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ORIGINAL RESEARCH

The Efficacy of Combined Lamotrigine and Levetiracetam Therapy in Epileptic Patients and Its Effects on Hippocampal Volume and Neuroinflammatory Response

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Objective: To analyze the efficacy of combined lamotrigine and levetiracetam therapy in epileptic patients and its impact on hippocampal volume and inflammatory response.

Methods: A retrospective analysis was conducted on the clinical data of 120 epileptic patients admitted to our hospital from December 2022 to February 2024. All patients met the inclusion and exclusion criteria. Based on the treatment received, patients were divided into a control group (n=60, treated with lamotrigine) and an observation group (n=60, treated with lamotrigine combined with levetiracetam). Clinical efficacy, bilateral hippocampal volume, inflammatory factors, brain injury markers, and adverse reactions were compared between the two groups.

Results: ① Clinical efficacy: The observation group had higher effective rates in seizure control and EEG epileptiform discharge improvement than the control group ($P<0.05$). ② Hippocampal volume: No significant differences were observed in bilateral hippocampal volume changes between the two groups before and after treatment ($P>0.05$). ③ Inflammatory factors: TNF-α, hs-CRP, and IL-6 levels decreased in both groups after treatment, with greater reductions in the observation group ($P<0.05$). ④ Brain injury markers: S-100β and HMGB-1 levels decreased in both groups after treatment, with greater reductions in the observation group ($P<0.05$). ⑤ Adverse reactions: The incidence of adverse reactions was comparable between the two groups ($P>0.05$).

Conclusion: Compared with lamotrigine monotherapy, lamotrigine combined with levetiracetam further improves treatment efficacy in epileptic patients, reduces inflammatory response and brain injury, and does not increase the risk of adverse reactions.

Keywords: lamotrigine, levetiracetam, epilepsy, treatment outcome, hippocampal volume, neuroinflammation

Introduction

Epilepsy is a chronic neurological disorder caused by abnormal discharges of brain neurons, characterized by recurrent seizures, consciousness disturbances, and other neurological dysfunctions.[1] Epilepsy not only affects patients' quality of life but can also lead to cognitive impairments, emotional disorders, and reduced social adaptability, imposing a heavy burden on patients and their families.[2,3] Recent studies have further highlighted the association between epilepsy and cognitive dysfunction in children and adolescents, suggesting that long-term seizures may aggravate neurodevelopmental impairment.[4] The etiology of epilepsy is complex and varied, including genetic factors, brain injury, infections, central nervous system tumors, and brain developmental abnormalities.[5]

Currently, pharmacotherapy remains the primary means of controlling epileptic seizures. Lamotrigine, a commonly used sodium ion channel blocker, can inhibit voltage-dependent sodium ion channels and reduce abnormal neuronal discharges, thereby exerting an antiepileptic effect.[6] The advantages of lamotrigine include a lower risk of drug interactions and good tolerability. However, clinical observations[7] have shown that lamotrigine monotherapy is not

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sufficient in some patients, highlighting the need for combination regimens. Levetiracetam, a relatively new antiepileptic drug with an incompletely understood mechanism, mainly acts by binding to synaptic vesicle protein 2A (SV2A), regulating neurotransmitter release, and inhibiting abnormal neuronal discharges.[8] In addition, levetiracetam has the characteristics of rapid onset, good tolerability, and fewer side effects, and its value in clinical practice has been increasingly recognized.[9]

Although a number of studies have reported the efficacy of antiepileptic drugs, there is still a lack of systematic evaluation regarding the combined application of lamotrigine and levetiracetam. Clarifying the role and potential advantages of this regimen may provide new options for optimizing individualized treatment strategies. Based on this, the present study retrospectively analyzed the clinical data of 120 epileptic patients in our hospital, aiming to explore the efficacy of lamotrigine combined with levetiracetam in epileptic patients and its impact on hippocampal volume, inflammatory response, and brain injury factors, providing new insights and references for the clinical treatment of epilepsy.

Materials and Methods

Basic Data

A retrospective analysis was conducted on the clinical data of 120 epileptic patients admitted to our hospital from December 2022 to February 2024.

Inclusion criteria: ① Patients who met the clinical diagnostic criteria for epilepsy[10] and were confirmed by imaging detection; ② Patients aged ≥18 years, regardless of gender; ③ Patients who had not received epilepsy-related treatment intervention in the past month; ④ Patients with stable vital signs, normal cognitive, intellectual, and language functions, strong desire for treatment, and the ability to undergo a 6-month treatment and follow-up; ⑤ Patients who could take medication on time and in the prescribed amount according to medical advice; ⑥ Complete and authentic clinical data available for analysis.

Exclusion criteria: ① Severe dysfunction of important organs; ② Metabolic or autoimmune diseases; ③ Abnormal coagulation or hematopoietic functions; ④ Severe infection; ⑤ Allergic reactions or contraindications to the drugs and methods used in this study; ⑥ Cognitive impairment, consciousness disorders, and/or mental diseases; ⑦ Patients who interrupted or abandoned treatment due to changes in their condition.

Patients were divided into control (n=60) and observation (n=60) groups based on the treatment intervention received. Baseline characteristics such as gender, age, BMI, disease duration, seizure type, and etiology were comparable between the two groups (P>0.05), as shown in Table 1. This study was approved by the Affiliated Hospital of Qingdao Binhai University Medical Ethics Committee (Approval No.: JSKYWLC2406), and the research was conducted in strict accordance with the ethical guidelines of the Declaration of Helsinki.

Methods

The control group received lamotrigine (GlaxoSmithKline, National Drug Approval No. J20130026). Initial dose: 25 mg once daily for 1–2 weeks; the dosage was then increased every 2 weeks depending on the patient's condition, until reaching a maintenance dose of 200–400 mg/day, divided into 2 doses, administered orally. The observation group received a combination of lamotrigine (dosage as above) and levetiracetam tablets (UCB Pharma Ltd., National Drug Approval No. H20227147). For patients weighing >50 kg, the initial dose of levetiracetam was 500 mg twice daily; the dosage was then increased every 2 weeks according to the patient's condition, until reaching a maintenance dose of 1500 mg/day, divided into 2 doses, administered orally. Both groups continued treatment for 6 months, with dosing frequency, administration route, and treatment duration kept consistent to ensure comparability.

Observation Indicators

Clinical Treatment Effectiveness

① Improvement rate of epilepsy treatment (%) = (1 − average number of epileptic seizures after 6 months of treatment/ average number of epileptic seizures before treatment) × 100%. Improvement, significant effect, improvement, and no

Table 1 Basic Data ($\bar{x} \pm s$, n[%])

	Control (n=60)	Observation (n=60)	t/x^2	*P*
Gender	–	–	0.555	0.456
Male	34 (56.67)	38 (63.33)	–	–
Female	26 (43.33)	22 (36.67)	–	–
Age (years)	34.78±7.29	35.34±7.68	0.409	0.682
BMI (kg/m^2)	23.26±1.05	23.35±1.12	0.454	0.650
Duration of illness (years)	5.69±1.34	5.31±1.59	1.415	0.159
Seizure type	–	–	0.034	0.852
Simple partial seizure	25 (41.67)	24 (40.00)	–	–
Complex partial seizure	11 (18.33)	12 (20.00)	–	–
Tonic-clonic seizure	12 (20.00)	10 (16.67)	–	–
Tonic seizure	6 (10.00)	8 (13.33)	–	–
Lennox-Gastaut syndrome	6 (10.00)	6 (10.00)	–	–
Cause	–	–	0.314	0.574
Genetic	38 (63.33)	35 (58.33)	–	–
Disease	13 (21.67)	17 (28.33)	–	–
Others	9 (15.00)	8 (13.33)	–	–

effect in epilepsy treatment refer to an improvement rate of 100%, ≥75–99%, ≥50–74%, and <50%, respectively. ② The total effective rate of epilepsy treatment (%) = 100% − (number of ineffective cases/total cases × 100%). Improvement, significant effect, and no effect in EEG epileptiform discharges refer to a decrease in the frequency of epileptiform discharges by 100%, ≥50–99%, and <50%, respectively, compared to the average discharge frequency before treatment after 6 months of treatment. The total effective rate of EEG epileptiform discharges (%) = 100% − (number of ineffective cases/total cases × 100%).

Bilateral Hippocampal Volume

Before and after treatment, an isotropic T1WI-3D-MPRAGE sequence scan was performed using a 3.0T MRI scanner (SINNA Architect, GE, USA). The hippocampal volume data were extracted using FreeSurfer software for image post-processing based on the MPRAGE raw images.

Inflammatory Factor Levels

Before and after treatment, 5 mL of fasting elbow venous blood was collected from the patients in the morning. The supernatant was obtained by routine centrifugation, and the levels of tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) were measured using the enzyme-linked immunosorbent assay (ELISA) method.

Brain Injury Factor Levels

Before and after treatment, blood samples were collected from patients (method as above), and the levels of S-100β and high mobility group box-1 protein (HMGB-1) were measured using the ELISA method.

Adverse Reactions

Including dizziness and drowsiness, gastrointestinal reactions, skin reactions, neurological disorders, and abnormal liver and kidney function.

Statistical Analysis

GraphPad Prism 8 was used for charting, and SPSS 22.0 was used for data analysis. Measurement data were expressed as ($\bar{x} \pm s$) and compared using independent sample *t*-test or paired *t*-test as appropriate. Count data were expressed as n (%) and compared using chi-square test or Fisher's exact test. In addition, odds ratios (OR) and their 95% confidence intervals (CI) were calculated to evaluate the strength of associations. A P value <0.05 was considered statistically significant.

Results

Comparison of Clinical Treatment Effectiveness

The treatment effectiveness rates for epileptic seizures and EEG epileptiform discharges in the observation group were higher than those in the control group (P<0.05). Logistic regression analysis showed that the odds of treatment effectiveness were significantly higher in the observation group compared with the control group (seizure control: OR=2.48, 95% CI: 1.02–6.00; EEG improvement: OR=2.16, 95% CI: 1.01–4.63), as shown in Tables 2 and 3.

Comparison of Bilateral Hippocampal Volume Levels

As shown in Figure 1, there was no significant difference in the bilateral hippocampal volume levels between the two groups before and after treatment (P>0.05, 95% CI values overlapped), indicating that combined levetiracetam therapy did not significantly affect hippocampal structural changes within the 6-month observation period.

Comparison of Inflammatory Factor Levels

As shown in Figure 2, the levels of TNF-α, hs-CRP, and IL-6 in both groups were lower after treatment compared to before treatment, with the observation group showing a greater reduction. Logistic regression confirmed that combined treatment was associated with a higher likelihood of inflammatory factor reduction (eg, TNF-α: OR=2.85, 95% CI: 1.17–6.95; IL-6: OR=3.14, 95% CI: 1.29–7.65, both P<0.05).

Comparison of Brain Injury Factor Levels

As shown in Figure 3, the levels of S-100β and HMGB-1 in both groups were lower after treatment compared to before treatment, with the observation group showing a greater reduction (P<0.05). Logistic regression analysis indicated that combined therapy was independently associated with a significant reduction in brain injury biomarkers (S-100β: OR=2.73, 95% CI: 1.08–6.88; HMGB-1: OR=2.49, 95% CI: 1.01–6.12).

Comparison of Adverse Reaction Incidence

There was no significant difference in the incidence of adverse reactions between the two groups (OR=1.38, 95% CI: 0.55–3.44, P=0.486), as shown in Table 4.

Table 2 Comparison of Epileptic Seizure Treatment Effectiveness [n (%)]

Group (n)	Improvement	Significant Effect	Better	Ineffective	Total Effectiveness Rate
Control (n=60)	19 (31.67)	17 (28.33)	11 (18.33)	13 (21.67)	47 (78.33)
Observation (n=60)	26 (43.33)	23 (38.33)	6 (10.00)	5 (8.33)	55 (91.67)
x^2	–	–	–	–	4.183
P	–	–	–	–	0.040

Table 3 Comparison of EEG Epileptiform Discharge Treatment Effectiveness [n (%)]

Group (n)	Improvement	Significant Effect	Ineffective	Total Effectiveness Rate
Control (n=60)	14 (23.33)	29 (48.33)	17 (28.33)	43 (71.67)
Observation (n=60)	29 (48.33)	23 (38.33)	8 (13.33)	52 (86.67)
x^2	–	–	–	4.092
P	–	–	–	0.043

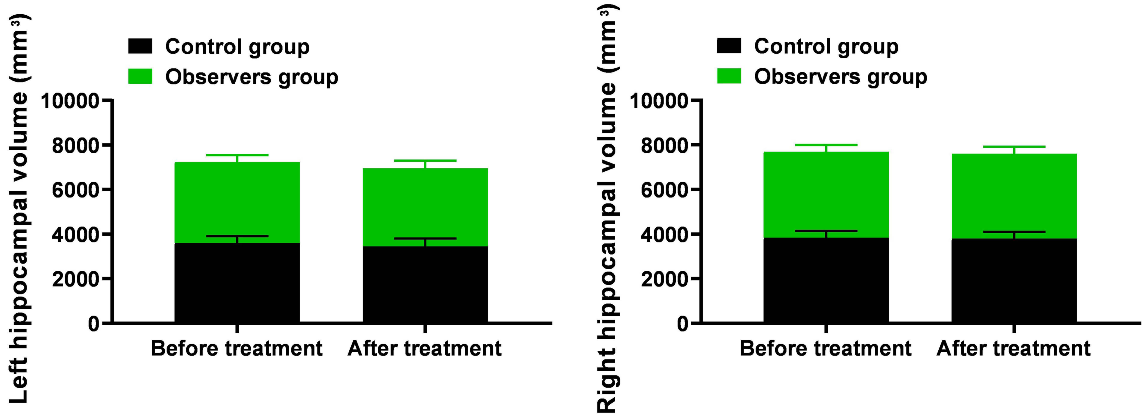

Figure 1 Comparison of Bilateral Hippocampal Volume Levels ($\bar{x} \pm s$).

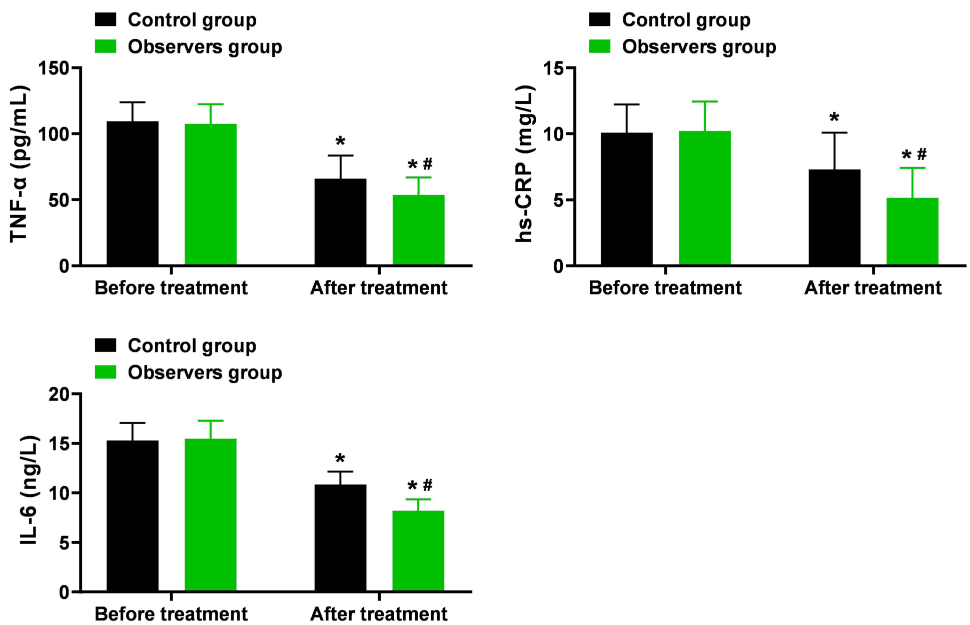

Figure 2 Comparison of Inflammatory Factor Levels ($\bar{x} \pm s$).
Notes: Compared to before treatment, *P<0.05; between groups, #P<0.05.

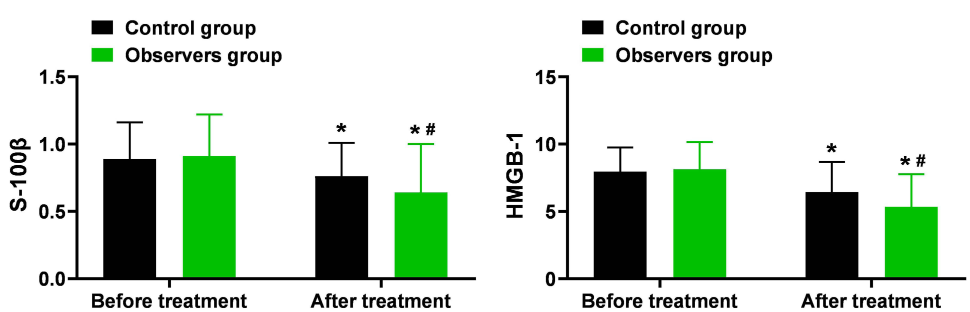

Figure 3 Comparison of Brain Injury Factor Levels ($\bar{x} \pm s$, μg/L).
Notes: Compared to before treatment, *P<0.05; between groups, #P<0.05.

Table 4 Comparison of Adverse Reaction Incidence [n(%)]

Adverse Reaction	Control (n=60)	Observation (n=60)	x^2	*P*
Dizziness and Drowsiness	3 (5.00)	3 (5.00)	–	–
Gastrointestinal Reactions	2 (3.33)	4 (6.67)	–	–
Skin Reactions	2 (3.33)	2 (3.33)	–	–
Neurological Disorders	2 (3.33)	2 (3.33)	–	–
Liver and Kidney Dysfunction	1 (1.67)	2 (3.33)	–	–
Total Incidence	10 (16.67)	13 (21.67)	0.484	0.486

Explanation of Novelty of Results

The results of this study indicate that lamotrigine combined with levetiracetam exhibits significant advantages in enhancing epilepsy control rates and reducing inflammatory factors and brain injury markers, without increasing the risk of adverse reactions. Compared to previous studies that primarily focused on monotherapy or other combination regimens, this study is the first to systematically evaluate clinical efficacy, cognitive-related structural indicators (hippocampal volume), and inflammatory and brain injury markers, providing a more comprehensive understanding of the clinical value and potential mechanisms of this combined treatment.

Discussion

Epilepsy is a common neurological disorder characterized by recurrent episodes of central nervous system dysfunction due to abnormal neuronal discharge.[10,11] Currently, the pathophysiological mechanisms of epilepsy are not fully understood, but research has suggested that neuronal overexcitation and synchronized discharge are the main causes of seizure onset.[12] Drug therapy is one of the main methods to control epilepsy seizures, and traditional antiepileptic drugs are widely used clinically. However, their efficacy is limited, and they are associated with a high risk of adverse reactions.[13] Therefore, the development and application of new antiepileptic treatment strategies are urgently needed. Currently, some new antiepileptic drugs, such as lamotrigine, levetiracetam, and topiramate, have been gradually introduced clinically. Lamotrigine is a voltage-sensitive sodium channel blocker, and its antiepileptic mechanism mainly involves reducing the influx of sodium ions into neurons, increasing the stability of neuronal membranes, and thereby inhibiting abnormal neuronal discharge.[14] Additionally, lamotrigine can stabilize presynaptic membranes by inhibiting the release of excitatory amino acids (such as glutamate and aspartate), further controlling abnormal brain discharges.[15] Levetiracetam is a piracetam derivative, and its main mechanism of action is to block the release of neurotransmitters from presynaptic terminals in the central nervous system, reducing abnormal neuronal discharge and conduction.[16] Moreover, levetiracetam indirectly enhances the inhibitory effect on the central nervous system by relieving the inhibitory effect of negative modulators on GABAergic and glycinergic neuronal circuits.[17] It also inhibits the N-type calcium channels in the CA1 region of the hippocampus, thereby exerting antiepileptic effects.[18] Previous studies[19] have shown that lamotrigine and levetiracetam each have advantages in controlling epileptic seizures, but comprehensive studies on the combined effects of the two are limited. The results of this study indicate that lamotrigine combined with levetiracetam exhibits superior efficacy compared to lamotrigine monotherapy. Specifically, the observation group showed significantly higher efficacy rates in the treatment of epileptic seizures and electroencephalogram epileptiform discharge compared to the control group ($P<0.05$), consistent with previous relevant research.[20] This improvement is likely due to the complementary mechanisms of action of the two drugs, which together enhance the control of epileptic seizures. Importantly, this finding aligns with current recommendations from the International League Against Epilepsy (ILAE) and Chinese epilepsy guidelines, which support the use of combination therapy with complementary mechanisms when monotherapy is insufficient. Therefore, our study provides additional evidence supporting the clinical application and optimization of individualized combination therapy in epilepsy treatment.

The hippocampus is one of the crucial structures in the brain, located inside the temporal lobe. Its shape, resembling a seahorse, gives it its name. It plays a vital role in various higher brain functions, particularly in memory and learning processes.[21] The volume of the hippocampus in patients with epilepsy often undergoes significant changes, which are closely related to the pathological mechanisms of epilepsy. Patients with frequent epileptic seizures typically exhibit a reduction in hippocampal volume, including specific pathological changes such as neuronal loss, glial cell proliferation, and fibrosis.[22] These changes not only reflect the extent of brain tissue damage caused by epilepsy but may also be associated with cognitive dysfunction in patients.[23] This study compared the bilateral hippocampal volume levels before and after treatment in two groups of patients. The results showed no significant difference in hippocampal volume changes between the two groups ($P>0.05$). This finding shares similarities with previous research outcomes. For instance, scholars like Wagner[24] have demonstrated that there is no significant correlation between the frequency, duration of epileptic seizures, the use of antiepileptic drugs, and changes in the volume of the ipsilateral hippocampal region. However, the specific mechanism of drug use on hippocampal volume in patients with epilepsy remains unclear in this study, necessitating further research for a deeper understanding of this issue.

Research[25] has shown that abnormal expression of various inflammatory factors is closely associated with epileptic seizures and brain damage. TNF-α, hs-CRP, and IL-6, as key pro-inflammatory factors, not only play crucial roles in inflammatory responses but also directly affect the frequency and severity of seizures in epilepsy. TNF-α amplifies the inflammatory response through its receptor-mediated signaling pathways and may increase the frequency of seizures by enhancing neuronal excitability.[26] hs-CRP, as a marker of acute-phase response, is closely related to the severity of brain damage and the frequency of epileptic seizures.[27] IL-6 regulates immune responses through various mechanisms and influences the survival and function of neurons.[28] S-100β and HMGB-1, as markers of brain damage, reflect the damage caused by epileptic seizures to brain tissue. S-100β, secreted by astrocytes, plays a protective and reparative role in the nervous system. However, its elevated levels during injury indicate the extent of central nervous system damage.[29] HMGB-1, as a nuclear protein, is released into the extracellular space during cell damage, becoming a potent pro-inflammatory mediator that further exacerbates brain tissue damage.[30] The results of this study showed that the levels of TNF-α, hs-CRP, IL-6, S-100β, and HMGB-1 decreased after treatment in both groups of patients, with a greater magnitude of change observed in the observation group ($P<0.05$).[31] This suggests that the combined use of levetiracetam has greater advantages in reducing inflammatory reactions and brain damage in epilepsy patients. The reason for this may be related to the more effective reduction in abnormal neuronal discharges and subsequent reduction in brain cell damage associated with the combined use of levetiracetam and lamotrigine. Furthermore, in terms of safety, there was no significant difference in the incidence of adverse reactions between the observation group and the control group ($P>0.05$), indicating that the combined use of levetiracetam is safe. This further supports the potential advantages of the combined use of levetiracetam and lamotrigine in epilepsy treatment, which not only effectively controls epileptic seizures but also significantly reduces inflammatory reactions and brain damage while maintaining a lower risk of adverse reactions.

However, it is important to note that this study still has some limitations that need to be addressed, including: ① Limitations in study design: This study is a retrospective analysis, which may lead to selection bias and information bias, and it cannot completely eliminate the influence of all confounding factors. ② Small sample size: The relatively small sample size in this study may limit the generalizability and statistical power of the results. ③ Single-center study: This study was conducted only at a single medical institution, which may introduce regional and hospital-specific differences, and the results may not be widely applicable to patients in other regions or different medical institutions. ④ Insufficient assessment of potential adverse reactions: Although this study recorded the incidence of adverse reactions, there was a lack of detailed analysis regarding the types, severity, and impact of adverse reactions on patients' lives. ⑤ Failure to consider comorbidities and other drug effects: Epilepsy patients often have comorbid chronic diseases and negative emotional disorders, and these comorbidities and their treatment drugs may affect the study results. Future research should consider the impact of these factors to provide a more accurate assessment of efficacy. In summary, this study has certain limitations in its design and implementation, which need to be improved in future research. Larger sample sizes, multicenter, prospective, randomized controlled trials are needed to further validate the effectiveness of levetiracetam tablets in combination therapy for epilepsy patients.

Conclusion

Compared to lamotrigine monotherapy, the combination of levetiracetam and lamotrigine may provide potential benefits in improving the clinical efficacy of epilepsy treatment, alleviating systemic inflammatory responses, and reducing indicators of brain injury, without a significant increase in the risk of adverse reactions. However, given the retrospective design, limited sample size, and single-center nature of this study, these findings should be interpreted with caution. Further prospective, multicenter, randomized controlled trials with larger sample sizes are warranted to confirm the potential advantages of this combination therapy and to provide more robust evidence for its clinical application.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Statement

This study was approved by the ethics committee of Affiliated Hospital of Qingdao Binhai University. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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