A Systematic Review of the Efficacy of Levetiracetam in Neonatal Seizures

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Abstract

Objective Seizures are the most common neurological complication in neonatal intensive care units. Phenobarbital (PB) remains the first-line antiepileptic drug (AED) for neonatal seizures despite known neurotoxicity. Levetiracetam (LEV) is a newer AED not approved for neonates. Retrospective and pilot studies have investigated the use of LEV in neonatal seizures. Our objective was to compare the efficacy of LEV to PB in neonatal seizures based upon published data.

Methods We searched PubMed to perform a systematic review. We found no studies of LEV with comparison or control groups; therefore, we utilized data from two randomized controlled trials of PB as our comparison group.

Results Five studies of LEV met all inclusion/exclusion criteria. The pooled sample size for LEV was 102 (48 received primary LEV, 54 received secondary LEV). The pooled sample size for primary PB was 52. Complete or near-complete seizure cessation was achieved as follows: primary LEV 37/48 (77%), secondary LEV 34/54 (63%), and primary PB 24/52 (46%).

Conclusion Our findings suggest that LEV may be at least as or more effective for neonatal seizures as PB. Our review, though limited, is the first to examine LEV efficacy compared with PB in neonates.

Keywords
- neonatal seizure
- levetiracetam
- systematic review

Introduction

Rationale

The incidence of neonatal seizures is estimated to be 1 to 3 per 1,000 for term infants and much higher for preterm infants.[1] Neonatal seizures are associated with high risk of death and chronic morbidities, such as epilepsy (up to 50%), cerebral palsy, developmental delays, and cognitive impairment.[1,2] Phenobarbital (PB), a first-generation antiepileptic drug (AED), remains the first-line therapy for neonatal seizures. However, PB is known to be associated with neuronal toxicity/apoptosis in animal models, and is associated with long-term cognitive and motor impairment.[3–6] Furthermore, its reported efficacy in complete resolution of seizures varies between 33 and 77%.[7]

Levetiracetam (LEV) is a second-generation AED that is U.S. Food and Drug Administration approved for the treatment of epilepsy in adults and children aged 1 month and older.[8] LEV has demonstrated a more favorable safety profile in both pediatrics and adults.[9] After neonatal exposure to PB and LEV, fewer cognitive and motor impairments were seen at 24 months in the LEV group when compared with the PB group.[6] Children exposed to LEV in utero may also have less risk of poor development.[10] Furthermore, unlike PB, LEV does not exhibit a proapoptotic effect in neurons.[11] Several small retrospective and pilot studies have investigated the use of LEV in the setting of neonatal seizures.[12,13] From these studies, some physicians elect to use LEV off-label for the treatment of neonatal seizures. Only one previous systematic review that examined all available therapies for neonatal seizures included

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LEV in its analysis.[14] However, only two retrospective studies were included from 2011, and several additional studies are now available for review. Given the off-label usage of LEV, lack of randomized controlled trials, and its potential to replace PB as a safer AED in the treatment of neonatal seizures, it is essential to investigate the efficacy of LEV with currently available data. Improved treatments for neonatal seizures may decrease morbidity and mortality associated with the disease.

Objectives

To perform a systematic review of published data examining the associations between LEV used to treat neonatal seizures and seizure resolution, seizure frequency, and seizure-related mortality. We will use standard outcome measures of AED efficacy, defined as complete electrographic seizure resolution and $\geq$ 50% electrographic seizure reduction.

Methods

Protocol

We performed a systematic review of the literature in accordance with the PRISMA statement.[15] To that end, the authors created a protocol in advance of performing the study specifying inclusion/exclusion criteria, outcome measures of interest, and analytical methods. Minor revisions were made regarding outcome measures of interest due to the heterogeneity of available publications. However, there were no major modifications with regards to the primary outcome measures.

Eligibility Criteria

We examined studies in which the primary objective was investigating the efficacy of LEV for treatment of neonatal seizures. Included studies met the following criteria: studies of neonates (defined as children $\leq$ 28 days old); investigated the use of LEV as primary or secondary/adjunctive therapy for seizure control; seizure diagnosis was electrographically proven; electrographically proven seizure response to therapy (e.g., complete or near-complete resolution, partial response, no response). Studies were excluded if they were single case reports or seizures were due to correctable electrolyte abnormalities.

Information Sources

The literature search was performed in April 2015 using PubMed, the Cochrane library, and reviewing reference lists of relevant publications.

Search

We used the following search terms in PubMed: (neonate* OR infant OR newborn) AND (seizure* OR epilepsy) AND (keppra OR levetiracetam). The filters "English" and "human" were applied to the results.

Study Selection

The authors independently reviewed search results by title and abstract and excluded all irrelevant results. Of the remaining studies, the authors used a standardized form to independently review them for the previously stated inclusion/exclusion criteria and evaluate for risk of bias utilizing Cochrane library recommendations. Disagreements between reviewers were resolved by consensus.

Data Collection Process

We developed data collection sheets utilizing the Cochrane Consumers and Communication Review Group template and modified it to collect all relevant measures for our review. The authors independently completed these data collection forms for all included studies and compared results. Disagreements were resolved by consensus.

Data Items

Data collection sheets included information regarding the study design, sample population (age, preterm vs. full term), sample size, documentation of electrographically proven seizures, LEV intervention (first-line vs. secondary, monotherapy vs. adjuvant, dosage, and route of administration), other AED therapy, control/comparison groups, outcome measures, and study strengths and limitations/risk of bias.

Strengths and Limitations

Each included study was assessed for strengths and limitations and risk of bias. Study strengths specifically targeted included prospective studies, continuous electrographic seizure monitoring, control/comparison groups, well-documented AED administration (including dosage, route of administration, adjuvant AEDs, etc.), and rigorous documentation and reporting of results. Commonly considered limitations included small sample sizes, retrospective studies, uncontrolled, nonblinded studies, heterogeneous AED administration, limited electroencephalographic monitoring, lack of control/comparison groups, and missing/unreported data. We assessed for risk of selection bias, confounding bias and design bias. Strengths, limitations, and risk of bias were assessed among individual studies and across all studies.

Summary Measures

Due to a lack of control and comparison groups among the included studies, we utilized historical data of standard therapy (PB) for neonatal seizures as a comparison group. A Cochrane library systematic review of AED therapy for neonatal seizures identified only two randomized controlled trials including PB for neonatal seizures.[16] We also searched PubMed for additional randomized controlled trials of PB but found none that reported response to PB along with electrographic confirmation of seizure reduction. We compared proportions of patients who responded to therapy from our included studies of LEV with published PB efficacy. Separate proportions were reported for LEV as first-line therapy and LEV as second-line therapy. We also reported upon $\geq$ 50% seizure reduction, mortality, and adverse events. Since all available studies of LEV constitute lower levels of evidence (retrospective studies, case series, no control groups, etc.), we were unable to perform direct comparisons (such as odds ratios) with the data from the PB randomized controlled trials.

Results

Study Selection

Our PubMed search yielded 153 results, and we identified two additional publications from reviewing references of relevant articles, for a total of 155 publications to be screened. No duplications were identified. Of these 155 publications, 141 were excluded based upon review of title and abstract most commonly for reasons, such as wrong treatment intervention and/or wrong patient population. The remaining 14 articles were evaluated in detail. Nine were found to not meet inclusion/exclusion criteria based upon wrong patient population, wrong intervention/outcome measure, lack of electrographic confirmation of seizure activity, survey-based study without appropriate outcome measures, and single case reports. The remaining five studies met all inclusion/exclusion parameters and were included in the final analysis.[17–21]

Study Characteristics

Study characteristics are summarized in ►**Table 1**. Of the included studies, four were retrospective (including one case series), and only one was prospective. There are a total of 102 patients combined among studies, with a combination of term and preterm neonates. All patients were treated during the neonatal period, from birth to 28 days old. A total of 54 patients were males, and 48 were females.

Use of LEV was heterogeneous within and across studies. A total of 48 patients received LEV as a first-line treatment and 54 received LEV as secondary treatment (including third-line therapy and beyond). All LEV was administered intravenously. The loading doses ranged from 5 to 50 mg/kg, and maintenance doses ranged from 10 to 60 mg/kg twice a day. The most commonly used AED in addition to LEV was PB, but several additional AEDs were used as well. These other AEDs were often given concomitantly with LEV. All studies lacked a control group.

The primary outcome measure of all included studies was electrographic seizure control, including both complete or near-complete seizure cessation and partial response ($\geq$50% reduction in electrographic seizure activity). One study provided an outcome classification as "excellent response," defined as $\geq$ 80% electrographic seizure reduction.[21] We were unable to determine based upon this publication which patients had complete seizure resolution, and which had $\geq$ 80% but less than complete seizure cessation; we elected to classify all patients in this category as complete or near-complete seizure cessation for simplicity. All five studies commented on adverse events and mortality, although it may not have been a defined outcome measure.

Strengths and Limitations Within and Across Studies

Strengths and limitations of individual studies are described in ►**Table 2**. Strengths found across most studies included good documentation of individual therapies and follow-up after hospital discharge. Common limitations across studies include small sample size, retrospective studies, lack of blinding, placebos, randomization and control groups, lack of a standard dosage of LEV, and heterogeneous use of other AEDs.

Table 1 Study characteristics

Source	Study type	Population	Gender distribution	Primary levetiracetam	Secondary levetiracetam	Loading dose	Maintenance dose	Other AEDs administered
Abend et al (2011)	Retrospective	Preterm and term neonates (35–41 wk)	11 M/12 F	4	19	10–20 mg/kg	5–40 mg/kg BID	PB, PHT, TPM, MDZ, FA
Ramantani et al (2011)	Prospective	Preterm and term neonates (23–42 wk)	24M/14 F	38	0	10 mg/kg	Up to 60 mg/kg	Up to two doses of PB 20 mg/kg
Khan et al (2011)	Retrospective	Term neonates	10 M/12 F	3	19	10–50 mg/kg	25 mg/kg BID or TID	PB, FP, LZP, MDZ
Khan et al (2013)	Retrospective	Preterm neonates (23–35 wk)	4 M/7 F	3	8	25–50 mg/kg	25 mg/kg BID	PB
Rakshasbhuvankar et al (2013)	Case series	Preterm and term neonates (22 wk–term)	5 M/3 F	0	8	5–10 mg/kg	10–35 mg/kg	PB, CZP, TPM, OXC

Abbreviations: CZP, clonazepam; F, female; FA, folinic acid; FP, fosphenytoin; LZP, lorazepam; M, male; MDZ, midazolam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate.

Table 2 Individual study strengths and limitations

Study	Strengths	Limitations
Abend et al (2011)	1. Detailed recording of individual patient treatments	1. Retrospective 2. Small sample size 3. Heterogeneous use of other AEDs 4. No standard LEV dosage
Ramantani et al (2011)	1. Prospective 2. Characterized EEG seizure types and severity 3. Standardized use of PB 4. Follow-up after discharge	1. Small sample size 2. Heterogeneous cohort (ages) 3. Lack of randomization, blinding, and control group
Khan et al (2011)	1. Detailed recording of individual patient treatments 2. Serial EEGs 3. Follow-up after discharge	1. Retrospective 2. Small sample size 3. Heterogeneous use of other AEDs 4. No standard LEV dosage
Khan et al (2013)	1. Detailed recording of individual patient treatments 2. Serial EEGs 3. Follow-up after discharge	1. Retrospective 2. Small sample size 3. Heterogeneous use of other AEDs 4. No standard LEV dosage
Rakshasbhuvankar et al (2013)	1. Detailed recording of individual patient treatments 2. Follow-up after discharge	1. Retrospective 2. Small sample size 3. Heterogeneous use of other AEDs 4. No standard LEV dosage 5. Lack of continuous EEG monitoring 6. Use of $\geq$ 80% seizure reduction

Abbreviations: AED, antiepileptic drug; EEG, electroencephalogram; LEV, levetiracetam; PB, phenobarbital.

Results of Individual Studies

Seizure control for individual studies is depicted in ►**Table 3**, categorized as complete or near-complete cessation of seizures, $\geq$ 50% reduction in electrographic seizure activity, or minimal or no response or unable to judge. Patients were divided as receiving LEV first-line or as secondary treatment. Within successful study treatment (defined as complete seizure or near-complete cessation of seizures or $\geq$ 80% seizure reduction) for first-line LEV ranged from 25 to 100% and for secondary LEV 32 to 84%.

A Cochrane library review of AEDs for neonatal seizures identified two randomized trials of PB in neonatal seizures. Since our review included studies that lacked a control group, we report data from these two trials as a published historical comparison (►**Table 3**). Painter et al found primary PB successfully controlled seizures (i.e., complete electrographic resolution) in 13/30 cases, and secondary PB successfully controlled 5/13 cases. Boylan et al reported primary PB successfully controlled seizures ($\geq$80% electrographic reduction) in 11/22 cases; no secondary use of PB was reported.

Synthesis of Results

A total of 48 patients received primary LEV across all studies. Of these, 37/48 (77%) achieved complete or near-complete seizure cessation (range: 25–100% within studies). A total of 54 patients received secondary LEV across all studies, with 34/54 (63%) achieving complete or near-complete seizure cessation (range: 32–84% within studies). Across the primary PB patients, 24/52 (46%) achieved complete or near-complete seizure cessation (range: 43–50% within studies). Only one study reported secondary PB results, with 5/13 (38%) patients obtaining complete or near-complete seizure cessation.

Insufficient data were available to perform a quantitative analysis or hypothesis testing between the LEV and PB studies due to heterogeneity between the types of studies available (case series and uncontrolled studies vs. randomized trials). Limited data are available regarding patients with $\geq$ 50% seizure reduction, mortality, or adverse events. Greater than 50% seizure reduction is characterized in ►**Table 3**. Across LEV studies, a total of three mortalities were reported during the acute treatment period out of 102 patients; however, mortality was not a clearly specified outcome measure in all studies. In total, only three adverse events were reported in the LEV studies: drowsiness, irritability, and transient conjugated hyperbilirubinemia. Across the PB studies, 4 deaths were reported out of a total of 65 patients; no other adverse events were reported.

Discussion

Summary of Evidence

The proportion of neonates obtaining complete seizure or near-complete cessation across all included LEV studies ranged between approximately two-thirds and three-quarters. This response rate may be inflated due to publication bias, and likely does not represent a true response rate of LEV that would be found in randomized controlled trials. However, this is the best available data regarding the efficacy of LEV for the treatment of neonatal seizures. Higher quality, though still severely limited, data exists regarding the use of PB in neonatal seizures. We found

Table 3 Results of individual studies

Source	Primary levetiracetam			
	Complete/near-complete cessation	≥50% Reduction	Minimal/no improvement or unable to judge	Total sample size
Abend et al (2011)	1 (0.25)	0 (0.0)	3 (0.75)	4
Ramantani et al (2011)	30 (0.79)	0 (0.0)	8 (0.21)	38
Khan et al (2011)	3 (1.0)	0 (0.0)	0 (0.0)	3
Khan et al (2013)	3 (1.0)	0 (0.0)	0 (0.0)	3
Rakshasbhuvankar et al (2013)	N/A	N/A	N/A	N/A
Total	37 (0.77)	0 (0.0)	11 (0.23)	48
Source	**Secondary levetiracetam**			
	Complete/near-complete cessation	**≥50% Reduction**	**Minimal/no improvement or unable to judge**	**Total sample size**
Abend et al (2011)	6 (0.32)	5 (0.26)	8 (0.42)	19
Ramantani et al (2011)	N/A	N/A	N/A	N/A
Khan et al (2011)	16 (0.84)	0 (0.0)	3 (0.16)	19
Khan et al (2013)	6 (0.75)	0 (0.0)	2 (0.25)	8
Rakshasbhuvankar et al (2013)	6 (0.75)	1 (0.13)	1 (0.13)	8
Total	34 (0.63)	6 (0.11)	14 (0.26)	54
Source	**Primary phenobarbital**			
	Complete/near-complete cessation	**≥50% Reduction**	**Minimal/no improvement or unable to judge**	**Total sample size**
Painter et al (1999)	13 (0.43)	N/A	17 (0.57)	30
Boylan et al (2004)	11 (0.50)	N/A	11 (0.50)	22
Total	24 (0.46)	N/A	28 (54)	52
Source	**Secondary phenobarbital**			
	Complete/near-complete cessation	**≥50% Reduction**	**Minimal/no improvement or unable to judge**	**Total sample size**
Painter et al (1999)	5 (0.38)	N/A	8 (0.62)	13
Boylan et al (2004)	N/A	N/A	N/A	N/A
Total	5 (0.38)	N/A	8 (0.62)	13

Abbreviation: N/A, not applicable.

the data from randomized trials suggesting that approximately one-third to one-half of neonatal seizures will achieve complete seizure or near-complete cessation with PB therapy.

Our findings suggest that LEV holds promise as a therapy for neonatal seizures, though further studies are needed before any definitive conclusions may be drawn. Since our analysis included patients who received LEV in addition to other AEDs, we utilized data from randomized controlled trials of PB including both patients who were treated successfully with PB first-line and those who achieved seizure cessation with PB plus an additional AED. This is not an optimal comparison group. However, studies of drugs used in neonates are difficult and often not performed for ethical reasons. We, therefore, think that this is the best comparison available given the limited data that are available.

Further investigation of LEV as a treatment for neonatal seizures is warranted based upon our results, as the data suggests that LEV has been used to successfully to control neonatal seizures. However, definite clinical recommendations cannot be made without randomized controlled trials. We compared published LEV efficacy to published PB efficacy. It is important to note that no direct statistical comparison can be made between these two groups due to the disparate nature of the LEV and PB studies. Our findings do suggest that clinical equipoise exists between treating neonatal seizures with LEV or PB. PB is not an optimal AED in the setting of neonatal seizures due to its known neurotoxic effects and potential for neurodevelopmental problems. Utilization of an AED that is equally or more effective than PB without known neurotoxicity or with fewer or less severe adverse effects is essential to improving outcomes in this patient population.

Our findings report minimal mortalities and adverse events. The lack of mortalities may be in part attributable to publication bias. Only three adverse events were reported across all studies, though it is likely that this represents underreporting, as it is difficult to accurately accrue such data in retrospective studies. Large-scale prospective trials are needed to better characterize the occurrence of adverse events.

Strengths and Limitations

The main limitation of this study is the lack of published studies investigating the use of LEV in neonatal seizures. The five included studies were all limited by small sample size, the retrospective nature of the studies (4/5), a heterogeneous use of additional AEDs, and a lack of control groups, randomization, and blinding. Another limitation is our comparison group (PB) was based upon data from the only two randomized controlled trials of PB in neonatal seizures. No direct comparisons can be made between the LEV and PB studies. Nevertheless, this study followed a strict protocol, utilized current guidelines (PRISMA), included studies with electrographically proven seizure activity, and included a variety of patient populations (full- and preterm). Moreover, this study is the first to attempt to characterize objective measures of seizure control with LEV compared with standard therapy (PB) in a patient population that is often not investigated in clinical trials due to ethical concerns.

Conclusions

We have found adequate data to support further investigation of LEV in the setting of neonatal seizures. Although our systematic review is based upon studies with lower levels of evidence compared with randomized controlled trials, this data are currently the best available evidence in this important field. Given the life-threatening nature of neonatal seizures, it is essential to investigate best practices and determine which AEDs are most effective and safe. Clinicians have long relied on the use of PB for neonatal seizures due to a lack of trials investigating newer alternative therapies, in spite of longstanding knowledge of the potential neurotoxic effects of PB. LEV appears not to be neurotoxic and may offer fewer and/or less severe long-term cognitive effects.

Neonatal seizure treatment is a severely understudied subject in child neurology. Our data demonstrate clinical equipoise between LEV and PB in the setting of neonatal seizures. Mortality and adverse events rates appear to be acceptably low in our review, though we were unable to perform a formal quantitative analysis. At the time of this report, we can identify two clinical trials of LEV in neonatal seizures. One is a prospective, single-arm phase 2 study of intravenous LEV (clinicaltrials.gov identifier: NCT02229123) and the other is a randomized controlled phase 1/2 trial of intravenous LEV versus intravenous PB (clinicaltrials.gov identifier: NCT01720667). Until the completion of these trials, and preferably phase 3 trials, the use of LEV in neonatal seizures remains speculative. Our systematic review, though limited, supports further investigation of LEV in the setting of neonatal seizures.

Conflict of Interest

None of the authors has any conflict of interest to disclose.

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