FULL-LENGTH ORIGINAL RESEARCH

Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy

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Summary

Objective: We aimed to compare the efficacy, safety, and tolerability of a modified Atkins diet (MAD) with the classic ketogenic diet (KD) for the treatment of intractable childhood epilepsy.

Methods: From March 2011 to March 2014, 104 patients aged 1–18 years who had refractory epilepsy were randomly assigned to each diet group (ClinicalTrials.gov, number NCT2100501). A seizure diary record was used to compare seizure frequencies with the baseline prediet seizure frequency at the third and sixth months after diet therapy initiation.

Results: Fifty-one patients were assigned to the KD and 53 patients to the MAD. The KD group had a lower mean percentage of baseline seizures compared with the MAD group at 3 months (38.6% for KD, 47.9% for MAD) and 6 months (33.8% for KD, 44.6% for MAD), but the differences were not statistically significant (95% confidence interval [CI] 24.1–50.8, p = 0.291 for 3 months; 95% CI 17.8–46.1, p = 0.255 for 6 months). Instead, for patients aged 1–2 years, seizure outcomes were consistently much more favorable in patients consuming the KD compared with those consuming the MAD. The rate of seizure freedom at 3 months after diet therapy initiation was significantly higher (53% for KD, 20% for MAD, p = 0.047) in these patients. The MAD had advantages with respect to better tolerability and fewer serious side effects.

Significance: The MAD might be considered as the primary choice for the treatment of intractable epilepsy in children, but the classic KD is more suitable as the first line of diet therapy in patients <2 years of age.

The ketogenic diet (KD) is an established treatment for drug-resistant childhood epilepsy.[1] However, it is difficult to implement in pediatric patients because its dietary regimen is too restrictive and causes worrisome side effects.[2] A more balanced and easily applied alternative dietary therapy in the form of a modified Atkins diet (MAD) has been utilized widely in these patients.[3,4] Results of numerous prospective and retrospective pilot studies have also indicated that the MAD is as effective as the classic KD for the control of intractable seizures.[5–7] However, some studies have found that the classic KD has an overall superior response rate.[5,8] For this reason, a randomized comparison between the two regimens is needed to aid physicians in making a more informed decision.

The objective of this study was to perform a randomized, comparative investigation of the efficacy, safety, and tolerability of the classic KD compared with the MAD.

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Methods

Study design

The study was designed as a randomized clinical trial (ClinicalTrials.gov, number NCT2100501). The primary end point was set as the determination of superior efficacy

Key Points

- The KD group had a lower mean percentage of baseline seizures compared with the MAD group, but the difference was not statistically significant
- For patients aged 1–2 years, the mean and median seizure frequencies in the KD group were significantly lower ($p = 0.008, 0.036$)
- The complication of hypercalciuria was presented more frequently in the KD group compared with the MAD group ($p = 0.004$)
- The MAD might be considered as the primary choice for treatment, but the classic KD is more suitable as the first line of diet therapy in patients <2 years of age

in seizure control between the classic KD and the MAD among children with drug-resistant epilepsy. The study sample consisted of a subset of patients who visited our tertiary epilepsy center from March 2011 to March 2014. Enrollment criteria included patient age in the range of 1–18 years, seizure frequency >4 seizures per month, and treatment failure of ≥2 prescribed antiepileptic drugs. The exclusion criteria included a history of previous dietary therapy, a history of hyperlipidemia, renal calculi, or any other medical conditions incompatible with dietary therapy. SAS PROC PLAN software (Statistical Analysis System [SAS] Version 9.2 Korean Edition Licensed to YONSEI UNIVERSITY, Site 0010503187; SAS Korea, Seoul, Korea) was used to generate a list of random numbers based on stratified permuted block randomization. A minimization method was used to ensure that the treatment groups among the three defined age-groups (1–2 years, 2–6 years, and 6–18 years) were balanced. Clinical study approval was obtained from the ethical clinical trial committee of Severance Hospital and the Severance Hospital Institutional Review Board. Written informed consent was obtained from the parents of all enrolled patients.

Procedures

Independent medical personnel blinded to the identity of the patient and the selected diet randomly allocated each patient to the KD or the MAD groups. Patients began the dietary therapy after a 4-week baseline period during which no changes were made to their previous therapeutic regimens. All enrolled patients were initially hospitalized to begin their respective diets, and were kept until they were adequately adapted to the diet. All patients in the KD group received dietary therapy with a 4:1 lipid to nonlipid ratio and nonfasting initiation protocol.[9] MAD group patients followed the Johns Hopkins protocol.[10] Carbohydrates were restricted to 10 g/day for the first month, and permitted to increase by only 5 g/day up to 10% carbohydrate by weight with an interval of at least 1 month. Unlike the Johns Hopkins protocol, however, calories were recommended to be restricted to 75% of recommended daily intake. Instead, patients with excessive lethargy were allowed a 100-calorie addition during the first 3 months of therapy. Other than that, all patients in both groups were supplemented with multivitamins, calcium at a dose of 30 mg/kg/day, vitamin D2 at a dose of 40 IU/kg/day, and L-carnitine at a dose of 66 mg/kg/day throughout the course of diet. Screening and follow-up examinations were performed according to the 2004 and 2005 Kang et al. protocols.[2,11]

All enrolled patients were assessed at the outpatient clinic during the 4-week baseline period, and at 1, 3, and 6 months after discharge. A seizure diary was recorded, and seizure frequency was compared at every visit with the baseline, prediet seizure frequency. The mean seizure number at a specific time point was calculated from the number of seizures at that particular time point and the number of seizures 4 weeks prior to that point. The results were expressed as a percentage of the mean baseline number of daily seizures. The proportion of responders who had >50% reduction in seizures, >90% reduction in seizures, and seizure freedom was analyzed using intention-to-treat criteria in both groups. The primary end point variables have been analyzed by intention-to-treat criteria. Patient compliance and presence of possible complications were also assessed at every visit. Antiepileptic drugs were maintained for 3 months without changes, and then dosages were reduced once in seizure-free patients.

Statistical analysis

This trial was designed as a comparative test to test the hypothesis that the classic KD might be more effective than the MAD. We used the results from a previous randomized controlled trial of the classic KD[1] to develop the null hypothesis that there would be no statistically significant difference in seizure control outcome between the two groups. We defined the clinically important minimum outcome difference to be a 25% reduction in seizure frequency. The estimated sample size for a comparison of two means was 47 patients per group to enable the detection of a difference significant at 5% with a power of 90%. The calculation was based on an expected outcome range of mean percentages of baseline seizures from 0% to 150% (standard deviation [SD] 37.5%). A sample of this size could detect a ≥25% difference in mean percentage of baseline seizures between the groups. Any difference greater than this would be regarded as clinically significant.

The mean percentages of baseline seizures between the KD and MAD groups at 3 and 6 months were compared using unpaired *t*-tests and Mann-Whitney *U* tests. Multiple linear regression analysis was used to assess the association between diet and the percentage of baseline seizures. The analysis included two seizure groups (epilepsy syndromes with generalized or focal seizures as well as focal seizures only, with or without secondary generalization),

two etiology groups (structural/metabolic and unknown), and the three age-groups (1 to <2 years, 2 to <6 years, and 6–18 years). The proportions of patients who showed greater than 50% or 90% seizure reduction and seizure freedom, were also compared between the two groups using the Fisher's exact test and the chi-square test. Spearman's correlation coefficient test was used to assess the associations between serum β-hydroxybutyrate level and seizure frequency. A p-value < 0.05 was considered to indicate a statistically significant result.

Results

Patients

Finally, 104 patients were randomly assigned to one diet group and 51 patients to the classic KD, and 53 patients to the MAD, group. The results for the baseline patient characteristics at enrollment are presented in Table 1. The mean age at seizure onset was 2.1 (±2.5) years in the KD and 2.4 (±3.1) years in the MAD groups. The mean age at the beginning of dietary therapy was 4.9 (±4.0) years in the KD group and 4.8 (±4.0) years in the MAD group. The mean seizure frequency was 4.6 times per month (4.2 in the KD group and 5.1 in the MAD group) and the mean number of antiepileptic medications was 3.0 (3.1 in the KD group and 3.0 in the MAD group).

Table 1. Baseline demographic characteristics of the patients allocated to each diet group

	Classic KD group (n = 51) (%)	MAD group (n = 53) (%)	p-Value
Sex			
Male	32 (63)	26 (49)	0.245
Female	19 (37)	27 (51)	
Age			
1 to <2 years	17 (33)	20 (38)	0.136
2 to <6 years	16 (31)	17 (32)	
6–18 years	18 (35)	16 (30)	
Seizure type			
Tonic	8 (16)	9 (17)	1.000
Tonic–clonic	4 (8)	2 (4)	0.432
Myoclonic	4 (8)	3 (6)	0.713
Atonic	2 (4)	1 (2)	0.614
Epileptic spasms	12 (24)	16 (30)	0.511
Focal	21 (41)	21 (40)	1.000
Epilepsy syndromes			
LGS	10 (20)	8 (15)	0.610
West syndrome	8 (16)	12 (23)	0.458
MAE	1 (2)	1 (2)	1.000
Dravet syndrome	2 (4)	4 (8)	0.678
Epilepsy unspecified	30 (59)	28 (53)	0.560
Etiology			
Structural/metabolic	23 (45)	26 (49)	0.699
Unknown cause	28 (55)	27 (51)	0.699

KD, ketogenic diet; MAD, modified Atkins diet; LGS, Lennox-Gastaut syndrome; MAE, myoclonic astatic epilepsy.

Complete data were available from 86 patients (39 from the KD group and 47 from the MAD group) at the 3-month follow-up. Complete data from 70 patients (34 from KD group, 36 from MAD group) were available at the 6-month follow-up. A total of 34 patients dropped out during the study (17 from KD group, 17 from MAD group) (Fig. 1).

Efficacy

At 3-month assessment, the KD group had 38.6% of baseline seizure frequency and the MAD group had 47.9% of baseline seizure frequency. At 6 months, the percentage was 33.8% in the KD group and 44.6% in the MAD group (Table 2). At 3 and 6 months, the KD group had a somewhat lower mean percentage of baseline seizures compared with the MAD group, but the differences were not statistically significant (95% confidence interval [CI] 24.1–50.8, p = 0.291 at 3 months, 95% CI 17.8–46.1, p = 0.255 at 6 months). Table 3 presents the results for the proportions of patients who achieved >50% and >90% reduction in seizure frequency, and for patients who achieved seizure freedom after 3 and 6 months. After 3 months of diet therapy, seizure freedom was achieved in 17 patients (33%) in the KD group and 13 patients (25%) in the MAD group, but the difference between the two groups (p = 0.374) was not statistically significant. The differences in the proportions of patients with >50% and >90% seizure reduction were also not statistically significant between the two groups (p = 0.527 for >50%; p = 0.314 for >90%). However, the overall numbers of responders who had >50% and >90% reduction in seizure frequency, or seizure freedom, were consistently higher in the KD group. We could also find this trend after 6 months of diet therapy.

The results for additional comparisons of efficacy between the two groups according to seizure type, epilepsy diagnosis, etiology, and age are presented in Tables 2, 3, and S1–S3. The analysis revealed that for patients aged <2 years, the mean and median baseline seizure frequencies in the KD group were much lower compared with the MAD group. This difference was not present in older patients. The difference in median value at 6 months after diet therapy initiation was statistically significant (interquartile range [IQR] 0–0, p = 0.036). Moreover, seizure freedom was achieved in 9 (53%) of 17 patients in the KD group and 4 (20%) of 20 patients in the MAD group after 3 months of diet therapy. The rate of seizure freedom was significantly higher in the patients consuming the KD (p = 0.047). This trend also occurred in patients with West syndrome (CI 95% 1.8–45.2, p = 0.126), but the result was not statistically significant.

Withdrawal and side effects

Nineteen patients from the KD group and 22 patients from the MAD group were withdrawn from dietary therapy at the 6-month follow-up. Six of (14%) the 51 patients who

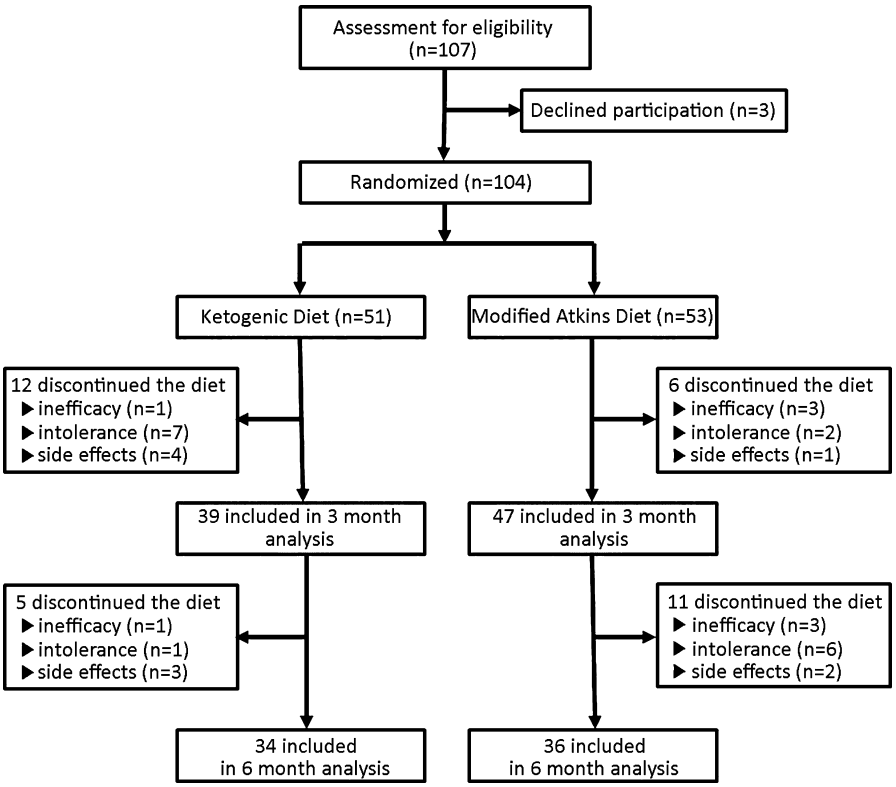

Figure 1.
The trial profile. Patient disposition by diet group.
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were allocated to the KD group failed to continue the diet due to life-threatening or disabling side effects. Three of these patients dropped out because of persistent metabolic acidosis: two patients due to development of serious infection, one due to renal calculus formation, and one due to development of osteoporosis. Only 3 (6%) of the 53 patients allocated to the MAD group dropped out due to serious side effects. Serious infection developed in two of these patients and an allergic reaction to food occurred in one patient. Intolerance and inefficacy were the other reasons for discontinuation. Eight patients (16%) in the KD group and eight patients (15%) in the MAD group withdrew due to intolerance. Two patients (4%) in the KD group and 6 patients (11%) in the MAD group withdrew because of limited or negative efficacy (Fig. 1).

The most common early (within 3 months of the diet) and late- (after 3 months of the diet) onset complications were gastrointestinal (GI) disturbances, and other notable side effects were lack of energy, hyperuricemia, dyslipidemia, infection, and metabolic acidosis, all of which presented similarly in both groups. Hypercalciuria was the only complication that presented more frequently in the KD group than in the MAD group. It occurred during the early and late periods of diet therapy ($p = 0.004$ during the first 3 months; $p = 0.085$ during the last 3 months). Renal calculus formation and osteopenia were also more frequent in the KD group during the late period of diet therapy ($p = 0.069$) (Table 4).

Blood ketosis

Table 5 presents the results for the mean serum β-hydroxybutyrate ketosis levels in patients at 3 and 6 months after initiation of dietary therapy. Mean blood ketosis level was higher in the KD group (67.4, SD 45.2 at 3 months; 72.9, SD 50.4 at 6 months) than in the MAD group (62.0, SD 48.3 at 3 months; 66.8, SD 48.0 at 6 months), but the difference in mean ketosis between the two groups was not statistically significant ($p = 0.165$ at 3 months, $p = 0.727$ at 6 months). The results for blood ketosis level measured at each visit correlated with seizure reduction were also not statistically significant ($p = 0.575$ at 3 months, $p = 0.631$ at 6 months).

Discussion

Our study revealed that the classic KD did not have definite advantage over the MAD in terms of efficacy. Instead, the MAD had advantages with respect to better tolerability and fewer serious side effects. We also found that the classic KD was superior to the MAD in producing more favorable seizure outcomes among patients aged <2 years. Similar to previous randomized trial,[1,4,12] however, our study was also limited in that it included an unblended design, and was missing masked outcome assessment. Our use of parental seizure records increased the risk of subjective errors. A pre- and postobjective long-term video–electroencephalography (EEG) assessment would have been the best method

Table 2. Percentage of baseline seizures in each diet group at 3 and 6 months of diet therapy, and percentage of baseline seizures by age

	Total			Ages								
				1 to <2			2 to <6			6–18		
	Classic KD	MAD	p-Value	Classic KD	MAD	p-Value	Classic KD	MAD	p-Value	Classic KD	MAD	p-Value
3 months after DT	n = 39	n = 47		n = 13	n = 17		n = 12	n = 16		n = 14	n = 14	
Mean percentage of baseline seizure (95% CI)	38.63 (24–51%)	47.93 (35–60%)	0.291	19.21 (−1–40%)	46.18 (25–68%)	0.070	32.10 (4–55%)	39.43 (15–64%)	0.675	59.62 (37–82%)	58.20 (36–80%)	0.916
Median percentage of baseline seizure (SD, IQR)	24.95 (42, 0–75%)	50.00 (42, 0–100%)	0.286	0.00 (34, 0–38%)	50.00 (42, 0–100%)	0.059	5.00 (43, 0–88%)	10.00 (46, 0–100%)	0.631	62.50 (38, 21–100%)	62.50 (38, 30–100%)	0.839
6 months after DT	n = 34	n = 36		n = 10	n = 14		n = 11	n = 13		n = 13	n = 9	
Mean percentage of baseline seizure (95% CI)	33.84 (18–46%)	44.62 (32–61%)	0.255	0.00 (−1–3%)	39.73 (16–63%)	0.008*	32.03 (4–56%)	44.34 (20–69%)	0.675	55.75 (31–80%)	61.05 (25–97%)	0.776
Median percentage of baseline seizure (SD, IQR)	10.00 (40, 0–63%)	37.50 (43, 0–100%)	0.596	0.00 (3, 0–0%)	25.00 (40, 0–75%)	0.036*	10.0 (39, 0–63%)	37.5 (43, 0–100%)	0.508	50.00 (39, 13–100%)	75.00 (47, 0–100%)	0.792

KD, ketogenic diet; MAD, modified Atkins diet; DT, diet therapy.

Table 3. The proportion of responders at 3 and 6 months of diet therapy and the proportion by age

	Total			Ages								
				1 to <2			2 to <6			6–18		
	Classic KD (51) (%)	MAD (53) (%)	p-Value	Classic KD (17) (%)	MAD (20) (%)	p-Value	Classic KD (16) (%)	MAD (17) (%)	p-Value	Classic KD (18) (%)	MAD (16) (%)	p-Value
3 months after DT												
Seizure-free	17 (33)	13 (25)	0.374	9 (53)	4 (20)	0.047*	6 (38)	7 (41)	1.000	2 (11)	3 (31)	0.385
>90% reduction in seizures[a]	19 (37)	17 (32)	0.314	9 (53)	5 (25)	0.101	7 (44)	9 (53)	0.968	3 (17)	3 (19)	1.000
>50% reduction in seizures[b]	22 (43)	22 (42)	0.527	10 (59)	8 (40)	0.191	8 (50)	10 (59)	0.999	4 (22)	4 (25)	1.000
6 months after DT												
Seizure-free	16 (31)	12 (23)	0.461	9 (53)	5 (25)	0.101	4 (25)	4 (24)	1.000	3 (17)	3 (19)	1.000
>90% reduction in seizures[a]	19 (37)	16 (30)	0.474	10 (59)	7 (35)	0.194	6 (38)	6 (35)	0.736	3 (17)	3 (19)	1.000
>50% reduction in seizures[b]	20 (39)	19 (36)	0.321	10 (59)	9 (45)	0.515	6 (38)	7 (41)	1.000	4 (22)	3 (19)	1.000

DT, diet therapy; KD, ketogenic diet; MAD, modified Atkins diet.
[a]Includes children who reported seizure-free.
[b]Includes children who reported >90% seizure reduction and seizure-free.
*p-Value < 0.05, statistically significant.

Table 4. Reported side effects in each diet group during the early 3 months and late 3 months of diet therapy

	3 months after DT			6 months after DT		
	Classic KD (n = 39) (%)	MAD (n = 47) (%)	p-Value	Classic KD (n = 34) (%)	MAD (n = 36) (%)	p-Value
Allergic reaction	0 (0)	1 (2)	1.000	0 (0)	0 (0)	
Vomiting	9 (18)	8 (15)	0.589	2 (4)	2 (4)	1.000
Diarrhea	5 (10)	3 (6)	0.459	1 (2)	0 (0)	0.486
Constipation	14 (27)	12 (23)	0.350	10 (20)	9 (17)	0.790
Lack of energy	13 (25)	10 (19)	0.230	2 (4)	1 (2)	0.609
Severe infection	3 (6)	0 (0)	0.089	0 (0)	2 (4)	0.493
Severe metabolic acidosis	3 (6)	2 (4)	0.655	0 (0)	0 (0)	
Renal stone	0 (0)	0 (0)		2 (4)	1 (2)	0.609
Hypercalciuria	22 (43)	12 (23)	0.004*	17 (33)	10 (19)	0.085
Hyperuricemia	2 (4)	5 (10)	0.448	4 (8)	7 (13)	0.515
Osteoporosis	0 (0)	0 (0)		3 (6)	1 (2)	0.350
Dyslipidemia	14 (27)	12 (23)	0.350	17 (33)	10 (28)	0.129
HyperChol	7 (14)	10 (19)	0.789	7 (14)	6 (11)	0.763
HyperTG	5 (13)	3 (6)	0.459	9 (26)	4 (8)	0.059
High LDL	4 (8)	4 (8)	1.000	3 (6)	2 (4)	0.669
Low HDL	2 (4)	1 (2)	0.588	0 (0)	0 (0)	

DT, diet therapy; KD, ketogenic diet; MAD, modified Atkins diet; HyperChol, hypercholesterolemia; HyperTG, hypertriglyceridemia; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*p-Value < 0.05, statistically significant.

Table 5. Mean serum β-hydroxybutyrate levels in each diet group at 3 and 6 months of diet therapy and correlations between blood ketosis and seizure frequency

	Mean serum β-hydroxybutyrate level, mg/dl (±SD)				
	Classic KD	MAD	p-Value	Correlation coefficient	p-Value
3 months after DT	67.41 ± 45.23	62.01 ± 48.28	0.165	0.075	0.575
6 months after DT	72.91 ± 50.42	66.83 ± 48.02	0.727	0.055	0.631

KD, ketogenic diet; MAD, modified Atkins diet; DT, diet therapy.

to assess the outcome, but unfortunately this was not feasible and was beyond the scope of our study.

Nevertheless, most of the previously published studies that used large prospective and retrospective designs to analyze the efficacies of the classic KD and MAD had results similar to the results of our randomized comparative trial.[3,5–7] However, compared with results from previously published studies employing randomized trials,[1,12] our study found a higher response rate among patients consuming the classic KD. These differences could be partly accounted for by the start of dietary therapy in our patients earlier in the clinical course of their disease. Our subject pool also included numerous younger patients in the range of 12 months to 2 years of age, so the result that patients <2 years were more likely to become seizure-free might have contributed to the superior efficacy of the diet.[13,14] In addition, the responder rate in our MAD group was also still higher than in the previous randomized trial.[4] The difference might be derived from the protocol we used for the MAD. Our protocol included calorie restriction, based on our previous clinical experiences, in which we observed more favorable outcomes among patients after a calorie-restricted MAD.[15] The effects of calorie restriction should be investigated further.

In addition, our study revealed that in the patient group aged <2 years, in which the benefits of the classic KD were more pronounced, the rate of seizure freedom was much higher in patients consuming the classic KD compared with those consuming the MAD. The same trend occurred in the patients with West syndrome, which occurs frequently in this age group. The central nervous system of children younger than 2 years, which is still in the process of rapid maturation, can be affected by serious epileptic encephalopathy if seizures are not controlled rapidly.[16] Hence, dietary therapy is usually urgently required to protect these children from the debilitating effects of epileptic encephalopathy.[16] The results of some studies have also suggested that compared with older children, dietary therapy implemented in this younger age group results in more favorable outcomes.[13,14] Multiple research reports have described the KD as a safe and effective treatment for infantile epilepsies.[13,14,17–19] Recently, the Johns Hopkins group has been offering the classic KD instead of the MAD for patients diagnosed with West syndrome, with the

maintenance of the higher fat diet shortened to 6 months.[13] Our experience supports this approach, and the use of a shorter 8-month course of the classic KD in patients with West syndrome who become spasm free appears to be justified.[20] We also recommend that because patients <2 years of age are more susceptible to epileptic encephalopathy caused by prolonged intractable seizures, rapid implementation of dietary therapy should be considered. The classic KD with the higher fat ratio should be given instead of the MAD.

No statistically significant difference was noted in the dropout rates between the two diet groups, but during the first 3 months, more patients in the classic KD group discontinued their dietary therapy due to intolerance and medical side effects. In the MAD group, even in those patients who eventually dropped out due to intolerance or side effects, dietary therapy was maintained longer than it was by the dropouts from the classic KD group. Commonly reported adverse side effects were typical of the diet therapies (i.e., gastrointestinal disturbances and lack of energy). Fortunately, gastrointestinal disturbances can be improved with conservative management, without stopping the diet. All patients who complained of lack of energy or excessive hunger could also maintain their diet without much difficulty after their calorie intake was increased, once, by 100 calories. We expected that lower fat content of the MAD would result in fewer abnormalities in lipid metabolism, and in fact we found hypertriglyceridemia less frequently in the MAD group. However, the frequencies of dyslipidemia were similar in both groups, and this result has occurred in other studies of long-term MADs.[3,4] Hypercalciuria occurred more frequently in the classic KD group during the early and late periods of diet therapy, so renal stones and osteopenia were frequent complications in the classic KD group later during the study period. Causes of abnormal calcium metabolism during consumption of a KD are not fully understood, but this effect is considered to be associated with persistent metabolic acidosis and a higher proportion of dietary unsaturated fat.[2,21,22]

A relationship between the level of ketosis and seizure control has been suggested by many authors, but some authors have questioned such a relationship.[10,12,23] Neal et al.[12] found that the extent of ketosis is not always proportionately correlated with better seizure outcomes. But it is generally believed that a consistent and high level of blood ketosis is important to obtain favorable seizure outcomes during diet therapy.[23] The MAD results have led to questions about the classic belief that a persistent, high level of ketosis is critical. Our results revealed higher blood ketosis levels in the classic KD group than in the MAD group, but the difference was not statistically significant. Our study also could not provide much insight about the correlation between blood ketosis level and the degree of seizure control.

In our trial comparing the classic KD and the MAD, we failed to detect superiority of the classic KD, and we suggested indirect evidence that the MAD was as effective as the classic KD for achievement of seizure control. In addition, the MAD had advantages with respect to better tolerability and fewer serious side effects. Therefore, like the dose of antiepileptic drug progressively increased in patients with uncontrolled seizure,[24] a MAD with a lower fat ratio might be considered as the primary choice because it is a well-tolerated and easily maintained treatment. But this recommendation of the MAD as primary choice does not apply to patients <2 years of age. The hyperexcitable brains of these patients require urgent stabilization to protect against epileptic encephalopathy; therefore, the classic KD with a higher fat ratio is a more suitable first-line treatment.

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Disclosure

All authors have no conflicts of interest to disclosure. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Clinical Trial Registration

Prospective Study of Comparison Between the Modified Atkins Diet and Classic Ketogenic Diet for Intractable Childhood Epilepsy, NCT02100501 https://clinicaltrials.gov/show/NCT02100501.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Percentage of baseline seizures in each diet group at 3 and 6 months of diet therapy, by seizure type, epilepsy syndrome, and etiology.

Table S2. Percentage of baseline seizures in each diet group at 3 and 6 months of diet therapy by epilepsy syndrome.

Table S3. The proportion of responders at 3 and 6 months of diet therapy by epilepsy syndrome.