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ARTICLE

Lack of response to treatment with levetiracetam in extreme preterm infants with seizures

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Abstract

Objective The aim of this study was to evaluate the effectiveness of monotherapy with levetiracetam (LEV) in achieving seizure cessation in a retrospective cohort of extreme preterm infants with seizures.

Study design Charts of infants with a diagnosis of neonatal seizures admitted to the NICU between 2013 and 2017 were reviewed. Seizures were diagnosed using continuous video electroencephalography. All infants were initially started on LEV and reached a dose of 80 mg/kg/day. Other ASMs were added to LEV if seizures continued after 2 days. Data on additional clinical variables were collected for each infant.

Result Sixty-one infants born <28 weeks of gestation met inclusion criteria. Seventy-four percent of patients did not respond to LEV monotherapy and required additional medications.

Conclusions LEV monotherapy stopped seizures in only a small portion of cases.

Introduction

Neonatal seizures are a common intensive care emergency, occurring in ~3 per 1000 term newborns and 11 per 1000 preterm neonates [1]. The neonatal period is the most common time of life during which an individual may develop seizures [2]. Neonatal seizure burden increases the risk for brain damage, epilepsy, and disability [3]. The etiology of neonatal seizures includes such conditions as hypoxic ischemic encephalopathy (HIE), intraventricular hemorrhage (IVH), periventricular leukomalacia, structural brain injuries and malformations, venous infarctions, metabolic disturbances (most often glucose and electrolyte abnormalities), and infections. A broad spectrum of etiologies coupled with few treatment options make management of neonatal seizures challenging. The FDA has not approved any antiseizure medication (ASM) for use in the neonatal period and a Cochrane report concluded that there was little evidence to support the use of any ASM currently available [4]. There are limited data from randomized controlled studies comparing antiepileptic treatments with regard to either efficacy or long-term outcomes. Phenobarbital has decades of historical precedence as the first ASM used for neonates based on extensive research in animal models. However, reports of negative long-term neurodevelopmental outcomes and side effects in neonates treated with phenobarbital [5] have shifted treatment preferences to other ASMs such as levetiracetam (LEV). Neonatal rat models have shown that LEV is not associated with apoptosis or cerebral palsy and may be even neuroprotective [6, 7]. A recent observational, cohort study suggested that LEV may be superior to phenobarbital for initial monotherapy of seizures in infants aged <12 months [8]. Earlier studies evaluating LEV efficacy in neonatal seizure management focused its use as a second- or third-line agent in mainly term infants [9–12]. At Pediatric Academic Societies in 2019, LEV was shown to have inferior efficacy compared with phenobarbital in the first-line treatment of EEG-confirmed seizures in term neonates [13]. Based on the scarcity of published data on LEV as a first-line agent for the management of seizures in extreme preterm neonates, our neurologists began to utilize LEV given the potential harm associated with phenobarbital.

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Given that more data has been published in neonates ≥ 36 weeks gestation [14], the primary objective of this retrospective cohort study was to evaluate the response to monotherapy treatment with (LEV) as a first-line agent in extreme preterm neonates with seizures. The secondary objectives were to identify pre- and postnatal risk factors associated with response to LEV monotherapy compared to infants requiring multiple ASMs for seizure control.

Materials and methods

This was a retrospective cohort study of infants with a diagnosis of neonatal seizures, born ≤28 weeks of gestation, between 2013 and 2017 and admitted to the NICU at Holtz Children's Hospital/Jackson Memorial/ University of Miami Medical Center. This study was approved by the Institutional Review Board of the University of Miami and Jackson Health System Clinical Research Office and they waived need for informed consent.

Seizure protocol

When there was suspicion for seizures by the clinical team, pediatric neurology was consulted and their recommendations regarding diagnosis and treatment were followed. The diagnosis of seizures was made using continuous video electroencephalography (EEG). All infants had at least 36 h of video EEG recording to allow for assessment of seizure freedom. Seizures were monitored electrographically and clinically, and a seizure-free state was defined by an EEG demonstrating absence of seizures after a minimum duration of 36 h from the first dose administration. The length and frequency of EEG monitoring was based on the discretion of the pediatric neurologists and by the clinical condition of the patient. LEV was used as a first-line agent in every infant presenting with seizures during the study period, with a loading dose of 40 mg/kg followed by a maintenance of 40 mg/kg/day. If electrographic seizures continued, another 40 mg/kg loading dose was given and maintenance dose increased to 80 mg/kg/day. Repeat LEV loads were deemed necessary if seizures were seen clinically and confirmed on EEG review by the pediatric epileptologist (every 6–8 h). If electrographic seizures continued for 12–24 h despite maximal LEV monotherapy, fosphenytoin, phenobarbital, and in rare refractory cases vitamin B6 or midazolam infusions were given.

Data collected

Data collected included the following prenatal and postnatal variables: singleton vs. twin gestation, gestational age (GA, based on prenatal ultrasound), birthweight, gender, small for gestational age (SGA, defined as birth weight < 10th percentile on Fenton growth curves), 5 min APGAR score, base deficit (BD < −12 on first arterial blood gas), ASMs used for seizure management, apnea requiring caffeine treatment, IVH (grade III–IV based on Papile's classification), PVL, hydrocephalus with or without ventriculoperitoneal shunt, diagnosis of HIE (based on history, metabolic acidosis, and Sarnat score), focal brain injury, hypoglycemia in the first 12 h (blood glucose <40 mg/dl), hypotension (mean arterial pressure < 5th percentile for age), genetic diagnosis, and survival to discharge. Additional neurologic data included day of life of seizure onset.

Statistical analysis

Descriptive statistics (mean, standard deviation, and frequency) were calculated and segregated into the defined LEV and multiple ASM groups. Characteristics of infants controlled on LEV monotherapy were compared with those of infants requiring multiple ASMs using binomial testing for categorical variables and *t*-test analysis for continuous variables. Odds ratio, β coefficient, and *p*-value were calculated. *P*-values < 0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics (version 24).

Results

Between January 2013 and December 2017, 779 infants were admitted to the NICU, 88 of which met seizure criteria and 61 were less than 28 weeks GA meeting inclusion criteria for this study (Fig. 1). Of the 61 neonates in the cohort, only 16 (26%) were successfully managed with LEV monotherapy, whereas 45 (74%) did not respond to initial LEV therapy alone and required multiple ASMs ($p < 0.0001$). Gestational age (GA) of study patients ranged between 22 and 28 weeks; mean GA did not significantly differ between infants who responded to monotherapy with LEV and those who did not (Table 1). Conceptional age at the start of LEV therapy was <28 weeks for the entire cohort (Table 1). Birthweight (BW) of study infants ranged between 428 and 903 g, and similarly mean BW did not significantly differ between patients who responded to LEV monotherapy and those requiring multiple ASMs (Table 1). Of infants in the study who were SGA, none responded to LEV monotherapy. Those requiring multiple ASM's had a higher incidence of base deficit <12 compared with the LEV group ($p = 0.016$) (Table 1). Presumed seizure etiology did not significantly differ between the two therapeutic response groups (Table 2).

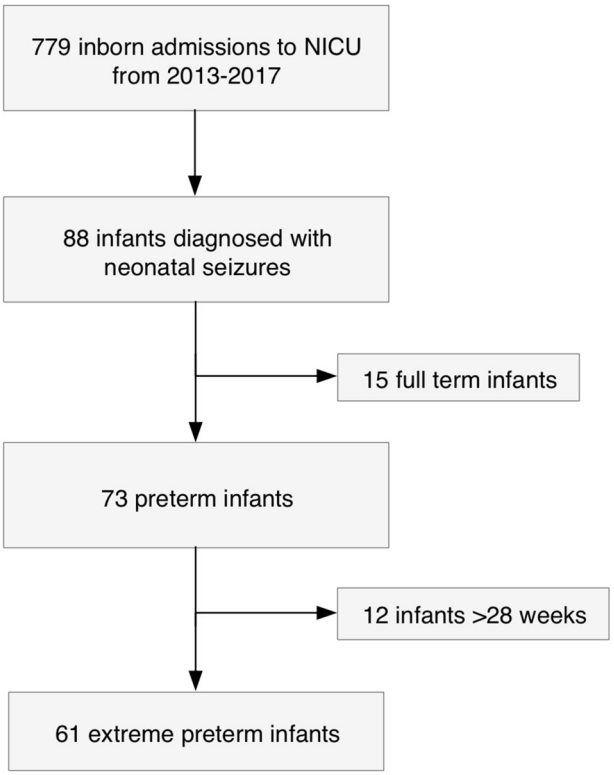

Fig. 1 Flow diagram indicating patients included in the study. Full term is defined as birth ≥37 weeks of gestation; preterm is defined as birth at <37 weeks of gestation; extreme preterm is defined as birth at <28 weeks of gestation

Discussion/Conclusion

LEV monotherapy was not successful in seizure control in 74% of patients. No study infant who was SGA responded to LEV monotherapy. Although the association between SGA and seizures in term and preterm infants has been shown previously [15–18], the significance of SGA in the context of refractory seizures is unclear at this time. No other risk factors for seizures, such as IVH or HIE were predictive of successful vs. unsuccessful LEV monotherapy response.

Table 2 Presumed seizure etiology of extreme preterm infants (<28 weeks of gestation at birth) included in the study

	Levetiracetam monotherapy	Multiple ASM's	*p*
Seizure etiology			
IVH grade III, *n*	1	2	0.77
IVH grade IV, *n*	6	12	0.60
HIE, *n*	1	3	0.95
Focal brain injury, *n*	4	17	0.36
Hypocalcemia, *n*	1	0	0.091
Hypoglycemia, *n*	1	2	0.77
Genetic condition, *n*	1	2	0.77

Brain abnormalities = presumed perinatal ischemic stroke, hemorrhagic stroke, and cerebellar infarcts, Genetic condition = Noonan's variant, VACTERL, and Klinefelter

IVH Intraventricular hemorrhage, *HIE* hypoxic ischemic encephalopathy

Table 1 Demographics and clinical characteristics of extreme preterm infants (<28 weeks of gestation at birth) included in the study

	Levetiracetam monotherapy	Multiple ASM's	*p*
Demographic data			
n	16	45	<0.0001
Birthweight (g), mean ± SD	719 ± 184	656 ± 194	0.27
Gestational age (weeks), mean ± SD	24.8 ± 1.5	24.6 ± 1.5	0.85
Male, *n* (%)	11 (69)	36 (80)	0.36
Female, *n* (%)	5 (31)	9 (20)	
Twin gestation, *n*	1	9	0.20
Clinical characteristics			
Small for GA, *n* (%)	0 (0)	13 (29)	0.015
BD < 12 on first gas, *n* (%)	3 (19)	10 (22)	0.016
Apgar 5, median	6	5	0.91
PVL, *n* (%)	1 (6)	7 (16)	0.34
Hydrocephalus, *n* (%)	3 (19)	10 (22)	0.77
Systemic infection, *n* (%)	4 (25)	11 (24)	0.96
Hypotension, *n* (%)	11 (69)	38 (84)	0.17
Conceptual age (weeks) at start of LEV treatment, median ± SD	26.1 ± 8.6	25.5 ± 26	0.40
Died, *n* (%)	6 (38)	21 (47)	0.48

SD standard deviation, *g* grams, *GA* gestational age, *BD* Base deficit, *PVL* periventricular leukomalacia

LEV's mechanism of action is not known, but its binding affinity to synaptic vesicle protein 2A correlates with its anticonvulsant activity. It is metabolized in the blood to inactive metabolites with no drug–drug interactions and is metabolized through plasma esterases. Commonly reported dosage information from published studies recommend a loading dose of 10–20 mg/kg, with a maintenance dose ranging 10–80 mg/kg/day. LEV dosing in the NEOLEV2 trial was 40–60 mg/kg [13]. Concerns over the long-term side effects of traditional ASMs such as phenobarbital and the potential safer side effect profile of LEV [5] has led to a transition towards usage of LEV as a first-line agent in neonates.

However, there is limited information on LEV use as a first-line therapy for premature neonates [19] and meager efficacy or safety profiles exist for preterm or full-term infants younger than one month. Ramantani et al. [9] attempted to prospectively evaluate the use of LEV as first-line therapy in neonates, but phenobarbital was administered in more than 50% of their study population during LEV dose titration and no simultaneous vEEG monitoring was performed. Han et al., in retrospective review of 37 preterm infants who received LEV, found that the anti-seizure medicine was effective in 57% of cases. The population in that study was however heavily weighted toward infants born >28 weeks of gestation [20]. A randomized controlled trial by Perveen et al. compared the efficacy of LEV and phenobarbitone in a population of 60 full-term infants with a clinical diagnosis of seizures and showed LEV to be efficacious in only 23.3% of cases [21]. Despite the lack of video EEG confirmation of seizures, this outcome is consistent with the low rate of seizure control observed in our cohort. A retrospective study evaluated LEV for acute neonatal seizures as a second-line agent after phenobarbital failure in term infants and reported that after phenobarbital failure, LEV adjuvant therapy achieved 100% complete seizure cessation by 72 h [10]. A retrospective cohort study of 23 term neonates with EEG-confirmed seizures used LEV as first-line therapy in only four patients [12].

Our results show that LEV monotherapy was effective for neonatal seizure control in only 26% of the study population of extreme preterm neonates. Limitations of this study include the fact that this was a smaller cohort size and that we were unable to calculate the seizure burden [22] and determine how much this burden was reduced by ASM use. The specific seizure etiology was presumed but may be unknown in some cases. In addition, despite statistical analysis that did not demonstrate increased illness in LEV nonresponders, it is possible that these infants were in some way clinically compromised. It will be of great importance to further investigate and validate the low therapeutic response to LEV as the first-line agent in extreme premature infant seizure control. Randomized controlled trials are needed to evaluate the effectiveness and safety of LEV in this complex and vulnerable population.

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Author contributions WK conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, was the drafter of the initial paper, and reviewed and revised the paper. BC conceptualized and designed the study, carried out the initial analyses, was a drafter of the initial paper, and reviewed and revised the paper. TD-M, AP, and IS were involved in the care of the infants described in this study and were involved in reviewing and revising the submitted paper; and all authors approved the final paper as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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