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Paediatrics

ROLE OF KETOGENIC DIET AND MODIFIED ATKINS DIET IN REFRACTORY SEIZURE DISORDER- A COMPARISION

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ABSTRACT Epilepsy is a chronic disorder of the brain due to abnormal excitability of neurons. It affects people of all ages, accounting for 1% global disease burden. Most of the Epileptic seizures are usually controlled by antiepileptic drugs, but 30% – 40% of people are resistant to the medications. Such type of patients are considered to have 'Refractory seizure disorder'. The drug-resistant seizure disorder is defined as 'failure of sufficient attempts of two tolerated, properly selected and used antiepileptic drug schedules (as monotherapy or in combination) to attain persistent seizure freedom'. Pharmaco-resistance in epileptic seizure could occur from a range of conditions, such as noncompliance, non-epileptic seizures, inappropriate use of medication, misdiagnosis of the seizure type or epilepsy syndrome and lifestyle issues. For patients who had drug resistance epileptic seizure, alternative treatments like dietary therapy in the form of Ketogenic diet and Modified Atkins diet were considered. The present comparative study aimed at studying the efficacy of dietary therapy (both ketogenic diet and modified Atkins diet) in seizure reduction.

KEYWORDS :

INTRODUCTION

"A Seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive neuronal activity in the brain". It contributes for one percent of global disease burden, depending on disability-adjusted life years, the number of person years lost because of disability and premature death(1).

In about 70% of patients, epileptic seizures were usually controlled by giving medication and the rest 30% – 40% who did not respond to the proper trial of 2 antiepileptic medication, either alone or in combination were diagnosed to have refractory epilepsy (2). Various studies from different parts of the world had found proportion of refractory seizures among patients between 6 to 35%[36]. "Drug-resistant epilepsy is defined as failure of sufficient attempts of two tolerated, properly selected and used antiepileptic drug schedules (whether as monotherapies or in combination) to attain persistent seizure freedom"(7).

Pharmaco-resistance in epileptic seizure could occur from a range of conditions, such as noncompliance, non-epileptic seizures, inappropriate use of medication, wrong diagnosis of the type of seizure and lifestyle issues(2). Medically refractory epilepsy was a major health problem not only for patients and their families, but also for society(2). Early effective interventions would offer the good opportunity for preventing the adverse social and psychological consequences of recurrent seizures, progressive deficits that lead to irreversible disability, and premature death(8).

Dietary therapy in the form of Ketogenic diet or Modified Atkins diet, or complementary and alternative approaches and psychosocial support services are offered by epilepsy centers for refractory seizure disorder patients. (2)Surgical treatment also offers an option for complete freedom for patients who had drug resistance epileptic seizures.

COMPOSITION

Ketogenic diet(KD) was first developed in the 1920's at the Mayo Clinic and Johns Hopkins found to have some efficacy in control of seizures. "The ratio of fats to carbohydrates and protein was 4:1 (classic ketogenic diet) or 3:1 (sometimes used in very young children below 2 years of age and in adolescents)"(6). Ketosis was produced in the hospital or at home and the diet could be maintained from months to years. Around 50% of children could experience control in seizure after dietary changes and benefits might persist even after the diet was stopped(2).

Modified Atkins diet(MAD) was less restrictive in comparison with Classical ketogenic diet and can be initiated on an outpatient basis (9,10). This diet permits about 60% of fat, 30% of protein, and 10% of carbohydrates without fluid or calorie restriction(11). However, Atkins diet was a good therapeutic option for older children and adolescents and much more "liberalized" as compared to ketogenic diet(12,13).

Current study had been planned with the aim of determining the effectiveness of the dietary therapy such as "ketogenic diet and modified Atkins diet" in reducing episodes of seizures in patients with refractory seizure disorder in a tertiary health care center of Pune, India.

MATERIAL AND METHODS

TYPE OF STUDY:

A Comparitive study to assess the effectiveness of dietary therapy in refractory seizure disorder

PLACE OF STUDY:

Dr. DY. Patil medical college, is a multispecialty hospital and research institute located in Pimpri, Pune.

SAMPLE SIZE:

Total of 30 Refractory seizure disorder patients who were fulfilling inclusion criteria were enrolled. Out of them-15 were enrolled in Ketogenic diet and the other 15 in Modified Atkin's diet.

DURATION OF STUDY: August 2016-August 2018

INCLUSION CRITERIA:

- Children with refractory seizure disorder with in the age of 2 years to 13 years, both male and female, were included in the study.
- "(Definition of Refractory Seizure disorder: According to Task Force of the ILAE Commission on Therapeutic Strategies (2010), it is defined as Failure of adequate trials of two or more tolerated and appropriately chosen and used anti-epileptic drugs (whether in monotherapies or in combination), in adequate strength and dosage for a sufficient duration of time to achieve sustained seizure freedom)"
- Patient's whose written informed consent has been obtained.

EXCLUSION CRITERIA

- Patients with confirmed or suspected metabolic disorder like Pyruvate carboxylase deficiency, Beta oxidation defects, Carnitine deficiency.
- Patients who were not willing or not giving consent for study.

INFORMED CONSENT:
The Purpose of the study and the details of protocols were explained to parents and an informed written consent was obtained.

DETAILED METHODOLOGY:
Clinical Assessment
Thirty paediatric patients suffering from refractory seizure disorder, fulfilling the inclusion criteria, were included into present study. Parents or caretakers were explained in detail about the diet and its various outcomes.Detailed history of patients was taken and complete clinical examination was performed as per the structured clinical proforma.

Randomization:
Randomization was done by picking up sealed opaque identical envelopes with odd and even numbered chits placed in them. Patient relatives who picked up odd numbers were given ketogenic diet and even numbers were given Modified Atkins diet

Pre diet counseling period and Investigations:
- During counselling ,various aspects of this dietary therapy including difficulties that could arise, cautious feeding in severely retarted patients, outcome of therapy, efficacy, adverse effects and the realistic goals of the dietary therapy were discussed in detail with parent's or care givers of the patient.
- Parents or care givers were instructed as how to record different types of seizures and how to maintain seizure chart to document the frequency of seizures on daily basis.
- Parents were instructed as how to check urinary ketone bodies of the patient and maintain a record on daily basis.
- All medications and tooth paste to be used should be sugar free.
- All the biochemical parameters including Complete blood picture with platelet count, Liver function tests with serum electrolytes, Total serum protein, Fasting Lipid profile, Vitamin D level with Calcium levels, Anti-seizure drug level(If applicable), Urine analysis should be done. Electrocardiogram (Consider If history of heart disease) ,
- Electroencephalogram (EEG) and Magnetic resonance Imaging (MRI) were also done.

INITIATING THE DIET
Ketogenic diet and Modified Atkin's diet:
- Dietary pattern of the patient including food choices, food habits and customary dietary recall of the patient was obtained from the parent's or guardian.
- Carbohydrate wash out diet: After overnight fasting of 10 to 12 hours 'carbohydrate wash out diet' was started. This diet was very low in carbohydrate (5gram or less than 5 gram) with normal proteins and increased fats. It was given for a span of 3-7 days, in which the patient usually had attained a state of ketoses (4+ ketones in urine).
- On reaching 4+ ketosis, patients were put on calculated Ketogenic diet or Modified Atkins diet.
- Total calorie requirement was considered based on patient's weight, height, ideal body weight, customary dietary recall and calories as per 75% of the RDA (Recommended dietary allowance).
- The keto ratio (Ratio of fat to protein+ carbohydrate) of 2:1 initially, was followed for all the patient's and if the urine ketone levels were not adequately high (less than 4), then the ratio or calories was increased. If the ketones were too high, then ratio was reduced. The calories were dependent on whether the patient was losing or gaining weight.
- For Modified Atkins diet, count of carbohydrate was important. The initial consumption of carbohydrate in MAD was approximately 10-15 gram per day with an increase to 20 gram per day, if possible.
- Use of weighing scale and other equipment's: Weighing scale should be accurate to weigh the food items.
- Patients on KD and MAD must receive multivitamin supplements with minerals (including trace minerals) and calcium preparations with vitamin D. Optional supplements include oral citrates (to prevent kidney stones) and carnitine as indicated.

Follow up's:
Following were noted at every month follow up
- Urine ketone chart: Average urinary ketones of every month were noted
- Height, weight were taken and Ideal Body Weight (IBW) was calculated. If the patient was either underweight as per IBW or losing weight, then we first increase the total daily calories and later ratio was increased if urinary ketosis of 4+ was not maintained.
- Patient's meal timings was checked.
- Seizure control was categorized as a) well controlled group (includes more than 50% control or complete cessation of seizures) and b) Poor control group (includes Uncontrolled Seizures and less than 50% control of seizures).
- Hydration status was assessed in terms of frequency of urine in a day and color of urine.
- Compliance of the patient to diet and accuracy of meal timings was checked.
- Weighing scale accuracy was checked.
- Number of Anti-epileptic drug's and its dosages were checked.

- **Investigations:**
- Urine –routine and microscopy done once in a month to check for any infection.
- Electroencephalogram(EEG) –once in every 3 month's
- Blood test's-including complete blood picture,
- Renal function tests, Liver function tests, Lipid profile, Blood venous gases were repeated once in every 3 months.

DATA ANALYSIS:
- Data was entered in MS Excel spreadsheet.
- It's analyzed with the help of software Open epi and IBM SPSS Statistics version 20.0
- Qualitative data such as Age group of the patients, Gender, EEG activity, urinary ketone level, Biochemical parameters, Seizure control, Number of AEDs requirement, assessed by using descriptive statistics such as frequency, percentage and cross tabulation.
- Chi square test applied to check the statistical association in cross tabulation that made between two qualitative data. “P value < 0.05 was taken as statistically significant”.
- Quantitative data such as values of age, height, weight were expressed in a mean and standard deviation (SD).
- The quantitative data between two groups can be compared by using Independent sample't' test. “P value less than 0.05 taken as statistically significant”.
- Paired sample test was applied for comparing mean values of height and weight at start and end of the study. “P value less than 0.05 was taken as statistically significant”.

RESULTS
1. Age and Gender wise distribution of all patients

Table 1: Age and Gender wise distribution of all patients

Age groups (Years)	Gender		Total (%)
	Male (%)	Female (%)	
0 – 3	4 (26.7)	1 (6.7)	5 (16.7)
4 – 6	8 (53.3)	10 (67.7)	18 (60.0)
7 – 9	3 (20.0)	3 (20.0)	6 (20.0)
10 – 12	0	1 (6.7)	1 (3.3)
Total	15 (100)	15 (100.0)	30 (100.0)

Among male patients (n=15), majority of the patients were 4 – 6 years old (53.3%), followed by 0 – 3 years old (26.7%) and 7 – 9 years old (20%). However, among female patients (n=15), majority of the patients were 4 – 6 years (67.7%), followed by 7 – 9 years old (20%), 0 – 3 years old (6.7%) and 10 – 12 years old (6.7%). (Table 1)

2) Distribution of patients based on Type of diet and Seizure semiology

Table 2: Distribution of patients based on Type of diet and Seizure semiology

Seizure semiology	Type of diet used		Total (%)
	KD (%)	MAD (%)	
Epileptic Spasms	4 (26.7)	4 (26.7)	8 (26.7)
GTCS	2 (13.3)	1 (6.7)	3 (10.0)
GTCS + Epileptic Spasms	4 (26.7)	5 (33.3)	9 (30.0)

GTCS + Myoclonic	1 (6.7)	1 (6.7)	2 (6.7)
Myoclonic + Epileptic Spasms	4 (26.7)	3 (20.0)	7 (23.3)
Atypical absence seizure	0	1 (6.7)	1 (3.3)
Total	15 (100)	15 (100.0)	30 (100.0)

Among the patients who were given ketogenic diet (KD), 26.7% had GTCS + Epileptic spasms, 26.7% had Myoclonic + Epileptic spasms, 26.7% had only Epileptic spasms, 13.3% had GTCS, and 6.7% had GTCS + Myoclonic seizure. However, among the patients who were given Modified Atkins diet (MAD), 33.3% had GTCS + Epileptic spasms, 26.7% had epileptic spasms, 20% had Myoclonic + Epileptic spasms, 6.7% had atypical absence seizure, 6.7% had GTCS, and 6.7% had GTCS + Myoclonic seizure.

3) Distribution of patients based on type of diet and Seizure control.

Table 3: Cross-tabulation of patients based on type of diet and Seizure controlled

Control of seizure		Type of diet used		Total (%)	P value
		KD (%)	MAD (%)		
At 1 month follow up	Poor controlled	15 (100.0)	15 (100.0)	15 (100.0)	----
At 2 months follow up	Well controlled	1 (6.7)	1 (6.7)	2 (6.7)	0.424
	Poor control	9 (60.0)	12 (80.0)	21 (70.0)	
	NA	5 (33.3)	2 (13.3)	7 (23.3)	
At 3 months follow up	Well controlled	4 (26.7)	2 (13.3)	6 (16.7)	0.454
	Poor control	6 (40.0)	7 (46.7)	13 (43.3)	
	NA	5 (33.3)	6 (40.0)	11 (36.7)	
At 4 months follow up	Well controlled	5 (33.3)	5 (33.3)	10 (33.3)	0.246
	Poor control	5 (33.3)	2 (13.3)	7 (23.3)	
	NA	5 (33.3)	8 (53.3)	13 (43.3)	
At 5 months follow up	Well controlled	7 (40.0)	5 (33.3)	12 (40.0)	0.924
	Poor control	1 (6.7)	2 (13.3)	3 (10.0)	
	NA	7 (46.7)	8 (53.3)	15 (50.0)	
At 6 months follow up	Well controlled	7 (46.7)	5 (33.3)	12 (40.0)	0.924
	Poor control	1 (6.7)	2 (13.3)	3 (10.0)	
	NA	7 (46.7)	8 (53.3)	15 (50.0)	

NA: Not applicable – These patients had stopped taking diet

Monitoring of seizure control at every months follow-up. At 1 month follow up among both groups, 100% patients had poor control of seizure.

At 3 months follow up- among the KD group, 26.7% had well control of seizure, 40% had poor control of seizure and 33.3% had stopped taking diet. While among MAD group-13.3% had well control of seizure, 46.7% had poor control of seizure and 40% had stopped taking diet.

At 5 & 6 months follow up among KD group, 46.7% had well control of seizure, 6.7% had poor control of seizure and 46.7% had stopped taking diet. While among MAD group, 33.3% had well control of seizure, 13.3% had poor control of seizure and 53.3% had stopped taking diet.

The relation of control of seizure activity at every months follow up was statistically non-significant between both groups.

4) Distribution of patients based on type of diet and No of AEDs required

Table 4: Cross-tabulation of patients based on type of diet and No of AEDs require

No of AEDs (Anti-epileptic drugs) require		Type of diet used		Total (%)	P value
		KD (%)	MAD (%)		
At 1 month follow up	Same	15 (100.0)	15 (100.0)	30 (100.0)	--
At 2 months follow up	Same	10 (66.7)	13 (86.7)	23 (76.7)	0.195
	NA	5 (33.3)	2 (13.3)	7 (23.3)	
At 3 months follow up	Same	10 (66.7)	9 (60.0)	19 (63.3)	0.705
	NA	5 (33.3)	6 (40.0)	11 (36.7)	
At 4 months follow up	Same	10 (66.7)	6 (40.0)	16 (53.3)	0.260
	Reduced	0	1 (6.7)	1 (6.7)	
	NA	5 (33.3)	8 (53.3)	13 (43.3)	
At 5 months follow up	Same	7 (46.7)	5 (33.3)	12 (40.0)	0.693
	Reduced	1 (6.7)	2 (13.3)	3 (10.0)	
	NA	7 (46.7)	8 (53.3)	15 (50.0)	
At 6 months follow up	Same	6 (40.0)	5 (33.3)	11 (36.7)	0.924
	Reduced	2 (13.3)	2 (13.3)	4 (13.3)	
	NA	7 (46.7)	8 (53.3)	15 (50.0)	

Monitoring was done for number of Antiepileptic drug (AED) requirement at every month's follow-up. At 1 month follow up among both groups, all patients required same no of AEDs.

At 3 months follow up among KD group, 66.7% patients required same no of AEDs and 33.3% had stopped taking diet. While among MAD group, 60% patients required same no of AEDs and 40% had stopped taking diet.

At 6 months follow up among KD group, 40% patients required same no of AEDs, 13.3% required reduced no AEDs and 46.7% had stopped taking diet. While among MAD group, 33.3% patients required same no of AEDs, 13.3% required reduced no AEDs and 53.3% had stopped taking diet.

DISCUSSION

Control of seizure activity after KD and MAD

In current study, At one month follow up there was poor control (includes <50% control of seizures or no control) of seizure in both the groups. At 3 months follow up 26.7% patients in KD group and 13.3% patients in MAD group had well control(includes >50% reduction of seizure or compete cessation of seizure.). At 6 months follow up among KD group, 46.7% had well control of seizure and among MAD group, 33.3% had well controlled seizure. The relation of control of seizure activity at every months follow up was statistically non-significant between both groups. In addition to seizure control parents have also found improvement in alertness,decreased impulsive and aggressive behavior, improved quality of sleep. A study by "Kim et al(14) had found that after 3 months, seizure freedom was achieved in 33% patients in KD group and 25% patients in the MAD group, but the difference between the two groups was not statistically significant. The overall numbers of responders who had >50% and >90% reduction in seizure frequency, or seizure freedom, were consistently higher in the KD group but this difference was statistically non-significant".

"Porta et al(15) had found that after 1 month, 59% children receiving the KD were >50% improved non-significantly as compared to 50% who received MAD. While after 3 months, 64% patients on the KD were improved significantly comparing to 20% with MAD. However, at 6 months, the difference was no longer significant". "Miranda et al(16) had found that at six months follow up among KD group 60% patients had more than 50% reduction in seizure, while 39% patients had more than 50% reduction in MAD group. However, this difference was statistically non-significant". "Kossoff et al(17) had found that 70% patients had at least a 50% seizure reduction after taking MAD, while 70% patients had more than 50% reduction in seizure among KD group".

Requirement of antiepileptic drug (AED)

In present study, among KD group, 6.7% were taking 3 AEDs, 26.7% were taking 4 AEDs, 20% were taking 5 AEDs and 46.7% were taking more than 5 AEDs. However, among MAD group, 40% were taking 3 AEDs, 33.3% were taking 4 AEDs, 13.3% were taking 5 AEDs and 13.3% were taking more than 5 AEDs. Monitoring of AEDs requirement was done at every month follow-ups. Requirement of number of AED was same at 1 month follow up in both groups, while at 3 months 66.7% patients in KD group and 60% patients in MAD group required same number of antiepileptic drugs. However, at 6 months among KD group, 40% patients required same number of AEDs, 13.3% required reduced number of AEDs, while among MAD group, 33.3% patients required same number of AEDs and 13.3% required reduced number of AEDs. The relation of control of seizure activity at every months follow up was statistically non-significant between both groups.

A study by "Kankirawatana et al(104) had found that reduction in number of AED requirement that used by each patients as a result of good control in seizure activity after providing KD". "Kossoff et al(101) had found that 6 patients among KD group and 3 patients in MAD group was able to discontinue Anticonvulsant drug". "Porta et al(98) study no difference in the number of anticonvulsants before and after dietary treatment. The occurrence of convulsive status epilepticus

significantly decreased after the diet initiation."

CONCLUSION

A comparative study conducted in thirty pediatric refractory seizure disorder patients attending tertiary health care center of Pune. These patients were distributed in two groups and provided Ketogenic diet and Modified Atkins diet.

The Follow up and clinical assessment in terms of seizure control was evaluated. In both groups, well control of seizure was achieved at 3 to 6 months of using continuous dietary therapy. The percentage of patients with well control of seizure (more than 50% of seizure reduction) was higher in KD group as compared to MAD group. KD is an effective treatment for refractory childhood seizure disorder, especially in the children who are not candidates for epileptic surgeries. The Modified Atkins diet is less restrictive as compared to Ketogenic diet and a good option in resource constraint settings with limited dietician support. However the response to the diet varies from one individual to other.

In both the groups, few patient's had left the diet. The reasons for withdrawal in KD group, was too much restrictiveness, inadequate response , Poor compliance , Family or financial problems. While in MAD group, reasons for stopping diet were inadequate response, Poor compliance, Family or financial problems.

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