Epilepsia, 50(5):1109–1117, 2009
doi: 10.1111/j.1528-1167.2008.01870.x

FULL-LENGTH ORIGINAL RESEARCH

A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy

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Summary

Purpose: To conduct the first randomized trial on classical and medium-chain triglyceride (MCT) versions of the ketogenic diet, examining efficacy and tolerability after 3, 6, and 12 months.

Methods: One hundred forty-five children with intractable epilepsy were randomized to receive a classical or an MCT diet. Seizure frequency was assessed after 3, 6, and 12 months. Treatment withdrawals were documented. Tolerability was assessed by questionnaire, and blood ketone levels were measured.

Results: Of the 61 children who started a classical diet and the 64 who started an MCT diet, data from 94 were available for analysis: 45 classical and 49 MCT. After 3, 6, and 12 months there were no statistically significant differences in mean percentage of baseline seizures between the two groups (3 months: classical 66.5%, MCT 68.9%; 6 months: classical 48.5%, MCT 67.6%; 12 months: classical 40.8%, MCT 53.2%; all $p > 0.05$). There were no significant differences between groups in numbers achieving greater than 50% or 90% seizure reduction. Serum acetoacetate and β-hydroxybutyrate levels at 3 and 6 months were significantly higher in children on the classical diet ($p < 0.01$); this was the case at 12 months for acetoacetate. There were no significant differences in tolerability except increased reports in the classical group of lack of energy after 3 months and vomiting after 12 months.

Discussion: This study has shown classical and MCT ketogenic diet protocols to be comparable in efficacy and tolerability; both ways of implementing the diet have their place in the treatment of childhood epilepsy.

KEY WORDS: Ketogenic diet, Epilepsy, Classical diet, Medium-chain triglyceride diet.

The ketogenic diet is a high fat, restricted carbohydrate regimen that was first used to treat epilepsy in the 1920s (Wilder, 1921). Following observations that fasting decreased seizure frequency (Guelpa & Marie, 1911), the diet was designed to induce a similar metabolic response, with the ketone bodies β-hydroxybutyrate and acetocetate becoming the primary energy source for the brain in the absence of adequate glucose supply. The diet has been shown to be effective in many retrospective and prospective studies (Freeman et al., 1998; Vining et al., 1998; Maydell et al., 2001; Coppola et al., 2002; Kang et al., 2005); and in one randomized controlled trial (Neal et al., 2008a).

There are two main ways of implementing the ketogenic diet. The classical diet is based on a ratio of fat to carbohydrate and protein, usually 3:1 or 4:1. The fat component is provided by long-chain triglycerides. Protein is kept to minumum requirements for growth, and carbohydrate is very restricted. A modification of this diet was introduced in the 1970s using medium-chain triglyceride (MCT) as an alternative fat source (Huttenlocher et al., 1971). MCT yields more ketones per kilocalorie of energy

Accepted August 13, 2008; Early View publication November 19, 2008.

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than its long-chain counterpart, it is absorbed more efficiently, and is carried directly to the liver in the portal blood. This increased ketogenic potential means less total fat is needed in the MCT diet, allowing inclusion of more carbohydrate and protein. In the traditional MCT diet, 60% of its energy is derived from MCT. This amount can cause gastrointestinal side effects in some children, with reports of vomiting, diarrhea, and abdominal pain (Huttenlocher, 1976; Trauner, 1985; Sills et al., 1986; Mak et al., 1999). For this reason, a modified MCT diet was developed, using 30% of energy from MCT, with an additional 30% from long-chain fatty acids (Schwartz et al., 1989a). Many centers using the MCT diet will use this modified version, although with a lower amount of MCT there may be problems obtaining adequate levels of ketosis.

Most studies on efficacy of the ketogenic diet have involved the classical diet, and there have been claims that this is more efficacious than the MCT diet (Livingstone et al., 1977; Berman, 1978; Freeman et al., 2000), although studies comparing the two types are limited. Schwartz et al. (1989a, 1989b) compared the clinical and metabolic effects of three types of the ketogenic diet—the classical 4:1 diet, the traditional MCT diet (60% energy as MCT), and a modified MCT diet (30% energy as MCT) in 55 children and 4 adults. They found all three diets equally effective in controlling seizures in children younger than 15 years of age. However, this study was nonrandomized, and results were obtained after only 3 weeks; there are no other data comparing the two diets on either a short or longer-term basis. Because the higher carbohydrate and protein allowances in the MCT diet may make it more acceptable and suitable for some children to follow, it is important that this protocol is not viewed as inferior on the basis of anecdotal claims alone. A randomized trial on the two diets is needed to ensure a good evidence base for decisions on choice. The aim of this study was to conduct the first such trial, addressing the questions of whether the classical ketogenic diet is more efficacious than the MCT ketogenic diet in controlling seizures, and whether there are any significant tolerability differences between the protocols.

Methods

Children were recruited and referred for consideration from epilepsy clinics at Great Ormond Street Hospital for Children NHS Trust, as well as from pediatric neurologists and pediatricians around the UK. Children were eligible for inclusion if they were between 2 and 16 years of age, experienced at least seven seizures per week, had failed to respond to at least two anticonvulsant medications, and had not been previously treated with the ketogenic diet. Exclusion criteria were a history of hyperlipidemia, renal stones, or organic acid deficiency syndromes; this did not apply to any referred children. Families or other caregivers needed to understand the implications of the diet, to be prepared to travel to the trial center, and to be contactable for regular monitoring at home.

Before an initial screening appointment, families were sent an information sheet explaining the ketogenic diet and the current trial. Children were then assessed with regard to epilepsy diagnosis and fulfilment of entry criteria by one of the two consultant pediatric neurologists (HC or RS). The main center was Great Ormond Street Hospital, London; a few additional children were seen at Central Middlesex Hospital, London, and the National Centre for Young People with Epilepsy, Lingfield (residential center). Children were randomized using a computer program that used the minimization method to ensure a close balance between the treatment groups for three defined age groups (2–6, 7–11, and 12–16 years), and for whether the child was at the residential center. The program randomized the children to receive either the classical or the MCT version of the diet. Neither the ketogenic diet team nor the parents or caregivers of the children were blinded as to the intervention allocated. This study formed part of a randomized controlled trial of the ketogenic diet in children with intractable epilepsy, in which children were randomized to receive a diet either immediately, or after a 3 month delay, with no other changes to treatment in the control group (Neal et al., 2008a).

All diets were calculated individually by a dietitian, after computer analysis of a 4-day food record and telephone consultation with parents or caregivers regarding current food preferences. Following a 4-week baseline period of seizure recording and a full-day outpatient visit for education and baseline investigations, diets were initiated at home. A nonfasting initiation protocol was used. Classical diets were started at a 2:1 ratio and gradually increased to a 4:1 ratio as tolerated over 1–2 weeks; in a few children the ratio was kept at 3:1 for longer because of tolerance problems. Protein was generally kept at World Health Organization (WHO) minimum requirements for age (World Health Organization, 1985). MCT diets were commenced on a full prescription for carbohydrate (generally 15% energy), protein (usually 10% energy), and long-chain fatty acids (usually 30% energy). The MCT fat was increased incrementally over a 7–10 day period as tolerated, to an initial level that was usually 40–45% of total dietary energy. Diets were fully supplemented with vitamins and minerals.

Subsequent to starting the diet, all children were reviewed as outpatients at 3, 6, and 12 months. They were also closely monitored by telephone between clinic visits. Diets were fine-tuned as necessary to improve ketosis and optimize seizure control. The parameters within which the two diets could be modified were defined before study commencement. Overall energy prescription was adjusted on both diets as needed. Ketogenic ratio on the classical

diets was kept between 2:1 and 5:1 (most classical diet children were on a 4:1 ratio, a few were on a 3:1 ratio, and two children needed a 2:1 ratio for a short period). Fine-tuning on the MCT diets involved adjusting the proportion of MCT and carbohydrate in the prescription. MCT was usually started at 40–45% of energy, and was increased up to 60% if necessary and tolerated. Carbohydrate was usually started at 15% of energy, and was reduced to a lowest value of 12% if necessary. Carbohydrate was reduced to improve ketosis only if an increase in MCT was not possible because of poor tolerance. Other modifications on both diets were fluid intake and meal distribution. Protein intake was increased as needed to meet requirements.

The primary outcome was efficacy, as assessed by a change in seizure activity. This was assessed by parental or caregiver seizure records using a chart with six categories (absence, myoclonic, atonic, tonic, tonic–clonic, and focal). Definitions of respective seizure types were clarified with parents at the start. Seizures were recorded daily for the 4-week baseline period and the study period. Efficacy was assessed at 3, 6, and 12 months: the 28 days prior to a time point were used to calculate mean daily seizure numbers at that time point and expressed as a percentage of baseline mean daily seizure numbers, that is, numbers during the 4 weeks before a child started the diet. No change in anticonvulsant medication was made during the 4-week baseline period or initial 3 months of the trial.

Withdrawals from the trial at any time were documented, and tolerability was assessed at 3, 6, and 12 months using a standardized questionnaire for parents or caregivers. Ketosis was assessed by blood measurements at clinic appointments, and twice-daily home urine testing using Ketostix (Bayer, Leverkusen, Germany). Routine hematology and biochemistry were performed at all outpatient reviews, and weight and height were also recorded to assess growth (Neal et al., 2008b).

This paper reports the results for efficacy and tolerability of the classical and MCT ketogenic diets after 3, 6, and 12 months.

Sample size and statistics

This trial was designed as comparative; the hypothesis being tested was that the classical diet might be more efficacious than the MCT diet as a treatment. Using a null hypothesis that the two diets were not significantly different in their effect on seizure control, and defining 25% as the minimum outcome difference of clinical importance, the sample size formula for comparing two means gave a necessary sample of 47 per diet group, allowing detection of a difference significant at 5% with a power of 90%. This was based on an expected outcome range of mean percentage of baseline seizures from 0–150% [standard deviation (SD) of 37.5%]. This sample would allow detection of a 25% or greater difference in mean percentage of baseline seizures in the MCT diet group as compared to the classical diet group; any difference greater than this would be regarded as clinically significant.

The following statistical analyses were performed.

The unpaired *t* test was used to compare mean percentage of baseline seizure numbers in the classical and MCT diet groups after 3, 6, and 12 months. Multiple linear regression analysis was used to examine the association between which ketogenic diet a child was following, and their percentage of baseline seizure numbers, taking into account sex and age group. Responder rates of greater than 50% and 90% seizure reduction were applied, and the Fisher's exact test was used to examine differences between the two diet groups in relation to these. In children who continued the diet for 12 months, linear regression was used in each child separately to determine the gradient of the line of best fit of their serial values of percentage baseline seizure numbers (3, 6, and 12 months). The resulting gradient value was used to represent the overall change in seizure numbers in that child over the 12-month period. The unpaired *t* test was used to compare the mean gradient of the line of best fit between the two diet groups. The number of children who had their medication dose reduced after 3 months of treatment was also compared between the two diet groups using the Fisher's exact test.

The unpaired *t* test was used to compare mean β-hydroxybutyrate and acetoacetate levels in the classical and MCT diet groups at baseline, and after 3, 6, and 12 months. Spearman's correlation coefficient was used to examine the association between a child's β-hydroxybutyrate and acetoacetate levels at each time point (3, 6, and 12 months), and their percentage of baseline seizures at that time.

Ethics

Ethical permission for the study was obtained from the ethics committees for each of the three centers involved. Parents or caregivers of all children enrolled into the study were asked to give written informed consent before the child was randomized into the study, and where appropriate, children were also asked to give their assent to treatment.

Results

Recruitment for the trial commenced December 2001, and closed July 2006. One hundred and forty-five children were randomized to treatment (Fig. 1). Of these, 73 were allocated to the classical diet arm and 72 were allocated to the MCT diet arm of the study. Twenty children did not receive their intervention: 10 changed their mind about participation in the study, diagnosis changed in three children, seizures improved in four children, one child died, and two were unable to travel to the study center. Twenty-five children

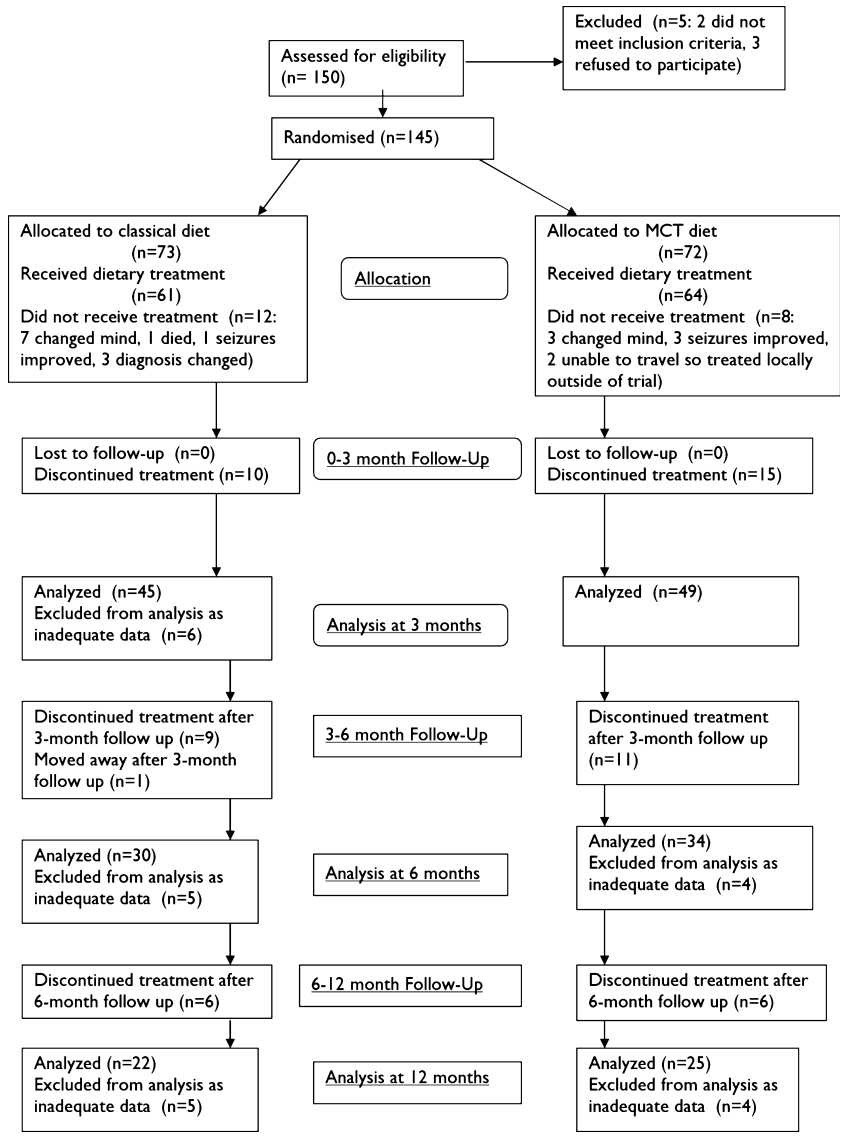

Figure 1.
Flow of children through the trial.
Epilepsia © ILAE

discontinued treatment before 3 months, an additional 20 children after the 3-month follow up, and 12 more after the 6-month follow-up. Data from 94 children was available for 3-month analysis (45 classical, 49 MCT), data from 64 children was available for 6-month analysis (30 classical, 34 MCT), and data from 47 children was available for 12-month analysis (22 classical, 25 MCT).

Baseline demographic characteristics of children randomized to and included in the 3-month analysis of each of the study groups are given in Table 1. Children were well matched for age and sex in both groups, with the majority of children aged between 2 and 11 years. At the time of study entry, six children were not taking any epilepsy medications, 20 children were taking one medication, 53 children two medications, 54 children three medications, 11 children four medications, and one child five medications. Children had a mean of 11.6 seizures daily (9.9 in classical diet group vs. 13.3 in MCT diet group). Eight children were recruited from the residential center. All others attended the hospital as outpatients

Table 1. Baseline demographic characteristics of children allocated to each study group

	Allocated to classical diet study group (n = 73)	Allocated to MCT diet study group (n = 72)
Boys n (%)	40 (54.8)	36 (50.0)
Girls n (%)	33 (45.2)	36 (50.0)
Age (y)		
2–6 n (%)	32 (43.8)	34 (47.2)
7–11 n (%)	31 (42.5)	28 (38.9)
12–16 n (%)	10 (13.7)	10 (13.9)

while living at home. Further detail on the epilepsy syndromes is given in Neal et al. (2008a).

Efficacy

Table 2 shows the results for percentage of baseline seizure numbers after 3, 6, and 12 months in the two diet groups. The mean percentage of baseline seizure numbers after 3 months was 2.35% lower in the classical diet group [95% confidence interval (CI) of difference −19.80 to 24.29, p = 0.834]. Using a linear regression model to take into account the sex and age group of the child, the difference between the mean percentage baseline seizures in the two diet groups increased very slightly to 3.45% (95% CI of difference −19.22 to 26.11), still not statistically significant (p = 0.763). There was one extreme outlier in the MCT diet group; on reanalysis excluding this outlier, the mean percentage of baseline seizures in the MCT diet group fell to 62.25% (SD 37.83%). This was 4.26% lower than the classical diet group (95% CI of difference 13.34–21.85), and still not statistically significant (p = 0.632). After 3 months of treatment, 26 children on the classical diet and 27 children on the MCT diet could have their antiepileptic medication dose reduced (p = 0.841).

The mean percentage of baseline seizure numbers after 6 months was 19.09% lower in the classical diet group (95% CI of difference −8.08 to 46.25, p = 0.165) and at 12 months 12.33% lower in the classical diet group (95% CI of difference −15.81 to 40.47, p = 0.382). When a linear regression model is used to take into account the sex and age group of the child, the differences between the mean percentage baseline seizures in the two diet groups remained very similar. This was lower in the classical group by 19.25% at 6 months (95% CI of difference −8.44 to 46.94, p = 0169), and by 12.53% at 12 months (95% CI of difference −16.09 to 41.14, p = 0.382). There were two extreme outliers in the MCT diet group at 6 months; on reanalysis excluding these outliers, the mean percentage of baseline seizures in the MCT diet group fell to 55.01% (SD 35.87%). This was 6.47% higher than the classical diet group (95% CI of difference 13.65–26.60, p = 0.522). These results show that after 3, 6, and 12 months of the ketogenic diet treatment there were no statistically significant differences between the two dietary protocols.

Table 3 shows the responder rates within each diet group of children achieving a greater than 50% or 90% seizure reduction after 3, 6, and 12 months, using the numbers of children who were allocated to either of the ketogenic diets as denominators, and, therefore, an intention to treat analysis. There was no significant difference between the two groups in the numbers of children who had >90% or >50% seizure reduction. The >90% group includes two children who were seizure free after 3 months (one classical and one MCT diet), one child who was seizure free after 6 months (classical diet), and seven children who were seizure free after 12 months (four classical diet and three MCT diet).

Table 2. Percentage of baseline seizure numbers at 3, 6, and 12 months in classical and MCT diet groups

	Percentage of baseline seizures (%)			
Time	Mean	Standard deviation	Range	Median
3 months				
Classical diet (n = 45)	66.50	47.34	0–200.00	58.14
MCT diet (n = 49)	68.85	59.47	0–385.71	58.12
6 months				
Classical diet (n = 30)	48.53	43.21	0–160.53	37.51
MCT diet (n = 34)	67.62	62.36	0–300.00	62.05
12 months				
Classical diet (n = 22)	40.83	37.77	0–123.72	36.55
MCT diet (n = 25)	53.16	55.10	0–196.52	31.29

n, number providing seizure data at that time point.

Table 3. Numbers of children in each diet group achieving greater than 50% and 90% seizure reduction at 3, 6, and 12 months, based on numbers allocated to each intervention

	Numbers (%) of children achieving cutoff points		
Time	Classical diet group (n = 73)	MCT diet group (n = 72)	p-value
3 months			
Greater than 90% seizure reduction	5 (6.8%)	2 (2.7%)	0.442
Greater than 50% seizure reduction[a]	18 (24.7%)	21 (29.2%)	0.578
6 months			
Greater than 90% seizure reduction	6 (8.2%)	4 (5.6%)	0.745
Greater than 50% seizure reduction[a]	18 (24.7%)	14 (19.4%)	0.549
12 months			
Greater than 90% seizure reduction	7 (9.6%)	7 (9.7%)	1.000
Greater than 50% seizure reduction[a]	13 (17.8%)	16 (22.2%)	0.539

[a]Includes those reporting >90% reduction (n, number who were allocated to intervention).

In children who completed 12 months of dietary treatment, the use of a gradient of the line of best fit allowed a value to be assigned to each individual that represented their overall pattern of change in seizure frequency during the 12 months. Although there was considerable variation between individuals in their pattern of change in seizure frequency, the mean gradient was similar in classical and MCT diet groups [−4.10 (range −7.96 to 4.28) and −3.08 (range −8.21 to 8.88), respectively]. Mean difference in gradient between the two groups was –1.02 (95% CI of difference −3.36 to 1.31); this was not statistically significant (p = 0.381).

Withdrawals from dietary treatment

Ten children on the classical diet withdrew from dietary treatment before completion of the initial 3-month period: four with increased seizures, three with behavioral food refusal, two because of parental unhappiness, and one with constipation. Fifteen MCT diet children withdrew from dietary treatment before completion of the initial 3-month period: four because of parental unhappiness; four with behavioral food refusal; three with diarrhea; and one each with increased seizures, problems with food texture, vomiting, and extreme drowsiness.

Of the 45 children on the classical diet and 49 children on the MCT diet who had seizure data analyzed at 3 months, 9 and 11, respectively, discontinued treatment after the 3-month follow-up visit. Reasons for discontinuation at this point were based on limited efficacy, the psychosocial costs of following the strict dietary regimen outweighing the benefit seen in terms of seizure reduction. After the 6-month follow-up an additional 12 children (6 on each diet) discontinued for the same reason. By 12 months, 57 children of the original 125 who started a dietary treatment (46%) had discontinued dietary treatment.

Tolerability

Table 4 shows side effects as reported by questionnaire at 3, 6, and 12 months. The main problems were constipation, vomiting, hunger, and taste. There were no significant differences between the two types of diet, except increased reports of lack of energy after 3 months and vomiting after 12 months with use of the classical protocol.

Ketosis

Table 5 shows mean serum acetoacetate and β-hydroxybutyrate levels in the children on the classical and MCT ketogenic diets at baseline, and 3, 6, and 12 months. The mean acetoacetate level was significantly higher in the classical diet group after 3, 6, and 12 months. The mean β-hydroxybutyrate level was higher in the classical diet group after 3, 6, and 12 months of treatment; this was significant at 3 and 6 months only. However, there was a wide range in individual values, with the highest level of β-hydroxybutyrate at all time points seen in a child on the MCT diet. The correlation between ketone levels and seizure control was examined for all children on a ketogenic diet (Table 6): this was significant for both ketone bodies at 3 months, but not at 6 and 12 months.

Discussion

This article reports the results of the first randomized trial comparing the classical and MCT versions of the ketogenic diet in the treatment of drug-resistant epilepsy. Our results show that the classical diet does not show any advantage over MCT in terms of efficacy, in agreement with those of the nonrandomized study by Schwartz et al. (1989a). At 3, 6, and 12 months, a wide range in percentage of baseline seizures was seen in both classical and MCT groups; however, the means were not significantly different. In addition, there were no significant differences between the groups in the numbers achieving greater than 50% and 90% seizure reduction, or reducing medication dose after 3 months.

The use of a gradient of line of best fit of serial measures in children who completed 12 months of dietary treatment is recommended as the appropriate statistical

Table 4. Reported side effects of the classical and MCT diets at 3, 6, and 12 months

	Time					
	3 months		6 months		12 months	
Side effect	Classical diet (n = 47)	MCT diet (n = 42)	Classical diet (n = 25)	MCT diet (n = 32)	Classical diet (n = 20)	MCT diet (n = 23)
Vomiting	13 (28%)	11 (26%)	9 (36%)	7 (22%)	9 (45%)[a]	3 (13%)[a]
Diarrhea	7 (15%)	6 (14%)	1 (4%)	4 (13%)	2 (10%)	4 (17%)
Abdominal pain	5 (11%)	8 (19%)	2 (8%)	4 (13%)	2 (10%)	4 (17%)
Constipation	21 (45%)	14 (33%)	12 (48%)	13 (41%)	9 (45%)	9 (39%)
Lack of energy	17 (36%)[a]	6 (14%)[a]	2 (8%)	5 (16%)	2 (10%)	3 (13%)
Hunger	12 (26%)	14 (33%)	6 (24%)	6 (19%)	5 (25%)	4 (17%)
Taste problems	10 (21%)	7 (17%)	4 (16%)	11 (34%)	3 (15%)	5 (22%)

[a]Statistically significant difference between two diets at $p < 0.05$ (n, number providing questionnaire data at that time point).

Table 5. Serum acetoacetate and β-hydroxybutyrate levels at 3, 6, and 12 months in children on classical and MCT ketogenic diets

Time	Mean ± SD ketone level (range), (number of children from whom data available at that time point)		
	Classical diet group	MCT diet group	p-value
Baseline			
Acetoacetate (mmol/L)	0.041 ± 0.030 (0.030–0.192) (n = 34)	0.063 ± 0.088 (0.008–0.570) (n = 42)	0.169
β-hydroxybutyrate (mmol/L)	0.08 ± 0.13 (<0.05–0.86) (n = 42)	0.07 ± 0.67 (<0.05–0.46) (n = 49)	0.596
3 months			
Acetoacetate (mmol/L)	1.182 ± 0.501 (0.033–1.949) (n = 37)	0.696 ± 0.475 (0.0028–2.004) (n = 39)	<0.0001[a]
β-hydroxybutyrate (mmol/L)	4.21 ± 1.73 (0.11–7.32) (n = 42)	2.71 ± 1.70 (0.05–8.22) (n = 45)	<0.0001[a]
6 months			
Acetoacetate (mmol/L)	1.255 ± 0.453 (0.183–2.180) (n = 31)	0.596 ± 0.382 (0.079–1.648) (n = 32)	<0.0001[a]
β-hydroxybutyrate (mmol/L)	4.21 ± 1.44 (1.10–6.84) (n = 32)	2.76 ± 1.81 (0.15–6.87) (n = 37)	0.001[b]
12 months			
Acetoacetate (mmol/L)	1.263 ± 0.692 (0.195–2.485) (n = 21)	0.709 ± 0.485 (0.095–1.806) (n = 21)	0.005[b]
β-hydroxybutyrate (mmol/L)	4.24 ± 1.69 (1.05–8.28) (n = 22)	3.37 ± 2.81 (0.05–9.65) (n = 22)	0.224

[a]Statistically significant at $p < 0.0001$ level.
[b]Statistically significant at $p < 0.01$ level.

Table 6. Correlation of serum ketone levels with percentage of baseline seizure frequency

Time (months)	Correlation with percentage of baseline seizure frequency			
	β-hydroxybutyrate		Acetoacetate	
	Correlation coefficient	p-value	Correlation coefficient	p-value
3	−0.238	0.036[a]	−0.312	0.009[b]
6	−0.058	0.673	−0.204	0.147
12	0.158	0.366	0.187	0.297

[a]Statistically significant at $p < 0.05$ level.
[b]Statistically significant at $p < 0.01$ level.

methodology for this type of data (Matthews et al., 1990), allowing a mean gradient to be obtained for the two diet groups, and, therefore, a statistical comparison of overall change in seizures to be made between the groups. The mean gradient in the 22 classical diet children was more negative than in the 25 MCT children, indicating more of a reduction in percentage of baseline seizures over the 12 months; however, this was not significant. Although a larger sample size would have been beneficial, these results do not support the hypothesis that the classical diet is significantly better in terms of seizure control. However, it is not possible from this study to conclude equal effectiveness. This would require an equivalence study design as opposed to a comparative study design, which would require a much larger sample size (Jones et al., 1996), only likely to be achievable by using a multicenter study design, run over many years.

The diet was stopped before 3 months in 25 children: 5 because of increased seizure activity; 3 because of diarrhea; and one each to vomiting, constipation, and extreme drowsiness. Although numbers were too small for statistical comparisons, it is of interest that four of the five patient withdrawals because of increased seizures were those on the classical diet, and all three children with excessive diarrhea were on the MCT diet. Other withdrawals included problems with the food texture in one child and behavioral eating problems in seven children, all of which were present prior to the child starting treatment, but worsened with the change in diet. Six other children were withdrawn from the study by parents who felt unhappy with the restrictions imposed on their child. In the future, we would recommend that the initial diet screening process should be more comprehensive, ensuring that children with pre-existing behavioral feeding problems have these appropriately managed before embarking on a restrictive dietary regimen.

After 3 months of treatment, the main reason for dietary withdrawal was limited efficacy. Problems with tolerability were still reported, but were not considered sufficiently severe to justify dietary withdrawal if seizure control had significantly improved. Tolerability was assessed by the reports of parents or caregivers. Although the use of our nonvalidated questionnaire could be questioned, and obviously this assessment method could be subject to a degree of bias because of its subjective nature, it did provide a useful way to serially assess the opinion of parents or caregivers on any side effects. There would be no advantage for a family to over- or underreport problems, and although questions were asked about any side effects from the diet in the outpatient clinic setting, the written responses to the questionnaire were not specifically discussed at these visits.

The results of this questionnaire do not support the idea that the MCT diet has a worse profile of abdominal side effects. There do seem to be more reports of diarrhea associated with this protocol in the first few weeks of treatment

and after 6 and 12 months, but the difference was not significant. Reports of abdominal pain were also higher in the MCT group at all time points, but again not reaching significance. Vomiting was reported to have occurred in more than one-fourth of diet children at 3 and 6 months, and by 12 months, the incidence was significantly higher in the classical diet group; this may be because of the higher overall dietary fat content. This high incidence does seem surprising; however, it does not mean a child was vomiting every day, most families who reported vomiting saw this as a minor problem that could occur occasionally, and certainly would not be a reason for discontinuing the treatment. A more significant problem could usually be resolved by dietary manipulation. Although our results for vomiting are similar to those reported by Kang et al. (2004) in their large study of classical diet children, our incidence of diarrhea was lower. Other studies on the MCT diet that report gastrointestinal side effects (Huttenlocher, 1976; Trauner, 1985; Sills et al., 1986; Mak et al., 1999) used 60% of energy from MCT in their diets. Although some children in our study did need this level of MCT to attain good ketosis and optimal seizure control, many others were able to achieve these goals on a lower amount. The children were generally commenced on 45% energy as MCT, and this percentage increased as needed, with the goal of providing the best balance between optimal seizure control and acceptable tolerability.

In our study, constipation was the most frequently reported side effect, at a much higher incidence than that seen in other studies (Kang et al., 2004; Keene, 2006), although it was overcome in most with dietary manipulation and medication. At 3 months, this was more of a problem on the classical diet, as would be expected given the reduced amount of carbohydrate and increased total fat content; however, by 6 and 12 months, reports were similar on both diets. There are no other literature reports of constipation being a problem on the MCT diet; indeed, this type of fat is often advocated as being of benefit as a treatment for the condition. It is not clear why our results did differ in this way from expected, but the low fluid intake of many of the children may have contributed. Although more generous than the classical diet, the limited carbohydrate intake may also have been a problem. Approximately one-third of all children were receiving medication for constipation at any time point.

It is not clear why significantly more children on the classical diet were reported as having a lack of energy at 3 months, but this difference was not present later in the study. Hunger was a problem in more than one-fourth of children at 3 months; this had fallen slightly by 6 and 12 months. Initially, there were more reports of taste problems with the classical diet, but by 6 months this was higher in the MCT group, although the difference was not significant.

Mean levels of β-hydroxybutyrate and acetoacetate in the blood were significantly higher in the classical diet group, although all diets were fine-tuned with the aim of children achieving a high level of urinary ketones (8–16 mmol/L), and very high blood ketone levels were found in certain individuals on both diets. The increased ketosis in the classical diet group is similar to that in previous reports (Schwartz et al., 1989b), and could be expected, as the MCT diet allows more carbohydrate, with a lower total fat level. The relationship between seizure control and ketosis, however, is still unclear. Whereas some authors suggest ketones must be at a sufficient level to achieve seizure control (Gilbert et al., 2000), the link between ketosis and seizure control has been questioned (Bough et al., 2000; Seo et al., 2007). Our results did show some correlation between seizure control and ketosis; however, this was only at 3 months. A linear relationship may not exist; other ketosis-induced metabolic changes may be more important in seizure control.

There are a number of limitations in the data analysis for this study. Total numbers of daily seizures were used, despite more detailed records being kept of numbers of six individual seizure types. A more complex seizure subgroup analysis is a goal in the future. Absence and myoclonic seizures are included in the current analysis. These are difficult to record accurately without accompanying 24-hour EEG data. The analysis also was based only on the daily seizures in the 28 days before each time point, and did not take into account the numbers over the entirety of the 3-month period. Although the use of parental or caregiver seizure records runs the risk of subjective errors, it is hoped that even if present, within-person recording would be consistent over the study period, both for seizure type and frequency. Numbers with regard to individual syndromes were too small to review response to individual diet type.

The use of a randomization process to allocate children using a minimization method to account for age group and treatment location, avoided any selection bias between the study groups. A double-blind randomization process would have improved study design, but it would have been impossible to blind either the dietician prescribing the diets or the parents or caregivers administering it. Despite these limitations, this study has shown in the first randomized trial that both classical and MCT protocols can be used with success.

Acknowledgments

Funding was received for this project from HSA, Smiths Charity, SHS International, and the Milk Development Council. UCL Institute of Child Health received funding as a National Institute for Health & Research Specialist Biomedical Research Centre.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

Conflict of interest: Professor J.H. Cross has received educational grants and honoraria for educational talks from UCB, Janssen Cilag, Eisai, and SHS International. The remaining authors have no conflicts of interest.

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