JPPT | Single Center Retrospective Study

Efficacy of Levetiracetam vs Phenobarbital as First Line Therapy for the Treatment of Neonatal Seizures

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OBJECTIVE Seizures are one of the most common neurologic complications seen in a neonate. Historically, phenobarbital has been the agent of choice, but can lead to adverse neurologic outcomes, which has contributed to the use of other agents. Levetiracetam has proven great efficacy with an excellent safety profile in older patients, causing interest of its use in neonates. The objective of this study was to determine if levetiracetam would provide similar neonatal seizure resolution rates as phenobarbital.

METHODS The study was a single-center, retrospective, cohort study from August 1, 2020 to August 31, 2022 investigating the efficacy and safety of using levetiracetam compared with phenobarbital as a first line treatment for neonatal seizures. The primary outcome was to assess overall seizure resolution after administration of levetiracetam or phenobarbital, without addition of a second antiseizure medication.

RESULTS There were 87 patients included in the study. Fifteen neonates (27.78%) achieved seizure resolution with phenobarbital compared with 9 neonates (27.27%) who received levetiracetam first line ($p = 0.959$). Neonates who received phenobarbital had higher rates of adverse effects. Neonates who received a benzodiazepine prior to administration of levetiracetam had lower seizure resolution rates ($p = 0.021$).

CONCLUSIONS These findings suggest there is no difference in using phenobarbital over levetiracetam to achieve complete seizure resolution in a neonate. Higher rates of adverse events were seen in the phenobarbital group. The use of a benzodiazepine prior to administration of levetiracetam may reduce the efficacy of levetiracetam.

ABBREVIATIONS ASM, antiseizure medication; BP, blood pressure; BZD, benzodiazepine; CGA, corrected gestational age; EEG, electroencephalogram; GABA, ɣ-aminobutyric acid; HIE, hypoxic-ischemic encephalopathy; LEV, levetiracetam; NICU, neonatal intensive care unit; OSH, outside hospital; PB, phenobarbital; SV2A, synaptic vesicle 2A

KEYWORDS benzodiazepine; levetiracetam; neonatal seizures; neonate; phenobarbital

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Introduction

Seizures are one of the most frequently encountered neurologic conditions in neonates. Neonatal seizures tend to differ from those of older children and adults, since they are often clinically subtle, inconspicuous, and difficult to recognize.[1,2] The neonatal period is the most vulnerable of all periods of life for developing seizures, particularly in the first 7 days of life.[2] The most common etiology of neonatal seizures is hypoxic-ischemic encephalopathy (HIE); however, infections, electrolyte and glucose disturbances, intracerebral hemorrhages, and inborn errors of metabolism have also been known to play a role.[3,4]

Phenobarbital has historically been recognized as the agent of choice for the treatment of neonatal seizures.[5] Phenobarbital is a long-acting barbiturate with sedative, hypnotic and antiseizure properties, that works to increase the length of time chloride channels are open on ɣ-aminobutyric acid (GABA)-A receptor subunits and hyperpolarize the membrane.[6] The 2011 World Health Organization (WHO) Neonatal Seizure Guidelines are the most recent clinical practice guidelines available for clinicians to follow. In these guidelines, phenobarbital and phenytoin are recommended to be used first line for the treatment of seizures in term and preterm neonates up to 44 weeks postmenstrual age.[5] A randomized, controlled trial showing that phenobarbital and phenytoin are equally effective in resolving seizures served as the basis for this recommendation.[7] The guidelines put preference on phenobarbital over phenytoin, due to the risks of severe hypotension and arrhythmias seen with phenytoin.[8] However, the use of phenobarbital is not without risk as this medication has been associated with respiratory depression, hypotension, neuronal apoptosis and poor neurodevelopment outcomes.[9] In addition, the guidelines do not offer

clinicians any guidance on the use of levetiracetam in this patient population.[5]

The concern for poor neurologic outcomes associated with phenobarbital has led to the use of alternative agents, such as levetiracetam. Levetiracetam works to inhibit voltage-gated-N type calcium channels and modulates glutamate release through binding of the synaptic vesicle 2A (SV2A).[10] Levetiracetam is seen as a safer alternative to phenobarbital due to the decreased rate of adverse neurologic effects.[10] A retrospective study of infants at 24 months corrected gestational age (CGA) who previously received phenobarbital or levetiracetam for neonatal seizures showed that increased exposure to phenobarbital resulted in worse Bayley Scales of Infant Development scores and higher incidence of cerebral palsy compared with levetiracetam.[11]

There have been a limited number of small, retrospective studies conducted that assessed the use of levetiracetam in comparison to phenobarbital for the treatment of neonatal seizures. These retrospective data have generally shown that levetiracetam provided comparable seizure resolution rates to phenobarbital, suggesting that levetiracetam would be a viable alternative to phenobarbital.[12–14] NEOLEV2 is the 1 randomized, controlled, phase IIb efficacy study completed in this patient population that assessed levetiracetam compared with phenobarbital. Results of this trial showed that phenobarbital was more effective than levetiracetam for first line treatment of neonatal seizures (80% vs 28%, $p < 0.001$), conflicting the results found in previous studies.[15] The purpose of this study was to analyze whether levetiracetam is an equivalent alternative for the treatment of neonatal seizures.

Materials and Methods

Study Design. This was a retrospective cohort study from August 1, 2020 to August 31, 2022 of neonates who received levetiracetam or phenobarbital first line for initial seizure presentation in a level IV neonatal intensive care unit (NICU) at an academic medical center. Typical neurology practice for a neonatal seizure at this institution allowed for the emergent administration of a benzodiazepine (BZD) and loading with a dose of phenobarbital 20 mg/kg, followed by an additional load of phenobarbital 10 mg/kg, with the option of adding levetiracetam 60 mg/kg for persistent or recurrent seizures 2 hours following the initial phenobarbital load; however, antiseizure medication (ASM) selection and dosing were not standardized due to neurologist preference and the retrospective nature of the study. Pharmacy administration records were used to identify all patients who received at least 1 dose of phenobarbital or levetiracetam during the study period. Patients were excluded if they were over 60 days of age or received an ASM at an outside hospital (OSH). Patients were also excluded if they received an ASM for any indication other than neonatal seizures or if they were found to have no seizure activity confirmed by electroencephalogram (EEG).

Data Sources. All data were collected via review of electronic medical records. Patient demographic information including gestational age at birth, gestational age at seizure onset, and dosing weight were all collected. Seizure characteristics such as etiology, whether patients with HIE received therapeutic cooling, and seizure resolution were based on documentation from the attending neurologist within the electronic medical record. Medical information collected included first line ASM choice and dosing, number of first line ASM loading doses given, and, if applicable, what second line ASM was given.

Outcomes and Statistics. The primary outcome of the study was seizure resolution after the administration of levetiracetam or phenobarbital, without addition of a second ASM. Seizure resolution was defined as normalization of EEG or absence of clinical features associated with seizures for 24 hours after administration of the ASM. Secondary outcomes included the proportion of seizure resolution with the addition of a second ASM and safety outcomes including respiratory depression, apneic event, hypotension, and increased diastolic blood pressure. Safety outcomes were collected through provider documentation within the electronic medical record. Statistical analysis was performed using SPSS Statistics version 29 (IBM, Armonk, NY). Continuous variables were compared between the 2 groups using the Mann-Whitney *U* test, while categorical data were assessed via the χ^2 or Fisher exact test. The predetermined level of significance was set at $\alpha = 0.05$.

Results

Enrollment. A total of 192 patients received levetiracetam or phenobarbital for the management of initial seizure onset. Based on pre-defined exclusion criteria, 105 patients were excluded from analysis. The most common reason for exclusion was patient age over 60 days of life at the time of seizure onset (n = 54). Of the 87 patients who met full inclusion criteria, 54 patients received phenobarbital and 33 received levetiracetam for first line management of their seizure (see Supplemental Figure).

Demographics. Baseline characteristics were similar in patients who received phenobarbital or levetiracetam first line (Table 1). In general, the phenobarbital group was about 1 week younger at birth (36.76 vs 37.52 weeks, $p = 0.300$) and at seizure onset (37.54 vs 38.92 weeks, $p = 0.163$) than the patients who received levetiracetam. Additionally, patients were similar in reference to the etiology of their seizure. The most common seizure etiology was HIE, affecting 37 of the 87 patients included in the study. Of those 37, 31 (83.78%) underwent therapeutic hypothermia. The number of patients with intracranial hemorrhage was

Table 1. Baseline Demographics of the Study Population

Demographic	Phenobarbital (n = 54)	Levetiracetam (n = 33)	*p* value
Weight, mean ± SD, kg	2.99 ± 0.99	3.15 ± 0.86	0.284
Gestational age, mean ± SD, wk	36.76 ± 4.25	37.52 ± 3.95	0.300
Age at seizure onset, mean ± SD, wk	37.54 ± 4.42	38.92 ± 4.09	0.163
Initial dose, median (IQR), mg/kg	20 (20–20)	60 (40–60)	—
Cumulative dose, median (IQR), mg/kg	20 (20–30)	60 (20–100)	—
Seizure etiology, n (%)			
Hypoxic-ischemic encephalopathy	22 (40.74)	15 (45.45)	0.670
Intracranial hemorrhage	15 (27.78)	3 (9.09)	0.037
Thromboembolic event	7 (12.96)	4 (12.12)	0.910
Epilepsy	1 (1.85)	2 (6.06)	0.302
Infection	2 (3.70)	0 (0)	0.269
Inborn errors of metabolism	2 (3.70)	0 (0)	0.269
Other*	4 (7.41)	6 (18.18)	0.129
Unknown	2 (3.70)	2 (6.06)	0.615
Patient cooled, n (%)	19 (35.19)	12 (36.36)	0.913

* Other: congenital brain malformation, electrolyte/laboratory value disturbance, brain injury.

higher in those that received phenobarbital for first line management (p = 0.037; Table 1).

Treatment. All 54 patients in the phenobarbital group received an initial first dose of 20 mg/kg. For the 33 patients who received levetiracetam, 23 received an initial loading dose of 60 mg/kg. In this analysis, patients could receive an additional loading dose of their selected first line agent if they were experiencing persistent or recurrent seizures 2 hours following the initial loading dose. The phenobarbital group typically received a second load of 10 mg/kg, with the levetiracetam group second loading dose ranging from 10 to 60 mg/kg. The phenobarbital group received a median cumulative dose of 20 mg/kg, while the levetiracetam group received a median cumulative dose of 60 mg/kg (Table 1).

Seizure Cessation Efficacy. Of the neonates who initially received phenobarbital, 15 patients (27.78%) achieved seizure resolution, compared with 9 patients (27.27%) who received levetiracetam first line (p = 0.959). In this analysis, patients who were unable to achieve seizure resolution with their selected first line agent subsequently could receive the alternative agent as second line therapy. Twenty-three of the 38 neonates (60.53%) who did not respond to phenobarbital achieved seizure resolution with the addition of levetiracetam. Conversely, among the 14 neonates who did not respond to levetiracetam first line, 11 achieved seizure resolution with the addition of phenobarbital (78.57%; Supplemental Figure). Administering a BZD prior to phenobarbital did not have a significant effect on seizure resolution rates (p = 0.733); however, patients who received a BZD prior to levetiracetam had a significant reduction in seizure resolution compared with those who received levetiracetam alone (p = 0.021). When the patients who received a BZD prior to their selected first line agent are removed from the analysis, seizure resolution rates favor those who received levetiracetam, with about 44% of those patients responding to levetiracetam, compared with 30% with phenobarbital (Table 2).

Safety Analyses. There were no reported instances of adverse events in the levetiracetam group. In patients who received phenobarbital, there was 1 report of apnea, while 14 (25.93%) patients experienced hypotension (p < 0.001) and 15 (27.78%) patients experienced respiratory depression (p < 0.001), both of which were significant compared with those who received levetiracetam (Table 3).

Discussion

In this single-center, retrospective chart review, we found that levetiracetam and phenobarbital provided similar rates of seizure resolution, adding to the limited yet growing evidence that levetiracetam may be an effective first line agent for the management of neonatal seizures. The previous reports of assessing levetiracetam efficacy for neonatal seizure in comparison to

Table 2. Seizure Resolution With Benzodiazepines

	No BZD	With BZD	*p* value
Phenobarbital (n = 54)	40	14	—
Seizure resolution, n (%)	12 (30)	3 (21.43)	0.733
Levetiracetam (n = 33)	18	15	—
Seizure resolution, n (%)	8 (44.44)	1 (6.67)	0.021

BZD, benzodiazepine

phenobarbital are mainly derived from retrospective cohort studies.[12,14] Rao et al[14] compared levetiracetam to phenobarbital for neonates experiencing seizures caused by HIE. This study found that levetiracetam was more effective in resolving neonatal seizures compared with phenobarbital; however, this study did not assess patients with other etiologies outside of HIE. A more recent retrospective study conducted by Wagner et al[12] found that when neonates did not receive an emergent BZD like lorazepam, both phenobarbital and levetiracetam achieved seizure resolution in approximately half of the cases. These cohorts comparing levetiracetam to the guideline recommended phenobarbital suggest that levetiracetam would be a viable alternative for first line management of neonatal seizures. However, NEOLEV2, a recent phase IIb randomized controlled trial has data that are conflicting to prior studies. This prospective study demonstrated significantly higher seizure resolution rates with phenobarbital compared with levetiracetam.[15] Additionally, the protocol of this study allowed for an initial loading dose of levetiracetam of 40 mg/kg, with the option of giving a second load to a total cumulative dose of 60 mg/kg.[15] This dosing differed from patients in our study, as under neurology recommendations, we commonly initiated patients on 60 mg/kg, with most patients receiving up to 120 mg/kg total if they required an additional levetiracetam load. In our assessment, patients who received smaller doses of levetiracetam did not have a lower response of seizure resolution compared with those who received larger doses. The authors of NEOLEV2 did conclude that optimal dosing of levetiracetam needed to be defined and further studies performed to assess if levetiracetam used in larger doses may achieve better seizure resolution rates than when used in more conservative dosing.[15] Overall, the results from our study are consistent with previous retrospective studies, showing that levetiracetam may be an effective and safe alternative to phenobarbital.

Regarding safety of these agents, there were no reported instances of adverse events in the levetiracetam group. Increased rates of hypotension and respiratory depression were observed in the phenobarbital group, which is consistent with previous literature.[13,15] The absence of any adverse effects in the levetiracetam group compared with those who received phenobarbital further shows the desirability of levetiracetam as a first line agent in the neonatal population.

The potential drug interaction between levetiracetam and benzodiazepines was introduced in a recent retrospective cohort. The study suggested that hyperpolarizing the membrane via GABA modulation by BZD use may reduce the occurrence of action potentials that levetiracetam needs to be effective given that its mechanism of action is action potential dependent.[12] The study further suggests that phenobarbital and BZDs may work synergistically at the GABA receptors by increasing both the frequency and the duration of the GABA receptor currents, which may lead to increased efficacy when used together.[12] Our study further supports that theory as the patients who received a BZD, typically lorazepam, prior to receiving levetiracetam had significantly lower rates of seizure resolution, while the phenobarbital group was not significantly affected. While the WHO neonatal seizure guidelines do not comment on using a BZD prior to the identified first line agent, preference of the attending neurologist and typical neurology practice at our institution allowed for the administration of a BZD, which potentially played a role in over half of the patients in the study receiving one.

A limitation of our study was that reportable outcomes were dependent on documentation within the electronic medical record. In the instance that seizure resolution was not properly documented, the results of the primary outcome could be affected. This may have also impacted the ability to assess safety outcomes in the treatment groups as well. Due to dosing being at the discretion of the neurologist on service, dosing of both phenobarbital and levetiracetam could not be standardized. This lack

Table 3. Medication Related Safety Outcomes

Adverse Effect	Phenobarbital	Levetiracetam	*p* value
Apnea, n (%)	1 (1.85)	0 (0)	1.000
Hypotension, n (%)	14 (25.93)	0 (0)	<0.001
Increased diastolic BP, n (%)	0 (0)	0 (0)	—
Respiratory depression, n (%)	15 (27.78)	0 (0)	<0.001

BP, blood pressure

of standardization resulted in various dosing regimens, particularly in the levetiracetam group. Timing of the administration of the ASM in relation to seizure onset could have affected outcomes as well. Phenobarbital is available and dispensed from automated dispensing cabinets in the unit, while levetiracetam requires preparation and dispensing from the pharmacy. The small sample size can be attributed to the single-center nature of the study. While the results of this study are comparable with other recent literature, a larger sample size may have helped account for any potential confounders. Additionally, power was not assessed in this analysis.

In the future, additional prospective randomized controlled trials are needed to confirm the results of this study. Within these studies, larger doses of levetiracetam should be included to define optimal dosing in neonates and its relation to seizure resolution. These trials should also assess long-term neurodevelopment outcomes to verify the potential benefit of using levetiracetam over phenobarbital in the neonatal population.

Conclusion

This retrospective study suggests that levetiracetam is as effective as phenobarbital for the initial management of neonatal seizures with significantly fewer side effects. If a benzodiazepine is administered prior to levetiracetam, seizure resolution rates may be impacted.

Article Information

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