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Original Article

Hematological and Renal Effects of Levetiracetam Versus Lamotrigine in Children With Epilepsy: A Randomized Clinical Trial

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Abstract

Background: Alterations in hematological and renal parameters have been reported with antiepileptic drugs (AEDs). This study aimed to evaluate the effects of lamotrigine (LTG) and levetiracetam (LEV) on these parameters in children with epilepsy.

Materials and Methods: This randomized clinical trial included children with a first-time diagnosis of epilepsy referred to Bandar Abbas Children's Hospital, Bandar Abbas, Iran, from 2017 to 2018. Participants' age, gender, and family history of epilepsy were recorded at the time of admission. Patients in the LTG group received 0.6 mg/kg of oral LTG in two divided doses for two weeks which continued with 1.2 mg/kg for another two weeks and then with a maintenance dose of 5-15 mg/kg daily. Patients in the LEV group received 10 mg/kg of oral LEV twice a day. When necessary, the dosage was increased to a maximum of 30 mg/kg twice a day. Treatment continued until seizures were controlled. Hematological and renal parameters were measured at baseline and 3 months after treatment. The total duration of treatment with each drug was noted as well.

Results: Of the 66 children evaluated in this study with a mean age of 8.51 ± 2.11 years, 31 (47%) were males. Age, gender, family history of epilepsy, treatment duration, and baseline hematological and renal parameters did not differ between the LTG (n = 26) and LEV (n = 40) groups. Patients in both groups were comparable regarding all the parameters after treatment. Finally, no significant change was observed after treatment compared to baseline in either group.

Conclusion: Overall, LTG and LEV appear to have no significant effect on the hematological and renal parameters of children with epilepsy.

Keywords: Epilepsy, Lamotrigine, Levetiracetam, Blood, Kidney

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Introduction

Epilepsy is a chronic neurological disorder, peaking at the extremes of age, namely, in the first years of life and the elderly. With a prevalence of 0.5%-1% and a lifetime incidence of up to 5%, it is considered a common condition (1). Seizure control is achieved in approximately 70% of children using antiepileptic drugs (AEDs), either with monotherapy as the first line or two or more AEDs when patients are nonresponsive to two trials of AED monotherapy (2).

The majority of patients with epilepsy can be treated with conventional AEDs. However, epilepsy remains uncontrolled with conventional AEDs in about 30% of patients (3). Levetiracetam (LEV) and lamotrigine (LTG) are among the second generation of AEDs, which have been approved by the Food and Drug Administration for use in epilepsy.

LEV is reported to be well tolerated, with a different mechanism of action compared to other AEDs; nevertheless, its function is not completely known. The adverse effects of LEV are generally mild; nonetheless, changes in the platelet count and function have been reported in patients taking LEV (4-6). Hematological changes have also been reported with LTG; nevertheless, concurrent use of other medications or AEDs, rapid dose escalation, and high doses of LTG could have influenced such changes (7).

Nephrotoxicity induced by AEDs occurs in less than 0.1% of patients, and its exact mechanism is unknown, but the direct action of AEDs on the kidney and idiosyncratic hypersensitivity have been proposed as potential causes (3). LEV is excreted by the kidney, and

monitoring of LEV has been recommended for patients with renal dysfunction (8). On the other hand, case reports have described nephrotoxicity secondary to non-hypersensitivity reactions in patients using LEV and LTG (9, 10).

Objectives

The current study sought to compare the hematological and renal effects of LTG and LEV in children with epilepsy.

Materials and Methods

Participants

This randomized clinical trial included children with a diagnosis of epilepsy referred to Bandar Abbas Children's Hospital from March 21, 2017, to March 20, 2018. The inclusion criterion was the first-time diagnosis of epilepsy by an expert pediatric neurologist. On the other hand, the exclusion criteria were any underlying hematologic, kidney, or liver diseases, and hypersensitivity to LTG or LEV. The sample size was calculated as at least 25 patients in each group based on the study by Dinopoulos et al (6), $\alpha = 0.05$, and $\beta = 0.2$.

Overall, 90 patients were assessed for eligibility, of whom 10 were excluded, and the remaining were randomly allocated to two equal groups (LTG and LEV) using random-generated numbers by the Random Allocation software. From the patients in the LTG group, parents/guardians of 8 did not cooperate, and 6 were lost to follow up; therefore, 40 and 26 patients in the LEV and LTG groups were included in the final analysis, respectively (Figure 1).

Study Design

Demographic features, including age, gender, and family history of epilepsy were recorded for each patient. Patients in the LTG group received 0.6 mg/kg of oral LTG in two divided doses for two weeks, which continued with 1.2 mg/kg for another two weeks. The maintenance dose was 5-15 mg/kg daily (maximum 400 mg daily in

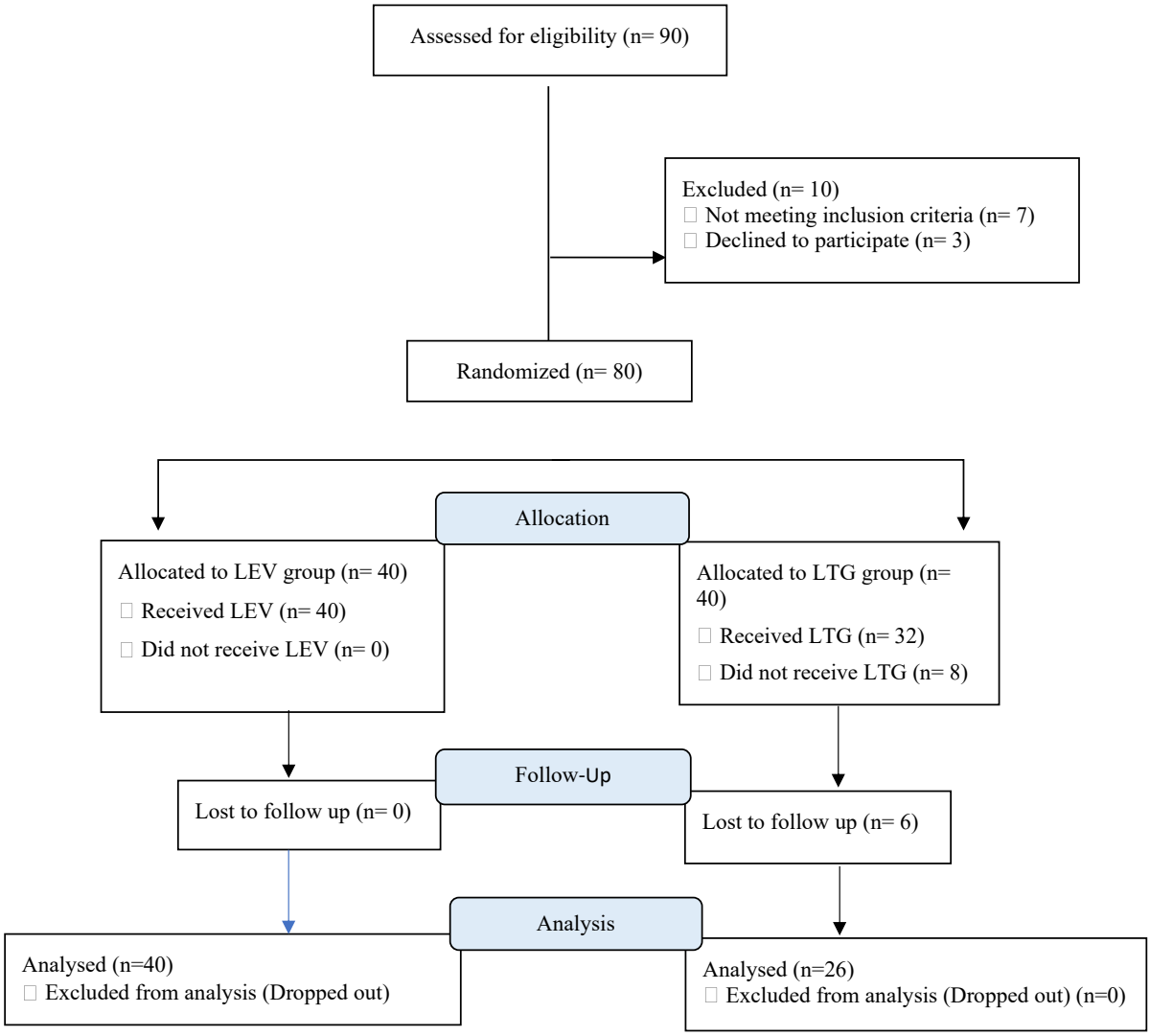

Figure 1. CONSORT Flowchart of the Study. *Note*. LEV: Levetiracetam; LTG: Lamotrigine.

two divided doses). Patients in the LEV group received 10 mg/kg of oral LEV twice a day. The dosage was increased by 10 mg/kg every two weeks to a maximum of 30 mg/kg twice a day when necessary. In case of seizure recurrence, the maximum dose was administered three times a day. Treatment continued until seizures were controlled. Random venous blood samples were collected from all the patients at baseline and three months after treatment. White blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hb), platelet count, creatinine (Cr), and blood urea nitrogen (BUN) were measured in the blood samples. The total duration of treatment with each drug was noted as well.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp.) was used for data analysis. Mean, standard deviation, frequency, and percentage was applied to describe the results. The chi-square test was employed to compare qualitative variables between the LTG and LEV groups. Based on the results of the Kolmogorov-Smirnov normality test, the independent *t* test was utilized to compare quantitative variables between groups. In addition, paired *t* test was used to compare quantitative variables before and after treatment in each group, and *P* values ≤ 0.05 were regarded as statistically significant.

Results

Of the 66 children included in this study, 31 (47%) were male and 35 (53%) were female. Their mean age was 8.51 ± 2.11 years. There were 26 (39%) and 40 (61%) patients in the LTG and LEV groups, respectively. The general characteristics of the study population are provided in Table 1. The two groups were comparable with respect to age (*P* = 0.352), gender (*P* = 0.425), family history of epilepsy (*P* = 0.622), and the duration of treatment (*P* = 0.371).

WBC (*P* = 0.498), RBC (*P* = 0.875), and platelet counts (0.344), as well as Hb concentration (*P* = 0.455), Cr (*P* = 0.795), and BUN (*P* = 0.567) levels were similar in both groups before treatment. WBC and platelet counts slightly decreased after treatment compared to baseline in both groups, while the Hb concentration and Cr level remained quite the same. The BUN level increased in the LEV group, while it decreased in the LTG group after treatment; however, none of these changes were statistically significant. Moreover, all the hematological and renal parameters were comparable between groups after treatment (Table 2).

Discussion

In the current study, it was found that neither LEV nor LTG was effective on the hematological and renal parameters of children with epilepsy. However, a slight but insignificant decrease in WBC and platelet counts was observed with both medications, as well as an insignificant increase of BUN with LEV.

LEV is a well-tolerated AED that has been effective in the treatment of myoclonic, generalized tonic-clonic, and partial-onset seizures. This medication is known for its acceptable bioavailability and rapid achievement of steady concentrations. It has been reported that after 24 hours, almost two-thirds of the administered LEV dose was found unchanged in the urine and approximately one-third as inactive metabolites. Therefore, LEV is almost exclusively eliminated by the kidneys (9). The most common adverse events reported with LEV include headaches, nausea, dizziness, fatigue, and somnolence (11). The findings of a large trial of LEV as an adjunctive treatment, including 1030 patients with partial-onset seizures demonstrated no kidney-associated adverse events (12). Furthermore, in line with our findings, no significant change in BUN or Cr concentrations was observed in two trials (11,13). However, in one of these trials, blood was found in the urinalysis of 10.9% of patients under LEV treatment (11). Rare reports of acute kidney failure have been found in patients on LEV treatment. In a 17-year-old female patient receiving 250 mg LEV twice a day for partial complex seizure, acute kidney injury and interstitial nephritis occurred 10 days after the initiation of treatment (14). In another case, Cr

Table 1. General Characteristics of the Study Population

Variables	Total (N = 66)	LEV (n = 40)	LTG (n = 26)	*P* Value[a]
Gender, No. (%)				
Male	31 (47.0)	22 (55.0)	9 (34.6)	0.425
Female	35 (53.0)	18 (45.0)	17 (65.4)	
Age (years), mean ± SD	8.51 ± 2.11	8.81 ± 2.10	8.04 ± 1.88	0.352[b]
Family history of epilepsy, No. (%)	12 (18.2)	6 (15.0)	6 (23.1)	0.622
Duration of treatment (months), mean ± SD	5.50 ± 2.01	5.33 ± 2.44	5.46 ± 2.30	0.371[b]

Note. N: Number; SD: Standard deviation; LEV: Levetiracetam; LTG: Lamotrigine.
[a] Analyzed by chi-square test; [b] Analyzed by independent *t* test.

Table 2. Comparison of Hematological and Renal Parameters Between Groups Before and After Treatment

Variables	Total (N = 66)	LEV (n = 40)	LTG (n = 26)	*P* Value[a]
WBC count (/μL), mean ± SD				
Before treatment	7.27 ± 2.22	8.98 ± 4.08	8.08 ± 2.47	0.498
After treatment	8.63 ± 3.54	7.12 ± 2.19	7.50 ± 2.31	0.511
P value[b]		0.124	0.220	
RBC count ($\times 10^6$/μL), mean ± SD				
Before treatment	4.29 ± 0.56	4.36 ± 0.52	4.22 ± 0.61	0.875
After treatment	4.30 ± 0.56	4.36 ± 0.52	4.19 ± 0.62	0.245
P value[b]		0.978	0.657	
Hb (g/dL), mean ± SD				
Before treatment	10.82 ± 1.42	10.92 ± 1.56	10.75 ± 1.56	0.455
After treatment	10.85 ± 1.55	10.95 ± 1.42	10.64 ± 1.44	0.395
P value[b]		0.825	0.794	
Platelet count ($\times 10^3$/μL) mean ± SD				
Before treatment	245.59 ± 71.81	278.05 ± 102.52	259.58 ± 62.07	0.344
After treatment	270.77 ± 88.71	253.7 ± 73.24	233.11 ± 69.07	0.258
P value[b]		0.158	0.221	
Cr (mg/dL) mean ± SD				
Before treatment	0.42 ± 0.15	0.47 ± 0.17	0.45 ± 0.16	0.795
After treatment	0.46 ± 0.16	0.47 ± 0.15	0.48 ± 0.15	0.880
P value[b]		0.866	0.798	
BUN (mg/dL)				
Before treatment	14.04 ± 6.46	13.67 ± 7.97	13.07 ± 5.07	0.567
After treatment	13.43 ± 6.94	14.83 ± 7.76	12.79 ± 3.43	0.213
P value[b]		0.555	0.481	

Note. SD: Standard deviation; WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; Cr: Creatinine; BUN: Blood urea nitrogen. [a] Analyzed by independent *t* test; [b] Analyzed by paired *t* test.

concentration significantly increased in a 45-year-old male patient receiving LEV for glioma, most probably as a result of acute renal failure due to interstitial nephritis. His renal function improved with the discontinuation of LEV (15).

As for the hematological effects of LEV, Dinopoulos et al reported no significant hematological alterations with a short-term monotherapy of LEV in children with epilepsy, except for a significant decrease in the lymphocyte count (6), which is consistent with our results. On the other hand, in a cross-sectional study by Bachmann et al, a significant decrease in platelet counts was observed in adult patients under LEV treatment for six months compared to controls (16). The difference in the study population, the sample size, and LEV dosing might be responsible for the discrepancy between the results of this study and those of ours. Moreover, it should be noted that aside from the number of platelets, their function can be influenced by LEV use, as reported in a woman who developed prolonged bleeding time and ecchymosis after the initiation of LEV treatment (5).

LTG appears to be safe in children with focal, myoclonic, tonic-clonic, and myoclonic absence seizures. Although the side effects of LTG are different for different patients, the most common side effects are nausea and/or vomiting, dizziness, headache, ataxia, and tremor (17). LTG is primarily metabolized in the liver and can rise to toxic levels in patients with underlying liver diseases (18). The LTG is mostly cleared from the body through glucuronide conjugation, and under normal conditions, a minor amount is converted by cytochrome P450 enzymes. The cytochrome P450 system is faster in children, while glucuronide conjugation is slower in adults, thus the pediatric population is at higher risk of idiosyncratic reactions induced by LTG (19). Very few studies have addressed the hematological and renal effects of LTG in humans; nevertheless, in a recent study on female albino rats, Hb concentration and WBC count significantly decreased after treatment with LTG (20). In the same study, the right and left kidney

weights significantly increased in the rats after treatment with LTG (20). Contrary to our findings, in a study by Biederman et al, the plasma Cr concentration and platelet count significantly increased after treatment in children and adolescents under LTG monotherapy for bipolar disorder (21). The reason for this inconsistency can be the condition for which children were treated with LTG in their study and ours, as well as the different doses and duration of treatment.

The primary strength of the current study was that it evaluated the hematological and renal effects of LTG and LEV; both effects have rarely been investigated in previous studies for any of these drugs. Furthermore, such effects have not been compared between these medications in previous investigations.

One limitation of the present study was that it did not evaluate the platelet function. Alterations in the platelet function have been reported with LEV, and this could have occurred in our study population despite the insignificant change in the platelet count. Another limitation was the relatively small sample size which questions the generalizability of the results.

Conclusion

Although LEV appears to be an effective treatment for epilepsy and is generally well-tolerated, based on the findings of the previous trials and case reports, as well as the slight increase in BUN in our study, it may have dangerous effects on renal function. Therefore, the close monitoring of patients, especially those with underlying kidney dysfunctions, is recommended while taking LEV. The hematological side effects of LEV were insignificant in the current study; however, the potentially decreased platelet function not evaluated in our study might be of concern in patients with pretreatment low platelet counts. This has to be investigated in future studies. LTG also had minimal effects on hematological and renal parameters. However, these findings have to be confirmed by larger clinical trials.

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Authors' Contribution

Conceptualization and study validation: ME, Implementation: SJ Supervision: AM, Data analysis and interpretation: GZ, Writing and reviewing: ME, All authors read and approved the final version of the manuscript.

Conflict of Interest Disclosures

There are no conflicts of interests.

Consent for Publication

Not applicable.

Ethical Statement

The study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences under the ethics code: IR.HUMS.REC.1396.74 and it complies with the statements of the Declaration of Helsinki. Written informed consent was obtained from the parents/guardians of the patients.

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