of kidney stones. Therefore, more attention should be to the side effects of KD treatment. Similar to the earlier data, 27 patients (5.5%) who started KD suffered mild nausea and vomiting. One child (1.8%) under 1-year-old who had not fasted beforehand experienced hypoglycemia, a substantially lower rate than in patients who had fasted before beginning the diet.[28] According to a Pakistani study by Mubarak et al.,[29] the ketogenic diet (high in fat and low in carbohydrates) was used in some types and severity of epilepsy

where seizures were drug-resistant. It has proven to be effective in managing all types of epilepsy in individuals of various ages, specifically in children, and it is used as a standard treatment for epilepsy that is refractory. Significant flaws in our study include a low number of patients and the use of only one institution. Nevertheless, to assess the effectiveness and safety of various diets, which may undoubtedly be helpful for those with refractory epileptic seizures, a large-sample study is required. Also, a multicenter prospective study can be more advantageous for future investigations.

CONCLUSION

According to the findings of our study, safe and effective therapy for Pakistani children with refractory epilepsy is a ketogenic diet combined with gradual commencement approaches. If the children can't respond to two adequate AEDs, they should consider the diet immediately. Effective initiation and consistent follow-ups may increase parents' adherence, which is helpful in seizure management.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

NA: Concept and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

FZ & ZuR: Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published.

MY: Acquisition of data, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request