Research Paper

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

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ABSTRACT

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

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. The participants' age, gender, and family history of epilepsy were recorded. The patients in the LTG group received 0.6 mg/kg 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. The patients in the LEV group received 10 mg/kg oral LEV twice a day. When necessary, the dosage is increased to a maximum of 30 mg/kg twice a day. The 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 also noted.

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

Discussion: LTG and LEV have no significant effect on the hematological and renal parameters of children with epilepsy.

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Introduction

Epilepsy is a chronic neurological disorder, peaking at the extremes of age, in the first years of life, and in the elderly. With a prevalence of 0.5% to 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 in 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 (FDA) 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; yet, changes in platelet count and function have been reported in patients taking LEV [4-6]. Hematological changes have also been reported with LTG. Nonetheless, 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; however, 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]. This study compares the hematological and renal effects of LTG and LVT in children with epilepsy.

Materials and Methods

Study 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 comprised the first-time diagnosis of epilepsy by an expert pediatric neurologist. Meanwhile, 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] with α=0.05 and β=0.2.

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

Study design

Demographic features, including age, gender, and family history of epilepsy were recorded for each patient. The patients in the LTG group received 0.6 mg/kg 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 two divided doses). The patients in the LEV group received 10 mg/kg oral LEV twice a day. When necessary, the dosage increased by 10 mg/kg every two weeks to a maximum of 30 mg/kg twice a day. 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 3 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 also noted.

Data analysis

The SPSS software (version 25, Armonk, NY: IBM Corp.) was used for data analysis. Mean±SD, frequency, and percentages were used to describe the results. The chi-square test was used 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 used to compare quantitative variables between groups. The paired t-test was used to compare quantitative variables before and after treatment in each group. $P \leq 0.05$ were regarded as statistically significant.

Results

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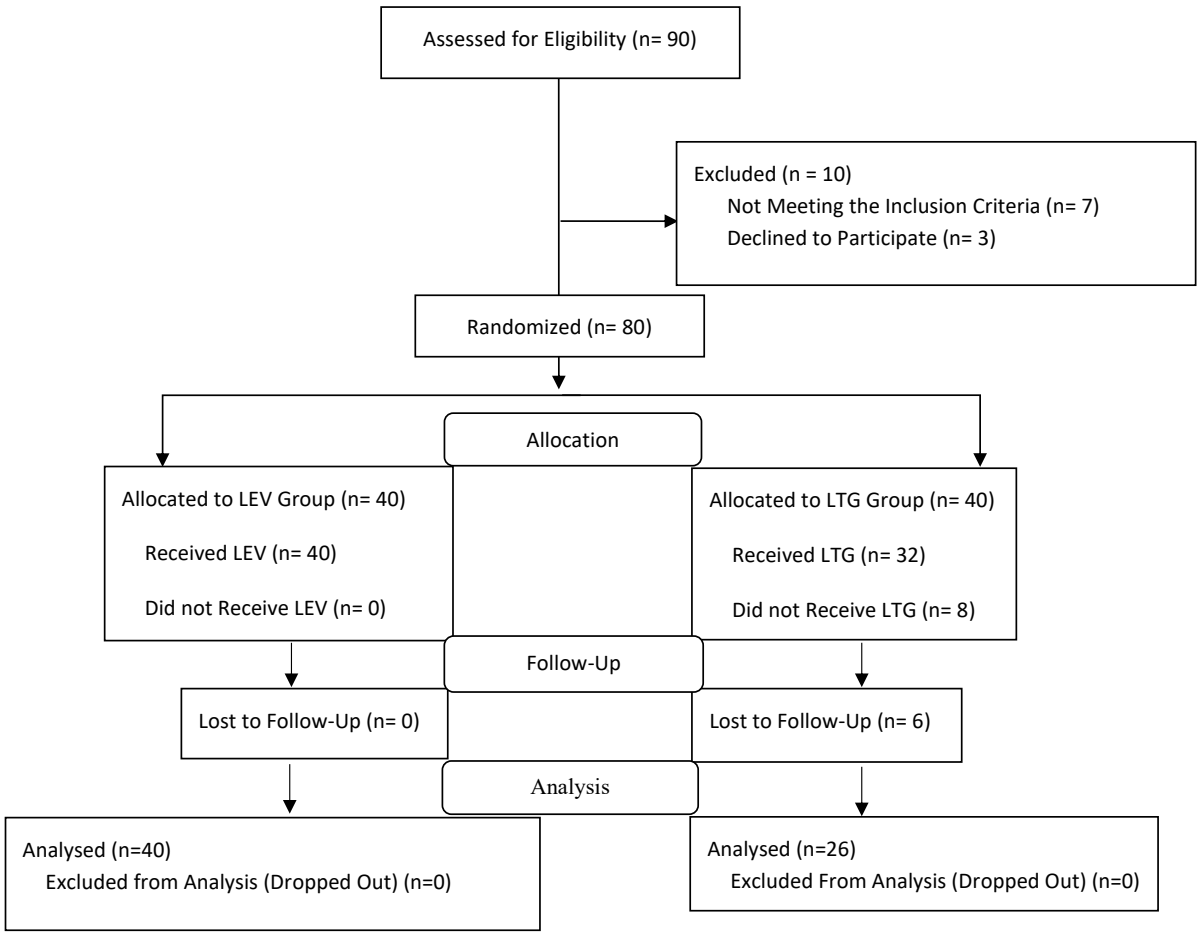

Figure 1. Study flowchart (CONSORT format)

LEV: Levetiracetam; LTG: Lamotrigine.

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 patients (39%) in the LTG group and 40(61%) in the LEV group. The general characteristics of the study population are demonstrated in Table 1. The two groups were comparable in terms of age (P=0.352), gender (P=0.425), family history of epilepsy (P=0.622), and 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 Hb concentration and Cr level remained quite the same. BUN level increased in the LEV group and 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

Neither LEV nor LTG were 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 good bioavailability and rapid achievement of steady concentrations. After 24 h, 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]. In a large trial of LEV as an adjunctive treatment, including 1030 patients with partial-onset seizures, no kidney-associated adverse events were

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Table 1. General characteristics of the study population

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

Abbreviations: N: Number; SD: Standard deviation; LEV: Levetiracetam; LTG: Lamotrigine.

*Chi-square test, †Independent t-test.

Table 2. Comparison of hematological and renal parameters between groups before and after treatment

Variables		Mean±SD			P*
		Total (n=66)	LEV (n=40)	LTG (n=26)	
WBC count (/µL)	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†		0.124	0.220	
RBC count (×10⁶/µL)	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†		0.978	0.657	
Hb (g/dL)	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†		0.825	0.794	
Platelet count (×10³/µL)	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†		0.158	0.221	
Cr (mg/dL)	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†		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†		0.555	0.481	

Abbreviations: SD: Standard deviation; WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; Cr: Creatinine; BUN: Blood urea nitrogen.

*Independent t-test, †Paired t-test.

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reported [12]. Also, in line with our findings, no significant change in BUN or Cr concentrations was demonstrated in two trials [13, 14]. However, in one of these trials, blood was found in the urinalysis of 10.9% of patients under LEV treatment [14]. Rare reports of acute kidney failure have been reported 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 [10]. In another case, Cr 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 discontinuation of LEV [15].

As for hematological effects of LEV, consistent with our results, 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 lymphocyte count [6]. 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 6 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 the current research. Moreover, 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 is 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 an underlying liver disease [18]. The clearance of LTG from the body is mostly done through glucuronide conjugation and under normal conditions, a minor amount is converted by cytochrome P450 enzymes. Since the cytochrome P450 system is faster in children while glucuronide conjugation is slower compared to adults, the pediatric population is at higher risk of idiosyncratic reactions induced by LTG [19]. 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., in children and adolescents under LTG monotherapy for bipolar disorder, plasma Cr concentration and platelet count significantly increased after treatment [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 dose 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 research.

Conclusion

Although LEV appears to be an effective treatment for epilepsy and is 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, close monitoring of patients, especially those with underlying kidney dysfunction, is recommended while taking LEV. The hematological side effects of LEV were insignificant in the current study; however, the potentially decreased platelet function which was 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.

Study limitations

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

Ethical Considerations

Compliance with ethical guidelines

This study received ethical approval from the Ethics Committee of Hormozgan University of Medical Sciences (Code: HUMS.REC.1396.74). It complies with the statements of the Declaration of Helsinki. Written informed consent was obtained from the parents/guardians of all patients.

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Authors' contributions

Conceptualization and study validation: Maryam Esteghamati; Study supervision: Alireza Moayedi; Implementation: Somayeh Jalilzadeh; Data analysis and data interpretation: Ghazal Zoghi; Writing and review: Maryam Esteghamati; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interests.

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