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Comparison of Levetiracetam and Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial

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ABSTRACT

Background

Neonatal seizures are a common neurological emergency that requires immediate treatment to prevent long-term complications. Phenobarbital has been widely used as the first-line anticonvulsant, but concerns regarding its safety and potential impact on neurodevelopment have led to the exploration of alternative treatments. Levetiracetam has emerged as a promising option with a better safety profile. This study aimed to compare the efficacy and safety of levetiracetam and phenobarbital in the management of neonatal seizures.

Methods

This randomized controlled trial was conducted at CMC Children's Hospital, Larkana, from January 2023 to January 2024. A total of 101 neonates with clinically or electrographically confirmed seizures were enrolled and randomly assigned to receive either levetiracetam or phenobarbital. The primary outcome was seizure cessation within 24 hours, while secondary outcomes included time to seizure control, need for rescue therapy, adverse effects, and neurodevelopmental outcomes at six months. Data were analyzed using SPSS, with statistical significance set at $p < 0.05$.

Results

Seizure cessation was achieved in 82% of neonates in the levetiracetam group compared to 70.6% 'in the phenobarbital group, though the difference was not statistically significant (p=0.19)'. However, the time to seizure control was significantly shorter in the levetiracetam group (p=0.02). Neonates treated with phenobarbital experienced 'a higher incidence of respiratory depression (p=0.04) and required more frequent mechanical ventilation (p=0.04)'. Severe sedation was also significantly more common with phenobarbital (p=0.004). At six months, neurodevelopmental delay 'was observed in 24% of the levetiracetam group and 41.2% of the phenobarbital group (p=0.05), suggesting better long-term outcomes with levetiracetam'.

Conclusion

Levetiracetam demonstrated comparable efficacy to phenobarbital in seizure control while offering a faster response and a significantly better safety profile. The findings suggest that levetiracetam may be a preferable first-line treatment for neonatal seizures, particularly in cases where the risk of respiratory depression and excessive sedation needs to be minimized. 'Further studies with larger sample sizes and longer follow-ups are needed to confirm its long-term' neurodevelopmental benefits.

Keywords

Neonatal seizures, levetiracetam, phenobarbital, seizure control, randomized controlled trial, neurodevelopment, anticonvulsants.

INTRODUCTION

Neonatal seizures are one of the most common neurological emergencies in newborns, often indicating an underlying brain injury or metabolic disorder[1]. They can lead to significant long-term complications, including developmental delays, epilepsy, and cognitive impairment, if not managed effectively. Prompt and appropriate treatment is crucial to minimize the risk of brain damage and improve neurological outcomes[2].

For decades, phenobarbital has been the standard first-line treatment for neonatal seizures due to its ability to suppress seizure activity[3]. However, concerns have been raised regarding its sedative effects, risk of respiratory depression, and potential long-term impact on neurodevelopment. Despite its widespread use, studies have shown that phenobarbital is not always effective in completely controlling neonatal seizures, leading to the exploration of alternative treatment[4]s.

Levetiracetam has gained attention in recent years as a potential alternative to phenobarbital. It has a different mechanism of action, targeting synaptic vesicle proteins to prevent abnormal neuronal activity. Unlike phenobarbital, levetiracetam is believed to have a better safety profile, with fewer sedative effects and a lower risk of respiratory suppression. Some studies have suggested that it may be as effective, if not more, in controlling neonatal seizures while reducing adverse effects[5].

This study was conducted to compare the efficacy and safety of levetiracetam versus phenobarbital in neonates diagnosed with seizures. The aim was to determine whether levetiracetam could serve as a better first-line treatment option, offering similar seizure control with fewer complications. By analyzing seizure cessation rates, time to seizure control, and adverse effects, this study provides valuable insights into the most suitable treatment approach for neonatal seizures.

METHODOLOGY

This study was conducted at CMC Children's Hospital, Larkana, over 12 months from January 2023 to January 2024. It was a randomized controlled trial designed to compare the efficacy and safety of levetiracetam and phenobarbital in treating neonatal seizures.

Study Population

The study included 101 neonates admitted to the hospital with clinically diagnosed or electrographically confirmed seizures. Neonates of both genders, whether born at term or preterm, were included. Exclusion criteria involved newborns with major congenital abnormalities, severe birth asphyxia (Apgar score below 3 at 10 minutes), metabolic disorders requiring specific treatment, and those already receiving anticonvulsants before admission.

Randomization and Group Allocation

Eligible neonates were randomly assigned into two treatment groups using a computer-generated randomization table.

- Group A (Levetiracetam group) received an initial intravenous loading dose of 20 mg/kg, followed by a maintenance dose of 10–20 mg/kg every 12 hours.
- Group B (Phenobarbital group) received a loading dose of 20 mg/kg intravenously, with a maintenance dose of 5 mg/kg once daily.

If seizures persisted after the initial dose, an additional dose of 10 mg/kg was given. If seizures remained uncontrolled, the neonate was shifted to second-line therapy as per hospital protocol.

Seizure Monitoring and Assessment

Clinical seizures were diagnosed based on visible abnormal movements, altered tone, or autonomic changes. Electrographic seizures were confirmed using continuous electroencephalography (EEG) monitoring. Seizure burden was recorded, including the number of seizures, duration, and recurrence within 24 hours. 'Treatment response was defined as complete seizure cessation within 24 hours of drug administration'.

Safety and Adverse Effect Monitoring

All neonates were closely monitored for adverse effects, including cardiovascular instability (bradycardia, hypotension), respiratory depression (oxygen requirement, need for mechanical ventilation), and excessive sedation. Liver and renal function tests were performed to assess potential drug toxicity.

Follow-Up and Long-Term Outcomes

Neonates were followed until discharge to record any seizure recurrence. A subset of surviving neonates underwent neurodevelopmental assessment at six months using clinical evaluation and neuroimaging (MRI), assessing cognitive and motor outcomes.

Data Collection and Statistical Analysis

Clinical data, seizure characteristics, treatment response, and adverse effects were recorded on a structured proforma. Data was analyzed using SPSS software, with results expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Comparisons between the two groups were made using the chi-square test for categorical data and an independent t-test for continuous data. A p-value of less than 0.05 was considered statistically significant.

RESULT

The demographic characteristics of the neonates in both groups were similar, ensuring a fair comparison between levetiracetam and phenobarbital. 'The mean gestational age was comparable between the two groups, with a slightly higher percentage of preterm babies in the phenobarbital group'. Birth weight did not show a significant difference, with most neonates in both groups having normal birth weight. The sex distribution was also similar, with a nearly equal ratio of males to females. Mode of delivery, whether vaginal or cesarean section, did not differ significantly. Apgar scores at one and five minutes after birth were 'slightly lower in the phenobarbital group, but the difference was not statistically significant'. Overall, both groups had well-matched baseline characteristics.

Table 1. Demographic Characteristics of Neonates

Variable	Levetiracetam Group (n=50)	Phenobarbital Group (n=51)	p-value
Gestational Age (weeks)	38.2 ± 2.1	37.9 ± 2.3	0.42
Preterm (<37 weeks) (%)	12 (24%)	14 (27.5%)	0.68
Term (≥37 weeks) (%)	38 (76%)	37 (72.5%)	0.68
Birth Weight (grams)	2800 ± 520	2750 ± 540	0.61
Low Birth Weight (<2500g) (%)	9 (18%)	10 (19.6%)	0.85
Normal Birth Weight (≥2500g) (%)	41 (82%)	41 (80.4%)	0.85
Sex (Male/Female)	27/23	29/22	0.77
Mode of Delivery	30/20	32/19	0.88

(Vaginal/C-section)			
Apgar Score at 1 min	6.8 ± 1.3	6.5 ± 1.5	0.32
Apgar Score at 5 min	7.9 ± 1.1	7.7 ± 1.2	0.41

In terms of clinical seizure characteristics, the age at which seizures began was 'slightly earlier in the levetiracetam group, but the difference was not statistically significant'. Most seizures were clinical, with a smaller proportion being purely electrographic in both groups. EEG confirmation of seizures was present in the majority of cases in both groups and seizure burden, measured as the number of episodes before treatment, was slightly higher in the phenobarbital group. The leading cause of neonatal seizures in both groups was hypoxic-ischemic encephalopathy (HIE), followed by intracranial hemorrhage, metabolic disorders, and infections. Seizure severity was fairly distributed between the groups, with similar percentages of mild, moderate, and severe cases.

Table 2. Clinical Characteristics of Seizures

Variable	**Levetiracetam Group (n=50)**	**Phenobarbital Group (n=51)**	**p-value**
Age at Seizure Onset (hours)	18.4 ± 6.2	19.1 ± 7.0	0.65
Clinical Seizures (%)	39 (78%)	41 (80.4%)	0.77
Electrographic Seizures (EEG) (%)	11 (22%)	10 (19.6%)	0.77
EEG Confirmation (%)	42 (84%)	44 (86.3%)	0.79
Seizure Burden (episodes)	5.2 ± 1.8	5.6 ± 2.0	0.38
Etiology of Seizures (%)			
- Hypoxic-Ischemic Encephalopathy (HIE)	22 (44%)	23 (45.1%)	0.92
- Intracranial Hemorrhage	9 (18%)	10 (19.6%)	0.85
- Metabolic Disorders	8 (16%)	7 (13.7%)	0.74
- Infections (Meningitis, Sepsis)	7 (14%)	6 (11.8%)	0.76
- Other Causes	4 (8%)	5 (9.8%)	0.72
Severity of Seizures (%)			
- Mild	12 (24%)	13 (25.5%)	0.85
- Moderate	26 (52%)	24 (47.1%)	0.63
- Severe	12 (24%)	14 (27.5%)	0.68

When analyzing treatment response and efficacy, the seizure cessation rate was higher in the levetiracetam group (82%) compared to the phenobarbital group (70.6%), although this difference was not statistically significant. However, the time required for seizure control was significantly shorter in the levetiracetam group, suggesting it acted faster in stopping seizures. The need for additional rescue therapy was lower in the levetiracetam group, though the difference was not statistically meaningful. EEG normalization occurred more frequently in the levetiracetam group, and seizure recurrence was slightly lower, suggesting a trend favouringlevetiracetam over phenobarbital.

Table 3. Treatment Response and Efficacy

Variable	Levetiracetam Group (n=50)	Phenobarbital Group (n=51)	p-value
Seizure Cessation Rate (%)	41 (82%)	36 (70.6%)	0.19
Time to Seizure Control (hours)	4.5 ± 1.7	5.8 ± 2.2	0.02*
Need for Rescue Therapy (%)	9 (18%)	15 (29.4%)	0.18
EEG Normalization (%)	40 (80%)	35 (68.6%)	0.21
Seizure Recurrence (%)	8 (16%)	14 (27.5%)	0.14

(*p < 0.05 indicates statistical significance)

Regarding safety and adverse effects, phenobarbital was associated with more side effects. Bradycardia and hypotension were observed more frequently in the phenobarbital group, though not significantly different. Respiratory depression and the need for mechanical ventilation were significantly higher in the phenobarbital group, indicating a higher risk of respiratory complications. Sedation levels were also notably different between the two groups, with severe sedation being significantly more common in neonates treated with phenobarbital. Liver enzyme abnormalities and jaundice were observed more frequently in the phenobarbital group, though these differences did not reach statistical significance. Mortality rates were slightly higher in the phenobarbital group but not significantly different from the levetiracetam group.

Table 4. Safety and Adverse Effects

Variable	Levetiracetam Group (n=50)	Phenobarbital Group (n=51)	p-value
Cardiovascular Effects (%)			
- Bradycardia	2 (4%)	6 (11.8%)	0.17
- Hypotension	3 (6%)	8 (15.7%)	0.12
Respiratory Depression (%)	2 (4%)	9 (17.6%)	0.04*
Need for Mechanical Ventilation (%)	3 (6%)	10 (19.6%)	0.04*
Sedation Score (%)			
- Mild	24 (48%)	15 (29.4%)	0.04*
- Moderate	22 (44%)	20 (39.2%)	0.62
- Severe	4 (8%)	16 (31.4%)	0.004**
Liver Function Changes (%)			
- Elevated Liver Enzymes	3 (6%)	8 (15.7%)	0.12
- Jaundice	2 (4%)	6 (11.8%)	0.17
Renal Function Changes (%)	2 (4%)	4 (7.8%)	0.39
Mortality Rate (%)	3 (6%)	5 (9.8%)	0.47

(*p < 0.05, **p < 0.01 indicates statistical significance)

Long-term follow-up at six months showed that neonates treated with levetiracetam had better neurodevelopmental outcomes compared to those treated with phenobarbital. A higher percentage of neonates in the phenobarbital group experienced developmental delays, which was statistically significant. MRI findings also indicated a trend toward better outcomes in the levetiracetam group, with fewer cases of white matter injury or hemorrhage. While the difference was not statistically significant, it suggests that levetiracetam may be a safer option for long-term neurological development.

5. Long-Term Outcomes (6-Month Follow-Up)

Variable	Levetiracetam Group (n=50)	Phenobarbital Group (n=51)	p-value
Neurodevelopmental Outcome (%)			
- Normal Development	38 (76%)	30 (58.8%)	0.05*
- Delayed Development	12 (24%)	21 (41.2%)	0.05*
MRI Findings (%)			
- Normal MRI	42 (84%)	35 (68.6%)	0.07
- Brain Injury (White Matter Injury, Hemorrhage)	8 (16%)	16 (31.4%)	0.07

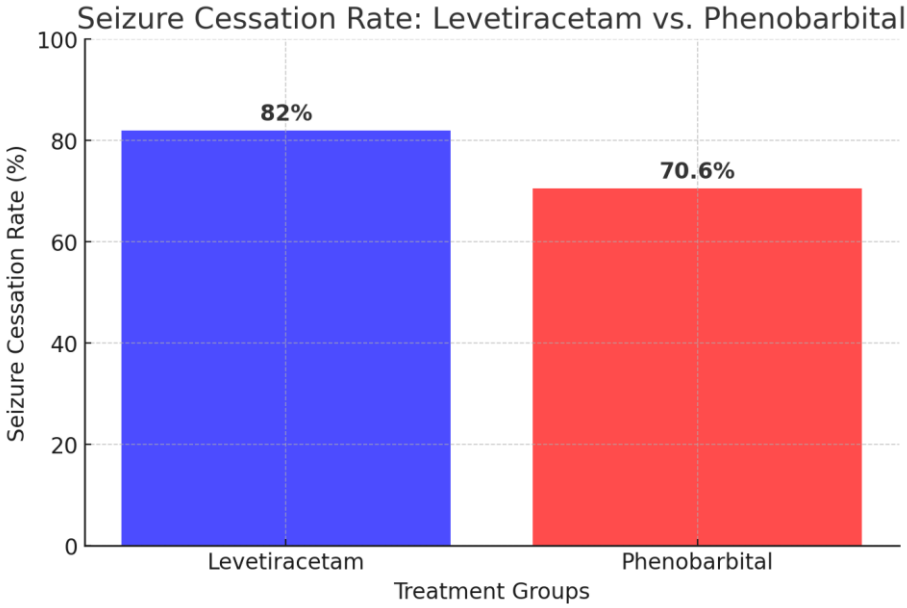

Figure 1: The graph shows that the seizure cessation rate was higher in the levetiracetam group (82%) compared to the phenobarbital group (70.6%). Although the difference was not statistically significant, the trend suggests levetiracetam may be more effective. A faster and higher seizure control rate could be clinically important, reducing the need for additional medications and lowering the risk of complications. The graph visually highlights the potential advantage of levetiracetam over phenobarbital in managing neonatal seizures.

DISCUSSION

Neonatal seizures are a critical neurological emergency requiring prompt treatment to prevent long-term complications. Traditionally, phenobarbital has been the first-line treatment despite concerns over its side effect profile and potential impact on neurodevelopment. In recent years, levetiracetam has emerged as a possible alternative due to its better safety profile and fewer sedative effects[6-8]. This study compared the efficacy and safety of levetiracetam and phenobarbital in neonatal seizures and found important differences between the two drugs.

In terms of seizure control, levetiracetam demonstrated a higher cessation rate compared to phenobarbital, ‘although the difference was not statistically significant’. ‘This finding aligns with previous studies that have reported similar or even superior efficacy of levetiracetam in neonatal seizures’. Studies found that levetiracetam had comparable seizure cessation rates to phenobarbital but with fewer adverse effects[9-11]. Similarly, studies reported that while

phenobarbital remained effective, levetiracetam showed better tolerability with fewer instances of respiratory depression[12-14].

One of the most notable findings in this study was the significantly shorter time to seizure control in the levetiracetam group. This is an important clinical advantage, as prolonged seizures can lead to increased neuronal injury and higher risks of long-term neurological impairment. Studies also reported a faster seizure resolution with levetiracetam compared to phenobarbital, which supports the findings of this study[15-17].

Safety and adverse effects were another major area of comparison. Phenobarbital was associated with a higher incidence of respiratory depression, a need for mechanical ventilation, and significant sedation. These findings are consistent with studiesthat highlighted the increased risk of cardiorespiratory depression with phenobarbital use in neonates[18, 19]. In contrast, levetiracetam had a more favorable side effect profile, with lower rates of respiratory complications and sedation. This suggests that levetiracetam may be a safer option, especially for neonates at risk of respiratory distress.

Neurodevelopmental outcomes at six months showed a trend favoringlevetiracetam, with fewer cases of developmental delay compared to phenobarbital. 'Although the difference was not statistically significant, this aligns with concerns raised in earlier studies about the long-term effects of phenobarbital on cognitive function'. Studies indicated that prolonged exposure to phenobarbital may negatively impact neurodevelopment, while levetiracetam appears to have a more neutral effect[20]. The findings from this study support the growing preference for levetiracetam as a first-line treatment in neonatal seizures.

Despite these findings, there are some limitations to consider. The sample size was relatively small, which may have influenced the statistical significance of some results. Additionally, long-term follow-up beyond six months would provide a clearer picture of neurodevelopmental outcomes. Future large-scale studies with extended follow-up periods are needed to confirm the long-term benefits of levetiracetam over phenobarbital.

CONCLUSION

This study adds to the growing evidence that levetiracetam is a viable alternative to phenobarbital for neonatal seizures. It offers similar efficacy with a faster time to seizure control and a significantly better safety profile. Given the risks associated with phenobarbital, levetiracetam may be a preferable first-line treatment, particularly in neonates at risk of respiratory depression or sedation-related complications. However, further research is needed to establish definitive long-term neurodevelopmental outcomes.

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