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Review Article

Efficacy of ketogenic diets in children with refractory epilepsy: a meta-analysis

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Abstract: Background and Purpose: Despite successful use of Ketogenic Diets (KD) in refractory epilepsy, its efficacy in children has been still limited. The aim of this meta-analysis was to summarize the scientific evidence of KD, especially the clinical efficacy of KD in children with refractory epilepsy. Methods: Electronic searches of PubMed, EMBASE, and the Cochrane Library were conducted to compare the efficacy of KD in children with refractory epilepsy in randomized controlled trails (RCTs) with that incare as usual (CAU); the included studies were reviewed. Meta-analyses were performed using RevMan 5.3 software. The proportion of 50%, 90% reduction in seizures frequency and free seizures were assessed by risk ratio (RR). The percentage of reduction in seizure frequency was evaluated by weight mean difference (WMD) and the 95% confidence interval (95% CI) was reported in all results. In addition, constipation and vomiting were assessed by risk ratio (RR), while other AEs were reported narratively. Results: 3 RCTs were included, with a total sample size of 295 children. Compared with the CAU group, the numbers of 50% reduction in seizures frequency (RR 4.65, 95% CI 2.75-7.85, P < 0.00001), 90% reduction in seizures frequency (RR 3.42; 95% CI: 1.61-7.29, P=0.001) and the free seizures (RR 3.12; 95% CI 0.91-10.70, P=0.07) were all statistically significantly higher in the KD group, while the percentage of reduction in seizures frequency was lower in the KD group (MD 46.41, 95% CI -62.03–30.78, P < 0.00001). Gastrointestinal symptoms were the most common adverse effects (AEs), while the cases of constipation (*RR 40.65, 95% CI 5.73-288.21, P < 0.0002*) and vomiting (*RR 18.1, 95% CI 2.42-133.98, P=0.005*) were all statistically significantly higherin the KD group than that inthe CAU group. Conclusion: The results indicate that a KD is a kind of promising complementary therapy for children with refractory epilepsy, while stricter monitor measures should be implemented for the potential AEs.

Keywords: Epilepsy, meta-analysis, efficacy, ketogenic diets, care as usual

Introduction

Epilepsy is one of the most common neurologic disorders featured with age-adjusted prevalence in the developed countries with a rate of 4-8 per 1000 people [1, 2], in particularly 20-30% of children with epilepsy suffered from treatment-resistant seizures [3]. Epileptic related surgeries also have been proved for limited effects with anatomic limitations [4]. Although the nimiety of anti-epileptic drugs (AEDs) is currently available and several efforts have been done to identify novel AEDs with higher efficacy and better tolerability [5], the prevalence of AEs is still on a increase [6, 7]. Therefore, non-pharmacological treatment strategies for refractory epilepsy are increasingly being considered as an alternative such as fish oil and KD.

The KD was developed in the 1920s as a treatment for refractory epilepsy when few AEDs were available. It is a high-fat and low-carbohydrate diet characteristic of fasting metabolic rate with normal calories. Body energy are met by lipolysis and β-oxidation of fatty acids rather than by the breakdown of carbohydrates in a KD [8]. Currently, the scientific and clinical attentions toward the role of the KD are ignored [9]. One important reason is that this treatment needs a medical team made up of trained and experienced nutritionists and neurologists. The access to this treatment is not always available. Another important reasonis that AEs in the KD have been reported by a range of studies. The most common AEs were gastrointestinal disturbance suffered by 12-50% of the patients [10, 11]. In addition, hyperlipidemia, nephrolithiasis,

bone mineralization and micronutrient deficiency are also published as AEs generated by KD [12-17]. Despite the controversy voice of strategies and AEs of KD, this dietary treatmenthas shown substantial efficacy for patients with refractory epilepsyin multiple observational studies and some RCTs [18-29]. Currently, besides the classic KD, there existthree other major subtypes of KD: the medium chain triglyceride (MCT) diet, the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT). That means the KD could be designed primarily to maintain efficacy in a less restrictive manner [30, 31].

Sometimes, dietary treatment strategies in epilepsyencounter challenges. For instance, the fish oil, a hotspot recently, has been reporteda higher proportion of 50% reduction in seizures frequency compared epilepsy patients who received fish oil with those in the placebo group, while there was still not enough evidence to support the efficacy of fish oil among patients with epilepsy [32]. How about the KD? The aim of this meta-analysis was to summarize the findings in published RCTs to identify the efficacy of a KD in children with refractory epilepsy, and to guide clinical practice with potential AEs.

Materials and methods

The meta-analysis was conducted in accordance with a predefined guidelines published by the Cochrane Collaboration [33].

Search strategy

We comprehensively identified studies through searching PubMed, EMBASE and the Cochrane Library up to September 2016 for all RCTs regarding to efficacy and AEs of the KD used in epilepsy. To identify other potentially eligible studies that had not been captured in our primary electronic searches, the referencelists of retrieved articles were also manually scanned to locate additional relevant studies.

The following key words were used for search: 1) ketogenicdiets, modified Atkins diet, medium chain triglyceride diet, low glycemic index treatment; 2) refractory epilepsy, seizure; 3) children. The literature language was restricted to English.

Study selection

Two investigators reviewed the title, theabstract, and the full text of all articles in dependently. All search results were manually screened by title and protocol for subject relevance and underwent the same selection procedure used for published results. Eligible trials were chosen according to the inclusion criteria. Any difference was resolved by consensus.

Inclusion and exclusion criteria

Studies were adopted if the following criteria were included: 1) study design: RCTs with the therapy of the KD compared with CAU; 2) participants: children less than 18 years old with refractory epilepsy; 3) outcomes including one of the followings: the number of 50% reduction in seizures frequency, the number of 90% reduction in seizures frequency and free seizures, the percentage of reduction in seizures frequency and the AEs in the KD; 4) definition: refractory epilepsy was defined as seizures not adequately controlled by optimal treatment with ≥2 AEDs and CAU was defined as children continuing to take their anti-epileptic drugs (AEDs) without other changes in the treatment.

Studies were excluded if the followingcircumstances occurred: 1) the trials did not trace the data of AEs or provide original data from which efficacy could not be calculated accurately; 2) the article was not complete with only abstract, letter, leading article, animal experiment, expert opinion, book section, case report, or lack of control group; 3) the studies compared classic KD with other subtypes of KD such as MCT and MAD or with different ratio of lipid: nonlipid.

Data extraction and quality assessment

The following items from each study were extracted into standardized data and form by two reviewers independently: first author's name, publication year, sample size, country of origin, and the subtypes of ketogenic diets and duration of treatment. The primary outcome was the number of 50% reduction in seizures frequency. Thesecondary outcomes were the numbers of 90% reduction in seizures frequency and free seizures, the percentage of reduction in seizures frequency, the number of constipation and vomiting, and other AEs. The

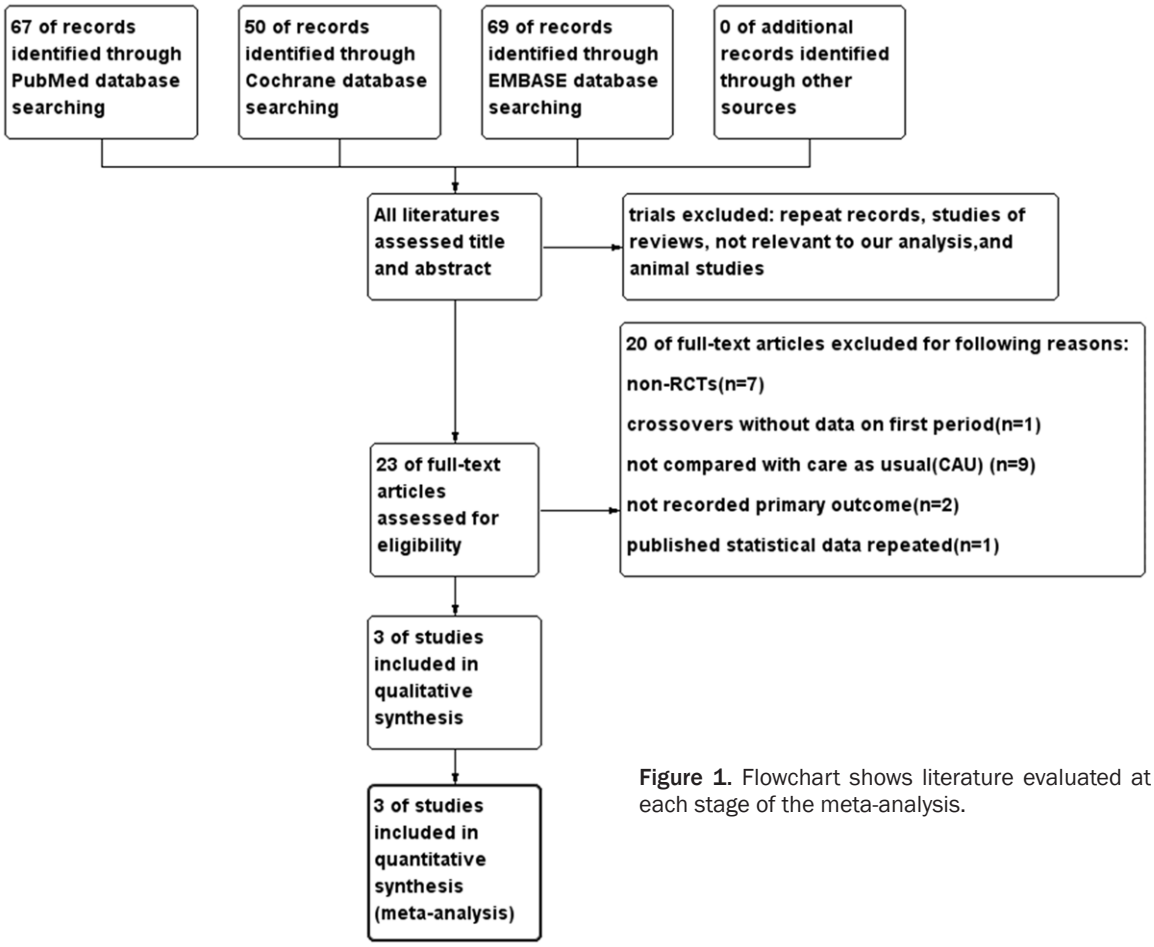

Figure 1. Flowchart shows literature evaluated at each stage of the meta-analysis.

methodological quality of each trial was evaluated by two researchers independently, and the Cochrane Handbook was used to assess the risks of bias.

Statistical analysis

The meta-analysis was conducted by the Review Manager software 5.3 for Windows (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). On the efficacy of KD for refractory epilepsy in children, because the endpoints of the number of 50% reduction in seizures frequency, the number of 90% reduction in seizures frequency and free seizures were dichotomous, risk ratios (RR) and their 95% CI can be reported. Because the outcome of the percentage of reduction in seizures frequency was continuous, the weight mean difference (WMD) and their 95% CI can be reported. To analyze the safety of KD in childhood refractory epilepsy,the number of constipation and vomiting were also dichotomous, so risk ratios (RR) and their 95% CI can be reported as well. Heterogeneity was assessed by Cochran's Q statistic and the I^2 test. Substantial heterogeneity was defined as $I^2 > 50\%$ or chi-squared test $P < 0.1$. When Substantial heterogeneity was observed,the datacan be analyzed throughthe random effects model. Otherwise, the fixed effects model was used.

Results

Search results

3 RCTs were included in the current meta-analysis from 186 potentially relevant literature which were screened from PubMed, Cochrane, and EMbase databases. The study selection process is depicted in **Figure 1**. To avoid missing studies, the lists of retrieved reviews were screened, unfortunately, there was no findings. After screening titles and abstracts, 163 studies were excluded due to repeated studies,

Table 1. Details of included studies

Author	Country	Research Type	Cases-Intervention Cases-CAU	Age (y)-Intervention Age (y)-CAU	Female-Intervention Female-CAU	Intervention methods	Duration of treatment
Neal EG 2008 [28]	UK	RCT	73	2-16	24 (44%)	Classical KD or MCT	3 months
			72	2-16	24 (49%)		
Sharma S 2013 [29]	India	RCT	50	4.7±2.8	9 (18%)	MAD	3 months
			52	5.2±3.3	15 (28.8%)		
Lambrechts DA 2016 [34]	Netherlands	RCT	26	2.1-16.5	8 (30.8%)	Classical KDor MCT	4 months
			22	1.1-15.7	13 (59.1%)		

Note: CAU means care as ususal, KD means ketogenic diets, MAD meansmodified Aktins diet, MCT means medium chain triglyceride diet.

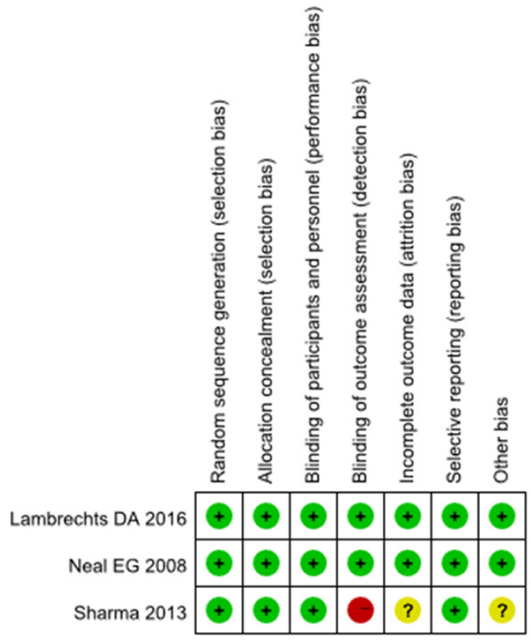

Figure 2. Risk of bias summary. Review authors' judgments about each risk of biasitem for each included study. + is "yes", - is "no", ? is "unclear".

reviews, not relevant to our analysis, or animal studies. Notably, 20 articles were excluded after full-text assessment for eligibility: 7 articles were non-RCT study, 1 article was crossover trail without first hand data, 9 articles were not compared with CAU, 2 articles did not reportthe primary outcome, and 1 RCT was repeated.

Characteristics and the quality of studies

The included 3 trials were published from 2008 to 2016 and enrolled an aggregate of 295 patients, including 149 patients in the intervention group and 146 in the control group. The details of included studies were summarized in **Table 1**. The KD group contained classical KD, MCT, and MAD. The treating duration was 3 or 4 months.

Neal EG 2008 [28] conducted a double-blind trial in the United Kingdom involving 73 children as participants randomized to classical KD or MCT and 72 participants randomized to CAU. The study had a duration of 12 weeks. Sharma S 2013 [29] conducted a single blinded trial randomizing 102 Indianchildren with drug-resistant epilepsy to MAD (a less restrictive alternative to the traditional KD) group and CAU group for 12 weeks. Lambrechts DA 2016 [34] conducted adouble-blinded, randomized trial in Netherlands. The study included 48 children who were 1-18 years old. In this study participants were also randomized to classical KD or MCT group and CAU group, witha duration of 16 weeks.

A summary of the risk of bias for each of the included studies was conducted. Three RCTs adopted a computer-generated method of sequence generation and allocation concealment and only one study was single-blinded. Three studies reported comparable drop-out rates across the groups: Neal 2008 and Lambrechts DA 2016 completed an ITT analysis. Other bias details were seen in **Figure 2**.

Effects of KD for childhood refractory epilepsy

50% reduction in seizures frequency: Three included studies reported the proportion of 50% reduction in seizures frequency after 3 or 4 months of KD treatment compared with CAU in children with refractory epilepsy. Because of the limited number of included trials, we evaluated the general efficacy with the meta-analysis on epileptic seizures regardless of the KD subtypes including classical KD, MCT and MAD.

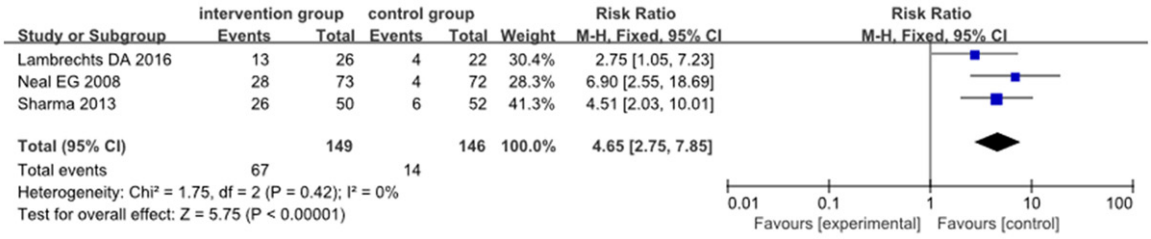

Figure 3. Forest plot of comparison: intervention group vs control group, outcome of efficacy: 50% reduction in seizures.

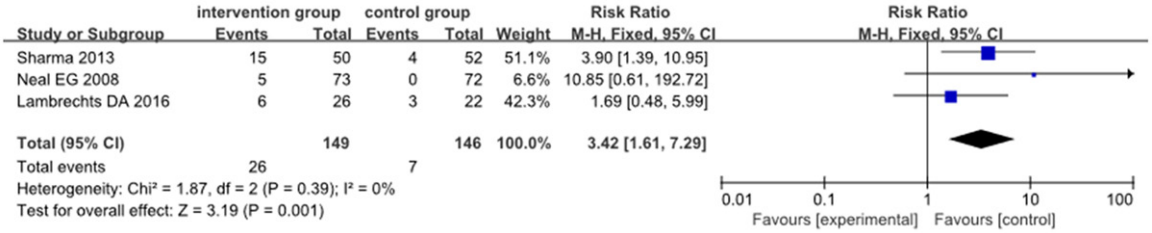

Figure 4. Forest plot of comparison: intervention group vs control group, outcome of efficacy: 90% reduction in seizures.

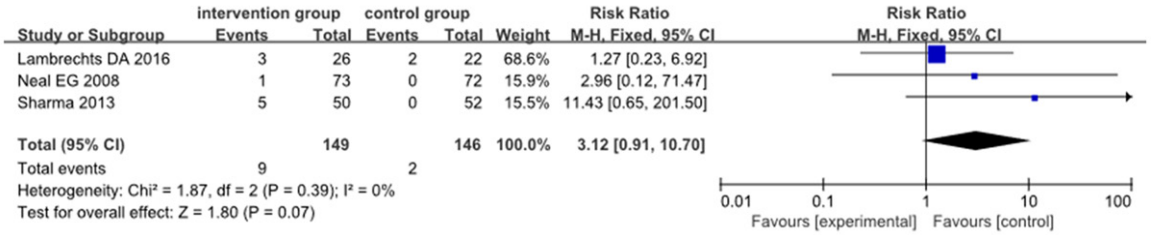

Figure 5. Forest plot of comparison: intervention group vs control group, outcome of efficacy: freeseizures.

The meta-analysis showeda total of 295 participants in three studies. There was no heterogeneity among these 3 studies (P=0.42, I^2=0%), so fixed model was adopted. The results showed that there was a higher rate in 50% reduction in seizuresamong the intervention group (RR 4.65, 95% CI 2.75-7.85, P < 0.00001) compared with that in the control group (**Figure 3**). It indicated there are significant benefits from supplementation of KD compared with CAU.

90% reduction in seizures frequency: Three included RCTs reported the proportion of 90% reduction in seizures frequency, and all these data were taken into analysis. A fixed model was used, as no heterogeneity was observed (P=0.39, I^2=0%). The meta-analysis showed the rate of 90% reduction in seizure frequency was higher in intervention group than that in control group (RR 3.42; 95% CI: 1.61-7.29, P=0.001; **Figure 4**).

Free seizures: At the same time, the proportion of free seizures during the treatment was reported in all included studies. In Sharma S study, 5 children in the diets group were seizure free compared with none in the control group after 3 months treatment. 11.5% of the children (n=3) in the KD group were free of seizures compared with 9.2% (n=2) in the control group in Lambrechts DA study. Free seizures were attained in one child in the diet group and none in the control group in Neal EG 2008. The result showed there was no heterogeneity (P=0.17, I^2=47%). The risk evaluation for seizures freeusing the fixed-effects model was RR 3.12 (95% CI 0.91-10.70), which indicated a significant difference between intervention group and con-

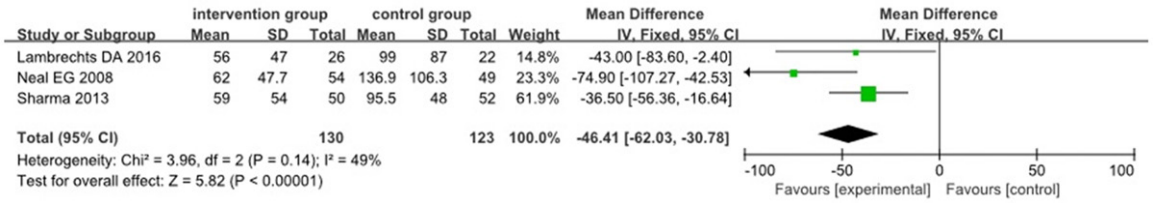

Figure 6. Forest plot of comparison: intervention group vs control group, outcome of efficacy: percentage of seizure frequency.

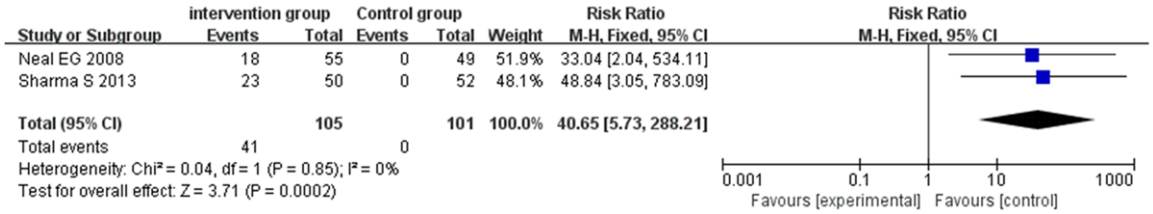

Figure 7. Forest plot of comparison: intervention group vs control group, outcome of AEs: cases of consipation.

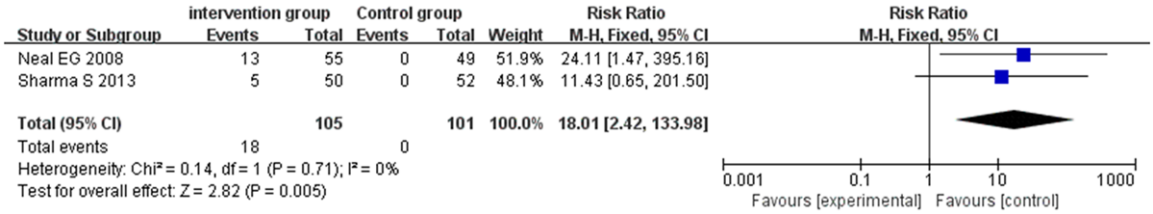

Figure 8. Forest plot of comparison: intervention group vs control group, outcome of AEs: cases of vomitting.

trol group (P=0.07) (**Figure 5**). As a result, the intervention group had a higher rate of free seizures.

Percentage of reduction in seizures frequency: All studies compared the mean percentage of seizures with their baseline and we combined these trials in the meta-analysis. We found there was a decreasein epileptic seizures frequency among children with refractory epilepsyin KD group (MD 46.41, 95% CI -62.03--30.78, P < 0.00001). However, a mild heterogeneity was found across the trials (P=0.14, I^2=49%, **Figure 6**). Interestingly, sensitivity analyses found there was no heterogeneity among the remaining studies after Neal EG 2008 study (I^2=0%) was excluded. Thus, this result should be interpreted with caution.

AEs of KD for childhood refractory epilepsy

In the current meta-analysis, AEs of the KD were commonly presented in the studies included. The most common side effects in three included articles were gastrointestinal symptoms, especially constipation and vomiting.

Constipation

In Neal EG 2008 and Sharma S 2013 study, constipation was the most frequent gastrointestinal disturbance, suffered by 33% and 46% patients respectively. We combined these trials in the meta-analysis. The result showed there was a significant difference in the incidence of constipation between intervention group and control group (RR 40.65, 95% CI 5.73-288.21, P < 0.0002) with no heterogeneity (P=0.85, I^2=0%, **Figure 7**).

Vomiting

The secondary AE was vomiting, with a record of 24% in Neal EG 2008 study and 10% in Sharma S 2013's. We combined these trials in the meta-analysis. The result also showed

Table 2. AEs described in three included articles in the intervention group

Adverse effect	Neal EG 2008 [28] n=55	Sharma S 2013 [29] n=50	Lambrechts DA 2016 [34]
Vomiting	13 (24%)	5 (10%)	The mean value of gastrointestinal symptoms increased from 3.08 at baseline to 3.14 after 4 months.
Diarrhea	7 (13%)	/	
Constipation	18 (33%)	23 (46%)	
Medication for constipation needed	13 (24%)	/	
Lack of energy	13 (24%)	/	2/21
Hunger	12 (22%)	/	/
Lethargy	/	3 (6%)	/
Anorexia	/	9 (18%)	/
Lower respiratory tract infections	/	2 (4%)	/
Hyperammonemic encephalopathy	/	1 (2%)	/
Total cholesterol increase	/	/	Higher than CAU group
Kidney stones	/	/	1/26

Note: AEs means adverse effects; CAU means care as usual.

there was a significant difference in the incidence of vomiting between intervention group and control group (RR 18.1, 95% CI 2.42-133.98, P=0.005) with no heterogeneity (P= 0.71, I^2=0%, **Figure 8**).

Other AEs were less mention in all three included studies, and there was no statistical comparability

In addition, the AEs of CAU groups were not recorded simultaneously in these three studies, sothere were no comparison statistics with intervention and control group. In the study of Lambrechts DA 2016, Side-Effects of Anti-Epileptic Drugs (SIDAED) were used to describe the AEs in intervention group and control group, and the result showed a statistically significantly higher score in the KD group than that in the CAU group on gastrointestinal symptoms. In addition, the AE called malnutrition also occupied a nonnegligible proportion. In Neal EG 2008 study, the proportion of lack of energy and feeling of hunger reached to 24% and 22% respectively. In Lambrechts DA 2016 study, among 21 children whose anthropometric values been traced, one child treated with the KD showed a clinically relevant decrease in height and one experienced weight reduction. Besides, neuropsychiatric system symptoms were also found such as lethargy (6%), anorexia (18%) and hyperammonemia, encephalopathy in (2%) in Sharma S 2013 study. In Lambrechts DA 2016 study and at group level, It is noteworthy that only the mean value for total cholesterol at 6-week treatment with the KD (5.01 mmol/L (SD 1.15)) was statistically significantly higher (P=0.03) than that of the children in the CAU group (4.31 mmol/L (SD 0.27)), while the long-term value for 4-months was similiar. Furthermore, lower respiratory tract infections and kidney stones were also reported, with 2 children in Sharma S 2013 study and 1 in Lambrechts DA's. Details see (**Table 2**).

Discussion

As a well-known dietary treatment for refractory epilepsy, the KD which has been developed into four subtle categorieshas suffered from great-controversy [35, 36]. There is apositive idea supported that the KD is an effective treatment for children and adults with epilepsy [37, 38], Taub KS advised the continual use of the KD for patients with initial seizure freedom to avoid seizures recurrence even after outbreakof seizures [39]. But whether KD could be a therapeutic selection in epilepsy needs more clinical evidence. The aim of this meta-analysis was to summarize the published RCTs to identify the efficacy and its potential AEs of the KD in children with refractory epilepsy regardless of its subtypes.

In the meta-analysis, the free seizures data, the proportion of 50% and 90% reduction in seizures frequency and the percentage of reduction in seizures frequency were analyzed. The results showed that 50% responder rates, 90% responder rates and free seizures of children with refractory epilepsy in the KD groupwere higher (RR 4.65, 95% CI 2.75-7.85, P < 0.00001) (RR 3.42; 95% CI: 1.61-7.29, P= 0.001) (RR 3.12, 95% CI 0.91-10.70, P=0.07)

than that in the CAU group, while KD showed a decreased epileptic seizures frequency compared with the baseline (MD 46.41, 95% CI -62.03--30.78, P < 0.00001).

Compared with the previous meta-analysis assessing the efficacy of KD in epilepsy, our study included all RCTs in current meta-analysis with a relative larger patient respondents. Martin K compared KD with other dietary treatments in adult patients with epilepsy [40]. However, it contained no quantitative synthesis in RCTs, and the outcomes were narratively presented with a poor overall quality of evidence. Ye F reported the efficacy of patient's compliance with a KD in adults with intractable epilepsy. Results indicated that KD was a promising complementary therapy for adults with intractable epilepsy. But the biggest limitation in the research was that the 12 included studies were all observational researches without control groups. Thusthe conclusion only ranked as the class III evidence [41]. Jackson CF meta-analysiswhich had analyzed KD interventions for people with epilepsy highlighted the need for well-designed randomized controlled trials to assess the effects of KD interventions on people with epileptic seizures [42]. Therefore, our meta-analysis summarized all RCTs about KD supplement for children with refractory epilepsy and further confirmed the significant effect of KD as a complementary treatment.

The mild heterogeneity in our meta-analysis about the percentage of seizures frequency could be at least partly attributable to the different subtypes of KD used in the studies. Kim JA designed a randomized clinical trial and compared the classic KD with the MAD involving 104 children with epilepsy. It was found MAD had advantages on better tolerability and fewer serious side effects while the classic KD is more suitable for the first line of diet therapy in patients < 2 years old [43]. But Maria MJ suggested that there was a trend of higher incidence of responders in the KD group than that of MAD group [44]. Although it may be necessary to compare the efficacy of different subtypes KD with CAU respectively, yet the detailed data could not be abstracted from the three included RCTs. Even so, our results showed children with epilepsy could benefit from supplementary KD and provided evidence with overall higher quality.

The main problem we need to consider in the clinical usage of KD is the AEs. The main side effects were gastrointestinal symptoms, including vomit, constipation and diarrhea, experienced by 12-50% of the patients and most of them were presented as mild, moderate or tolerable [11, 12]. Lambrechts DA reported that the weight reduction was 15% (4/27) and no kidney stones occurred during the treatment with the KD [45]. But in another research, the prevalence of kidney stones ranged from 3% to 10%. It's worth noting that after a long-term use of the KD, 21% of patients in the trial experienced fractures and 14% of them had a history of multiple fractures [14]. Notably, a number of researchers found the subtypes of KD resulted in different levels of AEs, El-Rashidy OF 2013 reported that 15.4% of participants suffered constipation in the MAD group and 25% in the classic group, but there was no statistic significance [46]. Kim JA 2016 reported similar AEs both in MAD group and classic KD group. Only hypercalciuria was the complication that presented more frequently in the classic KD group than that in the MAD group [43]. By combining the number of constipation and the number of vomiting, a meta-analysiswas made. Results showed there was statistic difference between KD group and control group (**Figures 7**, **8**). Even though varied AEs were reported from a large number of studies, most of the AEs could alleviate by dietary adjustment, but pancreatitis in association with hypertriglyceridemia has been described as a rare but serious complication of the KD that needs extreme caution. So, it was advisable that a trained and experienced medical team to manage KD in refractory childhood epilepsy.

Several limitations in our meta-analysis should be noticed. One potential limitation was the publication bias. It is possible that were stricted the liter ature language to English and included only 3RCTs. The original articles still had potential methodological limitations, such as the classical and modified KD which would have been analyzed respectively in the intervention group. Meanwhile, the small sample size may also be a limitation, which may lower the statistic power. Therefore, Large randomized controlled double-blinded clinicals tudies for different race and age populations still need to be given more powerful evidence.

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Disclosure of conflict of interest

None.

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