DOI: https://doi.org/10.47648/jswmc2025v15-02-123

Original Article

Efficacy and Safety of Using Levetiracetam and Phenobarbitone for the Treatment of Neonatal Seizure due to Hypoxic Ischemic Encephalopathy

* Uddin MS [1], Haque MR [2], Chowdhury FJ[3], Amin R[4], Rahman KMH[5]

Abstract:

Background: Timely diagnosis and management of a patient of neonatal seizure are challenging due to limited resources and adverse effects produced by the drugs used. Phenobarbitone is conventionally being using in pediatric department, while Levetiracetam is the newer one. This study compared the efficacy and safety between Phenobarbitone and Levetiracetam in treating neonatal seizure patients.

Methods: This open-labelled comparative study conducted in 100 cases of neonatal seizure in Sylhet Women's Medical College Hospital, Sylhet, Bangladesh. All the patients were full-term with normal birth-weight baby. They were grouped equally into Group-A (n = 50, Levetiracetam treated group) and Group-B (n = 50, Phenobarbitone treated group) by lottery method. Both Levetiracetam and Phenobarbitone were given intravenously at the dose of 20 mg/kg body-weight over 30 minutes initially. Based on the requirement, further administration was given with a maximum dose of 40 mg/kg body-weight.

Results: The response rate was 82% in Levetiracetam and 26% in Phenobarbitone treatment group. However, Levetiracetam treatment took significant shorter time to control the seizure event compared to the Phenobarbitone (11.44±11.17 minutes and 18.23±4.12 minutes respectively, p=<0.001). Adverse effects also observed significantly less in Levetiracetam treated group compared to the Phenobarbitone treated group (3/50 and 20/50 respectively, p=0.003) in this study.

Conclusion: Levetiracetam treatment found significantly more effective and relatively safe compared to the Phenobarbitone in the treatment of neonatal seizure.

Received date: 15 May 2025

Accepted date: 10 June 2025

Key words: Neonatal Seizures, Levetiracetam, Phenobarbitone, Efficacy, Safety.

How to cite this article: Uddin MS, Haque MR, Chowdhury FJ, Amin R, Rahman KMH. Efficacy and safety of using levetiracetam and phenobarbitone for the treatment of neonatal seizure due to hypoxic ischemic encephalopathy. Journal of Sylhet Women's Medical College. 2025 July; 15(02):37-41. https://doi.org/10.47648/jswmc2025v15-02-123

JSWMC 2025 [15(02)] P: 37-41

Introduction:

Seizures are the most frequently presenting complaints of any form of neurological disease in the neonatal life. Clinical patterns, electroencephalographic (EEG) features, causes and management approaches make neonatal seizures different from the adult patients.[1] It affects 1–3/1000 live births that may extents up to 10-130/1000 live births when babies are born prematurely.[2]

1. Dr. Md. Shahab Uddin, Associate Professor, Dept. of Paediatrics, Sylhet Women's Medical College
2. Prof. Dr. Md. Rashedul Haque, Professor and Head, Dept. of Paediatrics, Sylhet Women's Medical College
3. Dr. Farhana Jaya Chowdhury, Associate Professor, Dept. of Paediatrics, Sylhet Women's Medical College
4. Dr. Ruhul Amin, Assistant Professor, Dept. of Paediatrics, Sylhet Women's Medical College
5. Dr. K. M. Hafizur Rahman, Senior Lecturer, Dept. of Pharmacology & Therapeutics, Sylhet Women's Medical College

Corresponding author: Dr. Md. Shahab Uddin
Associate Professor, Dept. of Paediatrics Sylhet Women's Medical College
Email: drshahabuddin87@gmail.com

The commonest cause of neonatal seizures includes acute cerebral injury due to ischaemic encephalopathy, stroke and cerebral infection. However, transient alterations of brain metabolic or toxic product, congenital malformations and certain genetic disorders also leads to the development of neonatal seizures.[3]

Identification of neonatal seizures are challenging due to their subclinical manifestations, and untreated prolonged seizures events causing further brain injury[4], which may be associated with increased mortality or chronic morbidities (adult epilepsy, cerebral palsy, developmental delays, and cognitive impairment)[5].

Treatment of acute seizure attack and prevention of recurrence are the major goals in patient of neonatal seizure. Although, several drugs involving multiple mechanisms are available for adult patients, but the treatment options remain limited for the neonates. Barbiturates (Phenobarbital) and Na-channel blockers (Phenytoin and Fosphenytoin) are traditionally being used to treat neonatal seizures. However, their low efficacy (approximately 50%), short-term adverse effects, drug-drug interactions and requirement of frequent blood-level monitoring make difficulties of using these drugs. In contrast, Levetiracetam and Topiramate are relatively newer drugs to treat neonatal seizures with fewer adverse effects and ease of use.[6]

However, in some reports, it has shown promising efficacy in the acute phase of neonatal seizures.[7,8] Wide range of variation in success rate with or without reaching the level of significance demonstrated in earlier studies compared between Levetiracetam and Phenobarbitone in treating neonatal seizure.[9-11] Hence, this study aimed to compare both efficacy and safety of using Levetiracetam and Phenobarbitone in treating acute seizure events as primary drugs.

Methodology

This open labelled randomized clinical trial conducted on neonatal patients presented with seizures and got admitted into Sylhet Women's Medical College Hospital, Sylhet, Bangladesh, from January 2024 to December 2024. The patients who were full term (gestational age of more than 37 weeks), less than 24 hours age and with stage II Hypoxic-Ischemic Encephalopathy (HIE) enrolled in this study. HIE was diagnosed on the basis of Sarnat & Sarnat stages of hypoxic ischemic encephalopathy12. Neonate with lethargy, increased muscle tone and seizure was diagnosed as having stage II HIE. Preterm neonates, known hypersensitivity to drugs molecule, presence of selected biochemical abnormalities (such as hypoglycemia, hypocalcemia hypomagnesemia and metabolic disorders), and visible congenital anomaly were excluded from this study.

The enrolled cases were grouped into either Group-A (Levetiracetam treated group) or Group- B (Phenobarbitone treated group); simple lottery method was followed for the randomization. Group-A (n = 50) was treated with Injection Levetiracetam administered intravenously at the dose of 20mg/kg diluted in normal saline to achieve a concentration of 20 mg/mL and administered intravenously at a rate of 1 mg/kg/min under cardiorespiratory monitoring. If seizures terminated, Levetiracetam was continued as maintenance at 20 mg/kg/day in two divided doses. If seizures continued, another loading dose of Levetiracetam (20 mg/kg) was injected, and if seizures still persisted, patient was diagnosed as treatment failure and switched over to Phenobarbitone. Group-B (n = 30) was treated with Injection Phenobarbitone at a dose of 20mg/kg slow intravenous infusion over 30 minutes and waited or 10 minutes. If seizure persisted then the patient was reloaded with intravenous phenobarbitone 10mg/kg and waited for another 10 minutes. If seizure persisted then again was reloaded with intravenous Phenobarbitone 10mg/kg and waited for another 10 minutes. Total maximum of 40mg/kg Phenobarbitone was used. If seizure persisted neonate was recorded as a Phenobarbitone treatment failure case and crossed over to give intravenous Fosphenytoin at the dose of 20mg/kg slow intravenous infusion over 30 minutes for controlling seizure. Treatment failure was defined when the seizure became persistent even after administering for third times of the investigating drugs in this study.

Administration of drug was discontinued if any adverse effects of either of the drugs like respiratory depression, hypotension or bradycardia or hypersensitivity developed. Patients of both groups received other supportive care like O2 inhalation, maintenance of breathing and circulation, nutrition and fluids as per protocol of the unit. Each patient was under regular follow up. Once the baby was seizure free for 48 hours, anticonvulsant was stopped and patients was discharged after control of convulsions and establishment of oral feeding through sucking.

This study was performed under the principles of the Declaration of Helsinki and further ethical approval was taken from the institutional Ethics Committee of Sylhet Women's Medical College. Furthermore, signed informed written consent form obtained from the parents of each patient.

Statistical Analysis Data analysis was done using SPSS statistical software (version 23.0 for Windows; IBM SPSS Statistics, Armonk, NY, USA). The qualitative data were expressed as mean and standard deviation (mean ± SD) and compared using independent sample t-test. The quantitative data were expressed in frequency and percentage and compared using Chi-Square. The P-values under 0.05 were considered statistically significant.

Results:

There were 100 paediatric patients with neonatal seizure enrolled in this study and treated in wither group with Phenobarbitone or Levetiracetam. The comparative groups were statistically similar in terms of the patients mean age (p=0.329), gender distribution (p=0.838), mean gestational age (p=0.666), history of late cry after birth (p=1.000), history of moro-reflex status after birth (p=0.495), muscle tone on admission (p=1.000), pupil status on admission (p=0.232), consciousness on admission (p=1.000), body weight on admission (p=0.707), heart rate on admission (0.297), respiratory rate on admission (0.543), RBS on admission (p=0.496) and serum calcium level (p=0.089). Although there was a significant difference found in body temperature on admission (p=0.037), none of the patients had fever on admission (Table-1).

Table-1: Comparison of baseline characteristics of patients

Parameters	Group-A	Group-B	p-value
Age (mean±SD)	4.62±3.08	5.20±2.83	0.329
Gender (n, %) Male Female	 30 (60%) 20 (40%)	 31 (62%) 19 (38%)	0.838
Gestational age (mean±SD)	38.12±0.48	38.08±0.44	0.666
History of late cry after birth	50 (100%)	50 (100%)	
Moro reflex status after birth Strong Weak Absent	 1 (2.0%) 40 (98.0%) 0	 0 48 (96.0%) 2 (4.0%)	0.495
Muscle tone on admission Normal Hypotonic	 1 (0.2%) 49 (98.0%)	 0 50 (100.0%)	1.000
Pupil status on admission Mydriasis Miosis Unequal	 3 (6.3%) 44 (91.6%) 1 (2.1%)	 1 (2.0%) 49 (98.0%) 0	0.232
Level of consciousness on admission Hyper-alert Lethargic	 1 (0.2%) 49 (98.0%)	 0 50 (100.0%)	1.000
Body weight on admission	2.85±0.42	2.89±0.48	0.707
Heart rate on admission	130.86±15.45	134.32±17.47	0.297
Respiratory rate on admission	43.88±14.70	42.40±8.81	0.543
Body temperature on admission	98.28±0.53	98.06±0.51	0.037
RBS on admission	4.72±1.92	4.98±1.91	0.496
Serum Calcium level	8.19±0.81	8.41±0.38	0.089

The mean time to take complete seizure control in Levetiracetam treated group (11.44±4.37 minutes) observed significantly lowered (p=<0.001) compared to the Phenobarbitone treated group (18.23±4.12 minutes) (Figure-1). Similarly, time taken to oral feeding after the treatment also observed significantly (p=<0.001) lower in Levetiracetam treated groups (41.76±10.35 minutes) compared to the Phenobarbitone treated groups (71.52±3.39 minutes) in this study (Figure-2).

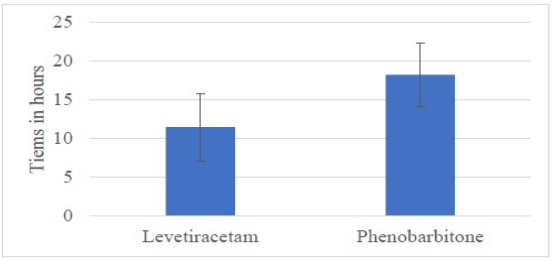

Figure-1: Comparative time taking to seizure control between the study groups

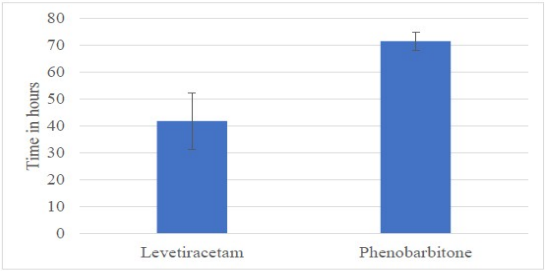

Figure-2: Comparative time taking to oral feeding between the study groups

Distribution of follow-up interval for seizure control also showed significant difference (p=<0.001) between Levetiracetam and Phenobarbitone treated groups (Table-2). There were 82% of Levetiracetam treated patient got seizure control by 16th hours, while 26.0% of Phenobarbitone treated patients became seizure free within 16th hours of drug treatment.

Table-2: Distribution of follow-up interval for seizure control after initiation of drug treatment

Follow-up interval	Group-A	Group-B
On 8th hour	23 (46.0%)	3 (6.0%)
On 16th hour	18 (36.0%)	10 (20.0%)
On 24th hour	6 (12.0%)	30 (60.0%)
On 36th hour	3 (6.0%)	7 (14.0%)

Among the Levetiracetam treated group, 7 (14.0%) patients developed adverse effects; 4 (8.0%) patients developed drowsiness and 3 (6.0%) developed lethargy. In contrast, 20 (40.0%) patients of Phenobarbitone treated group developed adverse effects; 8 (16.0%) patients developed bradycardia, 4 (8.0%) patients developed drowsiness and 8 (16.0%) patients developed lethargy. The difference between the occurrence of adverse effects between the study groups found statistically significant (p=0.003).

Discussion:

Neonatal seizures sometimes become a life-threatening condition of the paediatric patients. Prolong seizure events may progress to adult epilepsy, cerebral palsy cognitive decline etc.[13] Phenobarbitone conventionally being used to treat acute seizure event and also prevent further seizure events. In contrast, Levetiracetam is relatively newer agents with comparatively fewer side effects showed promising result in treating acute seizure events in neonate. This study compared efficacy and safety of using Phenobarbitone and Levetiracetam in the treatment of neonatal seizure.

The effectiveness and safety of using Levetiracetam found to be significantly better compared to the Phenobarbitone in this study. The treatment period for the Levetiracetam significantly lower than the Phenobarbitone treated group. Similarly, significantly early initiation of oral feeding observed in the Levetiracetam treated patient group in this study. However, most of the patient's seizure become controlled by the 24th hours in both Levetiracetam treatment (94%) and Phenobarbitone treated (86%) groups in this study.

Overall success rate was found to be 82% in Levetiracetam and 26% in Phenobarbitone treated patients in this study. However, earlier studies showed wide-variation in success rate. Gowda et al., reported 60% success rate in Levetiracetam and 50% in Phenobarbitone treated patients within first dose of drug administration. Opposite result reported by Sharpe et al., where 80% of Phenobarbital treated patients remained seizure free for 24 hours and 28% of Levetiracetam treated patients become seizure free in their study (p = <0.001).[10] Prakash et al. reported similar efficacy between Levetiracetam and Phenobarbitone in cessation of clinical seizure (66.6% and 81.5% respectively, p=>0.05). They further analyzed cross-over study those patient's seizure failed to control after first dose of investigated drug and observed statistically similar efficacy between them (95.2% and 97.3% respectively, p=>0.05).[11]

However, Tabassum et al.[14] and Mohammadi et al.[15] compared efficacy and safety between Levetiracetam and Phenytoin in treating neonatal seizure in their study. Tabassum et al. also reported that significantly (p=0.011) more patients got seizure control within first 24 hours in Levetiracetam treated group, while more patients of Phenytoin treated patients required more than 48 hours of treatment.[14] In contrast, Mohammadi et al. reported similar efficacy between the Levetiracetam and Phenytoin in their study (86.7% and 83.3% success rate respectively, p=1.00).[15]

In this study, occurrence of adverse effects observed significantly more in Phenobarbitone treated patient compared to the Levetiracetam treated patients (p=0.003). Prakash et al. also observed significantly (p=<0.05) higher rate of short-term adverse effects (cardiorespiratory depression and sedation) Phenobarbitone treated patients (20 of 38 patients) compared to the Levetiracetam treated patients (3 of 42 patients).[11] Gowda et al. reported a total of 10 adverse events in the Phenobarbitone group (hypotension, bradycardia and essentials of mechanical ventilation), but none in the Levetiracetam treated group.[10] However, Sharpe et al. and Mohammadi et al. did not find significant difference in occurrence of adverse effects in their study groups.[9,15] Sharpe et al. observed good number of patients developed adverse effects in both study groups (12 in Levetiracetam group and 13 in Phenobarbitone

group, p = 0.017), even death also in both study groups (two and one respectively), they were not found to be statistical significant. Death occurred in patients those were enrolled with severe hypo-ischemic encephalopathy.[9] Mohammadi et al. reported only the occurrence of adverse effect (3.3% in Levetiracetam and 6.7% in Phenytoin treated group, p = 1.00), they did neither elaborate the types of adverse effects nor describe the cause.[15] There are few studies compared the efficacy and safety between Levetiracetam and Phenobarbitone in neonatal seizure patients. This study showed significant difference both in efficacy and safety profile. However, this study has some limitations. First of all, it was a open-labeled clinical trial that may produce biasness in outcome measure. Other limitations include inability to monitor serum drug level and cerebral function, smaller sample size and unavailability of bedside EEG monitoring.

Conclusion

The study result demonstrated that the use of Levetiracetam is more effective and safer compared to the Phenobarbitone in managing acute seizure attack in neonates. However, studies with larger multi-center samplings and blindness in treatment are recommended to achieve definite and unbiased results. Further prospective study including prevention of further seizure attack is also hereby recommended.

Acknowledgement

The authors are thankful to all the guardians to allow to take part their children in this study.

Conflict of interest

The authors declared no conflict of interest.

References:

1. Abend NS, Wusthoff CJ, Jensen FE, Inder TE, Volpe JJ. Neonatal seizures. Volpe's Neurology of the Newborn 2025; 1:381-448.
2. Kaminiów K, Kozak S, Paprocka J. Neonatal seizures revisited. Children 2021; 8(2):155.
3. Tinggaard J, Pedersen SV, Larsen ML, Jensen AK, Greisen G, Hansen BM, et al. The risk of epilepsy after neonatal seizures. Developmental Medicine & Child Neurology 2025; Feb 19.
4. Pavel AM, Rennie JM, de Vries LS, Blennow M, Foran A, Shah DK, et al. Neonatal seizure management: is the timing of treatment critical? The Journal of pediatrics 2022; 243:61-68.
5. McHugh DC, Lancaster S, Manganas LN. A systematic review of the efficacy of levetiracetam in neonatal seizures. Neuropediatrics 2018; 49(01):12-17.
6. Slaughter LA, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: a systematic review. Journal of child neurology 2013; 28(3):351-364.
7. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: safety and efficacy in neonatal seizures. European Journal of Paediatric Neurology 2011; 15(1):1-7.
8. Han JY, Moon CJ, Youn YA, Sung IK, Lee IG. Efficacy of levetiracetam for neonatal seizures in preterm infants. BMC pediatrics 2018; 18:1-6.
9. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. Pediatrics 2020;145(6).
10. Gowda VK, Romana A, Shivanna NH, Benakappa N, Benakappa A. Levetiracetam versus phenobarbitone in neonatal seizures—A randomized controlled trial. Indian Pediatrics 2019; 56:643-646.
11. Prakash A, Richa R, Sahni GS. Neonatal seizures–Levetiracetam versus phenobarbital. Indian Journal of Child Health 2019; 6(11):605-608.
12. Sarnat HB, Sarnat MS. Neonatal Encephalopathy Following Fetal Distress: A Clinical and Electroencephalographic Study. Archives of Neurology 1976; 33(10):696–705.
13. Kim EH, Shin J, Lee BK. Neonatal seizures: diagnostic updates based on new definition and classification. Clinical and Experimental Pediatrics 2022; 65(8):387.
14. Tabassum A, Rafique A, Qadir W, Shahzad MS, Zaman MF, Sohail A. Comparison of Effect of Phenytoin and Levetiracetam in Neonatal Seizures. Journal of Fatima Jinnah Medical University 2024; 18(02):69-72.
15. Mohammadi M, Kadivar M, Sangsari R, Mirnia K, Saeedi M, Adhami P. Comparing the efficacy and safety of levetiracetam versus phenytoin for treating the acute phase of neonatal seizures. Iranian Journal of Child Neurology 2023; 17(1):65.