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Improving the effects of ketogenic diet therapy in children with drug-resistant epilepsy

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ABSTRACT

Purpose: To evaluate the retention rate, efficacy, and safety of ketogenic diet therapy for drug-resistant epilepsy in children and compare the results with those of a previous cohort at our institution.
Methods: A total of 634 children with drug-resistant epilepsy were included in this retrospective study. Patients were categorized into two groups. The previous cohort was included as a control group and included 317 children assessed between 2004 and 2011, whereas the current group included 317 children assessed between 2015 and 2019. The control group was provided care as usual, and the current group additionally adopted the goal and long-term management strategy. Outcomes were measured with respect to retention rate, seizure reduction, and adverse reaction.
Results: Patient demographics were consistent between both cohorts. Compared to the past ten years, the retention rate significantly increased over time (3 months: 62.8% *vs.* 82.0%, $p < 0.001$; 6 months: 42.0% *vs.* 60.6%, $p < 0.001$; 12 months: 24.3% *vs.* 34.1%, $p = 0.007$), and the response rate was significantly improved (3 months: 35.0% *vs.* 55.5%, $p < 0.001$; 6 months: 26.2% *vs.* 43.2%, $p < 0.001$; 12 months: 18.6% *vs.* 31.5%, $p < 0.001$). Constipation ($n = 79$, 24.9%) was the most common side effect in the current cohort. Food refusal and hypoproteinaemia reduced to 3.5% and 0.9%, respectively.
Conclusion: Goal and long-term management is effective for ketogenic diet therapy, which significantly improved the ketogenic diet retention rate, efficacy, and incidence of adverse reactions. This strategy has promising applicability in ketogenic diet therapy.
Clinical registration: ChiCTR-IIR-16,008,342.

1. Introduction

Epilepsy is a common neurological disease, which affects approximately 3.9–5.1‰ of children in China [1]. Antiseizure medication (ASM) is effective in most patients; however, some patients develop drug-resistant epilepsy. A meta-analysis evaluated that the pooled incidence proportion of drug-resistant epilepsy amongst children was 15% [2]. Drug-resistant epilepsy can result in cognitive and behavioural problems, autism, poor quality of life, and an increased risk of death [3]. The ketogenic diet (KD) is a high-fat, low-carbohydrate diet which also provides adequate amounts of protein and other nutrients, and it is effective and safe for children with drug-resistant epilepsy [4,5].

KD was first introduced to our institution in 2004. We have previously administered the KD to 317 children with drug-resistant epilepsy between 2004 and 2011 [6]. However, poor compliance was found in our patients. Since then, efforts have been made to improve this problem. Children and caregivers play an important role in the adherence of KD therapy. Factors related to children's compliance includes lack of KD efficacy, refusal to eat, unstable ketone levels, and KD side effects; for that of caregivers includes parents' attitudes towards KD, food tastes, and acceptance of KD dietary restrictions [4,7-10]. Thus, we adopted the goal and long-term management strategy focusing on children and their caregivers.

Goal setting has been incorporated into many self-management

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interventions for chronic diseases, and it could improve behaviour by enhancing the direction, self-regulation (use of tactics), and persistence of task-directed effort [11,12]. On the basis of a comprehensive assessment of our patients, we set five specific goals to assess the quality of children's ketogenic diet [13]. Since 2008, the International Ketogenic Diet Study Group has put forward the importance of long-term management of KD [14] and various studies have described their practice in the long-term management of KD [8,15,16]. Considering the high proportion of food refusal and hypoproteinaemia in our institution, we used a series of platforms to improve the ability of caregivers to prepare meals in addition to the regular follow-up of KD. To our knowledge, this goal and long-term management strategy was first applied to ketogenic diet and it proved helpful in the management of patients with KD. This study highlights our advancements in recent years with respect to KD therapy in children.

2. Materials and methods

In this retrospective study, patients were categorized into two groups as follows: 1) the current group, including 317 children diagnosed with drug-resistant epilepsy who underwent KD therapy between May 2015 and December 2019, and 2) the control group, including 317 children who met the inclusion criteria between October 2004 and August 2011. All patients or their parents provided informed consent before the treatment. This study was approved by the Ethics Committee of our hospital. Clinical registration: ChiCTR-IIR-16,008,342.

2.1. Ketogenic diet initiation

Children received the classical KD according to the Johns Hopkins Hospital protocol [17]. Before initiating KD therapy, children would fast for 12–24 h until blood beta-hydroxybutyrate (BHB) $\geq$2.5 mmol/L and urine ketone level reaches +++ or above [18]. The mass ratio of fat to carbohydrate and protein was adjusted between 2:1 to 4:1 as clinically necessary [13]. Meals were then typically advanced daily by 1/3 caloric intervals until full calculated calorie meals could be tolerated [5]. Total calorie intake was 60–80 kcal/kg per day and would be adjusted according to effect of seizure reduction and physical development. Children were recommended to use the standard KD products according to their age and preference. The products including Qitong ketogenic liquid milk, Qitong nutritional powder, Qitong ketogenic cookies, and ketogenic canned food (Zeneca). Children do not need to strictly limit the amount of water intake. Furthermore, oral supplementation of potassium citrate, multiple vitamins and trace elements were administered daily.

2.2. Patient management

Patients in the control group received care as usual (CAU) under the guidance of a multidisciplinary team including neurologists, nurses, and dietitians. Neurologists were responsible for the diagnosis, checking the indications and contraindications of KD, choice of treatment, effect of KD, monitoring of adverse events, medical interventions, and medications adjustment. Dietitians focused on guiding the selection of standard KD food and home-made cooking methods, evaluating and monitoring the physical growth and nutritional status of the children, and making decisions about dietary adjustments according to each individual's diet effect and tolerability. Nursing staff were mainly responsible for the diet therapy education, blood glucose and blood ketone monitoring, observation, and follow-up [19].

Besides care as usual, the current group also underwent goal and long-term management (GLTM+CAU). The goal was also used as a criterion to evaluate whether the KD was qualified or not. Briefly, the criteria for qualified KD are as follows: (1) Proper nutrition, physical growth with normal nutrition biomarkers; (2) Tasty food, patients and their families are willing to accept the therapeutic diets; (3) Ideal state of ketosis, urine ketone concentration remains above +++, blood ketone concentration approximately between 2.0–4.0 mmol/L, blood glucose is controlled at 4.0 mmol/L, ratio of blood glucose/blood ketone (Glucose-ketone Index, GKI) is approximately 1:1–2:1; (4) Reasonably balanced food composition, daily defecation one to two times; (5) No remarkable complication(s) [13]. Patients would be informed the goals during the initiation of ketogenic diet. Neurologists and dietitians would evaluate the quality of implementation during the follow-up and helped parents make adjustment to calories intake and ketogenic ratio accordingly [14].

Long-term management involves continuous guidance even as the children were discharged. A series of network platforms were used to provide health education for families. Every week, the platform delivered a KD-related article such as the food preparation procedure, food selection, adverse event identification, and relevant strategies. Each month, the online course taught parents how to prepare a tasty KD, and a catering software was used to match different types of diet. Furthermore, special dietitians would follow up families and offer continuous guidance.

2.3. Data collection and statistical analysis

Clinical data including sex, age of KD initiation, duration of epilepsy, diagnosis, number of ASMs administered previously, epilepsy aetiology, seizure frequency, retention rate, and adverse effects were collected from medical records, caregivers' diet records, seizure diaries, and parents' reports. The baseline data were defined as the 4 weeks before KD initiation. After KD initiation, patients would be followed up at 1, 2, 3, 6, 9, and 12 months. Seizure frequency 28 days before each follow-up was compared to the baseline. Efficacy was defined as the seizure reduction rate. For each follow-up, patients with a seizure reduction $\geq$50% and lasting at least 4 weeks were defined as responders. The overall response rate was calculated according to the last follow-up. Epilepsy aetiology was classified according to the International League Against Epilepsy (ILAE) 2017 classification [20]. We used an intent-to-treat analysis in this study. Patients who discontinued follow-up during the first three months were excluded.

A two-tailed *t*-test was used to test statistical differences of continuous variables and the Chi-square test was used for categorical data. The significance level for all tests was $p < 0.05$, and data analysis was performed using IBM SPSS Statistics 26.0.

3. Results

3.1. Patient characteristics

The patient characteristics of the control group have been described previously [6]. In the current group, 317 patients were included between May 2015 and December 2019. Baseline demographic characteristics of children in the current cohort are given in Table 1.

Of these 634 patients, 63.4% were male and 36.6% were female, 94.0% were younger than 10 years old, and 85.3% had a duration of epilepsy <5 years. No significant differences were noted between the groups regarding the baseline patient characteristics (Table 2).

3.2. Inter-group comparison of retention rate

The retention rate was significantly increased at 3, 6, and 12 months of follow-up in the current cohort. In particular, the 3-month retention rate improved to 82.0% (Table 3).

3.3. Efficacy in the current cohort and comparison of both groups

In the current cohort, KD was effective in 55.5%, 43.2%, and 31.5% of the patients at 3, 6, and 12 months after KD commencement, respectively (Table 4). Significant differences were noted regarding the

Table 1
Baseline characteristics of children with drug-resistant epilepsy in the current cohort.

	Values
Female/male n (%)	121 (38.2%)/196 (61.8%)
Age of seizure onset; years, median (IQR)[a]	0.7 (1.7)
Age of ketogenic diet initiation; years, median (IQR) [a]	2.6 (4.7)
Duration of seizure before ketogenic diet; years, median (IQR) [a]	1.3 (2.4)
Numbers of antiseizure medications tried; n, median (IQR) [a]	4.0 (2.0)
Epilepsy classification n (%)	
Dravet syndrome	31 (9.8%)
West syndrome	129 (40.7%)
Lennox-Gastaut syndrome	15 (4.7%)
Tuberous Sclerosis Complex with epilepsy	9 (2.8%)
Ohtahara syndrome	9 (2.8%)
Non-syndrome epilepsy	124 (39.1%)
Epilepsy aetiology	
Genetic	97 (30.6%)
Structural	117 (36.9%)
Metabolic	4 (1.3%)
Immune	9 (2.8%)
Infectious	12 (3.8%)
Unknown	78 (24.6%)

[a] IQR, interquartile range.

Table 2
Inter-group comparison of patient characteristics.

	Previous cohort(n = 317)	Current cohort(n = 317)	p value
Gender			
Male	206 (65.0%)	196 (61.8%)	0.410 [a]
Female	111 (35.0%)	121 (38.2%)	
Age during ketogenic diet commencement; years, mean (SD)[c]	3.30 (3.10)	3.79 (3.42)	0.059 [b]
Number of patients <10 years old during ketogenic diet commencement; n	299 (94.3%)	297 (93.7%)	0.738 [a]
Duration of epilepsy <5 years, n	265 (83.6%)	276 (87.1%)	0.217 [a]
Cerebral lesions			
Structural	100 (31.5%)	117 (36.9%)	0.873 [a]
Infectious	11 (3.5%)	12 (3.8%)	

[a] Categorical data were compared with a Chi-square test.
[b] Continuous variables were compared with a two-tailed t-test.
[c] SD, standard deviation.

Table 3
Inter-group comparison of retention rate.

	Control cohort(n = 317)	Current cohort(n = 317)	p value
3 months	199 (62.8%)	260 (82.0%)	<0.001*
6 months	133 (42.0%)	192 (60.6%)	<0.001*
12 months	77 (24.3%)	108 (34.1%)	0.007*

Categorical data were compared with the Chi-square test, *p <0.05 was considered statistically significant.

efficacy rates amongst different time points ($\chi^2 = 37.1$, p <0.001). At 3 months, ineffectiveness of KD was noted in 141 patients; amongst these patients, 65 retained KD until 6 months, and at 6 months, 35.4% (n = 23) of these patients responded to KD.

The Chi-square test results revealed that patients in the current group had significantly higher seizure reduction compared to the control group at different durations of follow-up (Table 5).

In our previous study, we found that children who started KD at ≥10 years of age were associated with reduced efficacy of KD compared to children who were <10 years of age when starting KD; however, we did not note this difference in the current study (Supplementary 1 -table 1). Compared the two cohorts with children who initiate ketogenic diet at <10 years of age, current cohort still showed a significant higher response rate than control cohort (Table 6).

Table 4
Efficacy at 3, 6, and 12 months after ketogenic diet initiation in the current cohort (n=317).

Seizure reduction	3 months n (%)	6 months n (%)	12 months n (%)
50–90%	55 (17.4%)	47 (14.8%)	24 (7.6%)
90–99%	38 (12.0%)	15 (4.7%)	15 (4.7%)
Seizure free	83 (26.2%)	75 (23.7%)	61 (19.2%)
Total	176 (55.5%)	137 (43.2%)	100 (31.5%)

Table 5
Comparison of the number of patients with seizure reduction ≥50% between both cohorts.

	Control cohort (n = 317)	Current cohort (n = 317)	p value
3 months	111 (35.0%)	176 (55.5%)	<0.001*
6 months	83 (26.2%)	137 (43.2%)	<0.001*
12 months	59 (18.6%)	100 (31.5%)	<0.001*

Categorical data were compared with the Chi-square test, *p <0.05 was considered statistically significant.

We tested the relationship between the aetiology of six categories (genetic, structural, metabolic, immune, infectious and unknown) and diet efficacy (responder and non-responder). The results showed that the aetiology was not statistically related with diet efficacy (p = 0.101).

In the current cohort, West syndrome was the most common type of epilepsy syndrome accounting for 40.7% of our patients. We did not observe significant differences between the seizure type and seizure response rate (p = 0.148). (Supplementary 1- Figure 1)

3.4. Adverse events

Gastrointestinal (GI) disturbances including constipation, nausea/vomiting, diarrhoea, and abdominal pain were seen in 181(57.1%) patients amongst current cohort. Constipation was the most common adverse event, occurring in 79 (24.9%) of the 317 patients; however, this could be controlled in most of the patients (68, 86.1%) within three months. Other GI disturbances included nausea/vomiting (50, 15.8%), diarrhoea (42, 13.2%), abdominal pain and distension (10, 3.2%).

Food refusal and hypoproteinaemia were observed frequently in the previous cohort. Currently, the percentage of food refusal has been reduced from more than 25% to 3.5%, and the percentage of hypoproteinaemia has been reduced from 12.3% to 0.9%. Six children were found hyperlipoidaemia, four were found elevation of liver enzyme.

Table 6
Inter-group comparison of the response rate in children aged <10 years during ketogenic diet initiation.

	Control cohort	Current cohort	p value
3 months			<0.001*
responder	109	164	
Non-responder	190	133	
6 months			<0.001*
responder	81	129	
Non-responder	218	168	
12 months			<0.001*
responder	57	95	
Non-responder	242	202	

Categorical data were compared with the Chi-square test, *p <0.05 was considered statistically significant.

Other adverse events included three each with electrolyte imbalance, increased rate of infection, allergy, hypocalcaemia; two each with osteopenia, lethargy, hyperuricemia; one each with myocardial damage, low creatinine, acidosis, renal stone, thrombocytopenia, hypoglycaemia and iron deficiency anaemia. (Supplementary 1- table 2.)

4. Discussion

In 2004, KD therapy was introduced to treat children with drug-resistant epilepsy in China. However, because the high proportion of fat in KD differed from that in traditional Chinese food, health education for parents was challenging. As mentioned by the International Ketogenic Diet Study Group, continuous nutritional support and management was necessary to ketogenic diet therapy [14]. After a decade, we additionally adopted the goal and long-term management strategy. As a result, the retention rate, response rate, and adverse events significantly improved over time.

The Ketogenic diet group concluded that KD therapy should be retained for at least 3 months to evaluate the efficacy [5]; however, our previous 3-month retention rate was 62.8%. Food refusal and hypoproteinaemia were common reasons for KD cessation, and hypoproteinaemia was possibly correlated with food refusal and protein deficiency [6]. Therefore, the three aspects of goal management for children include a proper nutrition state, provision of tasty food, and maintenance of balanced food composition. Adverse events accounted for 22.8% of our previous 158 patients who withdraw from KD; thus, we modified our goal management strategy accordingly.

Various studies have explored the effect of blood glucose and blood ketone concentrations on the curative effect of KD. Huttenlocher [21] found patients with mean beta-hydroxybutyrate levels of KD therapy above 2 mmol/L would have a better effect. European guidelines for infants with drug-resistant epilepsy indicated that the beta-hydroxybutyrate level in ketogenic diet therapy should not exceed 5 mmol/L [22]. A retrospective study in Japan pointed out that the mean serum beta-hydroxybutyrate level increased to 4 mmol/L at the first month of KD initiation and this level could be maintained during the diet [23]. These results were in line with our previous study, which revealed that children's beta-hydroxybutyrate level in the first week of KD therapy was generally 3.7 mmol/L (interquartile range 3.1–4.2 mmol/L) [24]. Hence, in our goal management we set the ideal beta-hydroxybutyrate at 2–4 mmol/L. Schoeler et al. [25] reported that the median blood glucose level in the first 3 months was 3.8 mmol/L, and the GKI was 1.0 in their patients. Meidenbauer et al. [26] considered that the GKI values approaching 1.0 may be most therapeutic in brain cancer. Combining these results with our experience, we set the goal of blood glucose at 4.0 mmol/L, and GKI at 1:1–2:1.

Furthermore, it is important for caregivers to understand and be willing to implement KD therapy [27]. Former health education focused more on KD initiation; however, families need continuous medical support such as a parent-mentor network, KD classes, and improved food selection [5,14,28]. Thus, long-term management is necessary in KD therapy. The development of internet technology has increased the availability of facets of long-term management such as communication with the multidisciplinary team and video teaching of new KD recipes. Moreover, this has also enabled the interaction of the families of patients with KD with experienced families, which comprises a new support strategy for KD management [29]. Additionally, the KD has increased in flexibility with respect to its type, and restrictions regarding the intake of calories and fluids have been reduced in recent years [5].

Regarding the goal and long-term management strategy, the retention rate in the current cohort significantly increased. The retention rate at 3, 6, and 12 months was 82.0%, 60.6%, and 34.1%, respectively; these values are comparable to results from other studies [4,30,31]. Meanwhile, food refusal reduced to 3.5% and hypoproteinaemia reduced to 0.9%; this confirmed our previous hypothesis about the relationship between hypoproteinaemia and food refusal. Notably, 23 children responded to KD until 6 months, indicating the importance of retaining KD in children for at least 3–6 months.

After a decade, the response rates in our patients significantly increased to 55.5%, 43.2%, and 31.5% at 3, 6, and 12 months, respectively. Efforts to increase patients compliance could also increase the efficacy of the dietary therapy [32]. Previously, KD therapy seemed to be more effective in children <10 years old. Within our current cohort, there was no significant association between therapeutic efficacy and age. One possible reason for this is that the current KD is tastier and more feasible than previous ones, and it may be easier for patients >10 years old to comply with the diet. The second possible reason is that the sample size of children >10 years old was not large enough, and further studies should increase the sample size to test the difference clearly.

In a meta-analysis of 70 studies, the response rate of classical KD was 50%, 42%, and 33% at 3, 6, and 12 months, respectively, with the intention-to-treat analysis approach, which was comparable with our findings [33]. The proportion of patients who attained seizure freedom in our study were 26.2%, 23.7%, and 19.2% at 3, 6, and 12 months, respectively, which were higher than those observed in other studies [33,34]. However, we did not identify the significant difference between treatment efficacy and age, as well as that between seizure type and epilepsy aetiology. Kim et al. found that the classical ketogenic diet was superior to the modified Atkins diet (MAD) amongst patients aged <2 years [35]; however, we did not identify this relationship. This may likely be due to the fact that most children <2 years old in our current cohort received classical KD.

GI disturbances constituted the most common adverse effect noted in our current patients, and this result was similar to those of other studies [4,36-38]. Beck et al. [39] found that children with ion channel-gene-linked developmental and epileptic encephalopathies have a high prevalence of GI symptoms. Seo et al. [40] found that a 3:1 KD would cause reduced GI disturbances compared with 4:1 KD. Moreover, physical factors and psychological resistance might also cause nausea and vomiting [41].

Constipation is more frequent in classical KD [14], and most patients in our current cohort could be relieved in three months. Avorio et al. [42] found higher constipation prevalence in patients with epilepsy than in healthy individuals (43.3 *vs.* 21.2%). Future studies could compare the prevalence of constipation with KD and other treatments in patients with epilepsy to exclude the influence of disease-related factors on constipation. They also found that most seizures occurred during periods of altered bowel movements, especially constipation [42]. However, we did not observe worse treatment efficacy in patients with constipation.

Acidosis and other adverse events were reduced in our cohort, however we note that different studies showed various proportion of adverse events. In our patients the beta-hydroxybutyrate level was physiological or nutritional, only one patient occurred acidosis, which was comparable with Kang et al. [43] and Li et al. [44]. However, Kim et al. [35]. found that the incidence of acidosis was 6% at 3 months; Lyczkowski et al. [45]. found that the proportion of metabolic acidosis was 39.4%. Heterogeneity may be caused by different sample size, follow-up time, individual differences and the ketogenic diet initiation protocol [37,40,46,47]. Meanwhile, there may have been incomplete information due to the retrospective design. Overall, gastrointestinal disturbances are the most common adverse effects in the ketogenic diet, and others are heterogeneous. More researches need to continue to find out the overall incidence and risk factors of side effects in ketogenic diet to derive more clinical benefit.

The retrospective design of this study is its primary limitation and parental reports of seizure reduction increased the risk of subjective errors. In the goal management strategy, we set goals regarding blood ketosis, blood glucose concentration, and GKI level; however, we did not examine the contribution of these factors to treatment efficacy in this study. Further studies would test the correlation between these two factors. Meanwhile, the goals we set in our institution were based on our previous experience, and there may be inter-institutional differences.

5. Conclusion

This large retrospective study summarized the five-year single-centre experience of KD therapy in our children's hospital. It provides new insights into the current implementation of KD in China. Regarding the goal and long-term management, we have improved our retention rate, seizure reduction, and incidence of adverse reactions significantly. The goal and long-term management could be a promising strategy within KD therapy.

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Declarations of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.10.021.

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