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Research Article

Effect of Perampanel Treatment on Immune Function and Seizure Frequency in Pediatric Epilepsy Patients

Tao Zhong and Shuping Huang

Department of Pediatrics, Ganzhou People's Hospital, Ganzhou 341000, China

Abstract

Background and Objective: The morbidity of pediatric epilepsy remains persistently high, with pharmacotherapy as a prevalent intervention. Perampanel aids in regulating neuronal overexcitation, yet there is scant research on its conjunction with conventional medications. To assess the clinical value of perampanel in the treatment of pediatric epilepsy and analyze the impact of interventions on the immune function and seizure frequency in affected children. **Materials and Methods:** Upon retrospectively selecting the clinical data from January, 2021 to June, 2023, pediatric epilepsy patients who received treatment in Ganzhou People's Hospital were collected as the research subjects. Forty cases undergoing treatment with levetiracetam were set as the control group and 40 cases receiving adjunctive perampanel were set as the research group. The clinical efficacy, epileptic seizure, discharge rate and serum levels of inflammatory factors before and after treatment were compared between the two groups. The incidence of adverse reactions was recorded and compared between the two groups. **Results:** The total effective rate of treatment in the research group was 97.50% (39/40), which was higher than 80.00% (32/40) in the control group ($p < 0.05$). Before treatment, the differences in seizure frequency, seizure duration, NHS3 scores, P300 latency, wave amplitude, HMGB1 and TNF- α levels were not statistically significant between the two groups ($p > 0.05$), while after treatment, children in the research group showed lower seizure frequency, shorter seizure duration, lower NHS3 score, shorter P300 latency, lower HMGB1 and TNF- α levels and higher wave amplitude compared with those in the control group ($p < 0.05$). The total incidence of adverse reactions of children in the research group was 17.50% (7/40), which was not statistically significant compared with 15.00% (6/40) of children in the control group ($p > 0.05$). **Conclusion:** The application of perampanel in the treatment of pediatric epilepsy is conducive to enhancing therapeutic outcomes, controlling the frequency and duration of seizures, reducing epileptic discharges, improving cognitive functions and lowering the serum levels of HMGB1 and TNF- α of pediatric patients. This approach exhibits a comparable safety profile to monotherapy, demonstrating a certain degree of clinical applicability for wider use.

Key words: Perampanel, epilepsy, clinical efficacy, seizure frequency, seizure duration, cognitive function, inflammatory factors, safety

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Corresponding Author: Shuping Huang, Department of Pediatrics, Ganzhou People's Hospital, No. 16, Mei Guan Street, Zhanggong, Ganzhou, Jiangxi 341000, China Tel: +86-18979773377

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Epilepsy, also known as “seizure disorder” or “convulsions,” is a chronic disease that involves sudden abnormal discharges of brain neurons caused by abnormally excessive or synchronized neuronal activity, leading to transient disruptions in brain function, which is one of the common disorders of the nervous system^{1,2}. Research indicates that approximately 60% of epilepsy cases start in childhood³. The overall prevalence of epilepsy in China is about 7.0‰, with an annual incidence of about 28.8 per 100,000 and the prevalence of active epilepsy, characterized by seizures within a year, is approximately 4.6‰⁴. Presently, there are about 9 million individuals in China living with epilepsy, among whom about 5-6 million experience active seizures and the annual increase in new cases of epilepsy is approximately 400,000⁵. Currently, epilepsy stands as the second most common neurological disorder after headaches in the field of neurology^{6,7}. Pharmacotherapy remains a common intervention for epilepsy, yet traditional antiepileptic drugs such as phenobarbital, primidone and phenytoin sodium have been less utilized in clinical practice due to their numerous side effects and strong drug interactions⁸.

Perampanel belongs to the class of non-competitive AMPA glutamate receptor antagonists and is currently utilized in clinical settings for partial seizures with or without secondary generalized seizures, as well as in adjunctive therapy for generalized tonic-clonic seizures⁹. Existing research validates the efficacy of perampanel in moderating neuronal hyperexcitability, affirming its value in managing epileptic seizures and demonstrates promising control in benign epilepsy in children¹⁰.

The aim of this study was to assess the differences in clinical efficacy and safety between levetiracetam alone and levetiracetam combined with perampanel in pediatric epilepsy patients by conducting a controlled analysis and analyze the changes in inflammatory status of the children following treatment, thereby providing a reference for the application of levetiracetam combined with perampanel in pediatric epilepsy management.

MATERIALS AND METHODS

Study area: This study was conducted in Ganzhou People’s Hospital, Ganzhou, Jiangxi, China.

Study design: Upon retrospectively selecting the clinical data from January, 2021 to June, 2023, 80 pediatric epilepsy

patients who received treatment in Ganzhou People’s Hospital were collected as the research subjects.

Ethical consideration: The study had obtained approval from the Ethics Committee of Ganzhou People’s Hospital and aligned with the principles of the Helsinki Declaration.

The specific inclusion and exclusion criteria are outlined as follows.

Inclusion criteria: (1) All subjects included met the diagnostic criteria for epilepsy as per Neurosurgery and Epilepsy¹¹ and presented corresponding clinical symptoms; (2) Patients had complete and comprehensive medical records (such as serum inflammatory factors, P300 latency, amplitude, etc.) and (3) Patients were confirmed through Electroencephalogram (EEG) and imaging examination.

Exclusion criteria: (1) Individuals with concurrent malignant tumors, (2) Those who had experienced central nervous system or systemic infections within the past month, (3) Patients accompanied by cerebral infarction and other diseases that might affect clinical efficacy evaluation, (4) Subjects allergic to investigational drugs, (5) Individuals who received treatment with other antiepileptic drugs in the month before enrollment and (6) Children with concurrent immune deficiency diseases.

Following screening the clinical data of children during the study period according to inclusion and exclusion criteria, 40 cases undergoing treatment with levetiracetam were set as the control group and 40 cases receiving adjunctive perampanel were set as the research group. Based on the medical records of enrolled pediatric patients, observation indices were compared between groups. The detailed research procedure was illustrated in Fig. 1.

Therapeutic regimen for children: The pediatric patients of the control group received treatment with levetiracetam tablets (manufacturer: Zhuhai United Laboratories Co. Ltd., Approval No. 202004032, specification 0.25 g/tablet). The initial dose was 10 mg/kg, twice daily. Every 2 weeks, the dosage was increased by 1 dose equivalent to the initial dose (for instance, the children were given 20 mg/kg, twice daily, starting in week 3 of treatment). The maximum dose was 30 mg/kg, twice daily, maintained for 6 months as the therapeutic dosage.

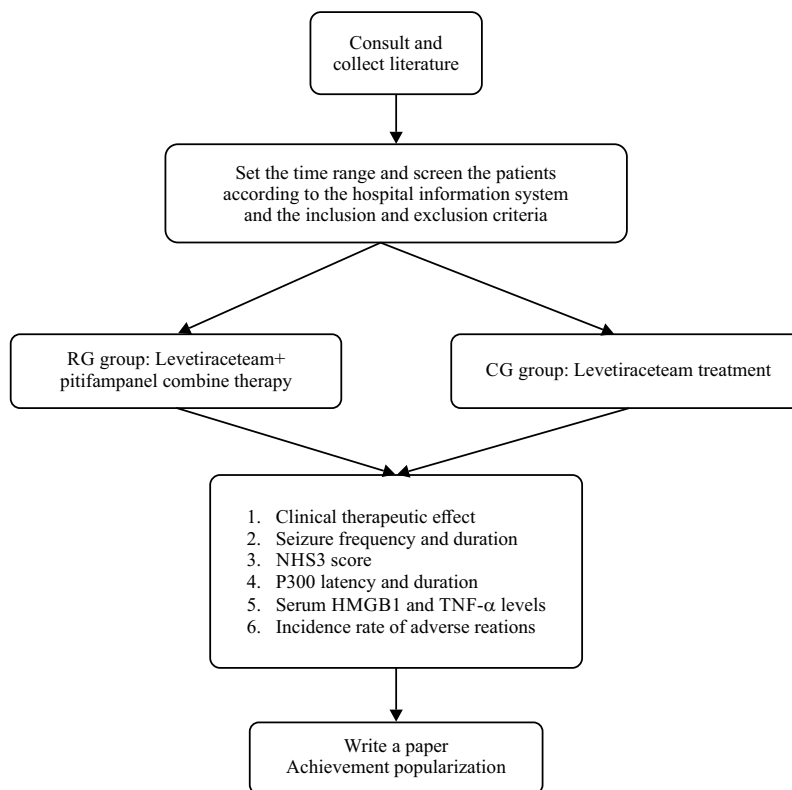


Fig. 1: Flow diagram of the study design

The pediatric patients of the research group were additionally administered with perampanel [manufacturer: Eisai Co. Ltd. (Kawashima Factory), Approval No. H20190053, specification: 2 mg/tablet) on the basis of the treatment in the control group. The dose administered was 2 mg/day (the dose was adjusted to 1 mg/day if the child's weight was <30 kg), taken orally before bedtime. The dosage was increased every 2 weeks until reaching the maintenance dose of 4 mg/day, maintained for six months as the therapeutic dosage.

Observation indices and assessment criteria

Clinical therapeutic efficacy: The therapeutic efficacy was divided into three categories: Significantly effective, effective and ineffective. Significantly effective denotes the difference value of pre- and post-treatment seizure frequency/pre-treatment seizure frequency $\geq 75\%$. Effective refers to $\leq 50\%$ the difference value of pre- and post-treatment seizure frequency/pre-treatment seizure frequency $< 75\%$.

Ineffective indicates the difference value of pre- and post-treatment seizure frequency/pre-treatment seizure frequency $< 25\%$.

Seizure frequency and duration before and after treatment:

The frequency (times/month) and duration (times/min) of seizures were recorded before and after treatment in both groups based on the follow-up information and compared between the groups.

NHS3 scores before and after treatment: The National Hospital Seizure Severity Scale (NHS3)¹² was employed to assess the improvement in seizure symptoms between two groups of pediatric patients before and after treatment. The NHS3 scale consists of seven dimensions, including loss of consciousness, falls, etc. This scale score ranges from 1 to 27, with a higher score signifying a more severe severity of seizure episodes.

P300 latency and wave amplitude before and after treatment: The P300 latency and wave amplitude of the two groups of pediatric patients before and after treatment were examined using the NDI-092 electromyography evoked potential instrument (manufacturer: Shanghai Haishen Medical Electronic Instrument Co. Ltd.) and P300 latency and wave amplitude of the two groups of pediatric patients before and after treatment were compared between the two groups.

Serum levels of inflammatory factors before and after treatment: Fasting blood samples (10 mL) of the two groups of pediatric patients were collected before and after treatment. The blood samples were centrifuged to measure HMGB1 and TNF- α levels using the HM-SY96S microplate reader. Both factors were tested using reagent kits purchased from ACON Laboratories, Inc. The differences in serum levels of inflammatory factors were compared between the two groups of patients before and after treatment.

Incidence of adverse reactions: The incidence of various types of adverse reactions such as dizziness and somnolence during the treatment period was recorded and compared between the two groups.

Statistical methods: Data statistics and analysis were performed using SPSS 22.0. The measurement data such as age, duration of disease and HMGB1 level conformed to normal distribution and were expressed using (Mean $\pm$ Standard Deviation) and inter-group and intra-group differences were evaluated using t-tests. The counting data such as gender and clinical efficacy were expressed as rates and analyzed using the Chi-square test. Statistical significance was set at $p < 0.05$.

RESULTS

Comparison of general clinical data between two groups of pediatric patients: The general clinical data of pediatric patients, including gender, average age, average weight, etc. were collected and compared between the two groups and the results showed no statistically significant differences in the above data ($p > 0.05$), suggesting good comparability, as shown in Table 1.

Comparison of clinical efficacy between two groups of pediatric patients: Of the pediatric patients in the research group, there were 12 significantly effective cases and

27 effective cases, with the total effective rate of 97.50% (39/40), which was higher than 80.00% (32/40) in the control group ($p < 0.05$), as indicated in Fig. 2.

Differences in seizure frequency and duration between two groups of pediatric patients before and after treatment: Before treatment, the differences in seizure frequency and duration were not statistically significant between the two groups ($p > 0.05$). After treatment, children in the research group showed lower epileptic seizure frequency (Fig. 3a) and shorter epileptic seizure duration (Fig. 3b) compared with those in the control group ($p < 0.05$), as shown in Fig. 3.

Differences in NHS3 scores between two groups of pediatric patients before and after treatment: Before treatment, the difference in NHS3 scores was not statistically significant between the two groups (Fig. 4a) ($p > 0.05$), while after treatment, children in the research group showed lower NHS3 score compared with those in the control group (Fig. 4b) ($p < 0.05$), as illustrated in Fig. 4.

Comparison of P300 latency and wave amplitude between two groups of pediatric patients before and after treatment: Before treatment, no significant difference was found in P300 latency between the two groups (Fig. 5a) ($p > 0.05$). After treatment, P300 latency of the two groups was significantly reduced compared with that before treatment and the difference was statistically significant ($p < 0.05$). In addition, the research group showed shorter P300 latency after treatment compared with the control group (Fig. 5b) ($p < 0.05$), as shown in Fig. 5. Before treatment, no significant difference was found in wave amplitude between the two groups (Fig. 6a) ($p > 0.05$). After treatment, wave amplitude of the two groups was significantly elevated compared with that before treatment and the difference was statistically significant ($p < 0.05$). In addition, the research group showed higher wave amplitude after treatment compared with the control group (Fig. 6b) ($p < 0.05$), as shown in Fig. 6.

Table 1: Comparison of general clinical data between two groups of pediatric patients ($\bar{x} \pm s$)/[n (%)]

General clinical data	Research group (n = 40)	Control group (n = 40)	t/ χ^2	p-value
Gender				
Men	26	28	0.228	0.633
Women	14	12		
Average age (years)	9.63 $\pm$ 2.65	9.51 $\pm$ 2.51	0.208	0.836
Average weight (kg)	35.62 $\pm$ 5.16	35.88 $\pm$ 4.98	0.229	0.819
Average duration of disease (years)	2.23 $\pm$ 0.51	2.19 $\pm$ 0.43	0.379	0.706

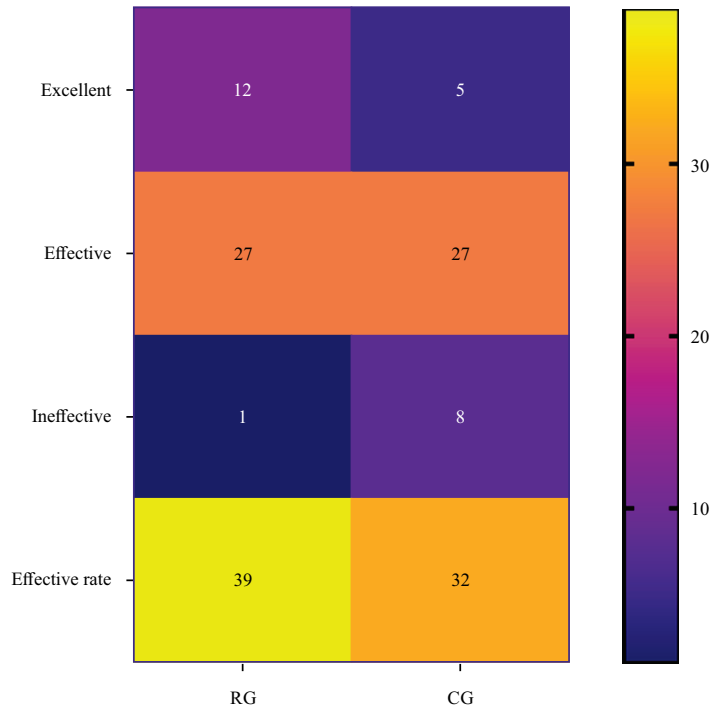


Fig. 2: Comparison of clinical efficacy between two groups of pediatric patients
Total effective rate of treatment in the research group was 97.50% (39/40), which was higher than 80.00% (32/40) in the control group ($p<0.05$); RG: Research group and CG: Control group

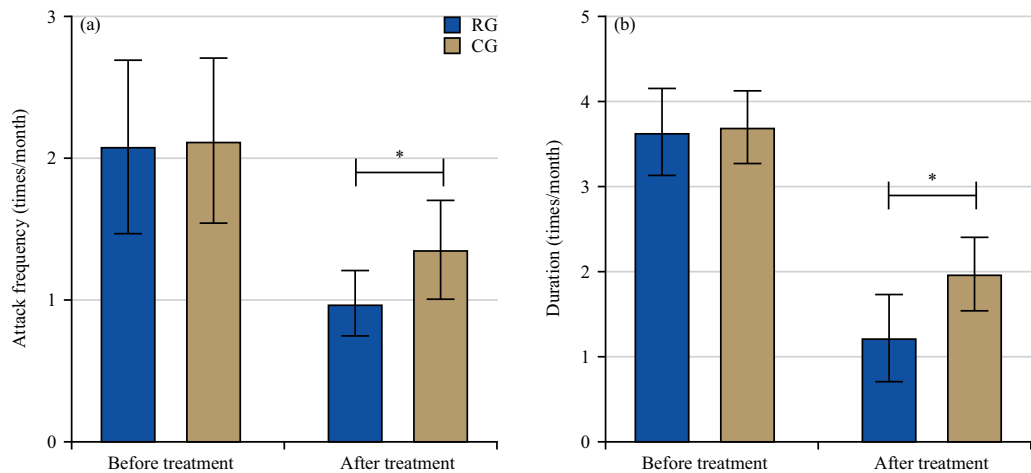


Fig. 3(a-b): Differences in seizure frequency and duration between two groups of pediatric patients before and after treatment. After treatment, (a) Frequency and (b) Duration of seizures in the research group were lower than those in the control group
* $p<0.05$

Comparison of serum inflammatory factor levels between two groups of pediatric patients before and after treatment: Before treatment, the differences in HMGB1 and TNF- α levels were not statistically significant between the two groups ($p>0.05$). After treatment, children in both groups

showed reduced levels of HMGB1 and TNF- α compared with those before treatment, exhibiting statistically significant difference ($p<0.05$). In addition, the levels of HMGB1 (Fig. 7a) and TNF- α (Fig. 7b) in the research group were lower than those in the control group ($p<0.05$), as shown in Fig. 7.

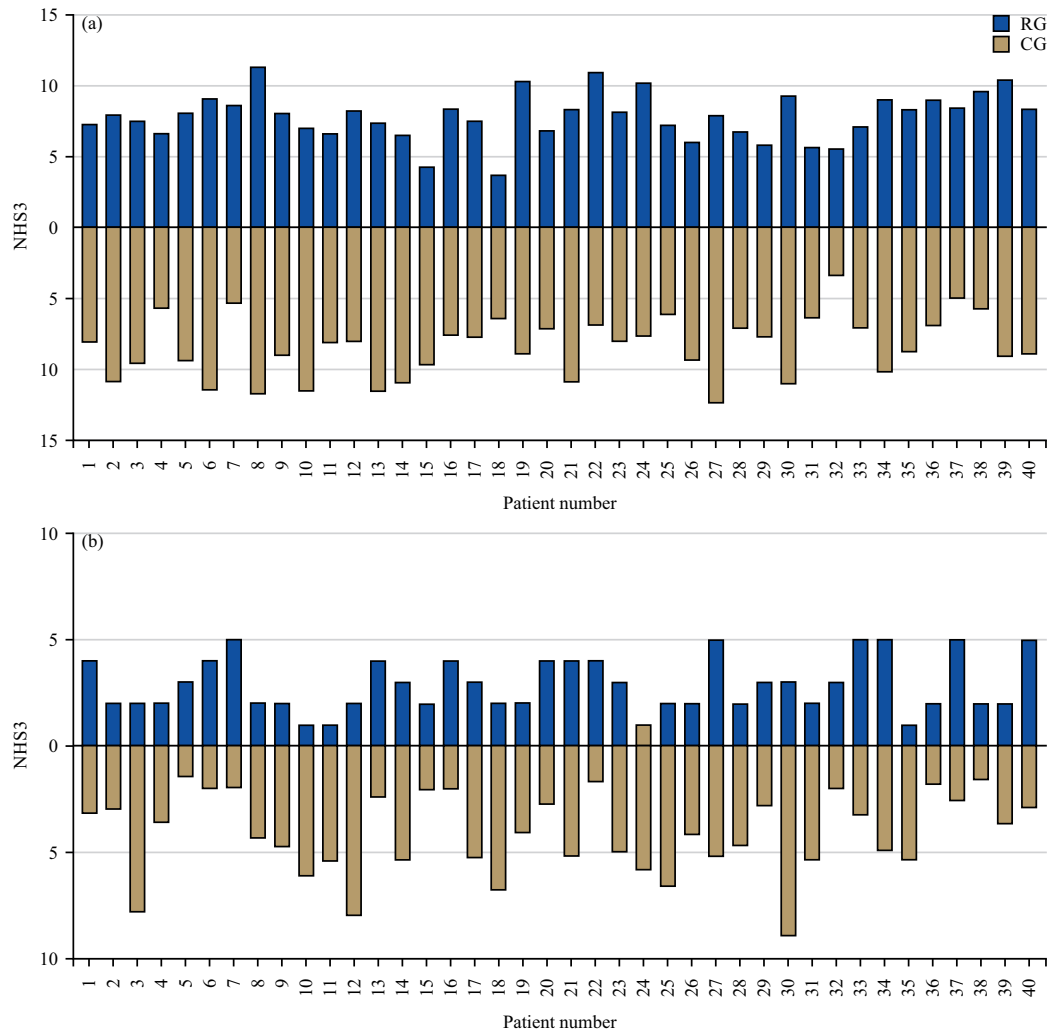


Fig. 4(a-b): Differences in NHS3 scores between two groups of pediatric patients (a) Before and (b) After treatment
There was no significant difference in NHS3 scores between the two groups before treatment ($p > 0.05$). The NHS3 scores in the research group were lower than those in the control group after treatment ($p < 0.05$)

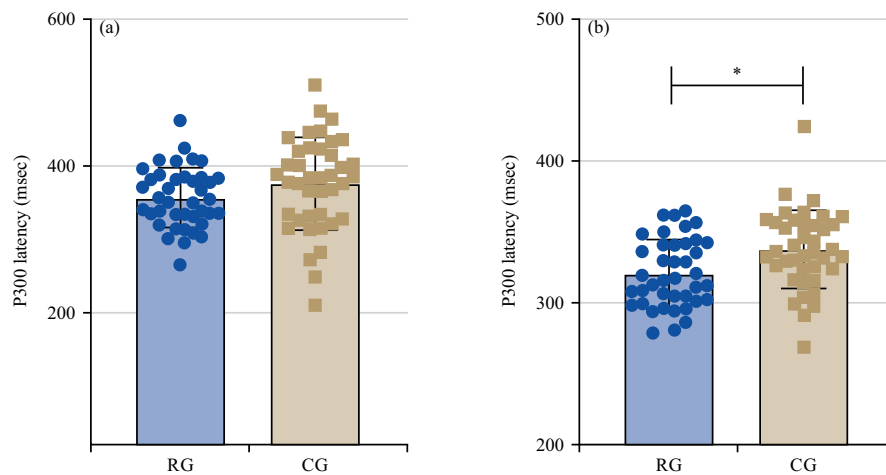


Fig. 5(a-b): Comparison of P300 latency between two groups of pediatric patients (a) Before and (b) After treatment
Before treatment, there was no significant difference in P300 latency between the two groups ($p > 0.05$); After treatment, P300 latency in the research group was lower than that in the control group ($p < 0.05$) and $*p < 0.05$

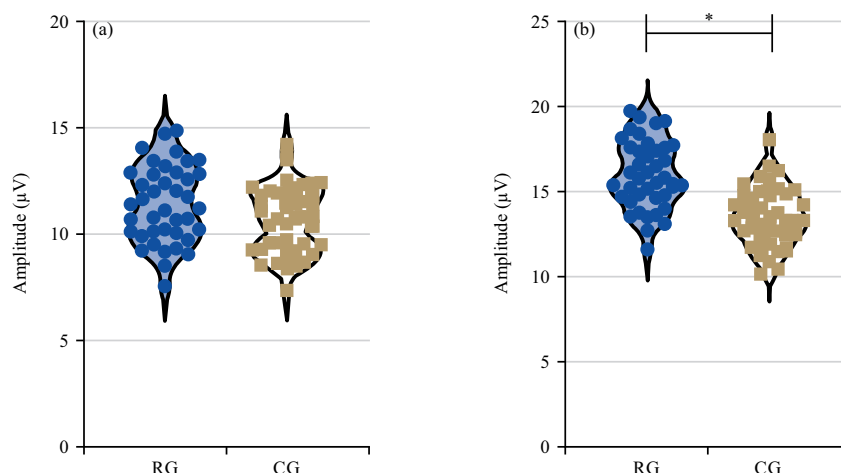


Fig. 6(a-b): Comparison of wave amplitude between two groups of pediatric patients (a) Before and (b) After treatment
Before treatment, there was no significant difference in wave amplitude between the two groups ($p>0.05$); After treatment, wave amplitude in the research group was higher than that in the control group ($p<0.05$) and $*p<0.05$

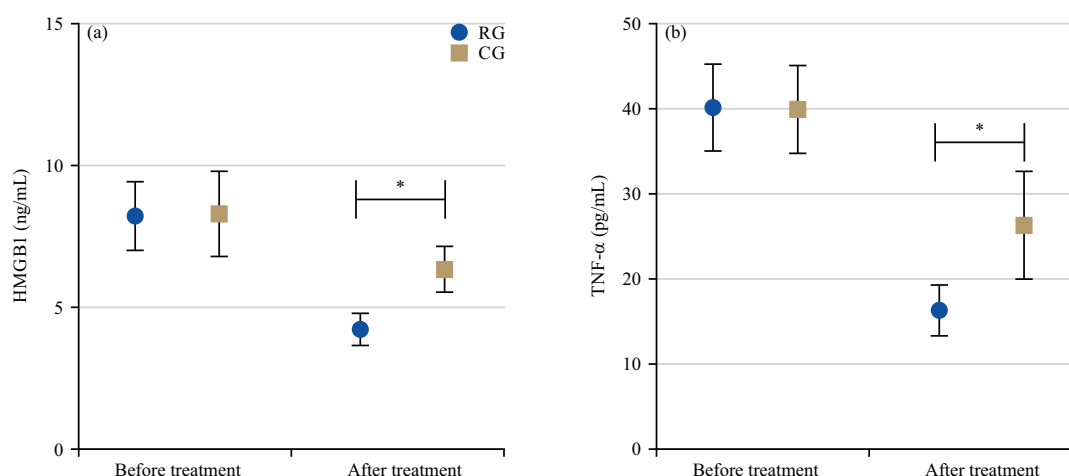


Fig. 7(a-b): Comparison of serum inflammatory factor levels between two groups of pediatric patients before and after treatment, (a) HMGB1 and (b) TNF- α

There was no statistically significant difference in HMGB1 and TNF- α levels between the two groups of pediatric patients before treatment ($p>0.05$); After treatment, the levels of HMGB1 and TNF- α in the research group were lower than those in the control group ($p<0.05$) and $*p<0.05$

Comparison of incidence of adverse reactions between two groups of pediatric patients: In the research group, there were 2 cases of somnolence, 2 cases of dizziness and 3 cases of anorexia, with a total incidence of adverse reactions of 17.50% (7/40), which had no statistical significance compared with 15.00% (6/40) in the control group ($p>0.05$), as shown in Fig. 8.

DISCUSSION

The findings of this study suggested that compared to the utilization of levetiracetam alone in treating pediatric epilepsy,

the combined therapy of levetiracetam with perampanel demonstrated a higher clinical efficacy, a more pronounced improvement in the inflammatory state of the body, a significant reduction in the frequency and duration of seizures and commendable safety profile in pediatric epilepsy patients. The subsequent section delineates the analysis and discussion of distinct outcomes.

In this study, a grouping and comparison method was adopted to analyze the clinical value of perampanel in the treatment of pediatric epilepsy and the results showed that compared with the control group treated with levetiracetam alone, the pediatric patients in the research group treated

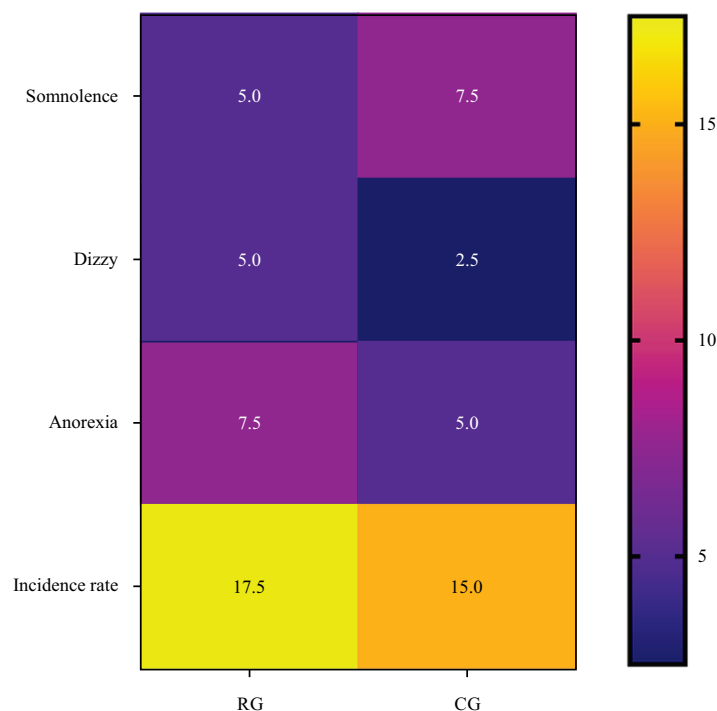


Fig. 8: Comparison of incidence of adverse reactions between two groups of pediatric patients

Total incidence of adverse reactions of children in the research group was 17.50% (7/40), which was not statistically significant compared with 15.00% (6/40) of children in the control group ($p > 0.05$)

with levetiracetam and perampanel had a significantly higher clinical efficacy rate (97.50 vs 80.00%); moreover, after intervention, the NHS3 scores for epilepsy patients in the research group were lower than those in the control group, indicating that the adjunctive perampanel treatment contributes to enhancing the effectiveness of the pharmacological interventions and effectively improves the cognitive function of the pediatric patients. Although surgical procedures have been made in the treatment of epilepsy in recent years, pharmaceutical intervention remains the most commonly employed method and the emergence of new antiepileptic drugs, characterized by fewer side effects and limited drug interactions, has been widely applied for various types of epileptic seizures since 1994^{13,14}. Perampanel is a novel antiepileptic drug. Recent clinical studies indicate that perampanel has demonstrated favorable effects in treating various types of seizures, including generalized tonic-clonic seizures and partial seizures, both in adults and children when administered either adjunctively or as a monotherapy^{15,16}. A research conducted on patients with secondary epilepsy after cerebral infarction¹⁷ revealed that patients treated with perampanel in group B demonstrated significantly higher clinical efficacy compared to those in group A treated with carbamazepine (94.20 vs 73.91%) and this study also highlighted that post-treatment neurological functional

deficits showed more noticeable improvement in group B patients than in group A. The authors of this study analyzed that perampanel belongs to the second generation of new broad-spectrum antiepileptic drugs, which exerts its antiepileptic effects mainly through the mechanisms of blocking voltage-dependent sodium and calcium ion channels, enhancing GABA_A receptor activity and augmenting partial voltage-gated and calcium-gated potassium ion channel influx¹⁸. Compared to traditional antiepileptic drugs, perampanel possesses the following advantages: (1) This medication exerts its effects by reducing excitatory responses in the nervous system, thereby helping to protect the patient's cerebral neural function, which is of positive significance in reducing the impact of epilepsy on patient's memory, language, executive abilities and computational skills, thus contributing to the protection of cognitive function^{19,20}; (2) Perampanel has the capacity to enhance the cognitive abilities of patients to a certain extent, consequently reducing the occurrence of epileptic episodes, which has a positive effect on improving clinical efficacy^{21,22}. Under the influence of the above mechanisms, the clinical efficacy of patients in the research group was significantly better than that of the control group. The cognitive function scores of the pediatric patients in the research group were also better than those of the control group after intervention.

In addition, the results of this study suggest that the addition of perampanel helps to improve the seizure frequency and duration in children with epilepsy and the research group showed shorter P300 latency and higher P300 wave amplitude compared with the control group after intervention. The authors of this study analyzed that perampanel mainly exerts its therapeutic effect on epileptic seizures by modulating Ca^{2+} channels and has multiple sites and multiple mechanisms of action in the body and that long-term use of perampanel in treating seizures allows the drug to bind to the synaptic vesicle protein SV2A to reduce the release of neurotransmitters, thereby inhibiting the occurrence of abnormal discharges and thus achieving the purpose of epilepsy treatment²³. In this study, the reduction of the intermittent epileptiform discharges in the EEG of the pediatric patients in the research group was more pronounced than in the control group after treatment, while the increase of intermittent epileptiform discharges in the EEG was significantly lower in the research group than that in the control group, which suggests that the efficacy of perampanel treatment is better and safer. A research conducted on epileptic children²⁴ revealed that compared to receiving treatment with levetiracetam, the addition of perampanel treatment reduced the impact of the drug on the EEG background activity of epileptic children, ensuring the normal EEG development in affected children, thereby benefiting the subsequent brain development of epileptic children.

Furthermore, the results in this study showed that the improvement of immune function in the research group was better than that in the control group after treatment with perampanel. Existing research indicates that immune response is one of the significant causes of epilepsy, which should not be disregarded. Clinically, neural-specific autoantibodies in serum or cerebrospinal fluid are often considered crucial indicators for diagnosing epilepsy. Liu *et al.*²⁵ compared 90 epileptic patients with 90 healthy volunteers and found that the levels of IgA, IgG and IgM in epileptic patients differed greatly from those of healthy individuals; to further validate the correlation between inflammatory factors and the condition of epilepsy, the scholars implemented follow-up treatment on epileptic patients and observed noticeable changes in the levels of IgA, IgG and IgM of epileptic patients after receiving treatment with oxcarbazepine, leading to significant improvement in their immune function and the scholars analyzed that immune response might play a certain role in the progression of epilepsy. The authors of this study analyzed that the pathogenesis of epilepsy is very complex. As early as 1977,

a study by Abenza-Abildúa *et al.*²⁶ proposed that the neuroendocrine system and the immune system are not isolated entities; the regulatory function of the neuroendocrine system and the defensive role of the immune system are integral components in the body's homeostatic regulation and epilepsy arises from the disruption of the neuroendocrine-immune network, thus theoretically suggesting the potential use of immunotherapy as an intervention for individuals with epilepsy, which is also corroborated by the results of Lim *et al.*²⁷. Finally, the comparison of adverse reactions between the two patient groups confirmed the commendable safety profile of perampanel in the treatment of epilepsy. The authors of this study analyzed that the adverse effects of drugs used for the treatment of epilepsy are particularly prominent and most patients exhibit significant side effects during the course of medication, with some even displaying resistance to treatment due to severe adverse reactions. This evidently impedes the prospects of prolonged treatment for the patients. The mechanism analysis for the reduced occurrence of adverse reactions through combined medication is as follows: Perampanel mainly plays a therapeutic effect by reducing the excitatory response of the nervous system in epilepsy patients and this mechanism, to a certain extent, can protect the cerebral neural function of the patients and has a minimal impact on the cognitive functions of the patients, such as language, calculation and comprehension²⁸. Furthermore, after oral administration, perampanel exhibits a prolonged half-life in small doses, enabling more thorough elimination and excretion from the body, which also significantly reduces the discomfort of patients after medication intake²⁹.

The shortcomings of this study are the small sample size and simple source. It is planned to conduct a large sample, multicenter, prospective randomized study, which will significantly enhance the accuracy of the research data.

CONCLUSION

The application of perampanel in the treatment of pediatric epilepsy is conducive to enhancing therapeutic outcomes, controlling the frequency and duration of seizures, reducing epileptic discharges, improving cognitive functions and lowering the serum levels of HMGB1 and $\text{TNF-}\alpha$ of pediatric patients. This approach exhibits a comparable safety profile to monotherapy, demonstrating a certain degree of clinical applicability for wider use.

SIGNIFICANCE STATEMENT

Epilepsy is the second most common neurological disorder in neurology. Pharmacotherapy remains a common intervention for epilepsy, yet traditional antiepileptic drugs have been less utilized in clinical practice due to numerous side effects and strong drug interactions. This study aimed to evaluate the clinical value of perampanel in treating pediatric epilepsy and analyze the impact of interventions on the immune function and seizure frequency in affected children. The findings revealed that compared with levetiracetam alone, the combined use of perampanel contributes to enhancing therapeutic outcomes, reducing frequency of seizures, improving inflammatory status of children with epilepsy and exhibiting higher safety profile. This research provides novel insights into pharmacotherapy for pediatric epilepsy, offering data support for the clinical application of perampanel.

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