RESEARCH PAPER

Modified Atkins Diet vs Low Glycemic Index Treatment for Drug-Resistant Epilepsy in Children: *An Open Label, Randomized Controlled Trial*

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Objective: To compare the efficacy of the modified Atkins diet (mAD) and low glycemic index treatment (LGIT) among children with drug-resistant epilepsy.

Design: Randomized, open labelled, controlled clinical trial. **Setting**: Tertiary care referral center.

Participants: Children aged 6 months to 14 years with drug-resistant epilepsy.

Intervention: mAD (*n*=30) or LGIT (*n*=30) as an add-on to the ongoing antiseizure drugs.

Main outcome measures: Proportion of children who achieved seizure freedom as defined by complete cessation of seizure at 12 weeks as primary outcome measure. Secondary outcome measures were proportion of children who achieved >50% and >90% seizure reduction at 12 weeks, and adverse effects of the two therapies.

Results: Of the 60 recruited children, 3 in the mAD group, and 3 in LGIT group were lost to follow-up. The proportion of children with seizure freedom [16.6% vs 6.6%; relative risk reduction (RRR) (95% CI), 1.5 (-10.9, 0.5); *P*=0.42] and >90% seizure reduction [30% vs 13.3%; RRR, -1.2 (-5.5, 0.2); *P*=0.21] was comparable between the mAD and LGIT group at 12 weeks. The proportion of children with >50% seizure reduction was significantly higher at 12 weeks among those who received LGIT as compared to the mADgroup [73.3% vs 43.3%; RRR (95% CI) 0.4 (0.1-0.6); *P*=0.03] although the effect size was small. The diet was well tolerated with lethargy being the most common adverse effect in children in mAD (53.3%) and LGIT (66.7%) groups.

Conclusion: The present study with limited sample size shows that seizure freedom at 12 weeks was comparable between mAD and LGIT for the treatment of drug-resistant epilepsy.

Keywords: *Dietary therapy, Efficacy, Ketogenic diet.*

Clinical Trial Registration: CTRI/2017/12/010898

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Ketogenic dietary therapies are useful non-pharmacological therapeutic options in the management of drug resistant epilepsy [1]. Types of dietary therapy for epilepsy include the classical ketogenic diet, modified Atkins diet, low glycemic index treatment, and medium-chain triglyceride diet [2]. The classical ketogenic diet (KD) is high-fat (80%), low protein (15%), and low carbohydrate (5%) diet effective in drug-resistant epilepsy [3-5]. However, KD is a tedious procedure with a need for dietician as it is a stringent diet, requires lot of calculations and weighing of the food items, which makes it challenging to administer in resource-constrained settings. The modified Atkins diet (mAD) is a more liberal, less restrictive, and more palatable type of diet, which yields high compliance and similar effectiveness as compared to classical KD [6-9]. However, compliance, and weighing of food items is a drawback of this diet as well.

The low glycemic index treatment (LGIT) was developed as a liberalized alternative to the KD and mAD for seizure management [10-12]. LGIT diet includes food with a glycemic index less than 50. The LGIT is gaining popularity for treatment for epilepsy due to its effectiveness, mild side effect profile and more palatability. Hence, the present study was designed with a hypothesis that the two groups (LGIT and mAD) would not have a significant difference in seizure control outcome.

Accompanying Commentary: Pages 811-12

METHODS

This open-label, randomized controlled trial was conducted in the Departments of Pediatrics and Neurology of a public sector tertiary-care referral center. The data were collected from February, 2018 to March, 2019. Ethical approval from the institutional ethics

committee was obtained, and a written informed consent was taken from the parents. Children aged six months to 14 years with drug-resistant epilepsy (failure of adequate trials of two tolerated, appropriately chosen anti-seizure drug schedules, whether as monotherapies or in combination to achieve sustained seizure freedom [13]) were enrolled. Children with known or suspected inborn error of metabolism, systemic illness, and severe acute malnutrition were excluded.

Eligible children were randomized to receive either mAD or LGIT along with their ongoing conventional anti-seizure drug. Each child was subjected to clinical history and examination. Seizure type, frequency, age at onset, perinatal details, family history, developmental status and treatment history was recorded. If the child was on any syrup formulation, it was converted to tablets to avoid sugar intake. Adrenocorticotropic hormone (ACTH) and oral steroids (if any) were tapered off two weeks before starting the dietary treatment. A baseline video-electroencephalogram (EEG), whenever possible for a minimum of 1 hour including at least one sleep-wake cycle was performed in all children at the time of enrolment.

Eligible children were randomized using a computer-generated random number list in two groups: mAD and LGIT. Both groups were subjected to baseline one-week observation period, during which parents were asked to maintain a daily seizure log. Anti-seizure medications remained unchanged unless medically indicated, e.g. drug toxicity, or status epilepticus, in which case appropriate changes were made and the same was documented. Children were reviewed as outpatients every two weeks during the trial period. A 24-hour dietary intake chart was reviewed at each visit to compute calorie and carbohydrate intake and to evaluate and reinforce compliance with the prescribed diet. Weight was checked at each visit.

Percentage reduction in seizure frequency as compared to the baseline was assessed as per the parental seizure records. Seizure frequencies were recorded daily by parents. The seizure frequency at 4 weeks and 12 weeks was calculated based on the average of last one week. Based on comparison of these frequencies with baseline one-week frequency, children were classified as seizure freedom, >50% seizure reduction (50-90% reduction) and >90% seizure reduction. Parents were asked to measure urine ketones twice weekly. EEG was repeated at 12 weeks. Tolerability of the diet and any adverse events was evaluated using parental interviews at each visit, specifically asking about vomiting, lethargy, poor appetite, refusal to feed and constipation, in addition to others parental concerns. Liver and renal function tests and fasting lipid profile were performed at baseline and repeated at the end of 4 weeks and 12 weeks.

The sample size was estimated by use of null hypothesis that the two groups would not have a significant difference in seizure control outcome and by defining 30% as the minimum outcome difference of clinical importance. We estimated a sample size of 27 in each group to enable detection of a difference that was significant at 5% with a power of 80%. Assuming 10% drop out, a sample size of 30 was computed in each group.

Statistical analysis: Univariate analysis was done to assess the distribution of data in groups and to choose the appropriate statistical test. The proportion of children with seizure freedom and greater than 50% and 90% seizure reduction were compared between groups using Fisher exact test or Chi-Square test. The effect size was expressed in terms of relative risk reduction (RRR) and 95% confidence interval. For the purpose of RRR calculation, mAD group was considered as intervention and LGIT group was considered as control; achievement of seizure freedom, >90% reduction and >50% reduction were considered as good outcome. An intention to treat analyses was performed. A *P* value of less than 0.05 was considered significant.

RESULTS

Of the 94 eligible participants, finally 30 children

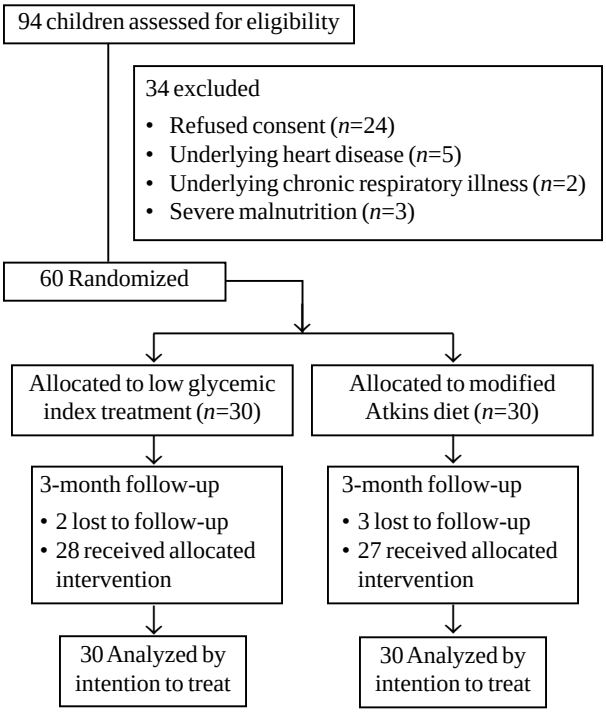

Fig.1 Study flow chart.

received mAD and 30 received LGIT, of which five were lost to follow-up at 12 weeks **(Fig. 1)**. The baseline characteristics were comparable the two groups. (**Table I**), except higher proportion of Microcephaly among children in mAD group (*P*=0.03).

The proportion of children who achieved seizure freedom at 12 weeks was comparable between the two groups (*P*=0.42), and the chance of seizure freedom with mAD was better [RRR (95% CI) = -1.5 (-10.9, 0.5)]. Similarly, the number of children who had more than 90% seizure reduction been also similar between the groups (*P*=0.21), but the proportion of children with 50-90% seizure reduction was significantly higher in LGIT group (*P*=0.03) at 12 weeks (**Table II**). However, the significance of LGIT superiority at 12 weeks needs to be interpreted in context of small effect size [RRR=0.4 (0.1-0.6)].

The diet was well tolerated in both the groups. Lethargy was the most common side effect. Two children in both groups had significant weight loss as compared to baseline and severe respiratory tract infections requiring hospitalization (serious adverse event).

DISCUSSION

The present randomized control study with a limited sample size shows that proportion of children with seizure freedom was comparable between low glycemic index treatment and modified Atkins diet for the treatment of drug-resistant epilepsy. LGIT diet was significantly more effective in achieving >50% reduction in seizure as compared to mAD diet at 12 weeks follow-up; although, with a small effect size (RRR=0.4).

Around 47-56% of patients on LGIT are reported to had achieved more than 50% reduction in seizure frequency [10-12]. In our cohort, 73.3% achieved more than 50% reduction in LGIT group probably because the previous studies were conducted among those with tuberous sclerosis and adults. In a pediatric study from middle east, 78% of children who received LGIT had achieved >50% reduction at the end of 2-month period [14]. The superiority of LGIT at 12 weeks in the present study needs to be interpreted in the context of the small effect size. LGIT in the present study had revealed disappointing results in terms of early seizure control within four weeks, or achievement of seizure freedom or >90% reduction. Most studies have used >50% reduction in seizure frequency as their study outcome instead of seizure cessation [10-12]. The other outcome measure includes percentage change in seizure frequency [15]. Minimal adverse effect profile, good tolerability of diet and efficacy in long term (3 months) are strong points to consider LGIT as an alternative to mAD in achieving seizure reduction [14-15]. However, cessation of seizure in DRE looks unrealistic, and LGIT does not promise to deliver the same.

Table I Baseline Characteristics of Children With Drug Resistant Epilepsy (*N*=60)

	Modified Atkins diet (n=30)	*Low glycemic index treatment (n=30)*
Age (mo)[a]	30 (12,60)	24 (23.5,51)
Male gender	22 (73.3)	25 (83.3)
Age at onset of epilepsy (y)[a]	0 (0, 3)	0.5 (0, 3)
Type of seizure [b]		
Tonic clonic	14 (46.7)	19 (63.3)
Epileptic spasms	13 (43.3)	9 (30)
Myoclonic	0	2 (6.7)
Focal	2 (6.7)	0
Neonatal problems	21 (70)	17 (56.7)
Birth asphyxia	11 (52.4)	15 (88.2)
Meningitis	6 (28.6)	2 (11.8)
Hyperbillirubinemia	1 (4.7)	0
Hypoglycemia	3 (14.2)	0
Microcephaly[c]	16 (53.3)	7 (23.3)
EEG findings		
Multifocal epilepsy	17 (56.7)	24 (80)
Hypsarrhythmia	11 (36.7)	6 (20)
LGS	2 (6.7)	0

EEG: Electroencephalography; LGS: Lennox-Gestaut syndrome; Data in no. (%) except [a]median (IQR); [b]Focal to bilateral tonic clonic one child in modified Atkins diet group; All P>0.05 except [c]P=0.03.

Table II Seizure Freedom and Adverse Effects Among Children With Drug Resistant Epilepsy

Outcome measure	*Modified Atkins diet (n=30)*	*Low glycemic index treatment (n=30)*	*RRR (95% CI)*
Seizure freedom[a]			
12 wk	5 (16.6)	2 (6.6)	-1.5 (-10.9-0.5)
50-90% seizure reduction			
4 wk[b]	19 (63.3)	7 (23.3)	-1.7 (-4.5, -0.3)
12 wk[c]	13 (43.3)	22 (73.3)	0.4 (0.1,0.6)
>90% seizure reduction[a]			
12 wk	9 (30)	4 (13.3)	-1.2 (-5.5, -0.2)
Adverse effects			
Lethargy	16 (53.3)	20 (66.7)	0.2 (-0.2, -0.5)
Constipation	15 (50)	9 (30)	-0.6 (-2.2, -0.1)
Vomiting	5 (16.7)	3 (10)	-0.7 (-5.4, -0.6)
Severe adverse effect	2 (6.7)	2 (6.7)	0 (-5.6, -0.8)

[a]None of participants achieved seizure freedom or >90% seizure reduction at 4 weeks. P<0.01; [c]P=0.03. RRR: Relative risk reduction.

WHAT IS ALREADY KNOWN?

- Modified Atkins diet is an efficacious and less restrictive alternative to ketogenic diet for management of drug-resistant epilepsy.

WHAT THIS STUDY ADDS?

- Proportion of children with seizure freedom was comparable between low glycemic index treatment and modified Atkins diet for the treatment of drug-resistant epilepsy.

Proportion of children with more than 50% reduction dropped from 63.3% at 1-month to 43.3% at 3-month in the present study. In contrast, previous studies have revealed slightly better efficacy (52-68%) [6-9] of mAD at 3-month follow-up. Although reported compliance with diet was satisfactory in the present study, it is difficult to provide an alternative explanation for marginally reduced efficacy of mAD and drop of efficacy from 1-month to 3-month follow-up. Studies have demonstrated efficacy of mAD to a tune of 45.5% at 6-month follow up [16]. We enrolled children with drug-resistant epilepsy and defined the same as failure of two adequate and appropriate anti-seizure medication. There has been lot of variation in the study inclusion in other studies. Many have used terms like medically intractable epilepsy [10], and many have adopted failure of three anti-seizure medication as their inclusion criteria [14]. Most children in present study were in the age group of 30 months in both the study groups. This means that we had included younger children with drug-resistant epilepsy. Many of them are either West syndrome or those progressing to Lennox Gestaut syndrome as evident from the type of seizure and their EEG findings. The adverse effect profile and frequency was similar to previous report [7-9].

A recent Indian study [15] compared mAD, LGIT and KD in a three-armed controlled trial. The study was conducted among 152 participants aged between 1-15 years with intractable epilepsy. They did not find any significant difference in seizure reduction at 24 weeks in the three groups. Nonetheless, patients on LGIT demonstrated >50% seizure reduction with a better safety profile [15]. Authors had considered percent seizure reduction as outcome measure limiting the comparability of findings to present study, but both have demonstrated comparable efficacy of mAD and LGIT.

Standardized definitions of drug-resistant epilepsy, and outcome parameters including seizure freedom, and more than 50% reduction in seizure were adopted to allow comparability of the results. Limitations of the study include small sample size, relatively short follow up period till three months, and lack of formal developmental and cognitive assessment. In addition, serial EEGs were not performed in the study to document improvement in the burden of epileptiform discharges. We did not find a statistically significant difference between mAD and LGIT in seizure freedom among children with drug resistant epilepsy. Numerical superiority of LGIT over mAD at 12 weeks for achieving >50% seizure reduction needs to be interpreted in the context of limited sample size, short follow up period and small effect size. Further multicenter randomized controlled trials may be considered with larger sample size and longer follow-up period.

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