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Original Research Article

Efficacy of Levetiracetam in the Treatment of Neonatal Seizures Presenting at Tertiary Care Hospital

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Abstract: *Neonatal seizures are the most frequent neurological emergency during the neonatal period and are associated with considerable morbidity and mortality. Conventional antiepileptic drugs, particularly phenobarbital and phenytoin, remain widely used but may have limited efficacy and a higher adverse-effect profile. Levetiracetam has emerged as a potential alternative because of its favorable safety profile and anticonvulsant activity.*
Objective: *To determine the efficacy and safety of levetiracetam in the treatment of neonatal seizures presenting at a tertiary care hospital and to compare its outcomes with conventional antiepileptic therapy using phenobarbital with or without phenytoin.* ***Methods:*** *This prospective, double-blinded, randomized, parallel-group controlled trial was conducted in the Neonatal Intensive Care Unit of Head Quarter Hospital, Dera Ismail Khan, from 25 October 2024 to 25 March 2025. A total of 260 neonates aged 0–28 days with clinically diagnosed neonatal seizures were enrolled and randomly allocated into two equal groups. Group A received intravenous levetiracetam, while Group B received phenobarbital with or without phenytoin according to clinical requirement. Treatment efficacy was assessed in terms of seizure cessation within 40 minutes, seizure freedom at 24 and 48 hours, seizure recurrence, and time to seizure control. Safety was evaluated by documenting adverse effects and mortality. Data were analyzed using SPSS version 23. Quantitative variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Chi-square test and independent sample t-test were applied where appropriate, and a p-value ≤0.05 was considered statistically significant.* ***Results:*** *Early seizure cessation within 40 minutes was significantly higher in the levetiracetam group than in the conventional antiepileptic group (64.7% vs. 52.3%, p=0.04). Mean time to seizure control was shorter in Group A compared with Group B (28 ± 12 minutes vs. 33 ± 15 minutes, p=0.05). Adverse effects were significantly less frequent among neonates receiving levetiracetam than among those receiving phenobarbital with or without phenytoin (8% vs. 18%), particularly sedation and poor feeding. Seizure freedom at 24 and 48 hours, seizure recurrence, and mortality were comparable between the two groups. Hypoxic-ischemic encephalopathy and sepsis were the most common underlying etiologies of neonatal seizures.*
Conclusion: *Levetiracetam demonstrated better early seizure control and a lower frequency of adverse effects compared with conventional antiepileptic therapy in neonates with seizures. It may be considered a safer and effective alternative to phenobarbital-based therapy, with comparable short-term seizure freedom and mortality outcomes.*

Keywords: Neonatal seizures, Levetiracetam, Phenobarbitone, Antiepileptic drugs

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Introduction

Seizures are a common neurological disorder in newborns, whose brains are still in early development. (1,2) Therefore, clinical manifestations of newborn seizures may differ from those of later age groups due to the distinct etiology and electrographic findings of these seizures. The onset of seizures in a newborn infant might indicate the presence of a more serious neurologic condition. (2) Therefore, managing emergency seizures and prompt diagnosis is necessary to avoid additional brain damage. (3) Neonatal seizures were reported, with subtle and tonic types being the most common. Most affected neonates recovered and were discharged, while 8.4% experienced severe neurologic deficits. (3,4) Newborn seizure treatment needs a full approach to control seizures, treat causes, and prevent long-term brain issues using medicines such as phenobarbital, phenytoin, or levetiracetam. (4,5) Continuous electroencephalogram monitoring is crucial for evaluating the effectiveness of treatment and providing guidance for adjustments in medication. (6) For situations where seizures are not responding to treatment or there is a suspicion of underlying causes that require definitive management, extended sedation has been used, but it may have negative effects on neurological development. (6,7) The exact mechanism of antiepileptic drugs is not fully known; however, levetiracetam is thought to produce its antiepileptic effects by binding to synaptic vesicle protein 2A, regulating neurotransmitter release, and stabilizing neuronal membranes. (7) Levetiracetam is different from other antiepileptic drugs because it has minimal interaction with liver enzymes and has a favorable absorption and pharmacokinetic profile. (7–9) A previous study reported that the efficacy of levetiracetam in controlling neonatal seizures was 64.7%. (8) In comparison, the efficacy of other antiepileptic drugs such as phenobarbital or phenytoin has been reported as 30% to 50%. (8)
Managing neonatal seizures presents a significant challenge in clinical practice due to their heterogeneity and diverse underlying etiologies. Due to the paucity of local literature on this subject, the goal of this study is to determine the efficacy of levetiracetam in the treatment of neonatal seizures presenting at our health setup. The results of this study will be helpful in understanding the efficacy of levetiracetam in order to reduce the morbidity and mortality associated with neonatal seizures. The findings of this study will also refine the clinical utility of levetiracetam, ultimately improving outcomes and quality of life for neonates living with seizures.
The main objective is to determine the efficacy of levetiracetam in the treatment of neonatal seizures presenting at a tertiary care hospital.

Methodology

This is a prospective double blinded randomized control parallel group study. This study is carried out in a neonatal intensive care unit in the

Department of Pediatrics, MTI District Head Quarter Hospital, Dera Ismail Khan which is tertiary teaching institute for one year duration.

WHO sample size calculator is used for the determination of sample size by keeping the following assumptions: Efficacy of Levetiracetam in controlling neonatal seizure was 64.7%. Margin of error 8.5%, and confidence level 95%. The calculated sample size is 122**.** (8) The study encompassed those who were male or female newborns, aged 0–28 days diagnosed with neonatal seizures. Excluded were those already on anti-seizure medication, or with congenital heart or kidney disease. We include 130 patients in each group after excluding 32 patients on the basis of exclusion criteria.

After ethical approval from the hospital board (IREB NO. 36/GJMS/4806), eligible newborns were enrolled. Study aims and benefits were explained to guardians, and written informed consent was obtained. Demographic details including age, gender, maternal education and occupation, socioeconomic status, and residence were recorded. Participants were randomly assigned to two groups Levetiracetam (Group A) and Phenytoin or Phenobarbitals (Group B), using a table of random numbers, with allocation concealed through sequentially numbered sealed opaque envelopes. Group A received Levetiracetam, while Group B was treated with either Phenytoin or Phenobarbitone. No crossover between groups occurred. For neonates in Group A, intravenous Levetiracetam was administered at 1 mg/kg/min, followed by 20 mg/kg diluted in saline (20 mg/mL). Upon seizure control, maintenance therapy was continued at 20 mg/kg/day. Efficacy was determined by the absence focal motor movement (focal interictal epileptiform discharges, such as spikes, sharp waves observe on EEG), protruding tongue (extension or displacement of the tongue observe on visual inspection), and eye deviation (abnormal positioning or movement of the eyes observe on visual inspection) were deciding variables in terms of efficacy. If seizures persisted, additional doses were given per group allocation. Failure to achieve seizure control within 40 minutes was classified as treatment failure. Initially, neonates (allocated in Group B) presenting with seizures were administered Phenobarbitone as the first-line antiepileptic drug. A loading dose of 20 mg/kg (tablet strength 30 mg or IV vial 60 mg/mL) was given, followed by a maintenance dose of 3 mg/kg/day in two divided doses, either orally or intravenously. In cases of persistent seizures, the maintenance dose was escalated to a maximum of 5 mg/kg/day. If seizures remained uncontrolled, combination therapy with Phenytoin was initiated (oral strength 30 mg/5 mL or IV form), starting with a loading dose of 20 mg/kg and maintenance dosing at 5 mg/kg/day in two divided doses, later increased to a maximum of 8 mg/kg/day when necessary. All evaluations were supervised by a consultant with at least five years of post-fellowship experience, and data were recorded using a structured proforma. All patients were monitored in the ICU for five days post-treatment and followed for 14 weeks. Any seizure recurrence after discharge was considered treatment failure and managed accordingly.

Data Analysis: Data were analyzed using IBM SPSS 23.0. Categorical variables (e.g., gender, efficacy, maternal factors) were summarized as frequencies and percentages. Numerical data (e.g., age, weight) were presented as mean ± SD or median (IQR). Normality was tested using the Shapiro-Wilk test. Demographic and other baselines feature of the both groups were compared by Stratification using Fisher's exact test or Chi-square for categorical variables and the Wilcoxon rank test for continuous variables. Results were presented in tables and figures.

Results

A total of 260 patients were included in the study after excluding 32 patients and equally divided into two groups: Levetiracetam (Group A) and phenobarbital or phenytoin (Group B). Table 1 shows that age distributed 38.4% of neonates in the group A were older than 28 days, compared to 19.2% in the group B. Most neonates were aged between 15-28 days in both groups. Males comprised 36.9% in Group A and 40.7% in Group B. The majority of neonates in both groups had birth weights between 1-2.49 kg (51.5% in Group A, 42.3% in Group B).

Figure 1. Shows the most common seizure type was tonic-clonic seizures (35%), followed by multifocal (29%), subtle (25%), tonic (7%), and clonic seizures (4%). These findings highlight the predominance of tonic-clonic and multifocal seizure presentations in the neonatal population studied.

Table 2 shows that term deliveries were slightly more common in group A (53.1%) than in the group B (42.3%), while preterm births were more frequent in the Phenobarbitone group (57.6%). No significant differences were noted in maternal gravidity or antenatal comorbidities, including gestational diabetes, hypertension, or thyroid disorders.

However, a significant association with birth asphyxia was observed in the Phenobarbitone group (27.7%) compared to Levetiracetam (18.5%).

Table 3 shows evaluation of the characteristics of seizure; that most seizures appeared between days 2-4 after birth. About half the neonates had two to three episodes, usually lasting under five minutes. EEG abnormalities were seen in roughly half of both groups, with no significant difference between them.

Table 4 and Figure 2 shows Levetiracetam demonstrated a higher early seizure cessation rate (64.7%) compared to Phenobarbitone (52.3%), which was statistically significant. Although seizure freedom at 24 and 48 hours was slightly higher in the Levetiracetam group, the difference was not significance. Adverse effects such as sedation and respiratory depression were frequent with Phenobarbitone (17.7%) than with Levetiracetam (8.5%). There was a significantly lower mean time taken by group A to control seizure. Thus, group A had shown fast and most effective seizure control and less frequent adverse effect compared to group B.

Table 5 and figure 3 shows that adverse effects were more frequently observed in the Group B, including hypotension, respiratory suppression and sedation or poor feeding compared with group A (4.6%, 3.8%, and 3%, respectively). These differences were statistically significant for sedation/poor feeding. Mortality was similar between both groups and not significant.

Figure 4 summaries that the majority of neonates had abnormal imaging findings which suggested Hypoxic-ischemic encephalopathy HIE, followed by metabolic and vascular causes, while a smaller proportion had normal scans or imaging not performed. Etiologically, HIE and sepsis were the predominant causes of neonatal seizures in both groups, with no statistically significant difference between them.

In summarizing the results, Levetiracetam provided faster and more effective seizure control with fewer adverse effects compared to Phenobarbitone. Both groups had similar demographics, seizure characteristics, and EEG findings. HIE and sepsis were the most common causes of neonatal seizures, with no significant difference between groups. Mortality was comparable, highlighting Levetiracetam's faster and safer profile.

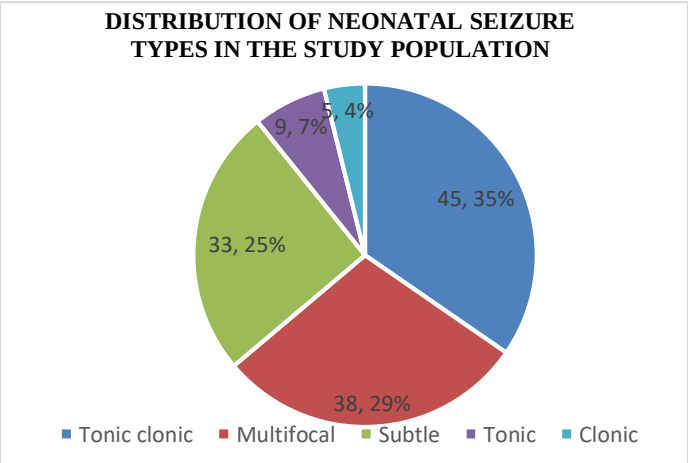

Figure 1: Distribution of Neonatal Seizure.

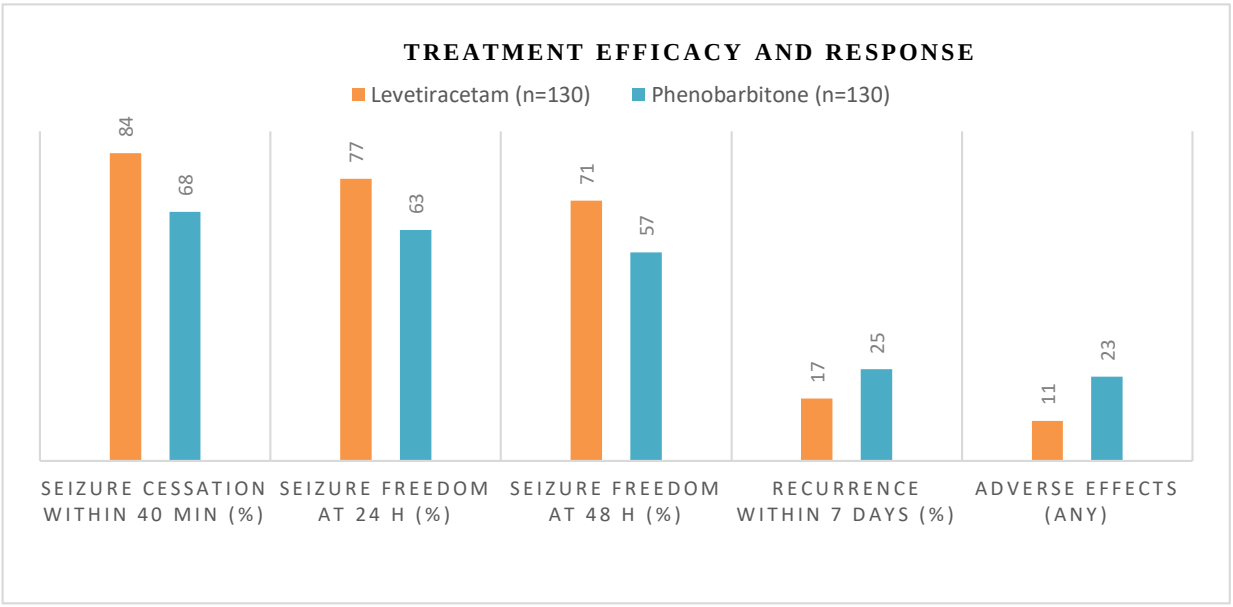

Figure 2: Efficacy and Response of Treatment

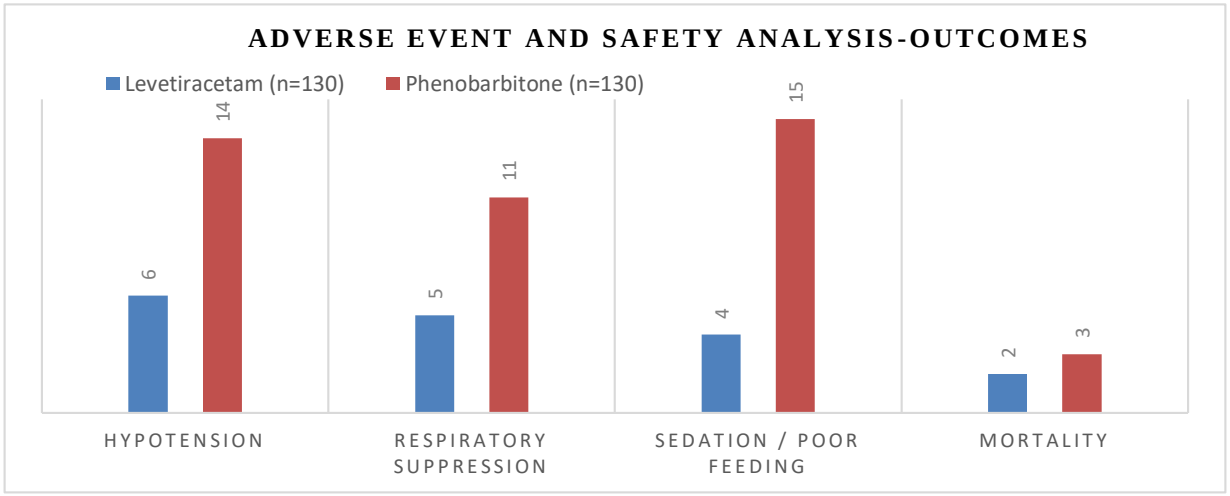

Figure 3: Adverse event and Safety Analysis-Outcomes

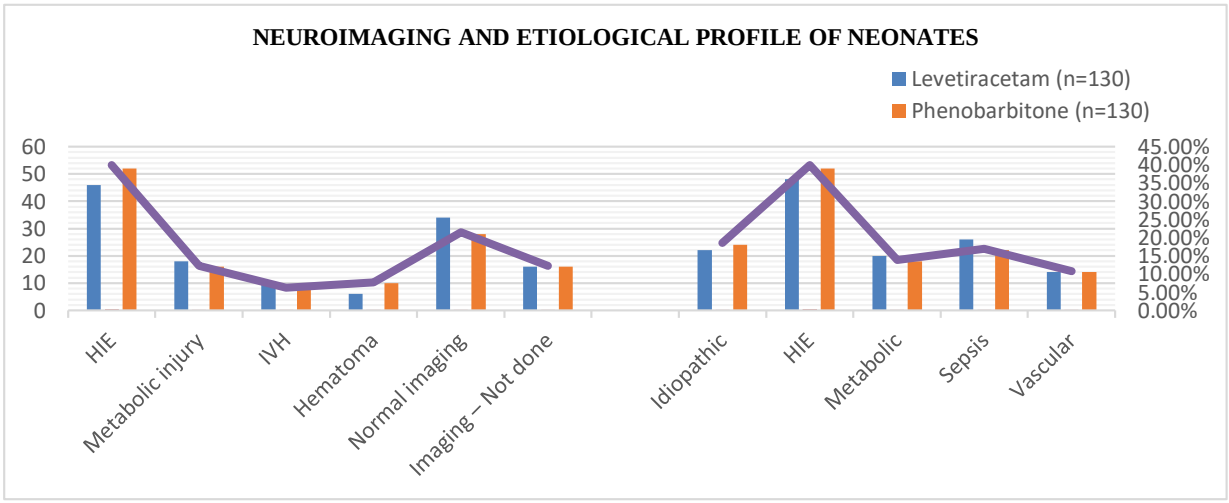

Figure 4: Neuro-imaging and Etiological features

Table 1: Demographic Characteristics of Neonates.

Characteristics	Group A (n=130)	%	Group B (130=)	%
Age (days)				
<7	19	14.6%	24	18.4%
8-14	28	21.5%	43	33.01%
15-28	33	25.3%	38	29.2%
>28	50	38.4%	25	19.2%
Gender				
Male	48	36.9%	53	40.7%
Female	82	63.1%	77	59.2%
Birth weight (in kg)				
<1	24	18.4%	29	22.3%
1–2.49				
	67	51.5%	55	42.3
>2.5	39	30%	46	35.4%

Table 2: Antenatal Risk factors (maternal) evaluation

Characteristics	Group A (n=130)	%	Group B (n=130)	%	p-value
Gestational maturity					
Term	69	53.07%	55	42.3%	0.333
Preterm	61	46.9%	75	57.6%	
Maternal gravid status					
Primigravida	68	52.3%	74	56.9%	
Multigravida	62	47.7%	56	43.1%	
Antenatal risk factors					
No risk factors	72	55.4%	64	49.2%	0.411
Gestational diabetes	16	12.3%	20	15.4%	0.493
Gestational hypertension	14	10.8%	18	13.8%	0.543
PROM	10	7.7%	14	10.8%	0.387
Thyroid disorders	8	6.2%	7	5.4%	0.785
Seizure disorders	10	7.7%	7	5.4%	0.462
Mode of delivery					
Normal delivery	74	56.9%	66	50.8%	0.482
Assisted vaginal delivery	12	9.2%	10	7.7%	0.654
Caesarean section	44	33.9%	54	41.5%	0.268
Association with asphyxia					
Yes	24	18.5%	36	27.7%	0.001
No	106	81.5%	94	72.3%	

Table 3: Evaluation and Characteristics of Seizures

	Levetiracetam (n=130)	Phenobarbitone (n=130)	p-value
Timing of onset of seizures			
Postnatal day 1	38 (29%)	42 (32%)	0.61
Postnatal day 2–4	47 (36%)	51 (39%)	0.74
Postnatal day 5–7	23 (18%)	20 (15%)	0.51
Postnatal day > 7	22 (17%)	17 (13%)	0.40
Number of episodes prior to AED			
1 episode	21 (16%)	19 (15%)	-
2 – 3 episodes	58 (45%)	61 (47%)	-
≥ 4 episodes	51 (39%)	50 (38%)	0.90
Average duration of episode			
< 3 min	33 (25%)	25 (19%)	0.27
3–5 min	42 (32%)	45 (35%)	0.70
5–10 min	35 (27%)	38 (29%)	0.80
> 10 min	20 (15%)	22 (17%)	0.69
EEG association			
Abnormal	62 (48%)	70 (54%)	0.35
Normal	53 (41%)	48 (37%)	0.59
Not done	15 (11%)	12 (9%)	0.52

Table 4: Comparative Outcome of treatment and efficacy in Group A and B.

	Levetiracetam (n=130)	Phenobarbitone (n=130)	p-value
Seizure cessation within 40 min (%)	84 (64.7%)	68 (52.3%)	0.04*
Seizure freedom at 24 h (%)	77 (59%)	63 (48%)	0.08

Seizure freedom at 48 h (%)	71 (55%)	57 (44%)	0.09
Recurrence within 7 days (%)	17 (13%)	25 (19%)	0.21
Mean time to seizure control (min ± SD)	28 ± 12	33 ± 15	0.05*
Adverse effects (any)	11 (8%)	23 (18%)	0.02*

Table 5: Table 5: Adverse Event and safety analysis-outcomes

	Levetiracetam (n=130)	Phenobarbitone (n=130)	Relative Risk (95% CI)	p-value
Hypotension	6 (4.6%)	14 (10.7%)	0.43 (0.17–1.05)	0.06
Respiratory suppression	5 (3.8%)	11 (8.4%)	0.45 (0.16–1.18)	0.09
Sedation / poor feeding	4 (3%)	15 (11.5%)	0.26 (0.09–0.76)	0.01*
Mortality	2 (1.5%)	3 (2.3%)	0.67 (0.11–4.03)	0.70

Discussion

Neonatal seizures can cause permanent neurological damage and therefore essentially require prompt diagnosis and appropriate treatment. (8,10) Certain medications, including phenobarbital, phenytoin, and levetiracetam, have been used to control seizures and prevent long-term adverse effects. (5,11) During emergency treatment, literature shows that EEG monitoring enables accurate detection of subclinical seizures and guides treatment decisions, which may significantly enhance the efficacy of antiepileptic therapy. (3,6,12,13) Previous studies exploring this relationship often lacked simultaneous EEG monitoring for confirmation and did not consistently document detailed electroclinical correlations for each seizure episode. This has also been documented by Nunes et al. (3) Pisani et al. reported that EEG is the gold standard for detecting subclinical seizures and evaluating treatment response. (6)

In this study, the efficacy of antiepileptic therapy was evaluated by the mean time taken to control seizures, need for second-line therapy, early resumption of breastfeeding, seizure freedom, and recurrence of seizures during follow-up. Seizures ceased within 40 minutes more frequently in group A than in group B, showing similar results to those reported by Ragunathan et al., Toptan et al., and Sharpe et al. (8,14,7) Similar to our findings, Akeel et al. and Ragunathan et al. reported that sedation and poor feeding were more frequent in the phenobarbital group than in the levetiracetam group, likely due to the sedative effects of phenobarbital, whereas levetiracetam demonstrated a more favorable safety profile in neonates. (8,15) Mruk et al. and Liu et al. similarly reported fewer adverse effects or no significant recurrence during follow-up with levetiracetam, supporting our finding that levetiracetam may provide faster, more effective, and safer seizure management in neonates. (16,17)

In general practice, phenobarbital remains the first-line antiepileptic drug, although evidence has raised concerns regarding its possible adverse effects on neurodevelopmental outcomes and neuronal apoptosis. (7,15,18) Previous evidence has suggested poorer cognitive and motor outcomes with phenobarbital exposure, while levetiracetam has shown a comparatively favorable safety profile. A survey of pediatric neurologists in the USA showed that levetiracetam is often considered for neonatal seizures, particularly after phenobarbital or phenytoin failure, although the available evidence remains inconclusive. (18)

The antenatal features in our study were somewhat different from the existing literature, which may be due to limited information for patients delivered outside the hospital. Most neonates were born at term, while preterm births were slightly higher in the phenobarbital group, consistent with findings by Pisani et al., who reported that prematurity is associated with increased seizure risk. (19)

Maternal factors such as gravidity and antenatal comorbidities were similar between groups, consistent with findings by Nemati et al., who reported that these factors do not strongly influence neonatal seizure occurrence. (20) Birth asphyxia was more frequent in the phenobarbital group, in line with Abate et al., highlighting that perinatal hypoxia increases seizure burden and may delay treatment response. (21)

Among fetal and neonatal risk factors in our study, hypoxic-ischemic encephalopathy was the most frequent etiology, followed by metabolic causes and intraventricular hemorrhage. These findings are consistent with earlier studies by Ramantani et al., Kaminiów et al., and Yau et al., who reported hypoxic-ischemic encephalopathy as a leading cause of seizures in term neonates, while metabolic and vascular causes are more common in preterm infants. (1,2,12)

Thus, levetiracetam appears safer and more effective than phenobarbital for neonatal seizures in emergency settings, providing prompt seizure control with fewer side effects; however, larger studies are needed to confirm these results. The limitations of our study include its single-center design and the fact that most participants were delivered outside the institution, which may have led to underreporting of perinatal information. In addition, long-term outcomes and adverse effects of levetiracetam were not evaluated. The study also focused mainly on EEG findings without considering drug levels or other contributing factors; therefore, the results cannot be generalized to all infants.

Conclusion

In conclusion, Levetiracetam is a safer and more effective alternative to Phenobarbitone for neonatal seizures, offering quicker seizure control, fewer adverse effects, earlier feeding resumption, no significant recurrence of seizures and better tolerance.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-DISM-203-24)

Consent for publication
Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

FA (Postgraduate Resident)
Data Collection, Manuscript drafting, Study Design,
FB (Professor)
Review of Literature, Data analysis, and Critical input.
GA (Postgraduate Resident)
Literature review and critical input
MS (Postgraduate Resident)
Literature review
MAK (Postgraduate Resident)
Revision and literature review.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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