ORIGINAL ARTICLE

Evaluate the Efficacy and Safety of Ketogenic Diet in Patients of Refractory Epilepsy

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ABSTRACT

Objective: To evaluate the efficacy and safety of the ketogenic diet in patients with refractory epilepsy.

Study Design: Prospective interventional study.

Place and Duration of Study: The study was conducted at The Children's Hospital, Lahore from Jan 2020 - Dec 2021.

Material and Method: Children with refractory epilepsy of aged 6 months to 18 years and both genders were included in the study while children with refractory epilepsy who also had hepatic, renal, cardiac issues, and hyperlipidemia and those who refused to take the ketogenic diet after explaining the benefits and side effects of the diet, were excluded from the study.

Results: Out of 50 patients, there was a male predominance (64%). In 48% of patients, the seizure burden reduced to 90% from the baseline. Seventy two percent presented with good compliance. Sixty percent patients presented with no side effects. Among the rest, constipation was the most common side effect. Good seizure control is associated with good compliance and good education status of parents.

Conclusion: Ketogenic diet is a good modality for the treatment of refractory epilepsy but its effectiveness is associated with good compliance.

Key Words: *Ketogenic diet, Refractory epilepsy*

INTRODUCTION

Epilepsy is one of the major neurological health disorders and is more prevalent in developing countries while in developed countries it is 0.5% to 1%.[1] Many comorbidities are associated with drug resistant epilepsy.[2] It is very important to define refractory epilepsy due to the associated risk factors and the failure to achieve seizure control after adequate trials of antiepileptic drugs, its incidence is 7 to 20% in children.[3-5]

Ketogenic diet (KD) is a diet, containing high fat, low carbohydrate and low protein diet which is used as a therapy for the treatment of refractory epilepsy.[6,7] Ketogenic diet helps in the production of ketone bodies and the human body uses ketones as a source of energy rather than carbohydrates.[8] It was first used in 1921 for the treatment of epilepsy. Other than classical ketogenic diet there are various other forms of ketogenic diet like medium chain triglycerides, modified Atkin diet and low glycemic index diet. These are not very strict diet and are easier to use but for better seizure control classical ketogenic diet should be considered.[7,8] Most of the time it was tried in patients who were on five or more

antiepileptic drugs.[9] The history of ketogenic diet is very old, even in Hippocratic era fasting was used as a therapy for the treatment of epilepsy. It also had a documented role mentioned in the Bible.[10] The classical ketogenic diet is used in precise calories and in a ratio of 2:1, 3:1, gradually increased to 4:1, out of these ratios 90% of the energy comes from fats and 10% combined of carbohydrates and proteins.[8,11] The outcome for the use of ketogenic diet for the treatment of refractory epilepsy is found to be good in both children and adults.[12] Ketogenic diet is indicated in GLUT-1 deficiency, pyruvate dehydrogenase deficiency, epileptic encephalopathies (like Dravet syndrome, Doose syndrome etc.).[13,14] While it is contraindicated in primary or secondary carnitine deficiency, pyruvate carboxylase, beta oxidation defects, small, medium or large chain acyl-dehydrogenase deficiency and porphyria.[14,15]

MATERIAL AND METHODS

It was a prospective, interventional study conducted over a period of two years at Pediatric Neurology Department, The University of Child Health Sciences and The Children's Hospital, Lahore from Jan 2020 - Dec 2021.Sampling technique was non-probability purposeful. The study was started after Internal Review Board (IRB) approval with reference no:2021-436-CHICH.

We included both genders of refractory epilepsy between 6 months to 18 years who are on more than three antiepileptics but still having uncontrolled fits. While Children of refractory epilepsy with associated hepatic, renal or cardiac issues, patients of hyperlipidemia and those who refused to take ketogenic diet after explaining the benefits and side effects of the diet were excluded. Total sample size of 50 patients were calculated with 95% confidence interval and 5% margin of error taking prevalence of refractory epilepsy as 7%.Their parents were counselled regarding ketogenic diet using a multidisciplinary approach, involving a pediatric neurologist, a nutritionist and a ketogenic diet staff nurse. The parents were counselled regarding the diet its preparation, how to measure the dietary portion, the associated side effects, monitoring of urinary ketones and blood sugar. The parents were counselled about the duration of the treatment and they were asked to maintain a keto diary to document the seizure frequency, blood sugar levels and urinary ketones. Before the initiation of therapy, the prerequisite detailed investigations including the CBC, liver and renal functions, serum electrolytes, anion gap, urine for ketones, fasting lipid profile, ultrasound abdomen, neuroimaging, EEG, ECG, echocardiography, serum ammonia, serum lactate, serum amino acids and urinary organic acids were carried out. After taking height, weight, BMI of patients we calculated the ketogenic dietary ratios, calories and fluid intake according to the age and weight of the patients. After the preliminary investigations, we started ketogenic diet on outpatient basis. Initially we put the patients on carbohydrate washout diet followed by 2:1, 3:1 and 4:1 after every 2 weeks interval, during this time interval we kept on counselling the parents regarding the maintenance of keto diary. We kept the patients on our regular follow up with the ketogenic team after every 15 days and we asked the parents to maintain a keto diary to document the seizures frequency and maintain the urinary ketones monitoring charts at home and the blood glucose monitoring. On our follow up we monitored the seizure frequency, their growth parameters any side effects. We also monitored the compliance as good or bad after checking the parents' diary containing urinary ketone, blood glucose charting and frequency of seizures and our dietitian assessed the adherence to prescribed dietary ratios in the previous visit.

RESULTS

A total of 50 children with refractory epilepsy were evaluated for the initiation of ketogenic diet. Among them 32 (64%) were male and 18 (36%) were female. Data were analyzed using SPSS version 26. The patients were stratified into 4 age groups at the time of ketogenic diet initiation, as shown in table 1. The majority of patients 22 (44%) were between 5 to 10 years. Sixteen patients (32%) were under 2 years of age, with the youngest being 7 months old.

Parental education was also assessed, and guardians were categorized into three groups: matriculate/intermediate education, graduate, postgraduate. Compliance to ketogenic diet was evaluated during follow up based on seizure control, urine ketone monitoring, parental record keeping, and adherence to prescribed dietary ratios. Compliance was classified as either good or bad as shown in the table 1.

TABLE 1: Demographic details of the study participants: their frequency and percentages.

Demographic details	Frequency	Percentage
Age in years		
<2 years (group 1)	16	32.0
2-5 years (group 2)	10	20.0
5-10 years (group 3)	22	44.0
10 years (group 4)	02	04.0
Gender		
Male	32	64.0
Female	18	36.0
Parental education		
Matric/Intermediate	20	40.0
Graduate	22	44.0
Postgraduate	08	16.0
Compliance		
Good	36	72.0
Bad	14	28.0

The frequency of seizure control was measured in these patients, so they were divided into 3 categories, those having >70% seizure control of seizure, 50-70% seizure control and the last group included patients with <50 % seizure control as shown in table 2

Patients with >50% seizure control were classified as good responders; those with <50% seizure control were labelled as poor responders or non-responders.

A comparison between seizure control and dietary compliance to the ketogenic diet. was performed using t test which showed a statistically significant association (p= 0.003).

TABLE 2: Showing frequency and percentages of seizure control

Seizure control	Frequency	Percentage
<50%	08	16.0
50-70%	18	36.0
>70%	24	48.0
Total	**50**	**100.0**

Safety of ketogenic diet was also assessed. Acute and chronic side effects were noted among patients, 30% and 60% reported no acute or chronic side effects respectively. while 16% patients presented with acute side effects like gastroesophageal reflux, 44% with constipation, 6% with diarrhea and 4% with irritability respectively as shown in (fig.1). In chronic side effects 34% patients presented with weight loss and 6% with hyperlipidemia as shown in (fig.2)

All the side effects were treatable and no serious side effects were noted, none of the patient expired during the study duration.

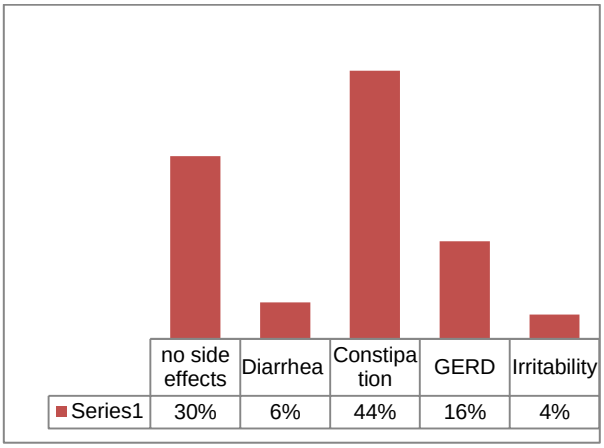

Fig 1: Percentages of acute side effects

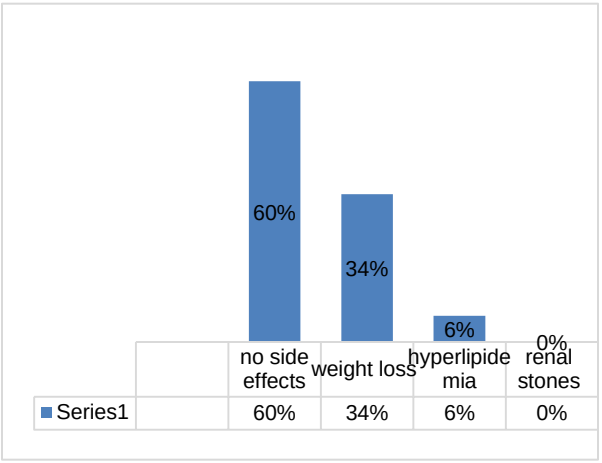

Fig 2: Percentages of chronic side effects

DISCUSSION

In this study we evaluated the efficacy and safety of ketogenic diet in a series of 50 patients who presented with refractory epilepsy in which the seizures were not controlled on more than 3 antiepileptics. The average age of initiation of ketogenic diet in our study was 5-10 years which was very much similar to a study on South Indian children where the median age was 6.16 yr.[15] We have noted that > 70 % reduction has been noted in 52% patients, while another study showed 33.7% patients in which >90% reduction in seizure frequency.[15] Another study done in Pakistan on 55

patients, showed that 25% patients had seizure free period while 29% patients from their study showed >75% seizure control.[16] The tolerance and compliance to the diet was mostly observed on western diet plan of ketogenic diet which will be difficult to transfer the patients on their traditional diet plans.[17] No serious side effects were noted in our study in contrast to a study where diarrhea, lipoid pneumonia and recurrent hypoglycemia was seen[15]. Our study showed constipation as the most commonly occurring minor acute side effect as seen in most of the other studies.[15,18] The role and efficacy of KD has also been studied in adult population for the management of refractory epilepsy and status epilepticus. KD also provides an added benefit in patients with acute status epilepticus.[19] The compliance towards ketogenic diet initiation and maintenance was found good (72%) in our study while the poor compliance was noted in Fang Ye at el which was 45%.[20] Regular monitoring and guidance is mandatory for the proper management of patients.[18.] It is found that good compliance is associated with good control of seizures and better satisfaction of the parents and the care givers

CONCLUSION

Ketogenic diet is a safe and effective treatment for the control of seizures in children having refractory epilepsy.

Conflict of interest: There were no conflicts of interest in our study.

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REFERENCES

1. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. Epilepsy Res 2009; 85(1):31-45.
2. Keezer MR, Sisodiya SM, and Sander Jaw. Comorbidities of epilepsy-current concepts and future perspectives. Lancet Neurol 2016; 15(1):106-115.
3. Berg AT. Identification of Pharmaco resistant epilepsy. Neurol Clin 2009; 27:1003-13
4. Berg AT, et al. Complete remission of childhood onset epilepsy: stability and prediction over decades. Brain 2014; 137:3213-22.
5. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Eng IJ Med 2000 ;342 :314-9
6. Williams TJ, Cervenka MC, The role for Ketogenic diets in epilepsy and status epilepticus in adults. Clinical Neurophysiology Practice. 2017; 2: 161-162
7. Leticia Pereira de Brito Sampaio. Ketogenic diet for epilepsy treatment. Arq.Neuropsiquitr.2016; 74:10
8. Kossoff EH, Zupec-Kania BA. et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia open. 2018 ;3(2):175-192
9. Martin K, Jackson CF. Ketogenic diet and other dietary treatments for epilepsy. Cochrane library 2016
10. Cervenka MC, Kossoff EH. Dietary treatment of intractable epilepsy. Continuum 2013; 19:756-766
11. Rho JM. How does the ketogenic diet induces anti-seizure effects? Neurosci Lett. 2017; 637: 4-10
12. Liu H., Yang Y., Wang Y., Tang H., Zhang Y., et al. Ketogenic diet for treatment of intractable epilepsy in adults: a meta-analysis of observational studies. Epilepsia open 2018;9-17
13. Laux L, Blackford R. The ketogenic diet in Dravet synd. J child Neurol.2013;28(8):104-4
14. Kelly S A, Kossof E H. Doose syndrome (myoclonic astatic epilepsy):40 years of progress. dev Med Child Neurol.2010;52(11):988-93.
15. Baby N, Vinayan K P, Pavithran N, Roy A G. A Programmatic study on efficacy, tolerability and longterm acceptance of ketogenic diet therapy in

74 South Indian Children with pharmacoresistant epilepsy. Seizure. 2018; 58:41-46

16. Anjum N, Zafar F, Yousuf M, Rehman ZU. Efficacy and safety of the ketogenic diet therapy in Pakistani children with refractory epilepsy. KMUJ 2023,vol 15 no.2
17. Nathan Jk, Purandare AS, Parekh ZB, Manohar HV. Ketogenic diet in Indian Children with uncontrolled epilepsy. Indian Pediatr 2009; 46:669-73
18. Yang R, Wen J, Wei W, Chen H et alI. Improving the effects of ketogenic diet therapy in children with drug resistant epilepsy. Seizure: European journal of Epilepsy.2022;94:183-188
19. Williams TJ, Cervenka M C. The role for ketogenic diets in epilepsy and status epilepticus in adults. Clin Neurophysiology Pract;2017; 2: 154–160.
20. 20.Ye F, Li XJ, JiangWL, SunHB and Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: A meta- Analysis. J Clin Neurol.2015;11(1):26-31