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Original Research Article

Efficacy and Safety of Levetiracetam versus Phenobarbitone as First-Line Antiepileptic Drug for the Treatment of Neonatal Seizures: A Randomized Controlled Trial from Eastern Bihar

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Conflict of interest: Nil

Abstract

Background: Neonatal seizures are the most common neurological emergency in the neonatal period, occurring in 1–5 per 1000 live births. Phenobarbitone (PB) has been the conventional first-line treatment, yet it controls seizures in fewer than half of affected neonates and is associated with significant adverse effects including neuronal apoptosis and cardiorespiratory depression. Levetiracetam (LEV), a newer antiepileptic drug with a favorable pharmacokinetic and safety profile, has emerged as a potential alternative.

Aim: To compare the efficacy and adverse effects of intravenous levetiracetam versus phenobarbitone as a first-line antiepileptic drug in the management of neonatal seizures.

Methods: This randomized controlled trial was conducted in the Level III NICU of Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India, from March 2025 to February 2026. Two hundred neonates (age 0–28 days) with clinical seizures were randomized (1:1) to receive either LEV (20 mg/kg IV) or PB (20 mg/kg IV). A repeat dose was administered if seizures persisted (LEV 20 mg/kg or PB 10 mg/kg), and crossover was undertaken upon failure of both doses. The primary outcome was seizure cessation after one or two doses with the assigned drug, and remaining seizure-free at 24 hours. Secondary outcomes included adverse drug reactions.

Results: Seizure cessation was achieved in 86 (86%) neonates in the LEV group compared with 62 (62%) in the PB group (RR 1.39; 95% CI 1.10–1.75; $P < 0.001$). Twenty neonates in the PB group developed adverse reactions (hypotension in 10, bradycardia in 6, requirement of mechanical ventilation in 4), whereas no adverse reactions were recorded in the LEV group ($P < 0.001$).

Conclusion: Levetiracetam was associated with higher seizure cessation rates compared with phenobarbitone as first-line antiepileptic therapy for neonatal seizures, and no adverse drug reactions were observed. LEV is a safe and effective first-line antiepileptic drug for neonatal seizures; however, further large-scale, blinded, randomized trials with electrographic monitoring and long-term neurodevelopmental follow-up are warranted.

Keywords: Antiepileptic Drugs; Levetiracetam; Neonatal Seizures; Phenobarbitone; Randomized Controlled Trial.

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Introduction

Neonatal seizures represent the most frequent and clinically distinctive manifestation of neurological dysfunction in the neonatal period. They occur in approximately 1–5 per 1000 live births, with most seizure activity occurring within the first few days of life.[1,2,3] The occurrence of seizures may be the earliest clinical indicator of underlying neurological disorders, and timely, effective management is essential to minimize secondary neuronal injury and long-term morbidity. The most common cause of symptomatic neonatal seizures is hypoxic-ischemic encephalopathy (HIE), which affects approximately 1–2 per 100 live births.[4] Other important etiologies include neonatal sepsis, meningitis, intracranial haemorrhage, metabolic derangements, and structural brain malformations. Neonatal seizures can be refractory to conventional antiepileptic drugs (AEDs), and their management remains variable in the absence of robust evidence-based guidelines.[5] Phenobarbitone (PB) has been

the cornerstone pharmacological treatment for neonatal seizures for several decades.[6,7] Despite its widespread use, its efficacy in achieving complete seizure resolution is modest, with reported rates ranging from 33% to 77%.[8,9] Moreover, PB is associated with significant dose-dependent adverse effects including respiratory depression, hypotension, bradycardia, and neuronal apoptosis in vitro.[11,12] These toxicological concerns are of particular relevance in the developing neonatal brain, where neurotoxicity may have lasting adverse consequences on neurodevelopmental outcomes.[10]

Levetiracetam (LEV) — chemically, (S)-α-ethyl-2-oxo-1-pyrrolidine acetamide — is a newer-generation AED that has received United States Food and Drug Administration (FDA) approval as adjunctive therapy for partial epilepsy for over a decade.[13,14,15] It demonstrates efficacy and safety as monotherapy in adult and pediatric epilepsy syndromes. Unlike PB and phenytoin, LEV does not cause neuronal apoptosis in infant rodents, does not induce hepatic microsomal enzymes, and has a more predictable pharmacokinetic profile in neonates.[11] Seizure cessation rates with LEV as a first-line agent have been reported to be approximately 77%, compared with approximately 46% with PB, based on existing systematic review evidence.[16,17] Despite this emerging evidence, published data on the use of LEV in neonatal seizures remain limited, and high-quality randomized controlled trials are scarce. This study compared the efficacy and safety of intravenous levetiracetam versus phenobarbitone as first-line antiepileptic therapy for neonatal seizures in a tertiary-care hospital in eastern Bihar, India.

Materials and Methods

Study Design and Setting: This was a prospective, open-label, randomized controlled trial conducted in the Level III Neonatal Intensive Care Unit (NICU) of Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur, Bihar, India — a tertiary-care academic institution — over a 12-month period from 5 March 2025 to 28 February 2026.

Eligibility Criteria: Outborn neonates aged 0–28 days presenting with clinical seizures were eligible for enrollment. Neonatal seizures were clinically defined as abnormal, stereotyped, paroxysmal dysfunction of the central nervous system occurring within the first 28 days of life.

Inclusion Criteria

- Neonates aged 0–28 days with clinical seizures admitted to the Level III NICU.
- Outborn neonates (born outside the study institution).
- Neonates in whom seizures persisted after correction of transient metabolic derangements (hypoglycemia, hypocalcemia, hypomagnesemia).
- Informed written consent provided by parents or legal guardians.

Exclusion Criteria

- Seizures resolving with correction of transient metabolic derangements alone (no pharmacological intervention required).
- Prior administration of any anticonvulsant therapy before enrollment.
- Major congenital malformations (congenital heart defects, neural tube defects, diaphragmatic hernia, choanal atresia, esophageal atresia, tracheo-oesophageal fistula, omphalocele, gastroschisis, intestinal obstruction, and imperforate anus).
- Refusal of consent by parents or guardians.

Sample Size: The sample size was determined using the standard formula for comparison of two proportions [17]: $n = [z\alpha/2 \times \sqrt{(2\bar{p}\bar{q})} + z\beta \times \sqrt{(p_1q_1 + p_2q_2)}]^2 / (p_1 - p_2)^2$ where p_1 = anticipated seizure cessation rate with LEV = 0.77, p_2 = anticipated seizure cessation rate with PB = 0.46 (derived from the systematic review by McHugh et al. [17]), $\bar{p} = (p_1 + p_2)/2 = 0.615$, $\bar{q} = 1 - \bar{p} = 0.385$, $z\alpha/2 = 1.96$ (two-sided $\alpha = 0.05$), and $z\beta = 0.842$ (power = 80%). Substituting: $n = [1.96 \times \sqrt{(2 \times 0.615 \times 0.385)} + 0.842 \times \sqrt{(0.77 \times 0.23 + 0.46 \times 0.54)}]^2 / (0.77 - 0.46)^2 = [1.96 \times 0.688 + 0.842 \times 0.652]^2 / 0.0961 = [1.349 + 0.549]^2 / 0.0961 = (1.898)^2 / 0.0961 = 3.602 / 0.0961 \approx 38$ per group Adding a 15% dropout allowance: $n = \lceil 38 / (1 - 0.15) \rceil = 45$ per group (90 total). To ensure adequate statistical power for secondary safety outcomes and to account for protocol deviations, a final sample size of 100 per group (200 total) was enrolled, providing greater than 99% power for the primary efficacy outcome.

Randomization and Allocation Concealment: Eligible neonates were randomly assigned in a 1:1 ratio to receive either LEV or PB using a computer-generated randomization schedule with allocation concealed in sequentially numbered, opaque, sealed envelopes. Envelopes were opened by a clinician independent of the study team at the time of enrollment.

Intervention Protocol: Following initial resuscitation and correction of hypoglycemia and hypocalcaemia, eligible neonates were randomized. In the LEV arm, levetiracetam was diluted in normal saline to achieve a concentration of 20 mg/mL and administered intravenously at a rate of 1 mg/kg/minute under continuous cardiorespiratory monitoring at a loading dose of 20 mg/kg. If seizures terminated, LEV was continued as maintenance at 20 mg/kg/day in two divided doses.

If seizures persisted after the first dose, a second loading dose of LEV (20 mg/kg) was administered. Persistent seizures after two doses of LEV prompted crossover to PB.

In the PB arm, phenobarbitone was diluted in normal saline (1:10) and administered intravenously at a rate of 1 mg/kg/minute under continuous cardiorespiratory monitoring at a loading dose of 20 mg/kg. If seizures terminated, PB was continued as maintenance at 5 mg/kg/day in two divided doses. A supplemental loading dose of PB 10 mg/kg was administered if seizures persisted after the initial dose. Failure after two loading doses of PB prompted crossover to LEV.

Outcome Measures: The primary outcome was the proportion of neonates achieving cessation of clinical seizures following the first or second dose of the assigned drug, and remaining seizure-free for the subsequent 24 hours. The secondary outcome was the proportion of neonates experiencing adverse drug reactions within two hours of drug administration. Clinical seizure termination was defined as the absence of abnormal movements, eyeball deviation, nystagmus, heart rate change, respiratory or oxygen saturation change, and autonomic dysfunction.

Adverse drug reactions recorded included desaturation, reduced respiratory rate, increased ventilator support requirement, arrhythmias, and haemodynamic instability (blood pressure or heart rate fluctuation >10% from the two-hour baseline). Increased ventilator requirement was defined as a tidal volume exceeding 6 mL/kg on a volume-controlled ventilator, peak inspiratory pressure (PIP) exceeding 22 cmH_2O (preterm) or 23 cmH_2O (term), or mean airway pressure (MAP) exceeding 12 cmH_2O on a pressure-controlled ventilator.

Investigations: Investigations performed included blood glucose, serum calcium, magnesium, electrolytes, complete blood count, C-reactive protein (CRP), liver function tests, renal function tests, arterial blood gas, serum lactate, ammonia, cranial ultrasonography, neuroimaging (brain MRI or CT where indicated), and electroencephalography (EEG) as clinically required.

Ethics: Informed written consent was obtained from parents or guardians of all enrolled neonates at the earliest feasible opportunity after eligibility assessment. The study protocol was approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar.

Statistical Analysis: Continuous variables were compared between groups using the independent samples t-test and are expressed as mean ± standard deviation (SD). Categorical variables were compared using the Chi-square (χ^2) test and are expressed as numbers and percentages.

Relative risk (RR) with 95% confidence intervals (CI) was computed for primary and secondary outcomes. A P-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 244 neonates presenting with clinical seizures were assessed for eligibility during the study period. Forty-four were excluded (metabolic seizures resolving with correction, n=28; prior anticonvulsant therapy, n=10; major congenital malformations, n=6). The remaining 200 neonates were randomized — 100 to the LEV group and 100 to the PB group. Baseline characteristics were comparable between the two groups (Table 1).

Table 1: Comparison of Baseline Characteristics of the Study Groups

Characteristic	Levetiracetam (n=100)	Phenobarbitone (n=100)	χ^2/t	P-value
Age (days), mean ± SD	2.1 ± 0.8	2.0 ± 0.9	0.71	0.479
Sex			0.00	1.000
Male	56 (56%)	56 (56%)		
Female	44 (44%)	44 (44%)		
Mode of delivery			0.10	0.752
Vaginal	70 (70%)	72 (72%)		
Caesarean	30 (30%)	28 (28%)		
Gestational age			0.61	0.435
Term (≥37 weeks)	80 (80%)	84 (84%)		
Preterm (<37 weeks)	20 (20%)	16 (16%)		
Birth weight (kg), mean ± SD	2.56 ± 0.64	2.73 ± 0.64	1.83	0.069
Etiology			—	0.612
HIE	40 (40%)	48 (48%)		
Neonatal sepsis/meningitis	36 (36%)	30 (30%)		
Intracranial haemorrhage	6 (6%)	4 (4%)		

Benign neonatal epilepsy	4 (4%)	2 (2%)		
Malignant neonatal epilepsy	2 (2%)	2 (2%)		
Cortical malformation	2 (2%)	2 (2%)		
Unknown	10 (10%)	12 (12%)		
Seizure type			—	0.954
Focal clonic	52 (52%)	48 (48%)		
Multifocal clonic	20 (20%)	22 (22%)		
Tonic	16 (16%)	18 (18%)		
Subtle	12 (12%)	12 (12%)		

SD: Standard deviation; HIE: Hypoxic-ischaemic encephalopathy; χ^2: Chi-square test; t: Independent samples t-test. Overall P values are reported for categorical variables. $P < 0.05$ considered statistically significant.

The commonest etiology for seizures in both groups was hypoxic-ischemic encephalopathy (HIE), accounting for 40% and 48% of cases in the LEV and PB groups respectively.

Focal clonic seizures constituted the most common seizure type, observed in 52% and 48% of neonates in the LEV and PB groups respectively. Gestational age, birth weight, sex, and mode of delivery did not differ significantly between the groups (all $P > 0.05$).

Primary Outcomes: Following the first dose of the assigned drug, seizures ceased in 60 (60%) neonates in the LEV group and 50 (50%) neonates in the PB group — a difference that did not reach statistical significance ($P = 0.126$). However, following one or two doses of the assigned drug, seizure cessation with continued seizure-freedom at 24 hours was achieved in 86 (86%) neonates in the LEV group compared with 62 (62%) in the PB group (RR 1.39; 95% CI 1.10–1.75; $P < 0.001$).

Treatment failure necessitating crossover to the alternate drug occurred in 14 (14%) neonates in the LEV group and 38 (38%) neonates in the PB group ($P < 0.001$).

Among the 14 neonates who failed LEV, 6 (43%) subsequently responded to PB. Among the 38 neonates who failed PB, 32 (84%) subsequently responded to LEV. Table 2 and Figure 1 summarize these efficacy outcomes.

Table 2: Comparison of Efficacy and Safety Outcomes between Levetiracetam and Phenobarbitone Groups

Outcome	LEV (n=100)	PB (n=100)	RR (95% CI)	P-value
Primary Outcomes				
Seizure cessation after 1st dose, n (%)	60 (60%)	50 (50%)	1.20 (0.95–1.52)	0.126
Seizure cessation after 1st or 2nd dose (seizure-free at 24h), n (%)	86 (86%)	62 (62%)	1.39 (1.10–1.75)	<0.001
Treatment failure — required crossover, n (%)	14 (14%)	38 (38%)	0.37 (0.21–0.63)	<0.001
Crossover Response				
Responded to PB after LEV failure, n (%)	6/14 (43%)		Not estimable	
Responded to LEV after PB failure, n (%)		32/38 (84%)	Not estimable	
Secondary Outcomes — Adverse Drug Reactions				
Total adverse events, n (%)	0 (0%)	20 (20%)	Not estimable	<0.001
Hypotension, n (%)	0 (0%)	10 (10%)	Not estimable	0.001
Bradycardia, n (%)	0 (0%)	6 (6%)	Not estimable	0.013
Requirement of mechanical ventilation, n (%)	0 (0%)	4 (4%)	Not estimable	0.044
Discharge Outcomes				
Discharged, n (%)	94 (94%)	92 (92%)		0.597
Left against medical advice, n (%)	4 (4%)	8 (8%)		0.232
Died, n (%)	2 (2%)	0 (0%)		0.157

LEV: Levetiracetam; PB: Phenobarbitone; RR: Relative Risk; CI: Confidence Interval. 'Not estimable' indicates zero events in one group precluding RR calculation. $P < 0.05$ considered statistically significant.

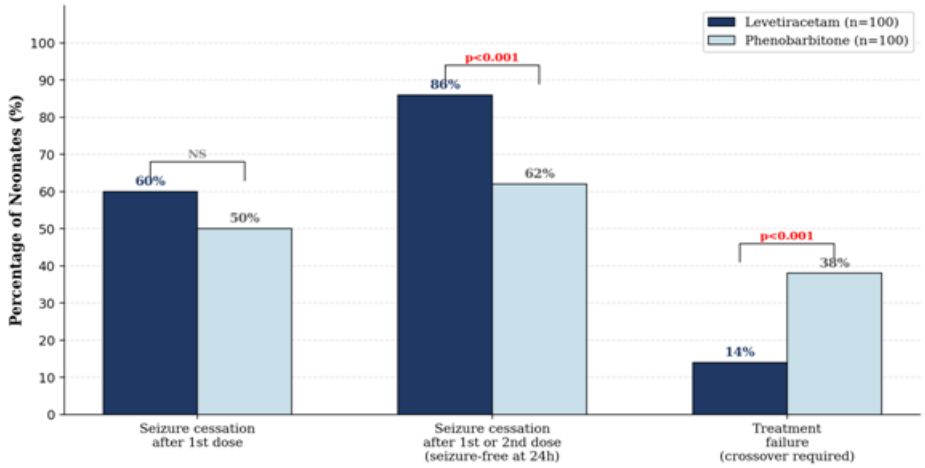

Figure 1: Comparison of Efficacy Outcomes between Levetiracetam and Phenobarbitone Groups

Secondary Outcomes — Adverse Drug Reactions: No adverse drug reactions were recorded in any of the 100 neonates who received LEV. In contrast, 20 of 100 (20%) neonates in the PB group developed adverse reactions, comprising hypotension in 10 (10%), bradycardia in 6 (6%), and requirement for mechanical ventilation in 4 (4%). The difference in adverse event rates between groups was statistically significant ($P < 0.001$). Figure 2 illustrates this comparison.

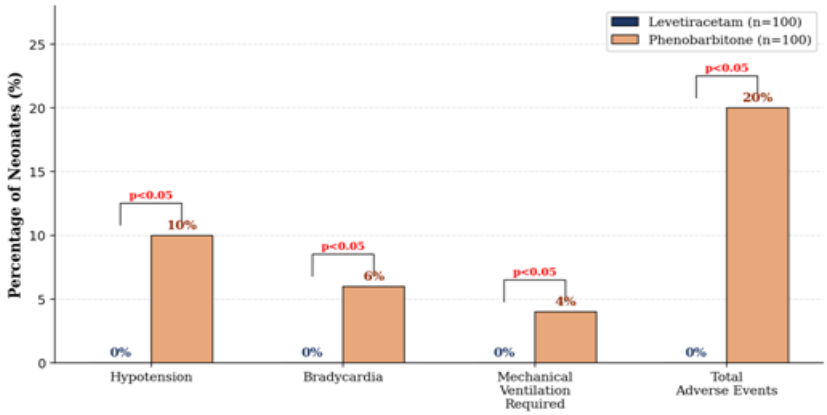

Figure 2: Comparison of Adverse Drug Reactions between Levetiracetam and Phenobarbitone Groups

Discharge Outcomes: In the LEV group, 94 (94%) neonates were discharged, 4 (4%) left against medical advice, and 2 (2%) died. In the PB group, 92 (92%) neonates were discharged and 8 (8%) left against medical advice; no deaths were recorded in the PB group. The differences in discharge outcomes between the two groups did not reach statistical significance (all $P > 0.05$).

Discussion

This prospective randomized controlled trial from a tertiary-care NICU in eastern Bihar provides evidence for the comparative efficacy and safety of intravenous levetiracetam versus phenobarbitone as first-line antiepileptic therapy in neonatal seizures. The principal findings are: (i) LEV was associated with significantly higher seizure cessation rates compared with PB (86% vs. 62%; $P < 0.001$); and (ii) no adverse drug reactions were recorded in the LEV group, whereas PB was associated with a 20% adverse event rate encompassing hypotension, bradycardia, and need for mechanical ventilation.

The seizure cessation rate of 86% with LEV in the present study aligns closely with the 86% reported by Khan et al. (2011) in 22 neonates receiving intravenous LEV, in whom seizure cessation was documented within one hour of administration.[20] Similarly, Ramantani et al. (2011) reported complete or near-complete seizure control in 78% (30/38) of infants treated with LEV, and observed no significant adverse effects.[19] McHugh et al. (2018), in a systematic review of LEV in neonatal seizures, reported a pooled seizure cessation rate of 77% with LEV as a first-line drug compared with 46% with PB — a finding consistent with the results of the present study.[17] Mruk et al. (2015), in a comprehensive narrative review, similarly concluded that LEV demonstrated a favorable safety and efficacy profile relative to conventional agents.[16]

The seizure cessation rate of 62% with PB in the present study is in keeping with the reported range of 33–77% in the literature. Van Rooij et al. (2013)

observed that PB, despite being the mainstay first-line treatment, achieves complete seizure resolution in fewer than half of neonates when outcome is defined by electrographic cessation.[8] Painter et al. (1999) demonstrated in a landmark randomized trial that PB and phenytoin achieve seizure control in 43% and 45% of neonates respectively when monitored by continuous EEG — a finding that underscores the limited efficacy of conventional agents and the need for alternative therapies.[6]

In contrast to the reassuring efficacy outcome, a minority study by Abend et al. (2011) reported a considerably lower LEV response rate of 35% in 23 neonates.[21] This discrepancy is likely attributable to the study design: LEV was employed as the sole first-line agent in only one neonate in that cohort, with the remainder receiving it as second- or third-line therapy after prior exposure to multiple antiepileptic drugs — a scenario where escalating drug resistance would predictably reduce response rates. The present trial, by administering LEV as a primary first-line agent in a pre-specified 1:1 randomized design, avoids this confounding limitation. The complete absence of adverse drug reactions in the LEV group in the present study is consistent with data from Li et al. (2011), who prospectively evaluated 120 infants (including neonates ≤1 month of age) receiving levetiracetam as mono- or combination therapy and concluded that it was both effective and well-tolerated.[24] Michaelides et al. (2008) similarly reported very good tolerability of intravenous LEV in a mixed neonatal and infant population.[25] Han et al. (2018) demonstrated efficacy and tolerability of LEV specifically in preterm neonates — a particularly vulnerable subgroup who may be at heightened risk of PB-associated cardiorespiratory complications.[18]

The 20% adverse event rate with PB observed in the present study — encompassing hypotension (10%), bradycardia (6%), and need for mechanical ventilation (4%) — is consistent with the established pharmacological profile of this agent. Bartha et al. (2007) documented significant practice variation in neonatal seizure management driven partly by clinician awareness of PB's adverse effect profile.[9] Kaushal et al. (2016) demonstrated that certain anticonvulsants, including PB, cause cell death in the developing white matter of the rodent brain — raising important concerns about the cumulative neurotoxic burden in a population whose white matter development is critically active.[12] Manthey et al. (2005) established, in contrast, that levetiracetam does not exert neurotoxic effects in the developing rat brain at therapeutic concentrations.[11]

The crossover data yield an additional important observation: when PB was employed as rescue therapy in LEV failures, only 43% (6/14) responded, whereas when LEV was used as rescue for PB failures, 84% (32/38) achieved seizure control. This differential rescue efficacy further supports the potential utility of LEV as a preferred first-line agent and as an effective rescue drug for PB-refractory seizures.

Table 3: Comparison of Levetiracetam Efficacy with Previously Published Studies on Neonatal Seizures

Study (Year)	Design	n LEV	n PB	LEV cessation	PB cessation	ADR (LEV)	Key finding
Present study (2025–26)	Randomized controlled trial	100	100	86%	62%	None	Higher seizure cessation with LEV (RR 1.39; P < 0.001)
Ramantani et al. (2011)	Prospective observational	38	NR	78%	NR	None	LEV safe and effective as add-on therapy
Khan et al. (2011)	Retrospective cohort	22	NR	86%	NR	None	Rapid cessation within 1 hour
McHugh et al. (2018)	Systematic review	48	52	77%	46%	Minimal	LEV superior as first-line agent
Abend et al. (2011)	Retrospective cohort	23	NR	35%	NR	None	Lower response; LEV used mainly as 2nd/3rd-line
Han et al. (2018)	Prospective cohort	42	NR	71%	NR	Minimal	Effective in preterm neonates
Mruk et al. (2015)	Narrative review	Pooled	NR	77%	46%	Favourable	Favourable safety and efficacy profile
Li et al. (2011)	Prospective observational	120	NR	NR	NR	Well tolerated	Safe in infants ≤1 month
Michaelides et al. (2008)	Retrospective cohort	Neonates and infants	NR	NR	NR	Well tolerated	IV LEV well tolerated in neonates

RCT: Randomized Controlled Trial; LEV: Levetiracetam; PB: Phenobarbitone; ADR: Adverse Drug Reaction; IV: Intravenous; —: Not applicable/reported.

Limitations

Several limitations of the present study merit acknowledgment. First, seizure cessation was defined clinically in the absence of continuous amplitude-integrated EEG (aEEG) or conventional EEG monitoring, which constitutes the gold standard for electrographic seizure detection and would have allowed identification of electroclinical dissociation — a recognized phenomenon where clinical seizure cessation may mask ongoing subcortical electrographic seizure activity, particularly following PB administration. While this limitation reflects the resource constraints prevalent across most NICUs in low- and middle-income settings, and thus enhances the generalizability of findings to such environments, it represents a methodological limitation with respect to outcome ascertainment. Second, the study was open-label and therefore carries an inherent risk of performance and detection bias, which would necessitate blinding in future trials. Third, long-term neurodevelopmental follow-up data were unavailable, precluding assessment of the comparative impact of LEV and PB on neurodevelopmental trajectories — arguably the most clinically relevant long-term outcome in neonatal seizure management. Fourth, therapeutic drug level monitoring of both PB and LEV was not performed. Fifth, the sample size, while adequately powered for the primary efficacy outcome, was insufficient to draw definitive conclusions regarding less frequent adverse event categories.

Conclusion

Intravenous levetiracetam was associated with higher first-line seizure cessation rates compared with phenobarbitone in neonatal seizures, with an 86% seizure cessation rate versus 62% for PB, and no clinically recorded adverse drug reactions. Phenobarbitone, by contrast, was associated with clinically significant cardiorespiratory adverse effects in one-fifth of treated neonates. LEV appears to be a safe and effective first-line antiepileptic option in neonates with clinical seizures. In resource-limited settings, where phenobarbitone may remain the mainstay of treatment on account of its lower cost and wider availability, its use should be accompanied by vigilant cardiorespiratory monitoring and efforts to limit cumulative exposure. Future research should prioritize large-scale, double-blind, placebo-controlled randomized trials with continuous electrographic monitoring, formal therapeutic drug level measurement, standardized long-term neurodevelopmental follow-up, and prospective cost-effectiveness analyses to guide definitive evidence-based first-line treatment recommendations for neonatal seizures.

Declarations

Conflicts of Interest: The authors declare no conflicts of interest.

Funding: This study received no external funding.

Ethical Approval: Approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar.

Data Availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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