Levetiracetam as monotherapy in the treatment of neonatal-onset seizures

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Seizures are the most common neurological emergency in neonates and associated with increased risk of abnormal neurodevelopmental outcomes, morbidity, and mortality.[1,2] Since the treatment with anti-seizure medications in neonates may be non-effective and even harmful for the developing immature brain, treatment strategy in neonatal-onset seizures is crucial .[3,4] However, there is no international consensus on when and how to treat neonatal-onset seizures. According to the World Health Association (WHO) guideline for neonatal-onset seizures (2011), phenobarbital (PB) still remains as the first-line anti-seizure drugs (ASDs) in the treatment.[5] Besides, there is great interest in the use of levetiracetam (LEV), which is a broad-spectrum ASD for neonatal-onset seizures in recent years. In the last ten years, numerous clinical studies revealed that LEV could be preferred as a first-line ASD in mono-and polytherapy for the treatment of neonatal-onset seizures because of its good pharmacokinetic characteristics and acceptable side effect profile.[6-8]

OBJECTIVES

Levetiracetam is a second-generation ASD approved by the “US Food and Drug Administration” for use as add-on therapy in patients older than one month of age.[9] Since animal studies showed that LEV does not lead to neuronal apoptosis in the immature brain or disrupt synaptic development unlike other ASDs, it is increasingly being used off-label in neonatal seizures.[10,11] However, the effects this agent in mono-and polytherapy on neurodevelopmental outcomes in neonates with seizures are not well-known. The present study aims to compare the patient characteristics and neurodevelopmental outcomes of the seizure-free group with LEV monotherapy and the treatment failure group.

MATERIALS & METHODS

The study was conducted on 139 infants who were seizure-free with LEV monotherapy or those with treatment failure with LEV monotherapy and followed-up in a pediatric neurology outpatient clinic in Western Türkiye from June 2014 to January 2022. Seizures were diagnosed based on bedside observation of clinical event by the neonatal intensive care unit health providers and/or analysis of amplitude-integrated EEG (aEEG) recording of events. Seizure semiology and etiologies were classified according to the International League Against Epilepsy 2021 classification of seizure types and the epilepsies: Modification for seizures in the neonate.[12] Levetiracetam was administered orally at a dose of 10 mg/kg/day initially. This dose was increased by 10 mg/kg/day up to 60 mg/kg/day in the monotherapy. In the evaluation of patients’ responses to LEV monotherapy, a decrease greater than 50% in seizure frequency was defined as “complete response”; a decrease less than 50% in seizure frequency as “partial response”; no change in seizure frequency as “no response”. In the treatment failure group, which is inadequate or no response to LEV monotherapy, diphenylhydantoin, PB, topiramate, carbamazepine or lamotrigine was added as a second drug, along with LEV therapy. Neurodevelopmental outcomes were assessed according to the “Denver-II developmental screening tool” results which were performed in the follow up. Demographic, clinical and follow-up data of the patients, brain magnetic resonance imaging (MRI), electroencephalography (EEG) records were collected from the PROBEL hospital information management system. The data were analyzed using the software Statistical Package for Social Science for Windows, version 22.

RESULTS

Of the 139 patients, 64% (n=89) were seizure-free with LEV monotherapy, and 36% (n=50) were seizure-free with other ASDs along with LEV therapy. Levetiracetam monotherapy was significantly more effective in patients with unknown etiologies than those with specific underlying etiologies (p=0.01). Abnormal pretreatment EEG and brain MRI findings were significantly more frequent in the LEV-failure group (p=0.001, p<0.001). The rate of psychomotor retardation was significantly higher in the LEV-failure group than the seizure-free group (p=0.001) (Table 1). Normal pretreatment EEG was the strongest predictor of seizure control under LEV monotherapy (OR=10; 95% CI=2.9–35.7; p<0.001). No adverse effects were reported in any patients in both groups.

Table 1: Comparison of the mono-and polytherapy groups

		Seizure-free group	LEV failure group	P value
Desimal age	[mean±SD (years)]	2.4±2.3	1.6±2	0.03
Gestational age (weeks)	<29	13 (14.6%)	8(16%)	0.7
	29-34	14 (15.7%)	10(20%)	
	≥34	62 (69.7%)	32(64%)	
Gender	Male	50 (56.2%)	31 (62%)	0.5
	Female	39 (43.8%)	19 (38%)	
Seizure semiology	Motor	65 (85.5%)	43 (91.5%)	0.18
	Non-motor	11 (14.5%)	4 (8.5%)	
Seizure type	Clinical	76 (85.4%)	47 (94%)	0.17
	Electrographical	13 (14.6%)	3 (6%)	
Seizure etiology	Specific etiologies	79 (88.8%)	50 (100%)	0.01
	Unknown etiologies	10 (11.2%)	0 (0%)	
Psychomotor retardation	Yes	17 (35.4%)	17 (81%)	0.001
	No	31 (64.6%)	4 (19%)	
Brain MRI	Normal	32 (44.4%)	4 (11.8%)	0.001
	Anormal	40 (55.6%)	30 (88.2%)	
Pretreatment EEG	Normal	35 (49.3%)	4 (14.3%)	<0.001
	Anormal	36 (50.7%)	24 (85.7%)	

LEV, levetiracetam; SD, standard deviation; MRI, magnetic resonance imaging; EEG, electroencephalogram

CONCLUSIONS

Our findings suggest that LEV monotherapy is effective for the treatment of neonatal-onset seizures, especially in the treatment of neonatal epilepsies with unknown etiologies. Neonates with abnormal EEG and brain MRI findings are less likely to be treated with LEV monotherapy. Immature nervous systems of neonates are especially vulnerable to ASD induced neurodevelopmental impairment. It is crucial to identify and minimize the short and long-term adverse effects of ASDs. On the other hand, it is difficult to determine whether the seizure etiology or ASD therapy is responsible for neurodevelopmental outcomes. Further prospective, randomized controlled trials are needed to evaluate the short and long-term effects of LEV in the monotherapy or polytherapy with the other ASDs.

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