Effectiveness of Levetiracetam as a First-Line Anticonvulsant for Neonatal Seizures

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OBJECTIVE Optimal treatment for neonatal seizures remains unclear, and management among US hospitals is highly varied. The purpose of this study was to evaluate the effectiveness of levetiracetam as a first-line treatment for seizures in a neonatal population.

METHODS A single-center, retrospective review of neonates at a tertiary medical center who received levetiracetam as a first-line agent after benzodiazepines for seizure control between 2015 and 2017 was conducted. Chart review was completed to analyze patient and treatment characteristics. The primary outcome was seizure control, defined as clinical seizure cessation and video electroencephalogram resolution, with no new seizures documented prior to discharge.

RESULTS A total of 36 patients met inclusion criteria. Seventeen patients (47%) had seizure control after intravenous levetiracetam as monotherapy. Eighteen patients required a second anticonvulsant, of which 13 (72%) had seizure control. In total, 30 patients (83%) had seizure control with levetiracetam monotherapy or combination therapy of levetiracetam plus fosphenytoin or phenobarbital.

CONCLUSIONS Levetiracetam monotherapy provided seizure control in about 50% of the patients reviewed. Overall, seizure control was observed in 83% of the study population that received either levetiracetam monotherapy or combination therapy of levetiracetam plus fosphenytoin or phenobarbital as a second-line agent. Further studies are warranted to directly compare historical therapies with levetiracetam for neonatal seizure control.

ABBREVIATIONS GABA, gamma-amino-butyric acid; HIE, hypoxic ischemic encephalopathy; UK, University of Kentucky; vEEG, video electroencephalogram

KEYWORDS anticonvulsant; levetiracetam; monotherapy; neonatal, seizure

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Introduction

Neonatal seizures arise from multiple causes, such as hypoxic ischemic encephalopathy (HIE), congenital malformations, infections, neonatal abstinence syndrome, intracranial hemorrhages, thrombosis, and inborn errors of metabolism.¹ Neonatal seizures place the neonate at an increased risk for neurologic impairment, developmental delay, and even death.² Optimal treatment for neonatal seizures remains unclear, and management among US hospitals is highly varied.^{3,4} Historically, the primary treatment option for neonatal seizures has been phenobarbital, followed by phenytoin or fosphenytoin.^{5,6}

Efficacy data for phenobarbital and phenytoin indicate that these medications successfully control neonatal seizures in fewer than 50% of patients when used as monotherapy.⁷ In combination or sequentially, they have been shown to be marginally more effective.⁷ Phenobarbital failure may be due in part to its mechanism and the unique characteristics of the neonatal brain, for example, underdevelopment of the gamma-amino-butyric acid (GABA) receptors and inver-

sion of the chloride gradient.⁸ Phenytoin possesses its own challenges in the treatment of neonatal seizures. Reduced protein binding, compared to that observed in adults, and variable metabolism of the drug in the neonate make standardized dosing and monitoring difficult.^{9,10} Additionally, in animal models, both phenobarbital and phenytoin were shown to trigger neuronal apoptosis—programmed cell death of neurons—in the developing brain.¹¹ Neuronal apoptosis is a potential mechanism that may lead to the neurodevelopmental deficits seen in neonates treated with these drugs.

Levetiracetam, a novel agent, provides a new target, the synaptic vesicle protein SV2a, which avoids the challenging characteristics in the neonatal brain that other antiepileptic medications encounter.⁸ In animal models, neurotoxicity was not seen in the developing brain with single doses of levetiracetam (up to 100 mg/kg/dose).¹² When looking at long-term effects in neonates treated for seizures, phenobarbital exposure was associated with worsening neurodevelopmental outcomes, which were not seen when compared to the results obtained with levetiracetam at 2 years.¹³

Additionally, levetiracetam possesses a more desirable pharmacokinetic profile for use in neonates due to its linear time-dependent kinetics, reduced protein binding, and renal-dependent clearance.^{8,14,15}

However, there are limited published data regarding use of levetiracetam in neonates. Khan et al¹⁶ retrospectively reviewed 22 neonates treated for seizures, 72% of whom received levetiracetam due to continued seizures following either phenobarbital or fosphenytoin therapy. All of the treated patients had cessation of seizures within 72 hours after receiving levetiracetam, with only 1 patient demonstrating increased irritability while on the medication, a potential side effect of levetiracetam, but one that is difficult to assess in the neonatal population. In another retrospective study, Yau et al¹⁷ reviewed 12 neonates who received levetiracetam for seizures after a loading dose of phenobarbital. Seventy-five percent of patients attained seizure resolution at 72 hours post-levetiracetam administration, and no adverse effects were seen associated with levetiracetam. In a prospective study, Ramantani et al¹⁸ administered levetiracetam as first-line therapy for seizures in 38 neonates. Seventy-nine percent of patients were seizure free at 1 week; however, 50% of patients received at least 1 dose of phenobarbital during therapy, and no severe adverse effects were reported.

Despite these studies and levetiracetam's favorable pharmacokinetic and safety profile, use of levetiracetam as a first-line agent for neonatal seizures is low nationally.⁴ Additionally, current guidelines for neonatal seizure management either do not list levetiracetam as an option or only list it as a second-line agent.^{5,6} Based on the favorable pharmacokinetics, safety profile, and available evidence with first- and second-line therapy, a protocol using levetiracetam as the first-line agent for neonatal seizures requiring treatment was initiated June 1, 2015, within the neonatal intensive care unit by the neurology and neonatology groups at our center. The primary objective of this study was to evaluate the effectiveness of levetiracetam as a first-line treatment for neonatal seizure control.

Materials and Methods

The study was a single-center, retrospective chart review of hospitalized neonates, 0 to 28 days postnatal age, with clinically or electrographically confirmed seizures who received levetiracetam as a first-line therapy during the period of June 1, 2015, to June 1, 2017. Pharmacy billing records were used to identify all patients who received at least one dose of levetiracetam within the institution during the study period. Additionally, while it was recommended per institution to obtain video electroencephalogram (vEEG) prior to levetiracetam load, patients could be loaded prior to vEEG if the vEEG was delayed. If seizures persisted, a second bolus of levetiracetam was to be given. If seizures continued despite a second levetiracetam load

then treatment was followed by either fosphenytoin or a neurology consult. Criteria for persistent seizures and consideration of additional levetiracetam were also guided by neurology consult. Institution guidelines provided levetiracetam dosing recommendations of 50 mg/kg loading dose followed by a maintenance dose of 20 mg/kg administered intravenously every 12 hours. An additional 20-mg/kg load of levetiracetam was recommended for persistent seizures despite initial levetiracetam load.

Patients were excluded if they received a medication other than levetiracetam (e.g., phenytoin or phenobarbital) as the first-line antiepileptic medication within the institution. In addition, patients were excluded if they received any anticonvulsant prior to transfer to the institution. Patients were not excluded based on the receipt of a benzodiazepine, as the institution's protocol allows for administration of a benzodiazepine prior to loading with levetiracetam or gestational age. The study was approved by the University of Kentucky Medical Institutional Review Board, with waiver of consent due to the retrospective nature of the study.

Data Collection. Individual patient information was collected via chart review of medical records. Patient demographic information, including sex, ethnicity, gestational age, type of delivery, birth weight, and age at seizure onset, was collected. Additional information regarding seizure characteristics, receipt of benzodiazepines prior to levetiracetam, loading and maintenance doses of levetiracetam, anticonvulsants used subsequent to levetiracetam, and any reported adverse effects was also collected. Seizure characteristics, such as etiology of seizure, clinical or electroencephalogram confirmation of seizure, and seizure control, were based on documentation from treating physicians within the institution's electronic medical record. Seizure control was defined as resolution of the clinical features associated with seizures (e.g., abnormal gaze or eye movement; tongue thrusting; apnea; and clonic, tonic, or jerking movements) and normalization of vEEG, if an abnormal vEEG had been documented, with no recurrence of seizures prior to discharge.

Statistical Analysis. An independent samples *t*-test was used to test the means between variables of patients with seizure control. Due to the small sample size in this study, 2 tests were used to compare categorical breakdowns of patients with seizure control. Chi-square and Fisher exact tests were used to compare the primary endpoint with individual patient variables. Descriptive statistics were calculated for frequencies, means, and standard deviations for all categories. The statistical software SPSS Statistics version 23 (IBM Corp, Armonk, NY) was used for data analysis.

Results

Of the 260 patients billed for a dose of levetiracetam during the study period, 36 met inclusion criteria.

Table 1. Patient Demographics*

Variable	Result
Male sex, n (%)	18 (50)
Race, n (%)	
Caucasian	32 (89)
Other	4 (11)
Gestational age, n (%)	
Preterm	10 (28)
Full-term	26 (72)
Birth weight, n = 33	
Mean $\pm$ SD, g	2989 $\pm$ 709
<2500 g, n (mean weight, g)	9 (2116)
$\geq$ 2500 g, n (mean weight, g)	24 (3317)
Delivery method, n (%)	
Vaginal	16 (44)
C-section	20 (56)
Age at seizure onset, n (%)	
$\leq$ 3 days	26 (72)
>3 days	10 (28)
Etiology of seizure, n (%)	
HIE	11 (31)
Infection	5 (14)
Unknown	11 (31)
Other†	9 (24)
Associated clinical features of seizure, n (%)	
Yes	32 (89)
No	4 (11)
Abnormal first vEEG, n (%)	
Yes	20 (56)
No	16 (44)

HIE, hypoxic ischemic encephalopathy; vEEG, video electroencephalogram

* n = 36 unless otherwise noted.

† Other causes included intracranial hemorrhage, cerebral infarction, neonatal abstinence syndrome, and congenital malformations.

Patients were excluded for the following reasons: 207 were outside of the age range (0–28 days birth age) at seizure onset; 9 had received an anticonvulsant (i.e., levetiracetam, fosphenytoin, or phenobarbital) prior to transfer to the institution; 4 involved a protocol deviation (i.e., levetiracetam not given as first-line therapy); and 4 were treated for an indication other than seizure management (i.e., prophylaxis). Demographic data are presented in Table 1. Patients were 50% male and had a mean gestational age of 37.7 weeks, with a range from 29 to 40.6 weeks. The primary known seizure etiology was HIE (n = 11, 31%), followed by infection (n = 5, 14%). Other causes of seizure included intracranial hemorrhage, cerebral infarction, neonatal abstinence syndrome, and congenital malformations. Thirty-one percent of patients had an unknown or unidentified cause for their seizures. Per chart review, 32 (89%) had clinical features of seizures, and 20 (56%) had

an abnormal first vEEG read at seizure onset. Sixteen (44%) patients had both clinical features of seizures documented and an abnormal first vEEG read.

Of the 36 patients, 10 (28%) received at least 1 dose of a benzodiazepine prior to levetiracetam, all of whom received lorazepam. The mean loading dose of intravenous levetiracetam was 49.8 mg/kg, with an initial maintenance dose of 24.8 mg/kg/dose administered intravenously every 12 hours. After treatment with levetiracetam, 17 (47%) had seizure control without administration of an additional anticonvulsant. Out of the 19 patients who continued to have clinical or vEEG confirmed seizures, 18 received an additional anticonvulsant; 1 patient died prior to further treatment. Fifteen of these patients received fosphenytoin, and 3 patients received phenobarbital. Of these 18 patients, 13 (72%) had seizure control with the addition of a second anticonvulsant, 10 of whom received fosphenytoin and 3 of whom received phenobarbital. In total, 30 patients (83%) had seizure control with levetiracetam monotherapy or combination therapy of levetiracetam plus fosphenytoin or phenobarbital. Treatment data are presented in Table 2.

Data analysis was performed to explore subgroups that may have benefited from levetiracetam therapy. When analyzing the patients who had seizure control with levetiracetam monotherapy, patients who did not receive benzodiazepine therapy prior to levetiracetam administration had a significantly higher rate of seizure control compared to those who received benzodiazepine therapy prior (16 of 20 patients [80%] vs 1 of 10 patients [10%], $p = 0.008$). A statistical difference was also found in patients with clinical seizure features only who had a normal initial vEEG. Data revealed these patients had a higher rate of seizure control compared to those with an abnormal initial vEEG (12 of 16 patients [75%] vs 5 of 20 patients [25%], $p = 0.006$). There was no statistically significant association with seizure control between subgroups for sex, gestational age, birth weight, method of childbirth, age at seizure onset, etiology, or when clinical features of seizures were associated with seizure onset. Subgroup analysis data are presented in Table 3. No adverse effects were identified during chart review. Patients were not followed after discharge to assess any future adverse effects or therapy adjustments.

Discussion

Levetiracetam is a novel agent for the treatment of neonatal seizures. Its mechanism differs from that of traditional agents, which may help overcome the challenges faced by other anticonvulsants due to the anatomy and physiology of the neonate.⁸ Levetiracetam also possesses favorable pharmacokinetics and safety profile, linear time-dependent kinetics, high oral bioavailability, reduced protein-binding, and renal-dependent clearance, which makes routine monitoring

Table 2. Treatment Characteristics*

Parameter	Value
Received benzodiazepine [†] prior to levetiracetam, n (%)	
Yes	10 (28)
No	26 (72)
Levetiracetam, mean $\pm$ SD (mg/kg)	
Loading dose (n = 36)	49.8 $\pm$ 11.4
Maintenance dose (n = 31)	24.8 $\pm$ 7.0
Seizure control with levetiracetam monotherapy, n (%)	
Yes	17 (47)
No	19 (53)
Additional anticonvulsant given after levetiracetam, n (%)	
Fosphenytoin	15 (83)
Phenobarbital	3 (17)
Seizure control following levetiracetam plus a second line agent, n = 18, n (%)	
Yes	13 (72)
No	5 (28)
Seizure control following addition of a specific anticonvulsant to levetiracetam, n (%)	
Fosphenytoin (n = 15)	10 (67)
Phenobarbital (n = 3)	3 (100)
Seizure control with monotherapy or combination therapy, n (%)	30 (83)

* n = 36 unless otherwise noted

[†] Lorazepam

unnecessary and, if needed, transition to oral therapy at discharge simple.^{8,14} Additionally, levetiracetam lacks significant drug interactions because of its minimal hepatic metabolism.⁸

In this study, neonates with documented seizures attained seizure control 47% of the time when intravenous levetiracetam was administered as a first-line monotherapy. Overall seizure control was seen in 83% of patients who received levetiracetam monotherapy or went on to receive combination therapy of levetiracetam plus fosphenytoin or phenobarbital. Treatment was tolerated in all patients, as no adverse effects were documented or identified during chart review.

Available literature has shown that levetiracetam's efficacy in controlling seizures in neonates may be comparable, if not better than, that of traditional agents utilized as first- or second-line treatment. In a randomized controlled trial of 30 patients comparing phenobarbital with phenytoin, Painter et al⁷ attained seizure control 43% and 45% of the time, respectively, with monotherapy. When looking at efficacy data for levetiracetam, Ramantani et al¹⁸ conducted a prospective study of levetiracetam first-line treatment in 38 patients. Thirty (79%) infants were seizure free at 1 week, and 27 of 30 (90%) patients remained seizure free at 4 weeks. However, the study protocol allowed for acute intervention, up to 2 doses of phenobarbital, for prolonged or recurrent seizures during up-titration of levetiracetam, and 19 (50%) patients received at least 1 dose of phenobarbital during treatment. In patients who did not

receive phenobarbital treatment after levetiracetam, 20 of 38 (53%) patients were seizure free at 1 week, and 19 of 20 (95%) patients remained seizure free at 4 weeks. This result is comparable to that of the current study, with about 50% of patients attaining seizure control with levetiracetam monotherapy.

There is additional literature that has investigated levetiracetam used as a second-line agent. Khan et al¹⁶ provided a retrospective study of 22 patients who received intravenous levetiracetam therapy for neonatal seizures. Fifteen (68%) patients received levetiracetam due to continued seizures on phenobarbital and 1 patient (5%) due to continued seizures on phenytoin. Seizure control was seen at 1 hour after levetiracetam administration in 7 of 22 (32%) patients and in 100% of patients by 72 hours. In another retrospective study, Abend et al¹⁹ analyzed 23 neonates who received levetiracetam for seizures. Only 4 (17%) patients received levetiracetam as first-line therapy, and all others received phenobarbital and/or phenytoin prior to levetiracetam. Seizure improvement, defined as a >50% reduction in electrographic seizures, after levetiracetam administration was seen in 35% of patients at 24 hours and in an additional 17% of patients between 24 and 72 hours after administration. Full seizure control was only seen in 9 (39%) patients. These studies reflect a wide range of protocols, with levetiracetam efficacy ranging from 53% to 79% with first-line therapy to 35% to 100% as a second- or third-line option. The results of the current study are within these ranges, showing

Table 3. Comparison of Variables in Patients After First-Line Levetiracetam Monotherapy With Seizure Control

Variable (n)	Seizure Control, n (%)	p Value
Sex		0.738*
Male (18)	8 (44)	
Female (18)	9 (50)	
Gestational age		0.836*
Preterm (10)	5 (50)	
Full-term (12)	12 (46)	
Birth weight		1.00†
<2.5 kg (9)	4 (44)	
≥2.5 kg (24)	11 (46)	
Delivery method		0.709*
Vaginal (16)	7 (44)	
C-section (20)	10 (50)	
Age at seizure onset		0.463†
≤3 days (26)	11 (42)	
>3 days (10)	6 (60)	
Etiology		0.417†
HIE (11)	4 (36)	
Unknown (11)	5 (46)	
Other (14)	8 (57)	
Received benzodiazepine prior		0.008†
Yes (10)	1 (10)	
No (26)	16 (62)	
Associated clinical features of seizure		0.605†
Yes (32)	16 (50)	
No (4)	1 (25)	
Abnormal first vEEG		0.006†
Yes (20)	5 (25)	
No (16)	12 (75)	

HIE, hypoxic ischemic encephalopathy; vEEG, video electroencephalogram

* Chi-square test.

† Fisher exact test (2-sided).

47% of patients with seizure control as first-line monotherapy and up to 83% when patients received either levetiracetam monotherapy or combination therapy with levetiracetam plus phenobarbital or fosphenytoin.

With the recent introduction of levetiracetam use for seizures in the neonatal population, there are no clear recommendations on standardized dosing protocols. The protocol used in this study provided guidance for treating physicians to choose an intravenous load of 50 mg/kg/dose, followed by a maintenance regimen of 20 mg/kg/dose administered intravenously every 12 hours. The averages seen in the study correlated well with the protocol, with an average loading dose of 49.8 ± 11.4 mg/kg and an average initial intravenous maintenance dose every 12 hours of 24.8 ± 7.0 mg/kg. These recommendations for dosing were identified based on the available literature that shows that variable doses of up to 100mg/kg/dose appear safe, with efficacy provided above.^{12,16–20} Merhar et al²⁰ conducted a pharmacokinetic study to collect safety data on the use

of levetiracetam in this population. Out of the 18 patients included, initial loading doses of levetiracetam ranged from 14 to 40 mg/kg/dose. Somnolence was the only adverse effect observed in some patients, but overall the medication was determined to be well tolerated. In Khan et al,¹⁶ 91% of patients received a loading dose of levetiracetam at 50 mg/kg/dose. Nineteen patients followed with an intravenous maintenance dose of 25 mg/kg/dose every 12 hours and one at 25 mg/kg/dose every 8 hours. Levetiracetam was well tolerated in this study, with only one patient noted to exhibit increased irritability. In a more recent study, Khan et al,²¹ reported a retrospective review of 12 preterm neonates who were administered levetiracetam loading doses ranging from 25 to 50 mg/kg/dose, followed by an intravenous maintenance dose of 25 mg/kg/dose every 12 hours. No adverse effects were reported. In the prospective study by Ramantani et al,¹⁸ levetiracetam was initiated at a 10 mg/kg/dose twice daily with a 3-day titration up to 30 mg/kg/dose. If patients had persistent seizures by

the end of the first week, the doses could be increased up to 45 to 60 mg/kg/dose. Drowsiness was the only reported side effect in this trial and was attributed in some cases to concomitant phenobarbital use. Abend et al¹⁹ observed no serious adverse effects in their study population, which received on average total daily dose of approximately 40 mg/kg/day.

Among traditional antiepileptics, neuronal injury has been associated with phenobarbital, fosphenytoin, and benzodiazepine administration in neonates.^{11,22} In the reported literature analyzed above, levetiracetam shows a favorable safety profile, with little or no adverse effects reported at various doses.^{12,16–21,23} This corresponds well with the findings of the current study, in which no adverse effects were identified by chart review during the patient's stay.

In the subgroup analysis, statistically significant higher rates of seizure control with levetiracetam monotherapy were seen in patients who did not receive a benzodiazepine prior to levetiracetam. In the literature, GABA agonists have shown to have reduced efficacy in the neonatal population.^{24,25} This may be due to the reversed chloride gradient seen in neonates, which has the potential to cause neuronal firing in response to GABA activation by benzodiazepines.^{8,22,25} This unique response to GABA activation can either prolong seizures or initiate new ones.^{8,22,25}

The other subgroup analysis with a reported statistical difference was seen in patients who had a normal initial vEEG. These patients had a higher rate of seizure control with levetiracetam monotherapy. However, only 56% of the study population had an abnormal initial vEEG read. Electrical seizure activity may have been missed due to a delay in vEEG capabilities, as the protocol in the study allowed for levetiracetam administration prior to vEEG if there was any delay in attaining vEEG for monitoring.

Limitations to the current study include lack of a control cohort, the retrospective nature of the study, and the use of individual chart review. The study lacked a cohort to compare efficacy of levetiracetam with our traditional agents, and both the retrospective nature and chart review methodology within the study provide opportunity for investigator bias during data collection. Another limitation is that 31% of seizures had no etiology identified, a higher number when compared to historical data reported for etiology of neonatal seizures.¹ The limited study period and retrospective nature may account for this percentage, as etiology may have been undocumented or identified with outpatient follow-up. Additionally, potential long-term adverse effects may have been overlooked, as patients were only monitored until discharge.

Conclusions

In conclusion, the current retrospective study is one of the larger reported in the literature, with 36 neonates

receiving first-line levetiracetam therapy for seizures. The results seen in this study reveal promising efficacy with levetiracetam as a first-line therapy for neonatal seizures. In addition, the safety profile seen in the current study along with other reports demonstrates that levetiracetam is a safe option in the neonatal population. Further studies are warranted to directly compare historical agents with levetiracetam therapy to assess efficacy for neonatal seizures.

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