Effects of levetiracetam and lacosamide on therapeutic efficacy and neural function in patients with epilepsy

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Abstract. The present study aimed to investigate the effects of levetiracetam tablets and lacosamide (LCM) on therapeutic efficacy and neural function in patients with epilepsy. We assigned 252 patients with refractory partial seizures admitted to our hospital to receive either levetiracetam tablets [120 patients, the control group (CG)] or levetiracetam tablets combined with LCM [132 patients, the joint group (JG)]. The bone mineral density and neural function between the two groups at 6 months before and after treatment were compared. The total response rate was higher in the JG than in the CG ($P<0.05$). There was no significant difference in the comparison of the multiple indexes between the two groups before treatment ($P>0.05$). The frequency of seizures was reduced after treatment in the two groups, however, it was lower in the JG compared with the CG ($P<0.05$). The levels of neurological indicators were significantly reduced after treatment in the two groups ($P<0.05$), however, the reduction was more marked in the JG than in the CG. The bone mineral density (BMD) of the femoral neck decreased after treatment in the two groups ($P<0.05$), but there was no difference between the two groups after treatment ($P>0.05$). The calcium content decreased after treatment in the two groups ($P<0.05$), but there was no difference between the two groups after treatment ($P>0.05$). The comparison of other bone metabolism markers between the two groups exhibited no significant differences. The combination therapy greatly increased the quality of life score and the 1-year drug retention rate. To sum up, levetiracetam tablets combined with LCM significantly enhanced the therapeutic effect and improved the neural function in patients with refractory partial seizures, however this therapy may cause a slight adverse effect on BMD and bone metabolism in the short term.

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Key words: levetiracetam, lacosamide, epilepsy, bone mineral density, neural function

Introduction

Epilepsy is a common chronic disabling neurological disease that affects more than 1% of the population of the world (1,2). It is mainly caused by abnormal discharge of brain neurons, characterized by transient dysfunction of the nervous system (3). If seizures of patients are not controlled for a long time and reoccur frequently, they are likely to cause brain damage (4). Advancements in medical technology have contributed to great accuracy in the diagnosis of epilepsy. Conventional anti-epileptic first-line drugs can control the seizures of most patients with epilepsy, but persistent seizures will occur in more than 30% of patients according to relevant statistics (2,5).

Clinically, an epileptic seizure is generally controlled by symptomatic treatment with long-term medication (6). Traditional antiepileptic drugs have adverse effects on the skeletal system of middle-aged and elderly patients, and the degree of abnormal bone mineral density (BMD) and bone metabolism increases with the medication time, leading to a higher risk of fracture (7,8). Levetiracetam, a pyrrolidone derivative with high water solubility and high permeability, can inhibit the spread of lesions by increasing the excitability threshold of normal brain tissue cells (9,10). It is quickly absorbed after the oral administration, exhibiting good efficacy for preventing seizures (9,10). Lacosamide (LCM) is a newly developed antiepileptic drug, which has been used as an adjuvant treatment for partial or systemic epilepsy in numerous countries in recent years (11). Unlike traditional sodium channel blockers, LCM is novel because it can selectively enhance the slow inactivation of voltage-gated sodium channels without affecting its rapid inactivation (12). In addition, it can selectively attenuate collapsin response mediator protein 2 (CRMP2)-induced tubulin polymerization (13) to exert an antiepileptic effect.

However, to date, levetiracetam combined with LCM has rarely been used in the treatment of senile epilepsy. In addition, the effects of this combination therapy on the efficacy and neural function of patients are not clear. In the present study, the therapeutic effect of levetiracetam combined with LCM in patients with epilepsy was explored, aiming to inspire new treatment options for epilepsy.

Patients and methods

Basic information. We assigned 252 patients with refractory partial seizures admitted to the 5th People's Hospital of Qingdao (Qingdao, China) to receive either levetiracetam tablets [120 patients, the control group (CG)] or levetiracetam tablets combined with LCM [132 patients, the joint group (JG)]. The CG was comprised of 64 males and 56 females, aged 55.42±4.98 years, with an average course of disease of 8.01±3.31 years, while the JG was comprised of 69 males and 63 females, aged 56.13±5.68 years, with an average course of disease of 8.57±3.17 years. The present study was carried out under the approval of the Ethics Committee of the 5th People's Hospital of Qingdao (Qingdao, China) (approval no. QD31344). All patients and their families signed the written informed consent.

Inclusion criteria were as follows: i) Patients diagnosed with refractory partial seizures; ii) patients older than 18 years; iii) patients with more than 4 seizures per month; iv) patients exhibiting a poor response to a stable administration of one or more first-line antiepileptic drugs; v) patients undergoing no adjustment in the drug treatment within 6 months prior to this study; and vi) patients whose plasma-drug concentrations were within the effective range.

Exclusion criteria were as follows: i) Patients with poor compliance with the treatment or the follow-up; ii) patients not accompanied by family members at the time of admission; iii) patients with other diseases or complications affecting the results of the study; iv) patients with incomplete clinical data; v) patients who were pregnant or lactating women; vi) patients with a known history of drug addiction or abuse; vii) patients with abnormal expression levels of indicators for liver and renal function.

Treatment plan. For the CG, on the basis of conventional treatment, patients were treated with levetiracetam tablets (UCB Pharma S.A.; China Food and Drug Administration Approval no. J20160085) at an initial dose of 250 mg, twice a day (500 mg/day), which was increased to 500 mg, twice a day (1,000 mg/day) after two weeks, and then increased to 1,000 mg, twice a day (2,000 mg/day) after another two weeks. Then the dose was maintained at 1,000 mg and adjusted according to the conditions of the patients.

For the JG, in addition to the levetiracetam tablets designed for the CG, patients were also treated with LCM (Aesica Pharmaceuticals GmbH; China Food and Drug Administration Approval no. H20180069) at an initial dose of 50 mg, twice daily. According to the response and tolerance of patients, the dose was increased by 100 mg (twice a day) every other week, and was maintained at 200 to 400 mg per day.

Detection method. Fasting venous blood samples were collected from all patients. Blood calcium (Ca) and blood phosphorus (P) were detected on the Beckman Coulter AU2700 Chemistry Analyzer. Serum Glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), alkaline phosphatase (ALP), and parathyroid hormone (PTH), S-100β protein (S-100β) were tested using the enzyme-linked immunosorbent assay (ELISA). GFAP, NSE, ALP, and PTH ELISA kits were purchased from BioSwamp Life Science Lab (cat. nos. HM10951, HM10786, HM10232, and HM10797, respectively). The S-100β ELISA kit was from Wuhan Yipu Biotechnology Co., Ltd. (cat. no. MM-13258H1). The results were analyzed on the ELISA analyzer manufactured by Beijing Linmao Technology Co., Ltd. (cat. no. BS-1101). According to the kit instructions, standards (50 μl) were added at various concentrations to the standard wells, 10 μl of samples and 40 μl of the diluent were added to the sample wells, and 50 μl of distilled water to the blank well. Then, 50 μl of enzyme-labeled reagent was added to the standard wells and the sample well, the reaction wells covered were covered with a sealer, and incubated for 1 h in a 37˚C water bath or incubator. Next, 50 μl of color reagents A and B were added to each well, the plate was shaken gently, and placed in a dark place at 37˚C for 15 min for color development. Finally, 50 μl stop solution was added to each well, the ELISA Microwell Plate Reader was adjusted to zero using the blank well within 15 min, and then the OD value of each well was measured at 450 nm within 25 min. All test procedures strictly followed the instructions of the kit.

Outcome measures. The following indicators were recorded at 6 months before and after treatment: i) The treatment efficacy in the two groups was assessed. A marked response indicated a complete remission of clinical symptoms, great improvements in vital signs, and a decrease in seizure frequency by >70%. A moderate response indicated a partial remission of clinical symptoms, moderate improvements in vital signs, and a decrease in seizure frequency by 30-70%. No response indicated no improvements in the clinical symptoms or vital signs, and a decrease in seizure frequency by <30% or even no decrease. The total response rate was calculated as follows: Total response rate=percentage of patients with a marked response + percentage of patients with a moderate response. ii) The frequency of seizures was recorded and compared between the two groups. iii) Serum levels of markers for neural function including GFAP, NSE, and S-100β in the two groups were assessed. iv) The BMD of different parts of the body (femoral neck, lumbar vertebra L2-4, femoral trochanter, and Ward triangle) and the expression levels of bone metabolism indexes (Ca, P, ALP, PTH) were monitored. v) Adverse reactions during the treatment and the quality of life scores were recorded. The quality of life was assessed using the Quality of Life in Epilepsy Inventory (QOLIE-31) (14), which is a 100-point scale assessing 6 items: Worries about seizures, emotional health, mental state, cognitive function, drug influence, and social function. A higher total score indicated a better quality of life. vi) Patients were followed up on the telephone or through the outpatient service, and the medication was recorded.

Statistical analysis. The statistical analysis was performed on SPSS v20.0 (IBM Corp.). Count data were expressed as [n (%)] and compared between the two groups by the chi-square test. Measurement data were expressed as the mean ± standard deviation (SD) and compared between the two groups by the independent sample t-test. Multiple comparisons between the two groups before and after treatment were analyzed using the one-way ANOVA, and the LSD t-test was used for the post hoc analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Comparison of the clinical general information (mean ± SD)/[n (%)].

	JG (n=132)	CG (n=120)	χ^2/t	P-value
Sex			0.028	0.866
Male	69 (52.27)	64 (53.33)		
Female	63 (47.73)	56 (46.67)		
Age (years)			0.115	0.735
≤55	60 (45.45)	52 (43.33)		
>55	72 (54.55)	68 (56.67)		
Average age (years)	56.13±5.68	55.42±4.98	1.051	0.295
BMI (kg/m^2)	23.61±2.78	23.97±2.69	1.043	0.298
Place of residence			0.037	0.847
Urban area	71 (53.79)	66 (55.00)		
Rural area	61 (46.21)	54 (45.00)		
Course of the disease (years)	8.57±3.17	8.01±3.31	1.371	0.172
Duration of education (years)	10.07±2.13	10.24±2.53	0.579	0.563
Creatinine (μmol/l)	63.48±8.74	65.37±9.02	1.689	0.093
Urine urea nitrogen (mmol/l)	6.03±1.51	6.13±1.71	0.493	0.623

JG, joint group; CG, control group.

Table II. Comparison of treatment efficacy n (%).

Response	JG (n=132)	CG (n=120)	χ^2	P-value
Marked	67 (50.76)	50 (41.67)		
Moderate	52 (39.39)	47 (39.16)		
No response	13 (9.85)	23 (19.17)		
Total response rate	90.15%	80.83%	4.457	0.035

JG, joint group; CG, control group.

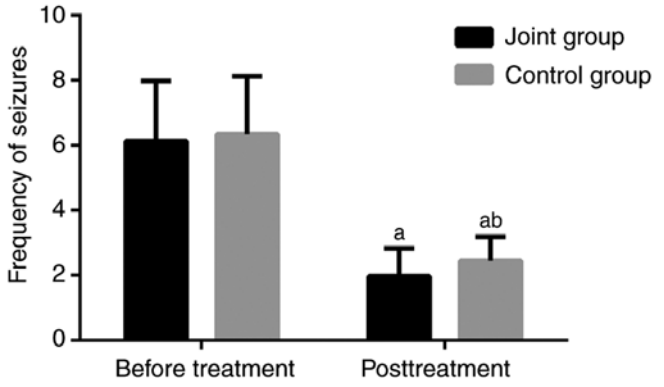

Figure 1. Comparison of the frequency of seizures before and after treatment between the two groups. The frequency of seizures decreased in both groups after treatment as compared with before treatment, with a higher frequency in the CG than in the JG (P<0.05). [a]P<0.05 compared with the data before treatment within the same group. [b]P<0.05 compared with the data in the JG posttreatment. CG, control group; JG, joint group.

Results

Comparison of general information. Details of the general information of patients are presented in Table I. Patients from the JG and patients from the CG were comparable since they were not markedly different in sex, age, body mass index (BMI), place of residence, course of the disease, duration of education, creatinine, and urine urea nitrogen (P>0.05).

Comparison of treatment efficacy. Details of the treatment efficacy in the two groups are presented in Table II. The total response rate was markedly higher in the JG than in the CG (90.15% vs. 80.83%, P<0.05).

Comparison of the frequency of seizures before and after treatment. Details of the frequency of seizures in the two groups are presented in Fig. 1. All patients met the inclusion criteria for the frequency of seizures. The JG and CG were not different in the frequency of seizures before treatment (P>0.05). After 6 months of treatment, the frequency of seizures decreased in both groups, with a slightly higher frequency in the CG than in the JG (P<0.05).

Comparison of neural function markers before and after treatment. The expression levels of neural function markers are presented in Fig. 2. The two groups were not different in the neural function before treatment. The expression levels of NSE, S-100β, and GFAP significantly decreased in the two groups after treatment (P<0.05), with lower NSE and S-100β levels in the JG than in the CG (P<0.05).

Comparison of BMD and bone metabolism before and after treatment. The BMDs of all patients after 6 months of treatment are presented in Table III. The JG and the CG were not obviously different in the BMD of different body parts before treatment (P>0.05). The BMD of the femoral neck decreased in both groups after a period of treatment (P<0.05), but there were no differences between the two groups (P>0.05). The comparison of the bone metabolism indexes are presented in Fig. 3. The JG

Table III. Comparison of BMD between the two groups (mean ± SD).

	JG (n=132)				GC (n=120)			
Body part	Before treatment	After treatment	t-value	P-value	Before treatment	After treatment	t-value	P-value
Femoral neck	0.73±0.16	0.67±0.21	2.828	0.005	0.71±0.15	0.66±0.16	2.247	0.025
Lumbar vertebra L2-4	0.72±0.18	0.70±0.23	0.834	0.405	0.74±0.20	0.71±0.16	1.193	0.234
Femoral trochanter	0.65±0.14	0.63±0.19	0.923	0.367	0.64±0.17	0.60±0.20	1.760	0.080
Ward triangle	0.66±0.18	0.64±0.22	0.876	0.382	0.67±0.19	0.63±0.14	1.670	0.096

BMD, bone mineral density; JG, joint group; CG, control group.

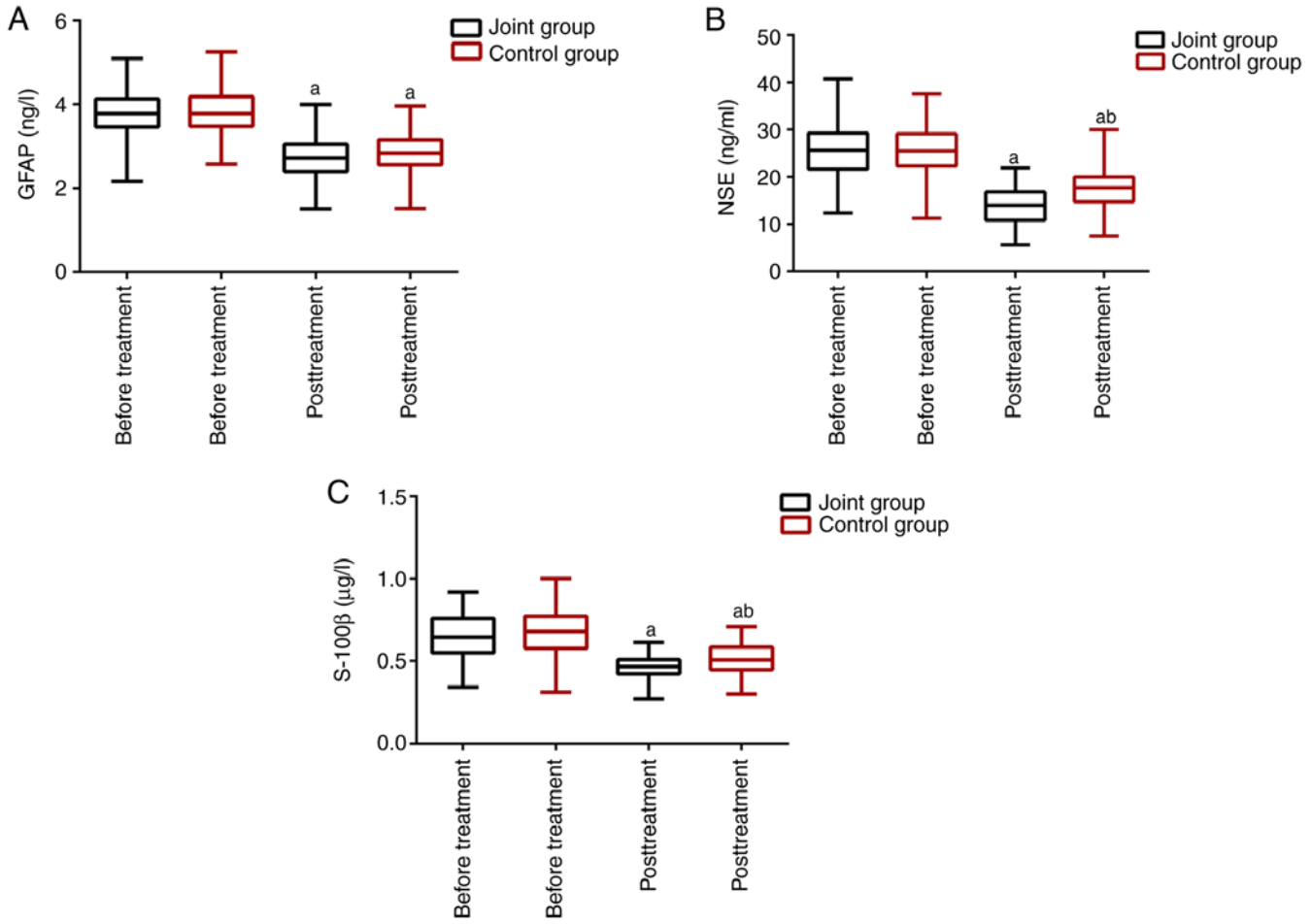

Figure 2. Comparison of neural function markers before and after treatment. (A) The GFAP level was significantly decreased in the two groups after treatment, but the two groups were not significantly different in the GFAP level before treatment nor after treatment (P>0.05). (B) The NSE level was significantly decreased in the two groups after treatment, with a lower NSE level in the JG than in CG (P<0.05). (C) The S-100β level was significantly decreased in the two groups after treatment, with a lower S-100β level in the JG than in the CG (P<0.05). [a]P<0.05 compared with the data before treatment within the same group. [b]P<0.05 compared with the data in the JG posttreatment. GFAP, glial fibrillary acidic protein; NSE, neuron-specific enolase; JG, joint group; CG, control group.

and the CG were not obviously different in the expression levels of bone metabolism indexes before treatment. There were no marked differences in the P and PTH levels between the two groups before and after treatment (P>0.05). In the JG, the ALP level after treatment was higher than that before treatment, but the difference was not statistically significant. In the CG, the ALP level after treatment was lower than that before treatment, but the difference was not statistically significant (P>0.05). The Ca level decreased in both groups after treatment (P<0.05), but there was no significant difference between the two groups after treatment (P>0.05).

Comparison of adverse reactions during treatment. Adverse reactions during the medication period are presented in Table IV. Adverse reactions occurring in the present study included nausea and vomiting, diarrhea, rash, leukocytosis,

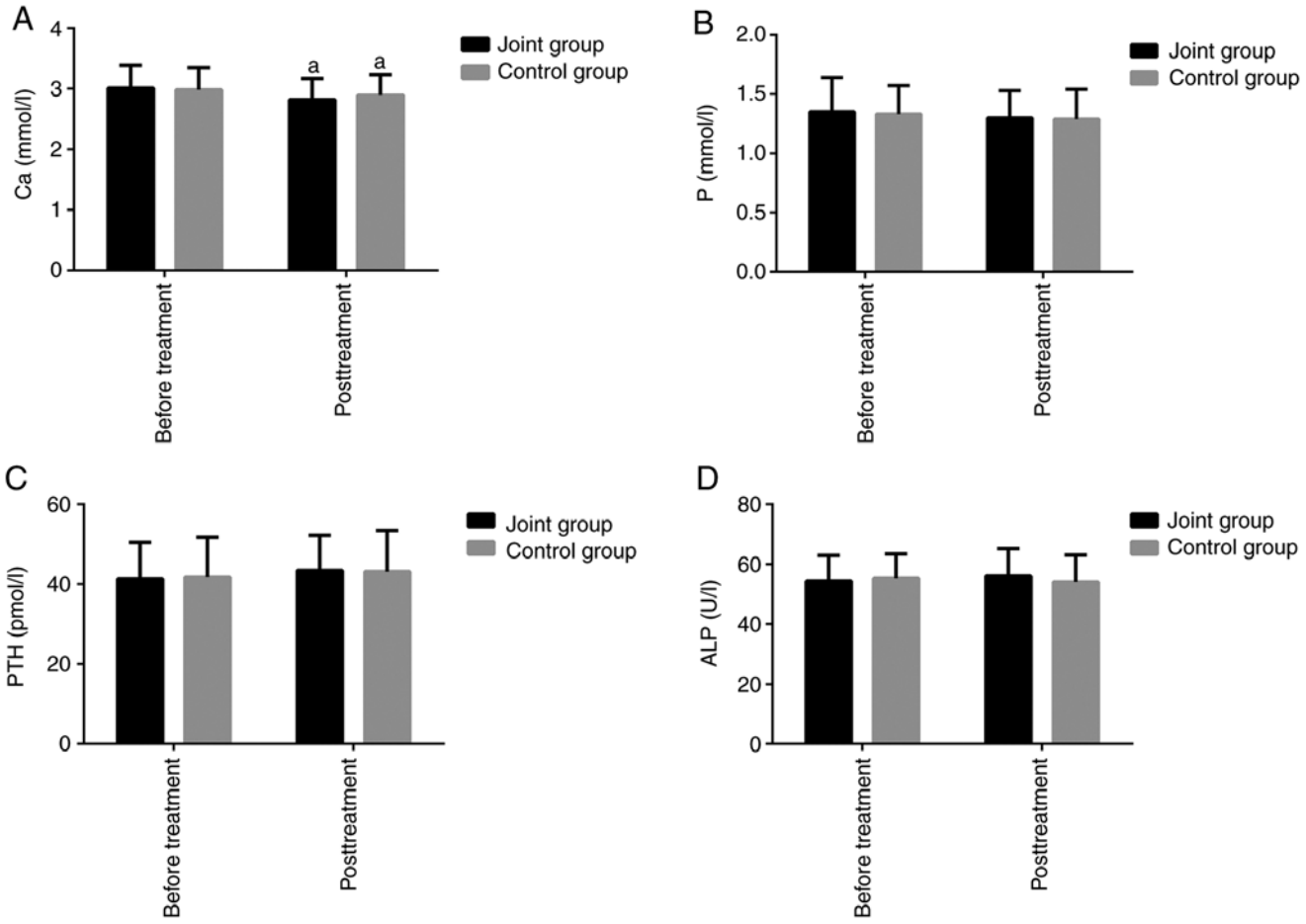

Figure 3. Comparison of bone metabolism indexes before and after treatment. (A) the Ca levels in both groups were lower after treatment than before treatment ($P<0.05$), but the two groups were neither different in the Ca level before treatment nor after treatment ($P>0.05$). (B) There was no marked difference in the P level between the two groups before and after treatment. (C) There was no marked difference in the PTH level between the two groups before and after treatment. (D) There was no marked difference in the ALP level between the two groups before and after treatment. [a]$P<0.05$ compared with the data before treatment within the same group. Ca, calcium; P, phosphorus; PTH, parathyroid hormone; ALP, alkaline phosphatase.

dizziness, and decreased appetite. The comparison of the total incidence of adverse reactions between the JG and the CG revealed no marked difference (20.46% vs. 25.83%, $P>0.05$).

Comparison of the quality of life before and after treatment. The scores of the quality of life before and after treatment are presented in Fig. 4. The JG and CG were not markedly different in the QOLIE-31 score before treatment ($P>0.05$). After treatment, the QOLIE-31 score significantly increased in the two groups, with a slightly higher QOLIE-31 score in the JG than in the CG, and the difference was statistically significant ($P<0.05$).

One-year drug retention rate and causes of drug withdrawal in the two groups. The 1-year drug retention rates in the two groups are presented in Table V and causes of drug withdrawal are presented in Fig. 5. The 1-year drug retention rate was 74.24% in the JG, with 34 cases of drug withdrawal (10 cases were caused by the poor curative effect, 11 by the untoward effect, and 13 by other reasons). The 1-year drug retention rate was 66.67% in the JG, with 40 cases of drug withdrawal (17 cases were caused by the poor curative effect, 12 by the untoward effect, and 11 by other reasons). The 1-year drug retention rate was higher in the JG than in the CG.

Discussion

Epilepsy is divided into systemic and partial seizures (15). Epilepsy is characterized by an acute but short onset, diverse clinical manifestations, a high risk of recurrence, and a complicated mechanism of seizures. Patients with recurrent seizures, whatever the cause is, are often attacked by a variety of psychological, physical, and social diseases that seriously impair their physical and mental health and quality of life (16,17).

In the present study, the treatment responses between two groups were compared to analyze the therapeutic effect of levetiracetam combined with LCM in patients with epilepsy. The results of treatment efficacy in patients with refractory partial seizures in the two groups after 6 months of treatment revealed that patients in the JG had improved treatment efficacy and markedly lower frequency of seizures. A previous study revealed that, in the cortical brain tissue of patients with refractory seizures, LCM can target GABAA receptors and play a synergistic effect with levetiracetam to relieve GABA functional impairment (18). LCM can reduce the frequency of seizures and improve the efficacy in the treatment for children with intractable epilepsy as an adjuvant drug (19). According to the results of the present study and the aforementioned studies,

Table IV. Comparison of adverse reactions, n (%).

Adverse reactions	JC (n=132)	CG (n=120)	χ^2	P-value
Nausea and vomiting	9 (6.82)	11 (9.17)		
Diarrhea	4 (3.03)	3 (2.50)		
Rash	4 (3.03)	6 (5.00)		
Leukopenia	2 (1.52)	3 (2.50)		
Dizziness	3 (2.27)	1 (0.83)		
Decreased appetite	5 (3.79)	7 (5.83)		
Total incidence	20.46%	25.83%	1.026	0.311

JG, joint group; CG, control group.

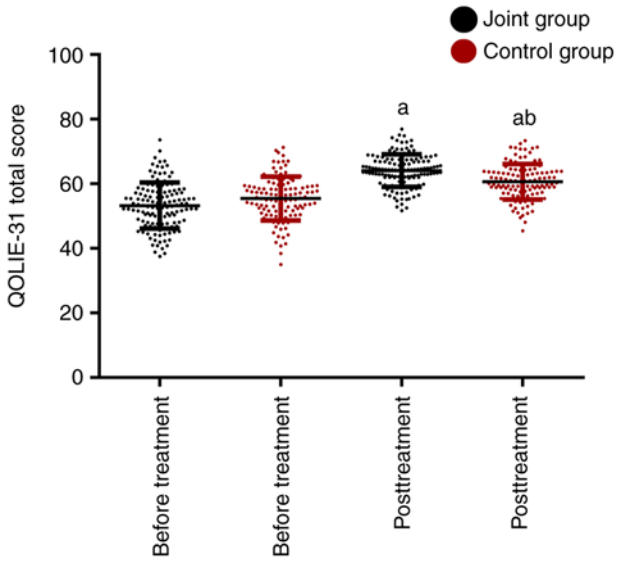

Figure 4. Comparison of the quality of life before and after treatment. The JG and CG were not markedly different in the QOLIE-31 score before treatment. The quality of life significantly improved in the two groups after treatment, with a higher QOLIE-31 score in the JG than in the CG (P<0.05). [a]P<0.05 compared with the data before treatment within the same group. [b]P<0.05 compared with the data in the JG posttreatment. JG, joint group; CG, control group; QOLIE, Quality of Life in Epilepsy Inventory.

it was theorized that levetiracetam can cooperate with LCM to expand the coverage of treatment of epilepsy, protect the neural function of patients, and improve the treatment efficacy. When a patient has a seizure, the nerve tissues are damaged, which causes a mass release of specific factors in the neuron and prompts those specific factors to enter the blood circulation through the damaged blood-brain barrier. The detection of serum nerve injury-related factors can quantitatively reflect the degree of nerve damage caused by seizures (20,21). GFAP is a specific marker for astrocytes, whose mass release can cause abnormal excitation of neurons and aggravate the progression of epilepsy (22). NSE that is present in nerve tissues and S-100β that is present in glial cells, which are upregulated at the onset of a seizure, can reflect the degree of neuronal damage (23). In the present study, the levels of NSE, S-100β, and GFAP were significantly reduced after treatment in the two groups, with a more pronounced reduction in the JG than in the CG. These results suggest that levetiracetam combined with LCM

Table V. Comparison of drug retention, n (%).

Drug use	JG (n=132)	CG (n=120)	χ^2	P-value
Drug retention rate	98 (74.24)	80 (66.67)	42.460	<0.001
Drug withdrawal rate	34 (25.76)	40 (33.33)	42.460	<0.001

JG, joint group; CG, control group.

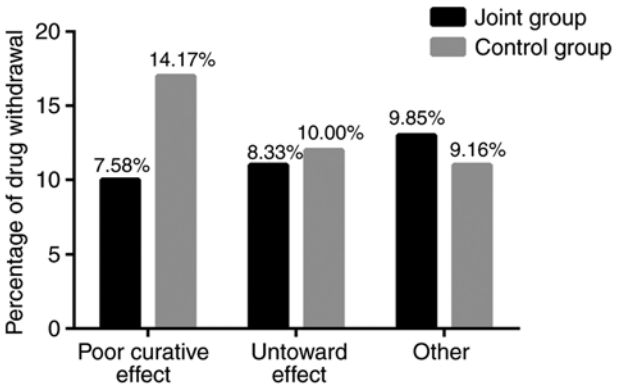

Figure 5. Causes of drug withdrawal in the two groups. In the JG, 7.58% of cases of drug withdrawal were caused by the poor curative effect, 8.33% by the untoward effect, and 9.85% by other reasons, while 14.17% of cases of drug withdrawal in the CG were caused by the poor curative effect, 10.00% by the untoward effect, and 9.16% by other reasons. JG, joint group; CG, control group.

can significantly improve neural function, reduce neural tissue damage, and better protect the brain.

The metabolism of bone is active. In the normal physiological environment, the formation and absorption of bone tissues are in a dynamic equilibrium (24,25). The maintenance of this equilibrium depends on the balance of multiple hormones or trace elements, including PTH, ALP, vitamin D, as well as other steroid hormones (24,25). Fractures in patients with epilepsy are most likely to be caused by a long-term use of antiepileptic drugs which can reduce BMD (26). Therefore, the exploration of the effects of long-term drug treatment on BMD is crucial to the prevention of adverse consequences. In the present study, the BMD and the expression levels of bone metabolism indicators were assessed in the two groups after 6 months of treatment. The results revealed that levetiracetam monotherapy caused a decrease in femoral BMD and Ca content, but caused no obvious changes in the BMD of other body parts or the expression levels of bone metabolism indicators. There was no significant difference between the two groups in the expression levels of bone metabolism indicators after treatment. A study by Beniczky *et al* (27) suggested that the BMD in patients treated with levetiracetam monotherapy is significantly reduced. However, in an animal model study by Anwar *et al* (28), they revealed that levetiracetam did not cause changes in BMD. The latest research has revealed a marked reduction in the BMD and levels of bone metabolism markers (ALP, Ca) in patients receiving levetiracetam monotherapy, and suggested that levetiracetam may alter bone marrow density by affecting the optimal mineralization of cartilage and thereby interfering with the maturation of bone tissue (29).

To date, there have been few studies on the effect of LCM on the BMD and metabolism in epileptic patients. According to the results of the present study, it was theorized that LCM does not aggravate the adverse effects on BMD and bone metabolism caused by levetiracetam.

In the present study, the incidence of adverse reactions was slightly lower in the JG than in the CG, but the difference was not statistically significant. Previous studies (30,31) have revealed that LCM does not aggravate the side effects of levetiracetam in the treatment of epilepsy, suggesting that there are no adverse effects of the combination of the two. But whether LCM can relieve the side effects of levetiracetam remains to be further studied. QOLIE-31 was used to assess the quality of life of patients after treatment. The results revealed that the quality of life of patients was improved in both groups after treatment, with a higher QOLIE-31 score in the JG. A former study concluded that LCM as an adjuvant treatment for levetiracetam can significantly increase the QOLIE-10 score of patients with refractory epilepsy and reduce the occurrence of anxiety and depression in patients (32). In addition, LCM as an adjuvant drug can improve cognitive function and the mental state of patients with epilepsy (33). The results of the present study and the aforementioned studies indicated that levetiracetam treatment supplemented by LCM can improve the mood and quality of life of patients with epilepsy. In the present study, the 1-year drug retention rate was 74.24% in the JG and 66.67% in the CG. According to previous studies, the 1-year drug retention rate was approximately 62.0% after long-term LCM monotherapy (34) and approximately 34.4% after long-term treatment with levetiracetam (35). In the present study, the 1-year drug retention rate was enhanced in patients with refractory partial seizures treated with levetiracetam combined with LCM. It is surmised that the increased 1-year drug retention rate may be due to the improved efficacy of levetiracetam treatment supported by LCM.

The present study mainly explored the effects of levetiracetam tablets and LCM on therapeutic efficacy and neural function in patients with epilepsy. However, at present only the related outcome measures after 6 months of treatment were assessed and a long-term follow-up was not conducted. Patients included in this study were middle-aged and elderly people. Therefore, whether levetiracetam and LCM can affect the BMD and bone metabolism in younger patients, and whether the BMD and bone metabolism vary among patients with different sexes and ages should be further explored. In the future, we will address these issues to provide a reference for future clinical treatment of epilepsy.

In summary, levetiracetam tablets combined with LCM significantly enhanced the therapeutic effect and improved the neural function in patients with refractory partial seizures, but it may cause a slight adverse effect on BMD and bone metabolism in the short term.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

AL conceived and designed the study. AL, QG and MW were responsible for the collection, analysis and interpretation of the data. QG drafted the manuscript. AL revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the 5th People's Hospital of Qingdao (approval no. QD31344). Signed written informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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