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Clinical efficacy of ketogenic diet combined with perampanel in epilepsy treatment: A randomized controlled trial

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Abstract

Objective: This study evaluated the therapeutic effectiveness and safety of combining the ketogenic diet with perampanel, a newly developed antiseizure medication, in individuals with epilepsy. *Methods:* A prospective randomized controlled trial enrolled 140 epilepsy patients at the department of neurology in a tertiary general hospital in Beijing, China from January 2022 to November 2024. Patients were randomly assigned to either a control or an observation group (n = 70 in each group). The epilepsy seizure counts and seizure duration, as well as serum biomarkers (BDNF, NSE, S100β), cognitive functions (MMSE, MoCA), clinical efficacy, and adverse reaction events were compared pre- and post-treatment. *Results:* Compared to the pre-treatment period, both groups exhibited significant reductions in epilepsy seizure counts and seizure duration, along with decreases in serum BDNF, NSE, and S100β levels ($P < 0.05$), as well as improvements in MMSE and MoCA scores post-treatment ($P < 0.05$). In addition, the intervention group displayed fewer epilepsy seizure counts and shorter epilepsy seizure durations, as well as lower levels of BDNF, NSE, and S100β, and higher MMSE and MoCA scores after treatment, compared to the control group (all $P < 0.05$). The intervention group demonstrated a significantly higher total effective rate and a lower incidence of adverse events compared to the control group (all $P < 0.05$).
Conclusion: Combining the ketogenic diet with perampanel showed good clinical effectiveness and a favorable adverse event profile in treating epilepsy.

Keywords: Ketogenic diet; perampanel; epilepsy; combination therapy; efficacy

INTRODUCTION

Epilepsy is one of the most prevalent neurological disorders, accounting for approximately 1% of the global disease burden.[1] Notably, about 90% of the affected individuals reside in developing countries.[2] This condition is characterized by recurrent seizures that occur spontaneously, rather than as a result of direct brain injury. Experiencing these seizures repeatedly can lead to various issues, including those related to brain function, cognitive abilities, emotions, and social interactions.[3] Epilepsy not only has a profound impact on the physical and mental health of the patient, but also places a heavy burden on the family and society.[4] Currently, pharmacotherapy is the first choice for antiseizure treatment.[5] Studies have confirmed the important role of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors in the mechanism of epileptogenesis.[6,7] Perampanel is a novel type of antiseizure drug. It functions by selectively blocking AMPA receptors, which are crucial in excitatory neurotransmission. This action reduces neuronal overexcitation and assists in controlling seizures.[8,9] Clinical studies have shown that perampanel is effective in managing epilepsy in both adults and children.[10] However, for patients with drug-resistant epilepsy, achieving optimal control often requires a combination therapy of antiseizure drugs with ketogenic diet, as single-drug treatment is frequently insufficient. This approach has become a major focus in recent research.[11]

The ketogenic diet alters the body's energy metabolism pathway by mimicking a starvation state, prompting the liver to produce ketone bodies. These ketone bodies serve as an alternative energy source for brain cells, decreasing their excitability to electrical signals and thereby reducing the

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frequency of epileptic seizures.[12] Studies have shown that the ketogenic diet significantly reduces seizure frequency in patients with refractory epilepsy.[13] As a result, the ketogenic diet in combination with medication can enhance the antiseizure effect.

This study aimed to investigate the clinical efficacy and safety of combining perampanel with a ketogenic diet in epileptic patients, seeking to provide a new direction for epilepsy treatment.

METHODS

Sample size estimation

The sample size was estimated based on the clinical efficacy rate, which served as the primary outcome index. Referring to previous clinical studies[14-16], it was known that the effective rate of perampanel alone in treating epilepsy exceeds 50%. It was anticipated that the effective rate of the combined treatment group in this study would be more than 75% (Total incidence of seizure-free = number of seizure-free individuals/total number of epileptic individuals). The test level was set at $\alpha = 0.05$ (bilaterally), and the test efficacy at $1 - \beta = 0.8$. Calculations for the minimum sample size per group using PASS 15.0 software indicated 55 cases. The final minimum sample size required for each group is approximately 64 cases, considering a potential 15% loss to follow-up during the study. Consequently, the total sample size required was at least 128 cases.

Study design

Patients diagnosed with epilepsy and admitted to the department of neurology in a tertiary general hospital from January 2022 to November 2024 were selected as study subjects. The Medical Ethics Committee of the hospital approved the study. All patients or their relatives have signed the informed consent form.

Diagnostic criteria: Met the diagnostic criteria for epilepsy as defined by the International League Against Epilepsy (ILAE):[17] (1) Had experienced at least two non-provoked seizures with an interval of more than 24 h. (2) One non-provoked (or reflex) seizure, with at least a 60% risk of recurrence within the next 10 years. This risk could be assessed based on a history of previous brain injury, epileptiform abnormalities on electroencephalography (EEG), epileptogenic changes in brain imaging, and whether the initial seizure occurred during sleep. (3) A confirmed epilepsy diagnosis was based on EEG, cranial CT, or magnetic resonance imaging findings showing signs of brain damage, epileptiform abnormalities, and structural cranial damage. (4) Diagnosis of a specific epilepsy syndrome.

Inclusion criteria: (1) Met the diagnostic criteria of epilepsy, and those who were diagnosed with epilepsy had been confirmed by EEG, cranial CT examination, and clinical diagnosis. (2) Were aged 18-70 years old. (3) The average number of seizures per month was ≥4 in the last 3 months. (4) Voluntarily participated in the study and signed the informed consent form.

Exclusion criteria: (1) Those suffering from severe hepatic or renal dysfunction, metabolic diseases, gastrointestinal diseases, and autoimmune diseases. (2) Pregnant or lactating women. (3) Previous psychiatric history or cognitive impairment. (4) Patients who were unresponsive to perampanel and those who were allergic to ketogenic diet components. (5) Presence of severe comorbidities (e.g., advanced heart failure, active cancer, or neurodegenerative diseases). (6) Used of other antiseizure drugs or the ketogenic diet within 3 months prior to enrollment.

Dropout/termination criteria: Serious adverse events during the study, patient request to withdraw, inability to continue participation for other reasons (e.g., sudden change in condition, transfer to another hospital), and failure to complete the prescribed treatment, which may affect the judgment of the results.

This was a prospective, single-anonymized, randomized controlled trial. Patients were randomly divided into two groups using a computer-generated random number table with a 1:1 randomization sequence. The results of the grouping were sealed in opaque, numbered envelopes. The allocation and randomization procedures were conducted by an off-site researcher who was not involved in any other aspects of this study. Due to the apparent differences in the intervention measures, it was not feasible to blind the patients and healthcare providers, but it is feasible to blind the researchers evaluating the results. The research management flowchart is shown in Figure 1.

A total of 156 patients with severe pneumonia and pulmonary atelectasis were initially selected for this study. After screening, three patients who refused to participate and four patients who did not meet the diagnostic criteria were excluded from the study. Eventually, 145 patients were selected

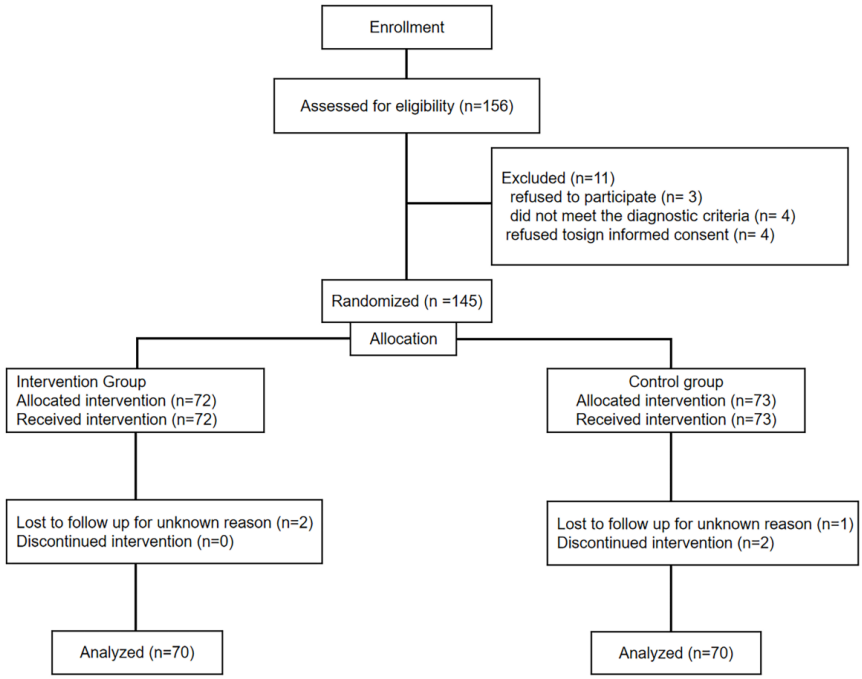

Figure 1. CONSORT flow chart

for the randomized controlled experimental study based on the inclusion and exclusion criteria. In the intervention group, two patients were lost to follow-up for unknown reasons. In the control group, one patient was lost to follow-up for unknown reasons, and two patients discontinued the intervention (medical condition changed and required additional treatment).

Treatment method

All patients were treatment-naive or had discontinued their previous antiseizure medications for at least 3 months before starting perampanel monotherapy.

Control group

The patients were given perampanel tablets (Viktor HJ20210063) for oral administration at an initial dose of 2 mg per day. The dosage was gradually increased according to the patient's age, body weight, adverse reactions, and disease control, at a rate of 2 mg per week, up to a maximum of 12 mg. The target dosage of perampanel was adjusted according to clinical efficacy and tolerability, and treatment continued for 3 months.[18] For elderly patients, a more conservative initial dose of 2 mg/day was used, with weekly increments of 1 mg, to reduce the risk of adverse reactions. Similarly, underweight patients (body mass index, BMI < 18.5) received cautious dosing (initial dose of 2 mg, with a weekly increase of 1 mg) due to their potentially lower body weight and metabolic rate. Patients with a normal BMI (18.5-24.9) were administered the standard regimen: an initial dose of 2 mg followed by 2 mg weekly increments. Although this protocol was deemed appropriate for most patients, close monitoring for adverse effects was maintained. For overweight patients (BMI > 24.9), the standard dosing regimen was applied (2 mg/day initial, 2 mg weekly increases), with intensified safety monitoring. More frequent follow-up assessments were conducted to ensure treatment tolerability.

Intervention group (perampanel + ketogenic diet)

Based on the control group, the ketogenic diet combined treatment was implemented simultaneously. All patients were treated with the classical ketogenic dietary regimen.[19,20]

(1) Pre-treatment assessment and dietary planning: Before treatment initiation, baseline seizure frequency was documented through retrospective analysis of two-month records for clinical assessment. Pre-treatment laboratory tests were performed to evaluate metabolic

tolerance for the ketogenic diet. The ketogenic diet program was implemented by certified dietitians and neurologists with specialized training. Individualized meal plans were developed according to body weight, metabolic parameters, and food preferences, with precise macronutrient calculations provided through standardized software Dietitians provided detailed guidance and training to patients and their families, covering food selection, proportion calculation, and dietary plan formulation, to help them fully understand the requirements and importance of the ketogenic diet. Weekly telephone follow-ups were conducted twice to review the patient's nutritional records (via photos), verify dietary compliance through blood ketone/urine ketone testing, and monitor for adverse events. All participating dietitians hold national certification and have completed training at international ketogenic diet centers or similar institutions, with at least two years of relevant experience. A physician reviewed the dietary plan, and a unified software was used to ensure precise proportions. In case of adverse reactions, dietitians had to respond within 24 h and adjust the plan accordingly.

(2) Initial ketogenic diet prescription: Within the first 3 days of the ketogenic diet, a customized dietary prescription was developed for each patient, taking into account their family's food preferences and staple foods. A gradual non-fasting approach was used to introduce the ketogenic diet. On the first day of the ketogenic diet, 75%-80% of the total daily energy requirement was provided, and this was gradually increased to the full energy level over 2 to 4 weeks.

(3) Structured implementation of the ketogenic diet: The ketogenic diet was implemented through the following structured methods to ensure standardization. The proportions of macronutrients were precisely controlled during calculation and diet composition. Fat was set to account for 80%-90% of total calories, with approximately 160-180 g/day at a 4:1 ratio. Protein intake was recommended at 1-1.2 g/kg of ideal body weight, accounting for about 10%-15% of total calories. Carbohydrate intake was strictly limited to less than 20 g/day, representing approximately 2%-5% of total calories. Fats mainly include animal fats (such as butter, lard, and cream), vegetable oils (such as olive oil and coconut oil), nuts (such as almonds and walnuts), seeds (such as chia seeds and flaxseeds), and high-fat meats (such as fried salmon and grilled meat). Proteins primarily came from meats (such as chicken, beef, and pork), fish (such as salmon, and cod), eggs (such as chicken eggs), and a small amount of legumes. Carbohydrates were primarily sourced from non-starchy vegetables (such as spinach, broccoli, and lettuce) and a small amount of low-sugar fruits (such as strawberries and blueberries). Example menu: Breakfast (3 fried eggs + 30 g butter + 100 g spinach); Lunch (150 g grilled salmon + 20 g olive oil + 100 g broccoli); Dinner (1 avocado + 200 g steak + 15 g coconut oil). In terms of energy targets, during the initial phase (days 1-3), energy intake was calculated based on the Harris-Benedict formula for basal metabolic rate (BMR), multiplied by 0.75. In the maintenance phase, energy intake was adjusted according to weight changes, with adults receiving 20-25 kcal/kg of body weight.

Two types of ketogenic diet initiation protocols were available, depending on individual tolerance. For adult patients with a BMI greater than 18.5, an adaptive fasting approach could be chosen, involving a short-term energy restriction over 16-24 h, during which only water and sugar-free electrolyte drinks were allowed. When the blood ketone level reaches or exceeds 1.0 mmol/L after fasting, the ketogenic diet could be started. For those who were intolerant to fasting, a gradual transition method could be used. On days 1-2, carbohydrate intake was reduced to 30 g/day, while the proportion of fat was increased to 70%. From day 3 onwards, the standard 4:1 ketogenic diet ratio was implemented.

(4) Monitoring during treatment: Throughout the treatment period, healthcare professionals closely monitored the patient's ketone levels. In the first week, urine ketone levels were measured twice daily (morning and evening) using ketone test strips. When urine ketone levels reached moderate to strong positivity (1.5-3 mmol/L), it indicated that the patient had entered a state of ketosis. Fasting blood glucose levels were monitored weekly to ensure they remained within the normal range. If symptoms of hypoglycemia (such as dizziness, palpitations, and sweating) occurred, the diet was adjusted promptly, or glucose supplementation was provided.

Observation indicators

(1) Baseline data: Gender, age, BMI, course of disease, epileptic seizures, epilepsy types, and syndromes. In 2022, ILAE defined epilepsy syndrome as a group of epileptic diseases with characteristic clinical and electroencephalogram phenotypes, and usually with specific etiologies (structural, genetic, infectious, metabolic,

immune), and the causes of seizures remain unknown.

(2) Seizure assessment: Monthly epilepsy seizure counts and epilepsy seizure duration were recorded at baseline (pre-treatment) and after 3 months of treatment (post-treatment). A standardized seizure diary (based on the ILAE-recommended template) was used to record the epilepsy seizure counts (with a clear distinction between seizure types), the epilepsy seizure duration (to the nearest minute), pre-seizure triggers (e.g., sleep deprivation, stress, etc.), and post-seizure status (time to recovery of consciousness, etc.) for all patients and their guardians on a daily basis. To ensure accurate recording, guardians (or adult patients themselves) were trained to recognize typical seizure symptoms (e.g., tonic-clonic, disorientation, etc.). Diary completeness was verified monthly by researchers, and suspicious records were identified through structured interviews. EEG monitoring was performed at month 3 of treatment to verify consistency of seizure type with diary entries. In addition, diary entries were cross-checked with clinic notes from healthcare professionals on a monthly basis to ensure data quality.

(3) Clinical efficacy:[21] Apparent effective: Post-treatment disappearance of symptoms (e.g., limb convulsions, hyperthermia, lethargy) with ≥70% reduction in seizure frequency and duration. Effective: All symptomatic improvement and 50-70% seizure reduction. Ineffective: <50% seizure reduction. Total efficacy rate = (number of marked improvement + effective cases) / total cases × 100%.

(4) Serological indexes: Blood was taken from all patients 1 day before treatment and 1 day after 3 months of treatment in a fasting state, centrifuged to obtain serum after standing, and stored at 4 °C for measurement. Serum levels of brain-derived neurotrophic factor (BDNF), neuron-specific enolase (NSE), and S100 calcium-binding protein β (S100β) were measured using enzyme-linked immunosorbent assay. The choice of measuring serum BDNF (brain-derived neurotrophic factor), NSE (neuron-specific enolase), and S100β as markers was based on the potential role of these metrics in epileptic pathophysiological processes. BDNF is the most ubiquitous growth factor in the central nervous system (CNS) and is essential for CNS development and neuronal plasticity. In addition, the peripheral actions of BDNF are primarily associated with the regulation of insulin sensitivity and glucose homeostasis. Therefore, BDNF is regarded as a metabolic factor because of its multiple effects on glucose metabolism, lipids, and other metabolic parameters.[22] NSE and S100β, on the other hand, are sensitive indicators of neuronal damage, and changes in their levels reflect the extent of neurological damage. It has been shown that they can be used as diagnostic markers for epilepsy.[23]

(5) Cognitive functions: all patients were assessed using the mini-mental state examination (MMSE)[24] and Montreal Cognitive Assessment (MoCA)[25] 1 day before treatment and 3 months after treatment. A score of 30 was assigned, and a score of less than 26 was considered cognitive dysfunction.

(6) Adverse events: The number of cases of nausea and vomiting, constipation, drowsiness, emotional irritability, and loss of appetite symptoms that occurred during the treatment period were recorded in both groups.

Statistical analysis

Data analysis was performed using IBM SPSS 27.0 statistical software. Categorical variables (gender, clinical efficacy, epilepsy etiology, epilepsy syndromes, seizure types, adverse events) were described using frequency counts and percentages. Continuous variables (age, BMI, duration of illness, time, epilepsy seizure counts, epilepsy seizure duration, serological indicators, MMSE, MoCA) were described using means and standard deviations. For categorical variables, the Pearson chi-square test was used for comparisons between the two groups if the data met the criteria of theoretical frequency greater than 5 and sample size of at least 40; otherwise, Fisher's exact test was used for comparisons between groups. For continuous variables that conform to normal distribution, the independent sample t-test was used for comparison between two groups, and the paired sample t-test was used for comparison within groups. For continuous variables that do not obey a normal distribution, nonparametric tests are used. Specifically, the Mann-Whitney U test was used for comparisons between two independent samples, and the Wilcoxon signed rank test was used for comparisons between two related samples. P-values less than 0.05 indicate statistically significant differences.

RESULTS

Baseline data

There was no significant difference in the clinical baseline data between the two groups ($P > 0.05$),

and the results of the study were comparable (Table 1).

Seizure assessment

The epilepsy seizure counts and epilepsy seizure duration in both groups after treatment were significantly lower than those pre-treatment ($P < 0.05$). Additionally, the epilepsy seizure counts and epilepsy seizure duration in the intervention group post-treatment were substantially lower than those in the control group ($P < 0.05$) (Table 2).

Clinical efficacy

The intervention group exhibited a significantly higher total effective rate (80.00% vs. 54.29%) than the control group ($P < 0.05$) (Table 3).

Serological indicators

Post-treatment analysis revealed significant decreases in BDNF, NSE, and S100β levels in both groups ($P < 0.05$), with the intervention group exhibiting notably lower concentrations of these biomarkers compared with the control group ($P < 0.05$) (Table 4).

Cognitive functions

Post-treatment MMSE and MoCA scores improved significantly in both groups compared to pre-treatment, with the intervention group demonstrating notably higher scores for both cognitive functions than the control group ($P < 0.05$) (Table 5).

Adverse events

Adverse event incidence rates were documented in 7/70 (10.0%) and 17/70 (24.3%) of the intervention group and control group, respectively, with the former demonstrating a significantly lower incidence ($P < 0.05$) (Table 6).

DISCUSSION

Epilepsy is a prevalent chronic neurological condition.[26] Although conventional antiseizure drugs can control seizures in some patients, drug resistance still exists in about 30% of patients, and long-term use of drugs is prone to side effects such as cognitive impairment, metabolic disorders, and liver damage.[27,28] In recent years, the ketogenic diet has been shown to assist in the pharmacological treatment of refractory

Table 1: Comparison of baseline data between the two groups [n (%)] (mean ± SD)

Variables	Intervention Group (n = 70)	Control Group (n = 70)	χ^2/t	*P*
Gender			0.110	0.735
Male	36 (51.43)	38 (54.29)		
Female	34 (48.57)	32 (45.71)		
Age (years)	33.77 ± 11.46	35.30 ± 9.56	-0.857	0.393
BMI (kg/m²)	23.01 ± 2.48	22.84 ± 2.03	0.443	0.658
Duration of epilepsy (years)	3.56 ± 0.47	3.68 ± 0.45	-1.531	0.128
Aetiology of epilepsy			1.942	0.879
Structural	15 (21.43)	12 (17.14)		
Genetic	23 (32.86)	21 (30.00)		
Infectious	1 (1.43)	2 (2.86)		
Metabolic	1 (1.43)	2 (2.86)		
Immune,	2 (2.86)	1 (1.43)		
Unknown	28 (40.00)	32 (45.71)		
Epilepsy syndromes			0.288	0.591
Yes	22 (31.43)	25 (35.71)		
No	48 (68.57)	45 (64.29)		
Seizure types			0.463	0.610
Focal seizures	41 (58.57)	37 (52.86)		
Generalized seizures	29 (41.43)	33 (47.14)		

Table 2: Comparison of seizures between the two groups (mean ± SD)

Variables		Intervention Group (n = 70)	Control Group (n = 70)	*t*	*P*
Epilepsy seizure counts (times/month)	pre-treatment	5.43 ± 1.11	5.54 ± 1.25	-0.243	0.808
	post-treatment	2.14 ± 0.35[#]	3.13 ± 0.48[#]	-9.362	<0.001
Epilepsy seizure duration (min/time)	pre-treatment	9.61 ± 1.45	9.83 ± 1.65	-0.839	0.403
	post-treatment	3.50 ± 0.32[#]	5.31 ± 0.51[#]	-25.258	<0.001

[#] indicates compared to pre-treatment, $P < 0.05$.

Table 3: Comparison of clinical efficacy between the two groups [n (%)]

Variables	Intervention Group (n = 70)	Control Group (n = 70)	χ^2	*P*
Apparent effective	11 (15.71)	0 (0)	-	-
Effective	45 (64.29)	38 (54.29)	-	-
Ineffective	14 (20.00)	32 (45.71)	-	-
Total effective cases	56 (80.00)	38 (54.29)	10.490	0.001

Table 4: Comparison of serological indicators between the two groups (mean ± SD)

Variables		Intervention Group (n = 70)	Control Group (n = 70)	*t*	*P*
BDNF (μg/L)	pre-treatment	24.05 ± 4.49	23.42 ± 4.26	0.852	0.396
	post-treatment	17.29 ± 3.08[#]	19.71 ± 3.27[#]	-4.504	<0.001
NSE (ng/mL)	pre-treatment	15.42 ± 4.32	15.03 ± 4.60	0.516	0.606
	post-treatment	5.84 ± 2.02[#]	7.19 ± 2.37[#]	-3.624	<0.001
S100β (ng/mL)	pre-treatment	1.60 ± 0.42	1.52 ± 0.50	1.016	0.311
	post-treatment	0.87 ± 0.31[#]	1.20 ± 0.37[#]	-5.680	<0.001

[#] indicates compared to pre-treatment, $P < 0.05$.

Table 5: Comparison of cognitive function scores between the two groups (mean ± SD)

Variables		Intervention Group (n = 70)	Control Group (n = 70)	*t*	*P*
MMSE	pre-treatment	23.33 ± 4.16	23.56 ± 3.90	-0.337	0.737
	post-treatment	27.21 ± 2.75[#]	26.16 ± 2.33[#]	2.437	0.016
MoCA	pre-treatment	24.43 ± 3.06	24.78 ± 4.20	-0.563	0.574
	post-treatment	27.85 ± 1.16[#]	27.23 ± 1.48[#]	2.759	0.007

[#] indicates compared to pre-treatment, $P < 0.05$.

Table 6: Comparison of the number of cases of adverse events between the two groups [n (%)]

Variables	Intervention Group (n = 70)	Control Group (n = 70)	χ^2	*P*
Nausea/Vomiting	2 (2.86)	5 (7.14)	-	-
Constipation	1 (1.43)	4 (5.71)	-	-
Drowsiness	1 (1.43)	3 (4.29)	-	-
Irritability	1 (1.43)	3 (4.29)	-	-
Decreased appetite	2 (2.86)	2 (2.86)	-	-
Total adverse reactions	7 (10.00)	17 (24.29)	5.029	0.025

epilepsy due to its mechanism of regulating neural excitability through the metabolism of ketone bodies.[29] It has been established that the ketogenic diet, in combination with antiseizure drugs, not only further reduces the number of seizures but also reduces the amount of antiseizure drugs.[30] Perampanel is a new antiseizure medication that blocks AMPA receptors and reduces glutamate activity, effectively treating multiple types of epilepsy.[7] However, Lim *et al*.[31] demonstrated that the adverse effects (e.g., dizziness and malaise) of its long-term use, as well as patient resistance, have limited some of its clinical applications. Therefore, in this study, the combination of ketogenic diet and perampanel was applied to patients with epilepsy, and its clinical efficacy and safety were analyzed.

In this study, it was found that the epilepsy seizure counts and epilepsy seizure duration were significantly reduced in both groups after treatment compared with before treatment ($P < 0.05$), with the intervention group exhibiting greater amplitude of clinical improvement relative to the control group. This result indicates that both perampanel monotherapy and combined ketogenic diet therapy can effectively improve seizures, and the effect of combined treatment is more significant. This is similar to the results of previous studies, which found that traditional antiseizure drugs combined with a ketogenic diet significantly reduced seizure frequency.[30] In addition, the analysis of clinical efficacy revealed that the total effective rate in the intervention group was significantly higher than that in the control group ($P < 0.05$), aligning with the findings of seizure improvement and further highlighting the advantages of the combined treatment. This may be because, on the one hand, the ketogenic diet regulates the level of inhibitory neurotransmitters such as γ-aminobutyric acid. It reduces neuronal excitability and improves mitochondrial function. These actions have a synergistic effect with the inhibition of AMPA receptor-mediated excitatory neurotransmission by perampanel, allowing for more effective seizure control.[32] On the other hand, the ketogenic diet both directly reduces seizures and boosts perampanel effectiveness by altering how the body processes the drug, leading to higher drug levels and stronger seizure control.[33,34] Overall, ketogenic diet combination therapy synergistically enhances the antiseizure effects of perampanel.

BDNF helps neurons survive and supports synaptic plasticity. However, in epilepsy, excessive BDNF can cause neurons to become more excitable by activating TrkB receptors. This can lead to abnormal changes in synapses and trigger seizures.[35] Reduced levels of BDNF in epileptic patients reflect the attenuation of neuronal excitatory damage caused by seizures. NSE and S100β are sensitive indicators of neuronal cell damage, and their reduced levels reflect the attenuation of nerve damage.[36] Thus, these serum markers are associated with the onset, development, and pathological processes of epilepsy, and measuring them can provide a preliminary understanding of pathophysiologic changes in patients with epilepsy and serve as a basis for assessing the efficacy of treatment. The results of the analysis of serological-related indexes in this study showed that both groups exhibited significant post-treatment declines in BDNF, NSE, and S100β levels, with the intervention group showing a more pronounced reduction than the control group ($P < 0.05$). These results indicate that both individual and combined treatments can reduce nerve damage in epilepsy patients, and the effect of combined treatment is more favorable. Previous studies have suggested that perampanel has neuroprotective effects against oxidative stress and neuronal apoptosis, and its effects may be related to the SIRT3 / FOXO3α, Akt / GSK-3β pathways.[37,38] In addition, the ketogenic diet has also been shown to reduce oxidative stress by inhibiting the mTOR pathway, while the ketone bodies generated also directly inhibit NSE release and attenuate neurological damage.[39] The more significant reduction of the above indicators when the two are combined may suggest that the ketogenic diet and perampanel may reduce neurological injury in epilepsy patients through synergistic anti-oxidative stress and anti-apoptotic effects.

It is estimated that about 70% of people with epilepsy have comorbid cognitive impairment, so cognitive impairment is also a major challenge in the treatment of epilepsy.[40] The results of this study showed that the MMSE and MoCA scores were significantly higher after treatment than before, and the scores were higher in the intervention group ($P < 0.05$). This indicates that a ketogenic diet combined with perampanel can significantly improve cognitive function in epilepsy patients. This is similar to the results of previous studies demonstrating that a ketogenic diet improves cognitive performance in patients with drug-resistant epilepsy.[41] The improvement in cognitive function during perampanel monotherapy may be attributed to its association with a reduction in the frequency of seizures.[42]

The ketogenic diet, when used with epilepsy treatment, can improve cognitive function in patients. It achieves this by enhancing brain energy metabolism, balancing neurotransmitters, and reducing oxidative stress.[43,44] The possibility of mechanisms was further analyzed. Ketogenic diet-induced ketosis improves the antioxidant capacity of the central nervous system in animal models and improves patient condition.[45] The ketogenic diet may regulate neuronal activity and transmission through various mechanisms, thereby affecting neurotransmitter homeostasis and gene expression.[46] Jiang *et al*.[47] found that the ketogenic diet improved cognitive function in APP/PS1 mice. It also reduced amyloid plaque formation and lowered proinflammatory cytokine levels. Additionally, it activated the Nrf2/HO-1 signaling pathway and suppressed the NF-κB pathway. Liao *et al*.[48] found that perampanel can help prevent changes in brain circuits before epilepsy develops in mice treated with pentylenetetrazole. This may occur by blocking BDNF/TrkB signaling and reducing inflammatory markers. This leads to temporary improvements in epilepsy-related behavior and brain chemistry.

Moreover, the incidence of adverse events in the intervention group was significantly lower than that in the control group ($P < 0.05$). The adverse events in this study were primarily nausea/vomiting, constipation, drowsiness, irritability, and decreased appetite. Lim *et al*.[31] reported that the adverse reactions arising from the use of perampanel were mainly dizziness and malaise. Janssen *et al*.[49] showed that the common adverse effects of the ketogenic diet were nausea, constipation, and headache, all of which were mild. They occurred mainly at the beginning of the diet, but none of them required any pharmacologic intervention and would not be a reason to discontinue the diet. In the present study, the adverse effects also occurred at the beginning of the diet. Differences in adverse reactions observed in this study and those of others may be due to a combination of factors, including patient characteristics, study design, treatment regimen, monitoring and reporting methods, sample size, and regional differences. This indicates that the ketogenic diet combined with perampanel treatment has a better safety profile. This result can be related to the fact that a ketogenic diet may reduce drug neurotoxicity by regulating the gut flora-brain axis.[50] Therefore, for patients with epilepsy, the combination of ketogenic diet and perampanel not only effectively enhances their cognitive function but also offers better safety and tolerability, providing an ideal treatment option for the comprehensive management of epilepsy. It is expected to be more widely applied in clinical practice to further improve the quality of life and prognosis of patients with epilepsy.

In addition, this study still has some limitations. The small sample size may affect the statistical validity of the results, the short intervention time, and the lack of long-term follow-up data. To compensate for these shortcomings, future studies need larger sample groups and more extended follow-up periods. A stratified analysis approach will be used to separately evaluate the independent effects of the ketogenic diet and perampanel, as well as their potential synergistic effects. This analysis will strictly control for key confounding factors, including baseline seizure frequency, patient body weight, disease duration, and treatment adherence. In the study, separate statistical analyses were not performed to isolate the effects of the ketogenic diet from those of perampanel. The primary analysis was focused on the combined effect of perampanel and ketogenic diet as a whole. However, the importance of understanding the individual contributions of each component in the combined therapy is recognized. To address this, further analyses will be conducted in future studies to specifically measure the additional effect of the ketogenic diet when used in conjunction with perampanel. This will help to better understand the synergistic effects and provide more detailed insights into the therapeutic contributions of each intervention. The MMSE and MoCA scales were employed in this study to assess cognitive functioning. While these tools provided a quantitative measure of overall cognitive status, their utility as general screening instruments may limit the detection of specific cognitive improvements relevant to epilepsy. The study design did not allow for clear differentiation between the independent cognitive effects of the ketogenic diet and perampanel. Future investigations should incorporate more targeted neuropsychological assessments to evaluate domain-specific cognitive changes and elucidate the distinct mechanistic contributions of each therapeutic intervention. Through the analysis of the physiological mechanisms of BDNF, NSE, and S100β in epilepsy, it is believed that the levels of these markers, BDNF, NSE, and S100β, can objectively reflect the therapeutic effect in the treatment of epilepsy. In the study, although improvements were observed in the levels of BDNF, NSE, and S100β after treatment, the direct causal relationship between the changes

of these markers and clinical outcomes remains unclear at present. In future research, we will conduct more targeted neuropsychological testing and detailed biomarker correlation analyses.

In conclusion, this study demonstrated that the ketogenic diet combined with perampanel was superior to perampanel monotherapy in the treatment of patients with epilepsy, as evidenced by increased seizure suppression, optimized therapeutic efficacy, some improvement in relevant neurological aspects (BDNF, NSE, and S100β) and cognition, as well as attenuated adverse effects. This study preliminarily investigated the effect of a ketogenic diet combined with perampanel in the treatment of patients with epilepsy, and the specific mechanisms involved need to be further analyzed.

DISCLOSURE

Ethics: The Medical Ethics Committee of Fu Xing Hospital, Capital Medical University, approved the study. All participants or their relatives have signed the informed consent form.

Data availability: Data supporting this study are available from the author upon reasonable request.

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Conflict of interest: None

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