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# Comparison Of Efficacy and Cost-Effectiveness of Phenobarbitone (PB) vs Levetiracetam (LEV) as First-Line Antiepileptic Drugs (AEDs) In Neonatal Seizures

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## ABSTRACT

**Background:** Phenobarbitone remains the recommended first-line antiepileptic drug (AED) for neonatal seizures in many low- and middle-income countries because of its low cost and long clinical experience. Levetiracetam is increasingly used as a perceived safer alternative, but comparative data incorporating both safety and cost from resource-limited neonatal intensive care units (NICUs) are limited.
**Methods:** This single-centre prospective observational study was conducted over 12 months in a rural tertiary NICU. Consecutive neonates with a first episode of clinically diagnosed seizures and no prior AED exposure were enrolled. Of 63 screened, 56 met inclusion criteria and received either phenobarbitone (PB; n = 28) or levetiracetam (LEV; n = 28) as first-line therapy. Primary outcome was clinical seizure cessation at 24 hours. Secondary outcomes included seizure cessation at 48 hours, recurrence, time to seizure control, duration of AED treatment, adverse events, daily drug cost and in-hospital outcome.
**Results:** Baseline demographic and clinical characteristics were broadly similar between groups. Seizure cessation at 24 hours was achieved in 22/28 (79%) PB-treated and 23/28 (82%) LEV-treated neonates (relative risk 0.96, 95% CI 0.74–1.24; p = 0.90). At 48 hours, cessation rates remained comparable (21.4% vs 17.9%; p = 0.52). Time to seizure control and duration of AED therapy did not differ significantly. Overall, 30 adverse events were recorded, 26 (86.7%) in the PB group and 4 (13.3%) in the LEV group (p = 0.009); all respiratory depression (n = 8) and hypotension (n = 7) occurred with PB. Mean daily drug cost was 168.82 ± 119.55 INR for PB and 800.08 ± 359.66 INR for LEV (p < 0.0001).
**Conclusions:** In this rural NICU, phenobarbitone and levetiracetam showed similar short-term clinical efficacy, but phenobarbitone was associated with substantially more cardiorespiratory adverse events and markedly lower daily drug cost. Levetiracetam appears to be a safer but more expensive alternative for first-line treatment of neonatal seizures.

***Keywords****: neonatal seizures, phenobarbitone, levetiracetam, adverse drug reactions, cost analysis, neonatal intensive care unit.*

## INTRODUCTION

Levetiracetam has emerged over the past two decades as an important intravenous option for the management of acute seizures and status epilepticus, with accumulating data supporting its efficacy, safety and economic acceptability in older children and adults. In a systematic review and meta-analysis of intravenous levetiracetam for status epilepticus, Yi et al. reported seizure control rates comparable to other second-line agents, with fewer treatment-limiting adverse events and, in several analyses, favourable or at least acceptable pharmacoeconomic profiles [1]. These findings have encouraged off-label use of levetiracetam in increasingly younger populations, including neonates, where safety and ease of dosing are critical considerations.

In contrast, current treatment paradigms for epilepsy and acute seizures are still heavily influenced by older agents such as phenobarbital. The ILAE evidence-based treatment guidelines for antiepileptic drug monotherapy highlight phenobarbital as an effective and inexpensive option for multiple seizure types, particularly in resource-limited settings where access to newer drugs is restricted [2]. Brodie and Kwan note that, although phenobarbital use has declined in many high-income countries because of concerns regarding tolerability and long-term cognitive effects, it continues to occupy an important niche globally due to its low cost, wide availability and clinician familiarity [3]. Broader paediatric pharmacotherapy reviews similarly describe a gradual shift towards newer agents such as levetiracetam, lamotrigine and topiramate, while emphasising that older drugs, including phenobarbital, remain widely used in children when cost, formulation and experience are decisive factors [4].

Historically, phenobarbital has played a central role in epilepsy care for more than a century. Yasiry and Shorvon describe how its introduction revolutionised epilepsy therapy, establishing it as a global standard for seizure control long before the era of modern antiepileptic polytherapy [5]. This long track record of efficacy, together with entrenched prescribing practices and procurement realities, explains why phenobarbital remains the default first-line agent for neonatal seizures in many institutions, despite increasing awareness of its adverse-effect profile. Importantly, frameworks for improving epilepsy care in low- and middle-income countries—from WHO mental health GAP approaches to national programs—highlight the continued reliance on long-established antiseizure medicines in routine and emergency care because they are more likely to be available, affordable, and supported by local implementation pathways [6]. Consequently, in many LMIC contexts, levetiracetam—though increasingly available—may remain constrained by higher cost and inconsistent supply outside major centres [3,6].

At the same time, there is growing concern that phenobarbital may not be the optimal first-line choice for vulnerable neonatal brains. Paediatric pharmacotherapy reviews highlight dose-dependent respiratory depression, hypotension, excessive sedation and potential adverse neurodevelopmental effects associated with early and prolonged phenobarbital exposure [3,4]. Levetiracetam, in contrast, is generally regarded as better tolerated, with minimal drug–drug interactions and a relatively benign side-effect profile dominated by mild sedation and behavioural change in older children and adults [1,4]. However, most comparative data on efficacy, safety and cost derive from older populations, and robust head-to-head studies in neonates—particularly from resource-limited NICUs—remain scarce.

In this context, there is a clear need for pragmatic data from real-world neonatal units where phenobarbital remains entrenched as first-line therapy but levetiracetam is increasingly available. The present study, conducted in a rural tertiary NICU, aimed to compare phenobarbital and levetiracetam as first-line antiepileptic therapy for neonatal seizures, focusing on three questions: (i) whether short-term clinical seizure control at 24–48 hours differs between the two drugs; (ii) whether levetiracetam offers a measurable short-term safety advantage over phenobarbital; and (iii) how the two agents compare in terms of direct drug costs in a resource-limited setting. By jointly evaluating efficacy, safety and economics, this work seeks to inform context-appropriate first-line treatment choices for neonatal seizures in LMIC environments where both drugs may be available but budgets and infrastructure are constrained.

## METHODS

### Study design and setting

This was a hospital-based cross-sectional study conducted in the Neonatal Intensive Care Unit (NICU) of Parul Sevashram Hospital, a rural tertiary care centre attached to the Parul Institute of Medical Sciences & Research (PIMSR), Parul University, Limda, Vadodara, Gujarat, India. The study was carried out over a 12-month period from October 2023 to October 2024.

### Study population and eligibility criteria

The study population comprised all neonates admitted to the NICU with clinically diagnosed neonatal seizures during the study period.

**Inclusion criteria were:**

Extramural and intramural neonates with a first episode of convulsion, and
No prior administration of any antiepileptic drug (AED) before the index admission, and
Availability of parental informed consent.

**Exclusion criteria were:**

- Neonates whose convulsions were primarily treated with an AED before hospitalisation at this centre.

During the study, 63 neonates presenting with seizures were screened. Seven were excluded for not meeting eligibility criteria, leaving 56 neonates who fulfilled all inclusion and exclusion criteria and were enrolled in the final analysis. All 56 received first-line antiepileptic therapy and completed in-hospital follow-up.

Although an a priori sample size of 150 was calculated and a time-bound convenience sampling strategy was planned, the final number of enrolled neonates reflected the actual number of consecutive eligible cases within the fixed 12-month study period.

**Treatment allocation and drug regimens**
Eligible neonates received either phenobarbitone (PB) or levetiracetam (LEV) as the first-line AED, according to unit practice and treating neonatologist discretion. There was no randomisation.

Dosing followed the NICU protocol, in line with published neonatal data. For the efficacy analyses, PB and LEV were categorised by weight-based loading dose ranges of 20–40 mg/kg for phenobarbitone and 40–60 mg/kg for levetiracetam as first-line therapy. Subsequent maintenance doses were prescribed by the treating clinician and recorded in the case-record form (CRF).

Rescue/second-line AEDs (e.g. an alternative first-line agent) were permitted in cases of persistent or recurrent seizures at the discretion of the treating physician, and their doses, timing, and response were also documented in the CRF.

Before or alongside AED administration, standard NICU protocols for acute metabolic and physiological stabilisation were followed for all neonates, including correction of hypoglycaemia, hypocalcaemia, hypomagnesaemia and other metabolic derangements where identified.

**Data collection and investigations**
Data were extracted from patient files using a predesigned proforma. Collected variables included demographic and perinatal details (sex, gestational age, type of delivery, birth weight and other anthropometry, nutritional status, type of admission, indication for NICU admission, and age at seizure onset) and seizure characteristics (clinical seizure type, number of episodes, timing of onset, and clinical/EEG confirmation). Perinatal physiological parameters at or around seizure onset (temperature, capillary blood glucose, and APGAR scores where available) were recorded, along with etiological investigations: EEG (RMS Clarity, 26 electrodes), cranial ultrasonography, routine laboratory tests (full blood count, C-reactive protein, serum electrolytes, random blood sugar, serum calcium and magnesium), CSF analysis and culture when indicated, and CT/MRI brain for suspected structural lesions or unclear etiologies. For each neonate, antiepileptic drug utilisation and cost data were also prospectively captured, including first-line AED used, loading and maintenance doses, time to seizure control, duration of treatment, average daily drug cost, total in-hospital drug cost, and details of any second-line AEDs.

**OUTCOMES**
**Primary efficacy outcome**
Seizure cessation at 24 hours, defined as the absence of any clinical seizure activity during the first 24 hours after administration of the first-line AED loading dose. This was coded separately for PB and LEV.

**Secondary efficacy outcomes**
- Seizure cessation at 48 hours, defined analogously for the 24–48 h period.
- Number of seizure episodes (single vs >1).
- Recurrence after first-line AED (yes/no).
- Time to seizure control, measured in minutes from first-line AED administration to the last observed clinical seizure.
- Duration of AED treatment, measured in days of in-hospital antiepileptic therapy.

**Safety outcomes**
- Incidence and type of adverse drug events attributed to PB or LEV (excessive sleepiness, respiratory depression, hypotension and other recorded events), with each event assigned to the suspected AED.

**Cost outcomes**
- Mean daily drug cost per neonate (INR/day) for PB and LEV, derived from the total daily dose (mg) multiplied by the unit cost per mg from the hospital pharmacy.
- Average daily dose (mg/day) and cost per mg (INR/mg) of PB and LEV.
- Drug amount per INR per day (mg/INR/day) as an efficiency metric (mg of drug delivered per rupee spent).

**In-hospital outcome**
- Final discharge status at the end of hospital stay (discharged alive, discharged against medical advice [DAMA], or death).

**Statistical analysis**

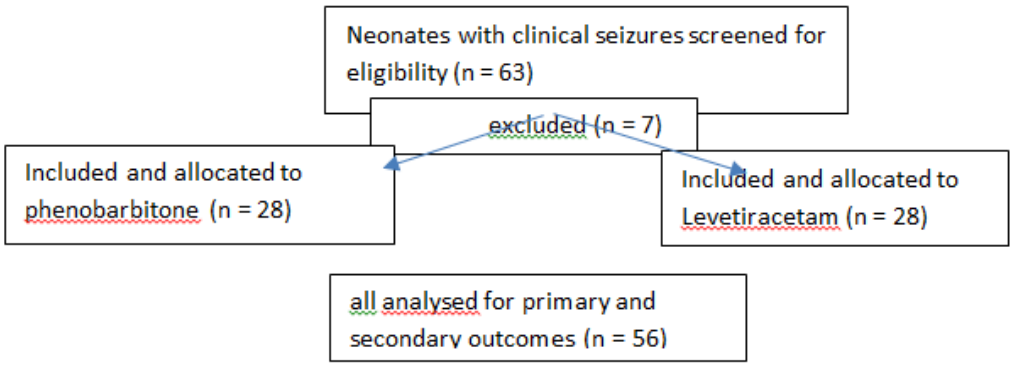
Data were entered into a spreadsheet and analysed using standard statistical methods.
Continuous variables (e.g. time to seizure control, duration of AED treatment, daily drug cost) were summarised as mean ± standard deviation (SD) and compared between the PB and LEV groups using the Student's t-test for independent samples, with 95% confidence intervals (CI) reported where appropriate.Categorical variables (e.g. 24-h and 48-h seizure cessation, recurrence rates, presence of adverse effects, discharge status) were expressed as counts and percentages, and compared using chi-square tests or Fisher's exact test as indicated by cell sizes; several tables explicitly used Fisher's exact test for proportion comparisons.

For selected outcomes, relative risks (RR) with 95% CI and p-values were calculated to quantify between-group differences.A two-sided p-value < 0.05 was considered statistically significant for all hypothesis tests. Given the modest sample size, some analyses (particularly for rare adverse events and subgroup outcomes) were interpreted descriptively.

**Ethical considerations**
The study was conducted as part of an MD thesis under the Department of Paediatrics, PIMSR, Parul University. The study protocol was approved by the institutional ethics committee, and the study period was explicitly defined as extending from ethics approval to one and a half years or until adequate sample size was reached. Written informed consent was obtained from parents or legal guardians before enrolment of each neonate, in accordance with institutional and university regulations.

## RESULTS

**Participant flow and sample description**
During the study period, 63 neonates presenting with clinical seizures were screened for eligibility. Of these, 7 were excluded because they did not fulfil the inclusion criteria (e.g. prior antiepileptic drug exposure or incomplete data), leaving 56 neonates who met all criteria and were enrolled in the study. All 56 infants received first-line antiepileptic therapy and were included in the final analysis.
The enrolled neonates were allocated to receive either phenobarbitone (PB; n = 28) or levetiracetam (LEV; n = 28) as first-line antiepileptic medication. There were no protocol deviations and no losses to follow-up during the acute treatment phase. The flow of participants through the study is summarised in Figure 1.




**2. Baseline characteristics of the neonates**
The baseline demographic and clinical characteristics of the 56 enrolled neonates are summarised in **Table 1**. Around two-thirds of the infants were male, and just over half were born at term, with the remainder almost evenly split between preterm and near-term gestations. Overall, the cohort represented a predominantly late preterm and term NICU population with moderately low birth weight.

Nearly two-fifths of neonates were small for gestational age, and two-thirds were referred from outside facilities. Birth asphyxia and respiratory distress were the leading indications for NICU admission, while surgical morbidities, feeding difficulties, metabolic disturbances and hypernatraemic dehydration accounted for smaller proportions of cases (Table 1).

**Table 1. Baseline demographic and clinical characteristics of the study cohort (n = 56)**

| Characteristic | Value |
|---|---|
| **Sex, n (%)** | |
| Male | 39 (69.6) |
| Female | 17 (30.4) |
| **Gestational age category, n (%)** | |
| Preterm (<37 weeks) | 12 (21.4) |
| Near-term | 13 (23.2) |
| Term | 31 (55.4) |

| | |
|---|---|
| **Gestational age, weeks** | |
| Mean ± SD | 36.0 ± 3.73 |
| **Anthropometry at birth** | |
| Birth weight, kg, mean ± SD | 2.29 ± 0.72 |
| Length, cm, mean ± SD | 46.11 ± 5.06 |
| Head circumference, cm, mean ± SD | 32.45 ± 3.46 |
| **Nutritional status, n (%)** | |
| Appropriate for gestational age (AGA) | 32 (57.1) |
| Small for gestational age (SGA) | 24 (42.9) |
| **Type of admission, n (%)** | |
| Extramural | 37 (66.1) |
| Intramural | 19 (33.9) |
| **Primary indication for NICU admission, n (%)** | |
| Birth asphyxia | 19 (33.9) |
| Respiratory distress | 18 (32.1) |
| Surgical morbidity | 6 (10.7) |
| Poor feeding | 5 (8.9) |
| Hypoglycaemia | 5 (8.9) |
| Hypernatraemic dehydration | 3 (5.4) |

**3. Seizure profile and etiologies**

**3.1 Age at onset and type of seizure**

In this cohort, seizures most commonly began between 1 and 7 days of life, accounting for just over half of all cases (53.6%). A smaller proportion of neonates presented with seizures within the first 24 hours after birth (26.8%), while the remainder developed seizures after 7 days of life (19.6%).

Subtle seizures were the predominant clinical type, observed in 64.3% of neonates. Clonic–tonic seizures were the next most frequent (23.2%), whereas purely tonic and purely clonic seizures were each seen in 5.4% of infants. Myoclonic seizures were uncommon, occurring in only 1.7% of the cohort. Together, these findings indicate that early-onset and subtle seizure manifestations formed the main seizure profile in the study population.

**3.2 Perinatal physiological derangements**

At the time of convulsion, **35.7%** of neonates were hypothermic and **14.3%** were hypoglycaemic. Evaluation of these parameters by gestational age showed no statistically significant differences in the frequency of hypothermia, hypoglycaemia or low APGAR scores between term and preterm infants, with all comparisons yielding p values > 0.05. These findings suggest that acute perinatal physiological derangements at seizure onset were common but not clearly clustered by gestational maturity.

**3.3 Etiology and investigations**

The most frequent underlying etiologies for neonatal seizures in this cohort were hypoxic–ischemic encephalopathy (HIE), identified in 37.5% of infants, and pyomeningitis/neonatal sepsis, present in 32.1%. Metabolic and structural causes were less common and included hypoglycaemia (8.9%), intracranial haemorrhage (5.4%) and hyponatraemic dehydration (5.4%), with isolated cases of other conditions such as hypocalcaemia and hydrocephalus.

Cranial ultrasonography was abnormal in 37.5% of neonates, most frequently demonstrating hydrocephalus or sequelae of HIE, with intraventricular haemorrhage and other focal abnormalities observed less often. Electroencephalography performed within 24 hours of seizure onset was abnormal in 38% of infants, typically showing features of mild encephalopathy, while a smaller proportion exhibited moderate-to-severe encephalopathic changes. Together, these findings indicate that perinatal asphyxial injury and systemic infection were the dominant etiological categories, with neuroimaging and EEG providing supportive evidence of underlying brain injury in a substantial subset of cases.

**4. Primary efficacy outcomes: seizure cessation at 24 and 48 hours**

Seizure control at 24 hours was achieved in 22/28 (79%) neonates in the phenobarbitone (PB) group and 23/28 (82%) in the levetiracetam (LEV) group (Table 2, Figure 2). There was no significant difference between PB and LEV for 24-hour seizure cessation (relative risk 0.96, 95% confidence interval 0.74–1.24; p = 0.90).

At 48 hours, seizure cessation rates remained similar between groups, at 21.4% for PB and 17.9% for LEV, again without a statistically significant difference (p = 0.52). The number of seizure episodes (single vs multiple), the proportion with seizure recurrence after first-line therapy, the mean time to seizure control, and the duration of antiepileptic treatment were also comparable between PB and LEV (Table 2).

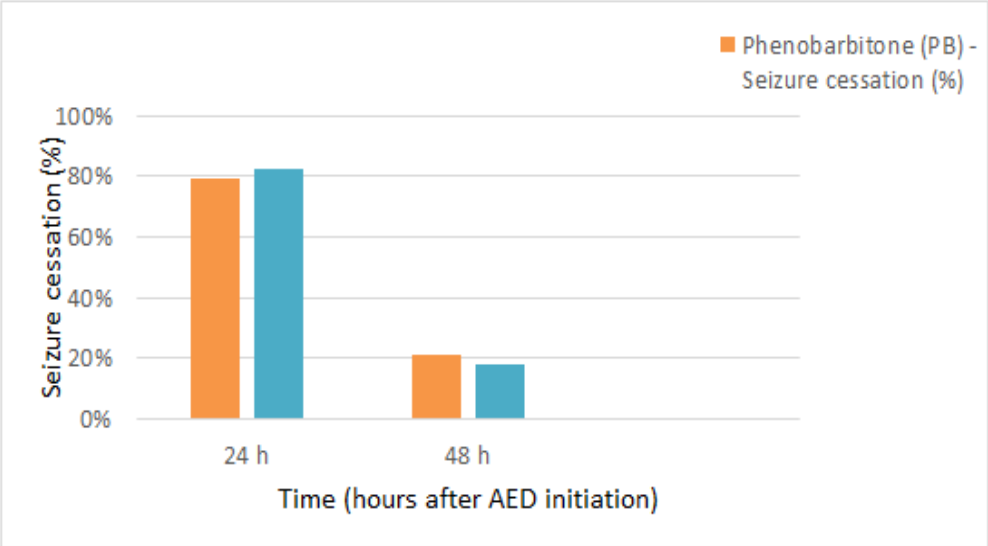



**Figure 2. Proportion of neonates with seizure cessation at 24 and 48 hours by treatment group**

**5. Safety outcomes: adverse effects of phenobarbitone vs levetiracetam**

Overall, 30 adverse drug events were recorded, of which 26 (86.7%) occurred in neonates receiving phenobarbitone and 4 (13.3%) in those receiving levetiracetam (Table 3). This difference in the overall burden of adverse events between treatment groups was statistically significant ($p = 0.009$).

Excessive sleepiness was the most frequently reported adverse effect, with 11 events in the PB group and 4 events in the LEV group. All recorded episodes of respiratory depression (n = 8) and hypotension (n = 7) occurred exclusively in neonates treated with phenobarbitone. Formal hypothesis testing was performed only for the composite outcome of "any adverse effect"; individual p-values were not calculated for specific adverse effects because of small event numbers and the absence of events in the levetiracetam group. All adverse events were transient and resolved after adjustment of the infusion rate or discontinuation of the drug.

**Table 3. Adverse effects in neonates receiving phenobarbitone vs levetiracetam**

| Adverse effect | PB (events, n) | LEV (events, n) | p-value | 95% CI for difference* |
|---|---|---|---|---|
| Excessive sleepiness | 11 | 4 | — | — |
| Respiratory depression | 8 | 0 | — | — |
| Hypotension | 7 | 0 | — | — |
| **Any adverse effect** | 26 | 4 | 0.009 | 11.4% to 90.0% |

*95% confidence interval for the difference in proportion of neonates experiencing at least one adverse effect between treatment groups. Individual confidence intervals and p-values were not calculated for specific adverse effects because of small numbers and absence of events in the levetiracetam group.

**6. Cost outcomes: daily and total treatment cost**

Drug utilisation and cost data are presented in Table 4. The mean daily drug cost was substantially higher in the levetiracetam group, at 800.08 ± 359.66 INR/day, compared with 168.82 ± 119.55 INR/day in the phenobarbitone group ($p < 0.0001$).

Although the average daily dose was slightly higher for levetiracetam (21.2 mg/day) than for phenobarbitone (16.8 mg/day), the combination of a greater dose requirement and a markedly higher unit price (4.80 vs 1.21 INR/mg) resulted in a much greater daily expenditure per neonate in the levetiracetam group. The metric of drug amount per rupee spent (mg/INR/day) further illustrates the difference in cost structure between the two agents.

Overall, these findings indicate that while phenobarbitone and levetiracetam showed comparable efficacy, phenobarbitone was considerably more economical as a first-line antiepileptic drug in this neonatal cohort.

**Figure 3. Mean daily drug cost per neonate for phenobarbitone vs levetiracetam**

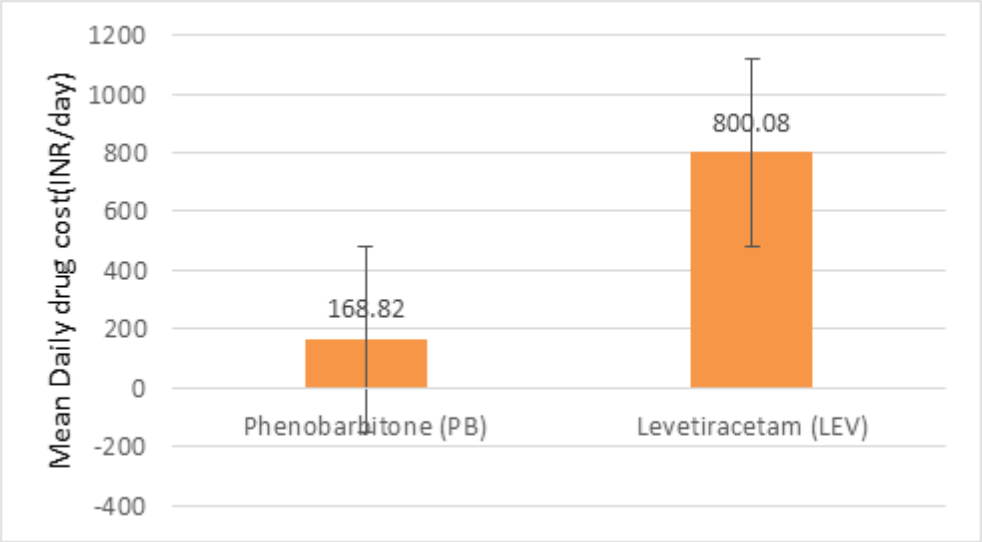



**Table 4. Comparison of antiepileptic drug utilisation and cost between phenobarbitone and levetiracetam**

| Variable | Phenobarbitone (PB) | Levetiracetam (LEV) | p-value |
|---|---|---|---|
| Mean daily dose, mg/day | 16.8 | 21.2 | < 0.0001 |
| Cost per mg, INR/mg | 1.21 | 4.80 | – |
| Mean daily drug cost per neonate, INR/day | 168.82 ± 119.55 | 800.08 ± 359.66 | < 0.0001 |
| Drug amount per INR per day, mg/INR/day | 20.3 | 101.8 | – |

*AED = antiepileptic drug; INR = Indian Rupee.*

**7. In-hospital outcomes**

At the end of the hospital stay, 31/56 (55.3%) neonates were discharged alive, 19 (34%) left against medical advice (DAMA), and 6 (10.7%) died during hospitalisation. The distribution of discharge status (discharged, DAMA, death) was broadly similar between male and female infants, with no clear sex-related pattern. Given the relatively small sample size and the heterogeneous, multifactorial etiologies underlying neonatal seizures in this cohort, the study was not powered to detect meaningful differences in mortality or discharge status between the phenobarbitone and levetiracetam groups, and these outcomes were therefore interpreted descriptively rather than subjected to formal comparative analysis.

## DISCUSSION

In this rural tertiary NICU cohort, phenobarbitone and levetiracetam achieved similar early clinical seizure control, with 24-hour cessation in 79% and 82% of neonates respectively, but with markedly different safety and cost profiles. Phenobarbitone generated most adverse events—particularly respiratory depression and hypotension—whereas levetiracetam was better tolerated but substantially more expensive. These findings sit within an evolving literature that is re-examining phenobarbitone as the default first-line agent in neonatal seizures [7–10].

Comparative efficacy data for these drugs are heterogeneous. In the NEOLEV2 randomized trial, Sharpe et al. reported that phenobarbitone produced ≥80% electrographic seizure reduction in about 80% of neonates, compared with roughly 30% for levetiracetam, albeit with more cardiorespiratory instability in the phenobarbitone arm [7]. Conversely, Bättig et al. found broadly similar clinical or electrographic control rates (around 60–70%) for first-line levetiracetam and phenobarbitone in routine practice, with fewer complications on levetiracetam [8]. Qiao et al.'s meta-analysis also suggested only modest differences, with seizure control around 50–60% for levetiracetam versus 40–50% for phenobarbitone, and overlapping confidence intervals [9]. Our near-identical 24- and 48-hour clinical control rates therefore align more with observational data and pooled analyses [8,9] than with the EEG-stringent RCT [7], likely reflecting differences in monitoring (clinical vs continuous EEG), illness severity and timing of assessment [9,10,14].

Current ILAE guidance still lists phenobarbitone as first-line therapy, largely on the strength of historical and electrographic evidence, while recognising levetiracetam as an increasingly used alternative [10]. Our results support this nuanced position: levetiracetam did not outperform phenobarbitone in short-term seizure control, but its safety profile was clearly more favourable. We recorded 30 adverse events in total, of which 26 (86.7%) occurred in phenobarbitone-treated neonates and only four (13.3%) in those receiving levetiracetam; all eight episodes of respiratory depression and all seven episodes of hypotension were confined to the phenobarbitone group. Ajayi et al. similarly described clinically important hypotension and impaired haemodynamic recovery in roughly one-third of term asphyxiated infants exposed to early phenobarbitone [13], and Qiao et al. reported that sedation, respiratory depression and hypotension were approximately two- to three-fold more frequent with phenobarbitone than with levetiracetam across pooled cohorts [9].

By contrast, our levetiracetam-related events were limited to transient excessive sleepiness, consistent with Ramantani et al., who found mainly mild sedation and serious cardiorespiratory events in fewer than 5–10% of treated neonates [11], and with Rao et al., who reported tolerable adverse event rates of around 10–15% in HIE-associated seizures [12].

Long-term data further strengthen the case for minimising phenobarbitone exposure. In a cohort followed to 24 months, Maitre et al. observed lower cognitive and motor scores in infants exposed to phenobarbitone for neonatal seizures, whereas levetiracetam exposure was associated with more favourable neurodevelopmental outcomes after adjustment for confounders [16]. Given that many of our seizures arose from HIE or structural lesions and that electrographic seizures are strongly linked to later neurologic sequelae [14], these long-term findings [16] reinforce the argument that, where available and affordable, safer agents such as levetiracetam should be preferred or at least used to limit cumulative phenobarbitone burden [9,10,16].

The etiologic and electroclinical profile of our cohort was typical of high-burden NICU populations: HIE and infection accounted for roughly 70% of cases, subtle seizures were the predominant clinical type, and most events occurred in the first week of life. Scher et al. similarly identified hypoxic–ischaemic injury and intracranial haemorrhage as dominant substrates for neonatal electrographic seizures, with subtle semiology particularly frequent in both preterm and term infants [14]. Our proportion of subtle seizures (64.3%) lies toward the upper end of the 40–70% range reported in other series and reflected in guideline discussions [10,14]. Regional differences in perinatal care and infection burden will shift exact proportions, but the broad pattern suggests that our findings are reasonably generalisable to other resource-limited NICUs.

A distinctive contribution of this study is the explicit assessment of drug cost. Mean daily drug cost was almost five-fold higher for levetiracetam than for phenobarbitone (about 800 vs 170 INR/day), driven by both a higher average daily dose (≈21 vs 17 mg/day) and a four-fold higher unit price (4.8 vs 1.21 INR/mg). While Qiao et al. and others emphasise levetiracetam's clinical and safety advantages [9], few analyses incorporate pharmacoeconomic data. Hooper et al., in a systematic review of levetiracetam as first-line therapy, highlighted its promise as a phenobarbitone alternative in high-resource settings but specifically noted the paucity of cost-effectiveness evidence from low- and middle-income countries [15]. Our data illustrate that tension: in a rural Indian NICU, levetiracetam appears safer and at least as effective, yet imposes a several-fold increase in per-day drug expenditure. For many hospitals, the incremental safety benefit must therefore be weighed carefully against sustainable budget impact.

This study has limitations. The sample size is modest compared with NEOLEV2 and the larger pooled cohorts in recent meta-analyses [7,9], limiting power to detect small differences in efficacy or mortality. Seizure diagnosis and outcome were primarily clinical, with conventional but not continuous EEG, so our 24-hour cessation rates likely overestimate electrographic control relative to EEG-based studies [7,10,14]. Treatment allocation was not randomised, leaving room for residual confounding despite broadly similar baseline characteristics, and our cost analysis was restricted to drug acquisition costs without accounting for potential differences in ventilation days, length of stay or long-term neurodevelopmental support.

Despite these constraints, the pattern of our findings is consistent with the broader literature. We observed comparable short-term seizure control with phenobarbitone and levetiracetam, echoing several cohort studies and pooled estimates [8,9,15], alongside a clearly more favourable safety profile for levetiracetam, in line with observational and developmental outcome data [9,11,12,16]. When situated within current guideline recommendations [10], this suggests that levetiracetam is a reasonable—and often preferable—alternative to phenobarbitone as first-line therapy where resources allow. In settings where levetiracetam cost or availability is prohibitive, phenobarbitone will remain central, but cumulative exposure should be minimised and cardiorespiratory monitoring optimised. Future work in similar low- and middle-income settings should prioritise adequately powered comparative studies with electrographic endpoints, long-term neurodevelopmental follow-up, and robust cost-effectiveness analyses to more precisely balance efficacy, safety and affordability for neonates with seizures [7–9,11,12,15,16].

## CONCLUSION

In this neonatal cohort, phenobarbitone and levetiracetam showed similar short-term clinical efficacy, with comparable 24- and 48-hour seizure cessation and recurrence rates. However, phenobarbitone was associated with substantially more adverse events, including all cases of respiratory depression and hypotension, while levetiracetam caused only transient excessive sleepiness. Despite this safety advantage, levetiracetam incurred an almost five-fold higher daily drug cost than phenobarbitone in our setting.

Overall, levetiracetam appears to be a safer but more expensive alternative to phenobarbitone for first-line treatment of neonatal seizures. In resource-limited settings, phenobarbitone will likely remain the mainstay, but its use should be accompanied by careful monitoring and efforts to limit exposure. Further large, preferably randomised, studies with electrographic monitoring, long-term neurodevelopmental follow-up and formal cost-effectiveness analyses are needed to guide definitive first-line treatment choices.

**REFERENCES**


1. Yi, Z. M., Zhong, X. L., Wang, M. L., Zhang, Y., & Zhai, S. D. (2020). Efficacy, safety, and economics of intravenous levetiracetam for status epilepticus: a systematic review and meta-analysis. *Frontiers in Pharmacology*, *11*, 751.
2. Glauser, T., Ben-Menachem, E., Bourgeois, B., Cnaan, A., Chadwick, D., Guerreiro, C., ... & Tomson, T. (2006). ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*, *47*(7), 1094-1120.
3. Brodie, M. J., & Kwan, P. (2012). Current position of phenobarbital in epilepsy and its future. *Epilepsia*, *53*, 40-46.
4. Verrotti, A., Loiacono, G., Coppola, G., Spalice, A., Mohn, A., & Chiarelli, F. (2011). Pharmacotherapy for children and adolescents with epilepsy. *Expert opinion on pharmacotherapy*, *12*(2), 175-194.
5. Yasiry, Z., & Shorvon, S. D. (2012). How phenobarbital revolutionized epilepsy therapy: the story of phenobarbital therapy in epilepsy in the last 100 years. *Epilepsia*, *53*, 26-39.
6. Katchanov, J., & Birbeck, G. L. (2012). Epilepsy care guidelines for low-and middle-income countries: From WHO mental health GAP to national programs. BMC medicine, 10(1), 107.
7. Sharpe, C., Reiner, G. E., Davis, S. L., Nespeca, M., Gold, J. J., Rasmussen, M., ... & NEOLEV2 INVESTIGATORS. (2020). Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. *Pediatrics*, *145*(6), e20193182.
8. Bättig, L., Dünner, C., Cserpan, D., Rüegger, A., Hagmann, C., Schmitt, B., ... & Ramantani, G. (2023). Levetiracetam versus phenobarbital for neonatal seizures: a retrospective cohort study. *Pediatric Neurology*, *138*, 62-70.
9. Qiao, M. Y., Cui, H. T., Zhao, L. Z., Miao, J. K., & Chen, Q. X. (2021). Efficacy and safety of levetiracetam vs. phenobarbital for neonatal seizures: a systematic review and meta-analysis. *Frontiers in Neurology*, *12*, 747745.
10. Pressler, R. M., Abend, N. S., Auvin, S., Boylan, G., Brigo, F., Cilio, M. R., ... & Hartmann, H. (2023). Treatment of seizures in the neonate: guidelines and consensus-based recommendations—special report from the ILAE task force on neonatal seizures. *Epilepsia*.
11. Ramantani, G., Ikonomidou, C., Walter, B., Rating, D., & Dinger, J. (2011). Levetiracetam: safety and efficacy in neonatal seizures. *european journal of paediatric neurology*, *15*(1), 1-7.
12. Rao, L. M., Hussain, S. A., Zaki, T., Cho, A., Chanlaw, T., Garg, M., & Sankar, R. (2018). A comparison of levetiracetam and phenobarbital for the treatment of neonatal seizures associated with hypoxic–ischemic encephalopathy. *Epilepsy & Behavior*, *88*, 212-217.
13. Ajayi, O. A., Oyaniyi, O. T., & Chike-Obi, U. D. (1998). Adverse effects of early phenobarbital administration in term newborns with perinatal asphyxia. *Tropical Medicine & International Health*, *3*(7), 592-595.
14. Scher, M. S., Aso, K., Beggarly, M. E., Hamid, M. Y., Steppe, D. A., & Painter, M. J. (1993). Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. *Pediatrics*, *91*(1), 128-134.
15. Hooper, R. G., Ramaswamy, V. V., Wahid, R. M., Satodia, P., & Bhulani, A. (2021). Levetiracetam as the first-line treatment for neonatal seizures: a systematic review and meta-analysis. *Developmental Medicine & Child Neurology*, *63*(11), 1283-1293.
16. Maitre, N. L., Smolinsky, C., Slaughter, J. C., & Stark, A. R. (2013). Adverse neurodevelopmental outcomes after exposure to phenobarbital and levetiracetam for the treatment of neonatal seizures. *Journal of Perinatology*, *33*(11), 841-846.