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Adverse Drug Reactions and Short-Term Clinical Outcomes in Preterm Neonates Treated for Seizures Following Perinatal Asphyxia

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Abstract

Background: Preterm neonates with perinatal asphyxia are at high risk of seizures, yet optimal first-line anticonvulsant therapy remains uncertain. Phenobarbitone has traditionally been used but carries significant adverse effects, while levetiracetam offers a potentially safer alternative. This study compared the efficacy and safety of levetiracetam versus phenobarbitone in preterm neonates with post-asphyxial seizures. ***Methods:*** This open-label randomized controlled trial enrolled 72 preterm neonates (31 to <37 weeks gestation) with convulsions due to perinatal asphyxia (HIE stage II/III). Neonates were randomized to receive either intravenous levetiracetam (20 mg/kg loading, 10 mg/kg/dose 12 hourly maintenance) or phenobarbitone (20-40 mg/kg loading, 5 mg/kg/day maintenance). Primary outcomes included seizure control, time to seizure cessation and adverse effects. ***Results:*** Seizure control with monotherapy was significantly higher in the levetiracetam group (72.22%) compared to phenobarbitone (44.44%) (p=0.004). The need for additional anticonvulsants was substantially lower in the levetiracetam group (27.78% vs. 55.6%, p=0.004). Seizure control within 12 hours was achieved in 83.33% of levetiracetam-treated neonates versus 50.0% in the phenobarbitone group (p=0.039). Adverse effects occurred significantly less frequently with levetiracetam (5.56% vs. 27.78%, p=0.024), with somnolence being the most common adverse effect in both groups. ***Conclusion:*** Levetiracetam demonstrated superior efficacy with more rapid seizure control and a significantly better safety profile compared to phenobarbitone in preterm neonates with post-asphyxial seizures. These findings support levetiracetam as a favorable first-line agent in this vulnerable population.

Keywords: Levetiracetam, Phenobarbitone, neonatal seizures, perinatal asphyxia, preterm neonates, adverse drug reactions.

INTRODUCTION

Perinatal asphyxia remains a significant contributor to neonatal morbidity and mortality worldwide, particularly affecting the most vulnerable preterm population [1]. The resulting hypoxic-ischemic encephalopathy (HIE) represents a spectrum of neurological injury that frequently manifests as neonatal seizures, which are among the most critical neurological emergencies encountered in the neonatal intensive care unit [2]. Preterm neonates are uniquely susceptible to both the initial hypoxic insult and its secondary neurological consequences due to the developmental immaturity of their cerebral vasculature, germinal matrix and subcortical structures [3]. Seizures in this population not only indicate significant underlying brain injury but also independently contribute to further neuronal damage through mechanisms such as excitotoxicity, metabolic exhaustion and impaired cerebral autoregulation [4].

The clinical management of seizures in preterm neonates with perinatal asphyxia presents a formidable challenge to neonatologists [5]. The overarching therapeutic goals include rapid seizure cessation to prevent secondary brain injury, while simultaneously minimizing iatrogenic harm from the anticonvulsant agents themselves. For decades, phenobarbitone has served as the cornerstone of neonatal anticonvulsant therapy, largely due to its established efficacy, familiarity among clinicians and extensive historical use

[6]. However, its pharmacokinetic profile in preterm infants—characterized by prolonged half-life, volume of distribution and hepatic metabolism—poses significant safety concerns [7]. Clinically, phenobarbitone is associated with a range of adverse effects including respiratory depression necessitating increased ventilatory support, hypotension, profound sedation and metabolic disturbances. These effects are particularly detrimental in preterm neonates who often have pre-existing respiratory compromise, hemodynamic instability and immature organ systems [8].

The emergence of newer anticonvulsant agents, particularly levetiracetam, has generated considerable interest in neonatal seizure management. Levetiracetam offers a distinct pharmacodynamic profile, acting through synaptic vesicle protein 2A, which provides a mechanistic divergence from traditional agents [9]. From a safety perspective, it appears to have a more favorable adverse effect profile, with a lower propensity for respiratory depression, sedation and hemodynamic instability [10]. This characteristic is especially attractive in the preterm population where preservation of spontaneous respiratory effort, stable blood pressure and adequate level of consciousness are paramount for successful neurological recovery. Furthermore, its more predictable pharmacokinetics and fewer drug-drug interactions offer practical advantages in complex neonatal intensive care settings where polypharmacy is common [11].

Given this clinical equipoise, there is an urgent need for robust comparative data examining not only the efficacy of anticonvulsant agents in achieving seizure control but also their safety profiles and impact on short-term clinical outcomes in preterm neonates following perinatal asphyxia. Understanding the balance between therapeutic benefit and iatrogenic harm is essential for optimizing treatment protocols, reducing neonatal morbidity and improving overall outcomes in this high-risk population.

METHODOLOGY & MATERIALS

This investigation was designed as an open-label randomized controlled trial, conducted at Bangladesh Shishu Hospital and Institute over a two-year period from July 2020 to June 2022. The study population comprised preterm neonates, ranging from 31st to less than 37 weeks of gestational age, who presented with convulsions secondary to perinatal asphyxia (specifically, stage II and III hypoxic-ischemic encephalopathy). Neonates were excluded if they presented with hypoglycemia, hypocalcemia, dyselectrolytemia, sepsis, major central nervous system malformations, or had a history of prior anticonvulsant exposure. Following approval from the institutional ethics committee and the procurement of written informed consent from parents or legal guardians, eligible neonates were randomized into two groups using a lottery method with sealed envelopes. A total sample size of 36 neonates was allocated to each treatment arm.

The intervention group received intravenous Levetiracetam at a loading dose of 20 mg/kg, followed by a maintenance regimen of 10 mg/kg/dose administered every 12 hours. Conversely, the control group received intravenous Phenobarbitone at a loading dose of 20-40 mg/kg, followed by a maintenance dose of 5 mg/kg/day in divided doses. Successful seizure control was defined as the complete cessation of convulsive activity without any recurrence within a 48-hour period. In instances where the initially assigned drug failed to achieve seizure control, additional anticonvulsants were introduced according to the established institutional protocol.

The primary outcome measures assessed included: the time required to attain seizure control, the occurrence of adverse effects within two hours of drug administration, the total duration of hospital stay, discharge status with clinical improvement and the necessity for more than one anticonvulsant agent. Documented adverse effects encompassed desaturation, cardiac arrhythmias, somnolence, respiratory depression and other observable complications. It is important to note that seizure diagnosis was made clinically, as continuous electroencephalography (EEG) monitoring was not utilized. Data collection was executed using a structured questionnaire and all gathered data were subsequently analyzed using SPSS version 26.0. Comparative analyses for categorical variables were performed using the chi-square and Fisher's exact tests, whereas continuous variables were compared using the unpaired t-test. A p-value of less than 0.05 was established as the threshold for statistical significance. Strict confidentiality of all patient-related information was rigorously maintained throughout the entire study process.

RESULTS

Table I: Stages of hypoxic ischemic encephalopathy (HIE) (n=72)

Stages	Group A (LEV) (n=36)	Group B (PHB) (n=36)	P value
II	34 (94.44)	33 (91.66)	0.405
III	2 (5.55)	3 (8.3)	

P value reached from fisher exact test

The distribution of hypoxic ischemic encephalopathy (HIE) stages among the study population is presented in Table I. Among the 72 preterm neonates enrolled, the vast majority presented with HIE

stage II, comprising 34 neonates (94.44%) in the Levetiracetam group and 33 neonates (91.66%) in the Phenobarbitone group. Only a small proportion of neonates had HIE stage III, with 2 cases (5.55%) in the LEV group and 3 cases (8.3%) in the PHB group. The difference in HIE stage distribution between the two treatment groups was not statistically significant (p=0.405), confirming that both groups were comparable at baseline with respect to the severity of encephalopathy.

Table II: Seizure types of neonates (n=72)

Seizure types	Group A (LEV) (n=36) No. (%)	Group B (PHB) (n=36) No. (%)	p-value
Clonic	24(66.7)	22(61.1)	0.804
Subtle	7(19.4)	8(22.2)	
Tonic	3(8.3)	5(13.9)	
Myoclonic	2(5.6)	1(2.8)	

Data were expressed frequency and percentage
p-value reached from chi square (χ^2) test

The distribution of seizure types among the study population is detailed in Table II. Clonic seizures were the most frequently observed type in both groups, occurring in 24 neonates (66.7%) in the Levetiracetam group and 22 neonates (61.1%) in the Phenobarbitone group. Subtle seizures were noted in 7 cases (19.4%) in the LEV group and 8 cases (22.2%) in the PHB group, while tonic seizures were observed in 3 neonates (8.3%) and 5 neonates (13.9%) respectively. Myoclonic seizures were the least common, affecting only 2 neonates (5.6%) in the LEV group and 1 neonate (2.8%) in the PHB group. The overall distribution of seizure types between the two treatment groups was not statistically significant (p=0.804), indicating that both groups were well-matched with respect to seizure semiology.

Table III: Response to anticonvulsant drugs in neonates (n=72)

Response to anticonvulsant drugs	Group A (LEV) (n=36)	Group B (PHB) (n=36)	p-value
Seizure controlled by 1 drug	27(72.22)	15(44.44)	0.004
Need of >1 drug for seizure control	9(27.78)	21(55.6)	
Time required to control seizure			
<12 hrs	30(83.33)	18(50.0)	0.039*
12-24 hrs	3(8.33)	8(22.22)	
25-36 hrs	1(2.78)	7(19.44)	
37-48 hrs	1(2.78)	2(5.56)	
>48 hrs	1(2.78)	1(2.78)	

p-value reached from chi square (χ2) test
*= p-value significant

The response to anticonvulsant therapy in the study population is presented in Table III. Seizure control was achieved with a single drug in a significantly higher proportion of neonates in the Levetiracetam group, with 27 neonates (72.22%) responding to monotherapy, compared to only 15 neonates (44.44%) in the Phenobarbitone group and this difference was statistically significant (p=0.004). Consequently, the need for more than one anticonvulsant agent for adequate seizure control was substantially higher in the PHB group, affecting 21 neonates (55.6%), whereas only 9 neonates (27.78%) in the LEV group required additional drugs, again demonstrating a significant difference between the groups (p=0.004). Regarding the time required to achieve seizure cessation, seizure control within the first 12 hours was achieved in 30 neonates (83.33%) in the LEV group, compared to only 18 neonates (50.0%) in the PHB group and this difference was statistically significant (p=0.039). Seizure control between 12 to 24 hours was observed in 3 neonates (8.33%) in the LEV group and 8 neonates (22.22%) in the PHB group, while control between 25 to 36 hours occurred in 1 neonate (2.78%) and 7 neonates (19.44%) respectively. Seizure control between 37 to 48 hours was noted in 1 neonate (2.78%) in each group and control beyond 48 hours was also observed in 1 neonate (2.78%) in both groups.

Table IV: Adverse effects of Levetiracetam and Phenobarbitone (n=72)

Adverse effect	Group A (LEV) (n=36) No. (%)	Group B (PHB) (n=36) No. (%)	p-value
Yes	2(5.56)	10(27.78)	0.024*
No	34(94.44)	26(72.22)	

Adverse effect	Group A (LEV) (n=36) No. (%)	Group B (PHB) (n=36) No. (%)	p-value
Types of adverse effect			
Somnolence	2(100.0)	9(90.0)	1.00
Shallow breathing	0(0.0)	1(10.0)	

p-value reached from fisher exact test
*= p-value significant

The adverse effects observed following anticonvulsant administration are presented in Table IV. Adverse effects were documented in significantly fewer neonates in the Levetiracetam group, occurring in only 2 neonates (5.56%), compared to the Phenobarbitone group where 10 neonates (27.78%) experienced adverse reactions and this difference was statistically significant (p=0.024). Among the neonates who developed adverse effects, somnolence was the most frequently reported manifestation, affecting both neonates (100%) in the LEV group and 9 neonates (90%) in the PHB group. Shallow breathing was observed exclusively in the Phenobarbitone group, affecting 1 neonate (10%), while no case of respiratory depression was documented in the Levetiracetam group. The distribution of specific adverse effect types between the two groups did not reach statistical significance (p=1.00).

DISCUSSION

The present study compared the efficacy and safety of levetiracetam versus phenobarbitone as first-line anticonvulsant therapy in preterm neonates with seizures following perinatal asphyxia. Our findings demonstrate that levetiracetam was associated with significantly superior seizure control and a substantially more favorable adverse effect profile compared to phenobarbitone.

Perinatal asphyxia remains a leading cause of neonatal morbidity and mortality, with preterm infants being particularly vulnerable due to cerebral immaturity and limited autoregulatory capacity [12]. The pathogenesis of hypoxic-ischemic encephalopathy involves a complex cascade of excitotoxicity, oxidative stress and neuroinflammation, ultimately resulting in neuronal injury and seizures [13]. In our study, the majority of neonates presented with HIE stage II in both groups (94.44% in LEV group vs. 91.66% in PHB group), confirming the predominant severity of encephalopathy in this preterm population. This distribution was comparable between groups (p=0.405), ensuring that baseline characteristics did not confound treatment comparisons.

The efficacy findings of our study are noteworthy. Seizure control with a single drug was achieved in 72.22% of neonates in the levetiracetam group compared to only 44.44% in the phenobarbitone group (p=0.004). Consequently, 55.6% of neonates in the PHB group required additional anticonvulsants versus only 27.78% in the LEV group. These results are consistent with the findings of Chaudhari *et al.,* who demonstrated superior efficacy of levetiracetam over phenobarbitone in neonatal seizure management [14]. Similarly, Akeel *et al.,* reported that levetiracetam was at least as effective as phenobarbital as first-line therapy, with a trend toward better seizure control [15]. Furthermore, our observation that 83.33% of neonates in the LEV group achieved seizure control within 12 hours, compared to only 50.0% in the PHB group (p=0.039), highlights the more rapid onset of action of levetiracetam. This rapid seizure cessation is clinically critical, as prolonged seizure activity independently contributes to additional neuronal damage through excitotoxic mechanisms and metabolic exhaustion [16].

Regarding adverse drug reactions, our study demonstrated a significantly lower incidence in the levetiracetam group, with only 5.56% of neonates experiencing adverse effects compared to 27.78% in the phenobarbitone group (p=0.024). Somnolence was the most frequent adverse effect in both groups, affecting 100% of affected neonates in the LEV group and 90% in the PHB group. Notably, shallow breathing was observed exclusively in the PHB group (10%), while no respiratory depression was documented in the LEV group. These findings align with the meta-analysis by Kumar *et al.,* who reported that levetiracetam had a significantly better safety profile with fewer adverse events compared to phenobarbitone [17]. The favorable safety profile of levetiracetam is particularly important in preterm neonates who frequently have pre-existing respiratory compromise, hemodynamic instability and immature organ systems, making them more susceptible to phenobarbitone-induced respiratory depression and sedation [18].

The pathophysiology of perinatal asphyxia involves not only hypoxic-ischemic injury but also subsequent reperfusion injury mediated by reactive oxygen species and inflammatory cytokines [13]. The choice of anticonvulsant may influence neurodevelopmental outcomes beyond seizure control alone. While therapeutic hypothermia has emerged as a standard neuroprotective strategy, the optimal anticonvulsant regimen in preterm neonates remains an area of ongoing investigation [19,20]. Gowda *et al.,* highlighted the potential role of neuroprotective adjuvants, though robust evidence remains limited [21]. The observation that phenobarbitone was associated with a higher need for additional drugs and more adverse effects suggests that its use as a first-line agent may inadvertently delay effective seizure control while exposing neonates to unnecessary harm [22].

The clinical implications of our findings are substantial. The superior efficacy and safety profile of levetiracetam support its consideration as a first-line agent in preterm neonates with post-asphyxial seizures. This is particularly relevant in resource-limited settings where continuous EEG monitoring may be unavailable [23]. The rapid seizure control achieved with levetiracetam may reduce the duration of seizure exposure, potentially mitigating secondary brain injury and improving short-term outcomes [24]. However, long-term neurodevelopmental follow-up is essential to determine whether the observed short-term advantages translate into sustained benefits [25].

Limitations of the study

Several limitations of our study warrant consideration. Seizures were diagnosed clinically without continuous electroencephalography (EEG) monitoring, which may have led to under-recognition of subclinical or electrographic seizures, potentially affecting the accuracy of seizure control assessment. The open-label design introduces the possibility of observer bias, although the objective nature of seizure documentation and adverse effect reporting partially mitigates this concern. Additionally, the relatively small sample size may limit the generalizability of our findings and the detection of less common adverse effects. The single-center setting further restricts the external validity of our results and the lack of long-term neurodevelopmental follow-up means we cannot ascertain whether the observed short-term advantages of levetiracetam translate into sustained improvements in cognitive and motor outcomes.

CONCLUSION

In conclusion, levetiracetam demonstrated significantly superior efficacy with a more favorable adverse effect profile compared to phenobarbitone in preterm neonates with seizures following perinatal asphyxia. Levetiracetam achieved higher rates of seizure control with monotherapy, more rapid seizure cessation and substantially fewer adverse drug reactions, particularly respiratory depression. These findings support the consideration of levetiracetam as a first-line anticonvulsant agent in this vulnerable preterm population, offering a favorable balance between therapeutic benefit and iatrogenic harm. However, larger multicenter trials with continuous EEG monitoring and long-term neurodevelopmental assessment are warranted to confirm these findings and guide evidence-based clinical practice.

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