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Neonatology Section

Levetiracetam versus Phenobarbitone as First Line Antiepileptic Drug in Management of Neonatal Seizures: A Retrospective Cohort Study

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ABSTRACT

Introduction: Neonatal seizures require urgent intervention, yet the optimal first-line treatment remains a subject of ongoing debate. While Phenobarbitone (PB) remains the traditional standard of care, its use is increasingly scrutinised due to adverse effects like respiratory depression and potential neurotoxicity in the developing brain. Levetiracetam (LEV) has emerged as a promising alternative with a more favourable safety profile and superior neurodevelopmental outcomes, but direct comparative data remain limited.

Aim: To compare the clinical efficacy and safety profiles of PB versus LEV in the management of neonatal seizures.

Materials and Methods: This retrospective cohort study was conducted over 1.5 years (April 2021 to October 2022) in the Neonatal Intensive Care Unit (NICU) at the Department of Paediatrics, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India, comparing 45 neonates treated for seizures with either PB (n=24) or LEV (n=21). Outcomes measured included clinical adverse events, breakthrough seizures, crossover protocols, discharge neurological status, and 6-month neurodevelopmental trajectories using Hammersmith Infant Neurological Examination (HINE) scores. Data entry and statistical analysis were performed using MedCalc software (v20.11), utilising Chi-square, Student's t-test, or One-way Analysis of Variance (ANOVA) with a significance threshold of $p<0.05$.

Results: Baseline demographics showed no significant differences between the PB and LEV groups regarding mean gestational age (38.87 vs 38.33 weeks), birth weight (2.84 vs 2.82 kg), male predominance, or mode of delivery. Immediate seizure cessation following the initial loading dose was achieved in 10/24 (41.67%) of the PB group compared to 3/21 (14.29%) of the LEV group ($p=0.04$). Additionally, a secondary reloading dose was required to attain seizure control in 14/24 (58.33%) of the PB cohort versus 18/21 (85.71%) of the LEV cohort ($p=0.04$). Retrospective data tracking revealed no statistically significant differences between the two treatment groups regarding documented in-hospital adverse effects, post-discharge breakthrough recurrence rates, or short- and long-term neurodevelopmental outcomes at the 6-month milestone.

Conclusion: The PB group showed better seizure control as first-line AED as compared to LEV.

Keywords: Breakthrough recurrence, Epilepsy, Neurodevelopmental outcomes, Respiratory depression, Treatment failure

INTRODUCTION

Neonatal seizures are clinically characterised as paroxysmal, stereotyped, and abnormal Central Nervous System (CNS) dysfunctions occurring within the first 28 days of life in full-term infants, or before 44 weeks of post-menstrual age in preterm infants. These events represent the most frequent clinical manifestation of acute neurological insults during the newborn period [1]. Notably, the underlying aetiologies and clinical presentations of neonatal seizures diverge significantly from those observed in older children and adults. Excluding rare benign familial and non familial neonatal seizure syndromes, the vast majority of cases arise secondary to severe intracranial pathologies [2].

Common aetiologies include Hypoxic-Ischaemic Encephalopathy (HIE), intracranial haemorrhage, CNS infections, inborn errors of metabolism, transient metabolic derangements, and malformations of cortical development. Among these symptomatic triggers, HIE remains the primary driver, affecting approximately one to two per 1,000 live births [3]. Despite the high clinical burden, universally accepted, evidence-based guidelines for pharmacological intervention remain limited, leading to substantial global variability in management practices [1].

The PB remains the historically established first-line mainstay for the management of neonatal seizures, as supported by conventional clinical guidelines. It exerts its therapeutic effects by binding to Gamma-Aminobutyric Acid (GABA) receptors, thereby enhancing gamma-aminobutyric acid-mediated inhibitory neurotransmission [4]. However, its clinical application is complicated by highly variable pharmacokinetics in newborns and a prolonged elimination half-life T1/2 ranging from 100 to 300 hours [5]. The therapeutic efficacy of PB is inconsistent, with complete seizure resolution rates fluctuating between 33% and 77% [6]. Furthermore, its use is heavily restricted by an unfavourable safety profile; acute adverse reactions include sedation, respiratory depression, cardiovascular instability, nystagmus, and ataxia, necessitating continuous cardiorespiratory monitoring [1]. Alarmingly, preclinical data have also linked PB exposure to accelerated neuronal apoptosis in the developing brain, raising significant concerns regarding its long-term impact on neurological and psychomotor development [7].

Concurrently, LEV has emerged as a promising therapeutic alternative, largely attributed to its unique mechanism of action and more favourable safety margins. LEV selectively binds to the Synaptic Vesicle Glycoprotein 2A (SV2A), inhibiting presynaptic calcium channels to modulate and reduce hypersynchronous neurotransmitter release. Crucially, unlike PB, animal models indicate that LEV does not induce widespread neuronal apoptosis in the developing brain, suggesting potential neuroprotective benefits [8]. It possesses a benign side-effect profile, primarily limited to transient sedation and irritability, while featuring minimal drug-drug interactions and an easily administered intravenous formulation.

Given the variable efficacy and compounding neurodevelopmental risks associated with conventional first-line PB therapy, evaluating the clinical utility, neuroprotective benefits, and safety profile of LEV in this vulnerable population has become a vital clinical directive [9].

Consequently, standard clinical guidelines recommend PB as the definitive first-line antiepileptic agent [10]; however, its inconsistent efficacy and documented negative impacts on long-term psychomotor and neurological outcomes have prompted a critical search for safer therapeutic alternatives [11]. LEV has emerged as a premier candidate under active clinical investigation due to its robust efficacy, favourable safety profile, and lack of pro-apoptotic neurotoxicity [8,9]. A direct clinical comparison between PB and LEV is essential to weigh the established, potent efficacy of conventional therapy against the superior neuroprotective safety margins of newer alternatives.

Conducting a retrospective cohort analysis will allow for the evaluation of these drugs within a real-world, pragmatic clinical setting, capturing institutional prescriptive behaviours and outcomes without the ethical and logistical challenges of randomised allocation in a critical care environment. Therefore, this study was undertaken to retrospectively evaluate and compare the therapeutic efficacy, safety profiles, and subsequent 6-month neurodevelopmental outcomes of PB versus LEV in neonates managed for acute seizures.

MATERIALS AND METHODS

This hospital-based, retrospective cohort study was conducted using medical records from the Neonatal Intensive Care Unit (NICU) at the Department of Paediatrics, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India, over a total study period of one and a half years from April 2021 to October 2022. The formal study planning, retrospective chart review, data analysis, and interpretation were executed from November 2022 to April 2023. The study protocol was approved by the Institutional Ethics Committee (Letter Number: SVIEC/ON/MEDI/BNPG20/D21092). The evaluation timeframe comprised a 1-year historical baseline enrolment window (April 2021 to April 2022) to identify eligible neonatal charts, followed by a subsequent 6-month historical tracking window (through October 2022) to extract follow-up data from outpatient or readmission records.

Inclusion criteria: The study included term neonates (chronological age ≤30 days; corrected gestational age >37 weeks and <44 weeks) retrospectively identified from the institutional database. Eligible neonates must have had a diagnosis of neonatal seizures with or without Electroencephalography (EEG) confirmation, received either PB or LEV as their initial Antiseizure Medication (ASM).

Exclusion criteria: Conversely, neonates were excluded from the study if they received a first-line ASM other than PB or LEV.

Sample size: A formal a priori sample size calculation was not performed due to the retrospective nature of the study; instead, a convenience sampling approach was applied, screening all consecutive records within a fixed chronological window (April 2021 to October 2022) to capture the maximum available cohort.

Seizure diagnosis was clinically confirmed by attending neonatologists or paediatricians based on documented focal or generalised motor semiology (e.g., clonic, tonic, myoclonic movements, or motor automatisms) or non motor paroxysmal events (e.g., autonomic changes or behavioural arrest) [1]. For a subset of patients where neurophysiology tracking was accessible, the clinical diagnosis was supplemented by bedside amplitude-integrated EEG (aEEG) or standard conventional EEG tracking demonstrating repetitive, evolving ictal waveforms lasting at least 10 seconds [12].

Study Procedure

Treatment and clinical assessment: Patients meeting the predefined inclusion criteria were identified and enrolled through a standardised medical chart review process. Because acute bedside EEG monitoring was unavailable in the NICU, initial seizure diagnoses were based on clinical presentation. Follow-up EEGs to guide medication discontinuation were performed at one month post-discharge using the hospital's centralised outpatient diagnostic facility. To standardise these clinical observations and minimise misclassification, features were strictly validated against the Volpe classification system, which categorises semiologies into four distinct observable types: subtle (e.g., ocular movements, pedaling), clonic, tonic, and myoclonic [13]. The sequence of Anti-Epileptic Drug (AED) administration was determined by the pertinent institutional treatment protocol and the discretion of the attending physician in the neonatal intensive care unit; the investigators did not participate in any clinical decision-making. To minimise potential retrospective interpretation and extraction biases, data collection was performed by two independent reviewers utilising a highly structured, predefined electronic proforma with rigid objective definitions. Discrepancies in data extraction or clinical symptom classification were resolved through a consensus-based adjudication process involving a third senior clinician who was blinded to the primary study objectives.

Abnormal neurological examination at the time of seizure manifestation was strictly defined by documented abnormalities in consciousness, tone, and reflexes, as recorded by the treating clinicians in the medical charts [14].

Investigators did not participate in clinical decision-making or patient management, strictly observing and extracting documented treatment outcomes from the institutional database.

Antiepileptic Drug (AED) administration protocols: Clinical data extraction revealed that weight-based dosing and escalation pathways followed specific institutional protocols, which were standardised across both treatment cohorts. Neonates in the PB cohort received an initial intravenous loading dose of 20 mg/kg, followed by a maintenance regimen of 5 mg/kg/day delivered in two divided doses; if clinical seizures persisted, an intravenous reloading dose of 10 mg/kg was administered while maintaining the same daily dose, with rescue LEV introduced if control failed [15]. Conversely, neonates in the LEV cohort received an initial intravenous loading dose of 20 mg/kg, followed by an initial maintenance dose of 20 mg/kg/day delivered in two divided doses; uncontrolled seizures prompted an intravenous reloading dose of 15 mg/kg and an increased maintenance dose of 30 mg/kg/day in two divided doses, with rescue PB initiated if clinical seizures remained uncontrolled [16].

Medication discontinuation and diagnostic criteria: The AED discontinuation followed a strict retrospective chart-review framework based on clinical stability. For neonates remaining seizure-free for 72 hours with a normal neurological assessment while on monotherapy, the drug was discontinued immediately. If a neonate was on dual therapy and remained seizure-free for 72 hours, the last introduced drug was ceased, while the primary drug was continued for a total duration of one month. At the one-month checkpoint, therapy was tapered and discontinued over a two-week period if the infant was seizure-free and neurologically normal. For infants presenting with abnormal neurology at one month, a follow-up EEG using scheduled Outpatient Department (OPD) machines was performed, and a two-week tapering schedule was pursued only if the EEG findings were documented as normal.

Outcomes

Primary outcome measures: Treatment efficacy was evaluated using standardised, mutually exclusive seizure control endpoints during the index hospitalisation, defined as follows:

- **Complete seizure control on initial loading dose:** Defined as the complete clinical cessation of all seizure activity within 24 hours following the administration of the initial loading dose of the first-line ASM (PB or LEV) without requiring any further medication escalation or dose repetition.

- **First-line medication reloading requirement:** Defined as a partial response where breakthrough seizures occurred despite the initial loading dose, necessitating the administration of a secondary reloading dose of the same first-line agent to achieve control within 24 hours of initial loading.
- **Requirement for additional therapy (secondary and tertiary escalation):** Defined as the necessity to escalate treatment by adding a 2nd or 3rd ASM due to persistent seizure activity despite optimised first-line dosing during the acute stabilisation period (first 48 hours).

Secondary Outcomes:

- **Adverse event profile (safety evaluation):** Drug safety was evaluated via medical charts, nursing notes, and laboratory records based on predefined parameters: cardiorespiratory stability (respiratory depression, bradycardia, or hypotension); neurological sedation and behaviour (documented clinical lethargy or hypotonia, poor feeding, or irritability); and hepatic safety (biochemical liver function tests including Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) elevations).
- **Seizure recurrence rate:** The incidence of documented breakthrough seizures occurring after initial control was achieved, tracked through subsequent emergency department visits or readmission records during the follow-up window of six weeks.
- **Length of hospital stay:** Calculated as the total number of inpatient days from the date of index admission to the date of official hospital discharge.

Neurological outcomes:

- **Short-term:** Neurological status at the time of hospital discharge, extracted from physician objective exams.
- **Long-term:** Neurological functionality documented during follow-up outpatient neurology clinic visits at six months post-discharge.

Primary efficacy outcomes extracted from medical records included successful clinical seizure control and documented side-effect profiles. Short-term neurological outcomes at discharge were evaluated using Hammersmith Neonatal Neurological Examination (HNNE) scores [17], while long-term neurological outcomes were assessed using HINE global scores recorded at six months of age [18]. The HNNE evaluates 34 items across tone, posture, reflexes, movements, and behaviour, with raw scores converted to an optimality system (range 0 to 34) where higher compound scores indicate typical performance [17]. The HINE at six months consists of 26 items spanning five domains (cranial nerves, posture, movements, tone, and reflexes) for a maximum global score of 78. HINE scores were interpreted using established age-dependent cut-offs: scores >70 were classified as optimal, scores between 60 and 69 as suboptimal, and scores <59 indicated a high-risk for cerebral palsy or severe neuromotor delay [18]. Long-term neurodevelopmental milestones at six months were further quantified using Developmental Quotients (DQ) for both motor and mental domains.

Demographic and clinical baseline variables- including gestational age, birth weight, gender, delivery location and mode, seizure semiology, and therapeutic timelines- were systematically collected from institutional records using a standardised data extraction proforma.

STATISTICAL ANALYSIS

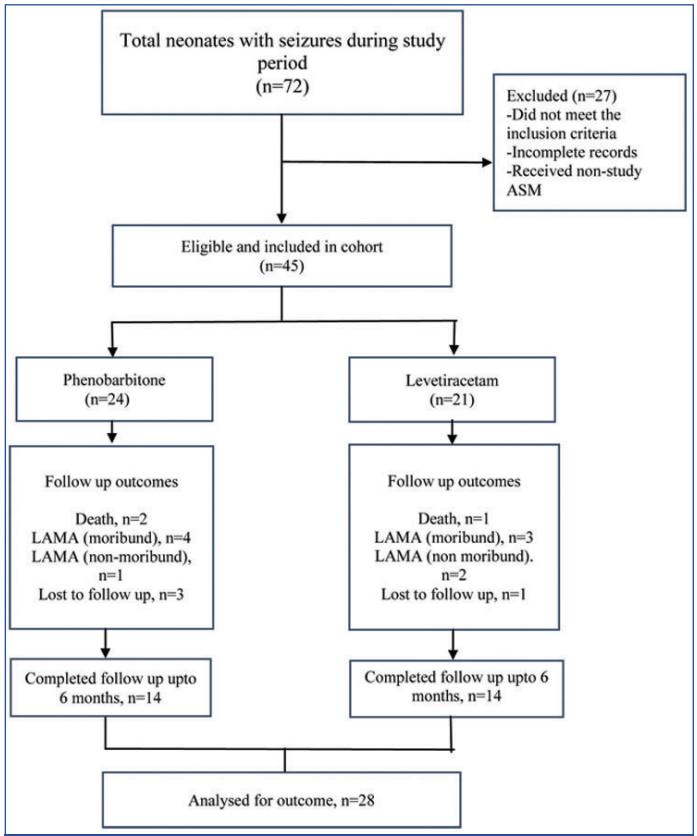
The data was primarily gathered in the form of a structured proforma and details were entered in excel sheet. Following which a detailed statistical analysis was done to attain the results of the study. Categorical variables were summarised using percentages. Continuous variables were summarised using means and Standard Deviations (SD). Chi-square test was used for analysis and comparison of categorical data. Student t-test or One-way ANOVA test was used to analyse and compare continuous data. All the statistics were done using MedCal software 20.11 version. All p-values are two-tailed and p-value of <0.05 was considered statistically significant.

RESULTS

During the overall study period a total of 72 neonatal medical records with a documented diagnosis of seizures were screened. Of these, 45 neonates met all eligibility criteria and were included in the final analysis.

The remaining 27 neonates were excluded from the study based on predefined criteria were excluded due to prematurity (<37 weeks of gestation), seizures secondary to transient or uncorrected metabolic abnormalities (such as hypoglycaemia, hypocalcaemia, or hypomagnesemia). Notably, bedside EEG monitoring was feasible and performed for only two patients out of the entire cohort during the acute phase.

The flow algorithm is shown in [Table/Fig-1]:



[Table/Fig-1]: Study flow algorithm.
ASM: Anti-seizure medication, LAMA: Leave against medical advice

Baseline characteristics of both groups including gender distribution, birth weight, gestation age, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at one and five minutes were compared and no significant difference were found between the groups. Majority of patients admitted in both groups were of birth asphyxia with HIE [Table/Fig-2].

A statistically significant difference was observed in initial seizure control between the two treatment cohorts (p=0.04). In the PB group, 10 out of 24 neonates (41.67%) achieved complete seizure control following the initial loading dose of the first AED. Conversely, in the LEV group, only three out of 21 neonates (14.29%) achieved control on the initial loading dose. For neonates with refractory seizures, treatment escalation followed a similar pattern across both cohorts, with 2 patients in the PB group (8.33%) and 2 patients in the LEV group (9.52%) requiring a

third-line AED intervention in the form of a continuous midazolam infusion [Table/Fig-3].

Variables	PB (Mean±SD) n=24 n (%)	Levetiracetam (LEV) (Mean±SD) n=21 n (%)	p-value
GA (mean±SD)	38.87±1.51	38.33±1.65	0.25
Birth weight			
Mean±SD	2.84±0.34	2.82±0.40	0.86
Male (n)	19 (79.16%)	14 (66.67%)	0.35
Female:	5 (20.84%)	7 (33.33%)	
Mode of delivery			
Vaginal (n)	18 (75%)	15 (71.4%)	0.79
LSCS	6 (25%)	6 (28.6%)	
Aetiology			
Birth asphyxia (n)	20 (83.34%)	19 (90.48%)	0.49
Meningitis (n)	1 (4.16%)	1 (4.76%)	0.92
MIS-N	2 (8.34%)	0	0.18
Hypoxic brain injury	1 (4.16%)	1 (4.76%)	0.92
Type of seizures			
Subtle and the respective values	21(87.50%)	19 (90.47%)	0.75
Clonic	2 (8.33%)	2 (9.52%)	0.88
Myoclonic jerks	1 (4.1%)	0 (0.00%)	0.35
APGAR (Mean±SD)			
At 1 min	2.14 (2.26)	1.57 (1.94)	0.55
At 5 min	4.57 (2.14)	3.64 (1.94)	0.33

[Table/Fig-2]: Demographic profile of patients in both groups.
MIS-N: Multisystem inflammatory syndrome-neonate; LSCS: segment caesarean section; APGAR: Appearance, pulse, grimace, activity, respiration

Seizure control	Phenobarbiton (PB) (n=24) n (%)	Levetiracetam (LEV) (n=21) n (%)	p-value
Seizure control on loading 1st AED	10 (41.66%)	3 (14.28%)	0.04
Need for reloading of 1st AED	14 (58.3%)	18 (85.71%)	0.04
Need for 2nd AED	7 (29.16%)	13 (61.9%)	0.02
Need for 3rd AED	2 (8.33%)	2 (9.52%)	0.88

[Table/Fig-3]: Primary outcome of seizure control with AEDs in both group.
Pearson Chi-square test

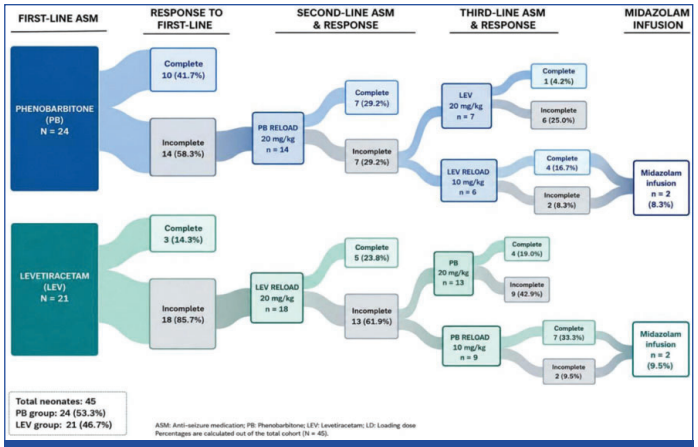
Short-term secondary outcomes did not differ significantly between the two treatment cohorts. Regarding safety profiles, there was an absence of documented treatment-limiting clinical adverse events or drug-related side effects in the inpatient records for either group.

Of the initial cohort, a total of 28 patients (14 in each group) had complete outpatient records available for analysis up to six months of age, while the remaining patients were lost to follow-up. No statistically significant difference was found in HNNE score and Development Quotient (DQ) of motor and mental milestones [Table/Fig-4]. Post-discharge development of microcephaly was identified in five patients overall, comprising 3 patients (12.50%) in the PB group and 2 patients (9.52%) in the LEV group [Table/Fig-5].

Treatment response flowchart below shows requirement and upgradation of AEDs as needed in both arms.

Secondary outcomes	Phenobarbitone (PB) (n=24)	Levetiracetam (LEV) (n=21)	p-value
Duration of hospital stay (days) (mean±SD)	11.09 (7.39)	9.65 (7.43)	0.52
Discharged (n)	17 (70.83%)	15 (71.42%)	0.96
HNNE score at the time of discharge (mean±SD)	28.08 (3.45)	28.63 (2.48)	0.61

[Table/Fig-4]: Secondary outcomes.



[Table/Fig-5]: Treatment response flowchart (Sankey Flow diagram).

The clinical management pathway and treatment responses of the 45 neonates are summarised in the flowchart [Table/Fig-5]. Initially, 24 neonates (53.3%) received PB and 21 (46.7%) received LEV as first-line therapy. Complete seizure control with the initial loading dose was achieved in 41.7% (n=10) of the PB group compared to 14.3% (n=3) of the LEV group. Among the non-responders, a second-line reload dose (20 mg/kg) successfully controlled seizures in an additional 29.2% (n=7) of the PB arm and 23.8% (n=5) of the LEV arm. Subsequent sequential treatment lines involving cross-over strategies with LEV (n=7) or PB (n=13) and secondary reloads resolved seizures in five and 11 additional infants, respectively. Ultimately, standard sequential ASM therapies failed in two neonates from each initial treatment group, requiring escalation to a continuous midazolam infusion to achieve definitive seizure control [Table/Fig-6].

Variables	Phenobarbitone (PB) (n=14)	Levetiracetam (LEV) (n=14)	p-value
HINE score (mean±SD)	68.35 (3.99)	69.64 (3.17)	0.35
Head circumference			
< -3 SD (n)	3 (21.42%)	2 (14.28%)	0.62
Mean±SD	41.67 (2.54)	42.21 (2.14)	0.54
Development Quotient (DQ) of motor milestones at 6 months (mean±SD)	76.66 (24.61)	81.56 (23.77)	0.59
Development Quotient (DQ) of mental milestones at 6 months age (mean±SD)	79.92 (21.26)	84.67 (21.63)	0.56

[Table/Fig-6]: Long-term outcomes at 6 months follow-up.

DISCUSSION

The present study demonstrates significantly superior initial seizure control with PB over LEV (41.67% vs. 14.29%, p=0.04) as a first-line agent, consistent with findings by Sharpe et al., Perveen et al., and Qiao MY et al. [9,19,20] Immediate clinical seizure cessation is paramount to prevent acute excitotoxicity and metabolic strain in the vulnerable neonatal brain, explaining why rapid stabilisation remains vital even though the present 6-month gross neurodevelopmental outcomes ultimately converged. Furthermore, LEV's lower initial efficacy has direct institutional resource implications. Because LEV failed to control seizures on the first load in 85.71% of neonates, it triggered a cascading requirement for secondary reloading and multi-drug escalation (61.9%). This higher failure rate directly impacts the healthcare facility by increasing internal pharmacy utilisation, prolonging NICU bed occupancy, and compounding specialised nursing and clinical monitoring demands.

Data revealed a significantly lower requirement for drug titration in the PB cohort (p=0.04). Following the initial load, a secondary reloading dose of the same agent was required in 14/24 (58.33%) of patients in the PB group, compared to 18/21 (85.71%) of patients in the LEV group.

Hnaini M et al., conducted a retrospective study on use of high-dose of LEV for neonatal seizures and concluded that seven out of 15 neonates required a higher dose of LEV for seizure control. As a first line drug, seizures were controlled in six out of 10 neonates, two of whom had complete seizure cessation only after escalation to higher doses of 80-100 mg/kg/day. Hence, it was concluded that in neonates not responding to standard used LEV doses, dose increment may be considered [21]. Sharpe C et al., also warranted escalation of Levetiracetam dose for better control of seizures [9]. Consistent with the present study findings, multiple studies have confirmed the clinical superiority of PB for optimised seizure control when utilised as a second-line therapeutic agent [19,20].

Due to the retrospective design of the data collection, the LEV cohort did not receive the higher dosing regimens (50 mg/kg loading; 40 mg/kg/day maintenance) recommended by the Indian Academy of Paediatrics (IAP) Guidelines late in 2022 [22]. This relative underdosing creates a distinct pharmacokinetic imbalance between the groups, which heavily accounts for the higher reloading and treatment escalation rates observed in the LEV arm.

Literature evaluating the long-term neurodevelopmental outcomes of neonates treated with AEDs for neonatal seizures remains exceptionally limited. In the present study, longitudinal assessment at the 6-month milestone demonstrated an upward trend in clinical improvement for both cohorts; however, the differences in HNNE scores and DQ for motor and mental milestones did not reach statistical significance.

This lack of short-term disparity contrasts slightly with the findings of Falsaperla R et al., who reported a significantly positive impact of LEV on early neurodevelopmental trajectories-specifically regarding muscle tone and posture-measured via HNNE scores, whereas the phenobarbital cohort exhibited no corresponding short-term improvement at one month of age [23].

The potential long-term neurodevelopmental divergence between these two agents is further highlighted by Maitre NL et al., [11]. In their evaluation of infants at 24 months corrected age using the Bayley Scales of Infant Development, the authors concluded that increased, cumulative exposure to phenobarbital was independently associated with poorer neurodevelopmental outcomes, a higher risk of cerebral palsy, and increased mortality compared to LEV exposure. While the present 6-month retrospective data did not demonstrate a statistically significant variance in neurological integrity or microcephaly rates between the groups, the existing literature emphasises the necessity for extended, longitudinal follow-up to fully capture the subtle, time-dependent neuroprotective or neurotoxic phenotypes associated with these treatments [23].

Limitation(s)

This study has several limitations. First, a post-hoc power analysis yielded a statistical power of 52.6%, reflecting a small sample size that limits the generalisability of the findings. Second, seizures and their cessation were determined strictly on a clinical basis without continuous EEG confirmation, though clinical monitoring remains the standard paradigm in resource-limited developing nations. Third, the longitudinal follow-up was capped at six months, whereas a 24-month window is required to definitively assess long-term neurodevelopmental trajectories. Consequently, the apparent therapeutic superiority of PB in the present study must be interpreted strictly within the boundaries of this prior institutional dosing paradigm.

CONCLUSION(S)

First-line PB provides significantly superior immediate clinical seizure control and reduces the need for secondary drug escalation compared to LEV. However, in-hospital safety profiles and 6-month neurodevelopmental outcomes did not differ significantly between the two cohorts. To validate these findings, large-scale, multicentre randomised controlled trials are warranted to directly compare long-term efficacy and specific domain-based neurodevelopmental trajectories beyond infancy. Future studies should also integrate continuous video-EEG monitoring to systematically evaluate the comparative impact of both agents on subclinical, electrographic seizure burdens.

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