Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Paediatrics & Neonatology

Levetiracetam Versus Phenobarbitone in the Treatment of Seizure in Preterm Neonate

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DOI: https://doi.org/10.36347/sjams.2026.v14i07.009 | **Received:** 03.06.2026 | **Accepted:** 18.07.2026 | **Published:** 25.07.2026

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Abstract **Original Research Article**

Background: Neonatal seizures are the most common neurological emergency, with higher risk in preterm than term neonates, mostly due to hypoxic-ischemic encephalopathy. Levetiracetam may be a safe alternative for treating seizures in preterm neonates. This study aimed to compare the effectiveness and adverse effects of Levetiracetam versus Phenobarbitone in preterm neonates with seizures due to perinatal asphyxia. ***Methods:*** This randomized controlled trial was conducted at Bangladesh Shishu Hospital and Institute from June 2020 to July 2022 among preterm neonates (31st to <37 weeks gestational age) with seizures due to perinatal asphyxia. Of 100 enrolled neonates, 72 were randomized into two groups of 36 each. The study group received intravenous Levetiracetam 20 mg/kg loading followed by 10 mg/kg 12-hourly maintenance, while the control group received Phenobarbitone 20-40 mg/kg loading and 2.5 mg/kg/dose 12-hourly maintenance as first-line therapy. Primary outcomes included time to seizure control, adverse effects within 2 hours, length of hospital stay, and need for more than one anticonvulsant. ***Results:*** The two groups did not differ statistically for age, sex, weight. Male neonates were affected more than female (61.1 % male in group A and 63.9 % male in group B). Seizure control is significantly higher in Levetiracetam in comparison to Phenobarbitone group (72.22% vs 44.44%). Need for more than one drug was significantly lower in Levetiracetan group (p = 0.004). Length of hospital stay was shorter and adverse effects were found significantly (p = 0.024) lower in Levetiracetam group (5.56 % vs 27.78 %). No serious adverse effect was observed in any group. ***Conclusion:*** In the present study, Levetiracetam is more effective and safer than Phenobarbitone in the treatment of seizure in preterm neonate due to perinatal asphyxia.

Keywords: Seizure, Perinatal Asphyxia, Levetiracetam, Phenobarbitone.

INTRODUCTION

During the neonatal period seizures are the most common manifestation of neurological insult [1]. In neonatal period seizures occur more frequently than any other time of life [2]. Neonatal seizures have an adverse effect on neurodevelopmental progression and predispose to cognitive, behavioral problem or epilepsy in later life [3]. There is greater risk of seizures in preterm than full-term infants [4].

The common etiologies of neonatal seizures are such as hypoxic ischemic encephalopathy (HIE), intraventricular hemorrhage (IVH), periventricular leukomalacia, structural brain injuries and malformations, venous infarction, metabolic disturbances (most often glucose and electrolyte abnormalities) and infection. A broad spectrum of etiologies and few treatment options make management of neonatal seizures difficult [5].

Hypoxic-ischemic encephalopathy (HIE) due to asphyxia is the most common cause of seizure in the neonatal population, approximately two-thirds of neonatal seizures [6]. In near-term newborns prevalence of HIE is 40 – 60% [7]. The onset of seizures in neonates with HIE is usually within 2 days of birth and neonatal seizures are associated with long-term seizure risk and poor neurological outcomes [8].

Seizures in the neonatal period can be classified into one of three categories, as clinical only, electrographic only and both. Neonatal seizures differ considerably from seizures observed in older children,

probably because the immature brain is less capable of propagating electrical discharges. The neonatal electroencephalography (EEG) is probably one of the best and most useful investigation of detecting neonatal seizures. Neonatal EEG recordings and interpretations require the special skills of trained physicians and technologists. Video EEG recordings revealed that upto 80% of electrographic seizures in neonates lack a clinical correlation [9].

Neonatal seizures, as any other type of seizure, are paroxysmal, repetitive and stereotypical events. They are usually clinically subtle, inconspicuous and difficult to recognize from the normal behaviors of the inter-ictal periods or physiological phenomena. There is no recognizable post-ictal state. Generalized tonic clonic seizures (GTCS) are exceptional [10]. There are four types of neonatal seizures, such as subtle, tonic, clonic and myoclonic.

Preterm newborns are more prone to develop severe complications and they are less responsive to treatment with conventional medications because of age-specific pharmacokinetic and pharmacodynamic features. In spite of these differences between preterm and full-term infants, there is no difference in treatment strategies in clinical practice [7].

Phenobarbitone (PB) remains as the first choice of treatment in neonatal seizures though PB is effective in less than 50% of cases [11,12]. Due to negative long-term neurodevelopmental outcomes and side effects of Phenobarbitone, other antiseizure medication such as Levetiracetam is prefered in neonatal seizure [5]. Neonatal seizures frequently fail to respond to the most common treatments, phenobarbital and phenytoin. Acute side effects of phenobarbital include hypotension, respiratory suppression and sedation. Chronic exposure to phenobarbital may cause decreased cognitive ability [13].

Levetiracetam (LEV) is a novel antiepileptic agent well-tolerated and effective in focal, generalized and neonatal seizure. Currently it is licensed as adjunctive therapy in the treatment of children and infants with epilepsy starting from 1 month of age in partial onset seizures and in children aged 4 years or above for other indications [2]. There are hardly any reports of severe, life-threatening side effects, with most frequently observed adverse effects include irritability, somnolence and behavioral problems [14].

Levetiracetam seems to be safer than Phenobarbitone in animal models. Phenobarbitone exposure with similar dosages used in humans induce neuronal apoptosis in the developing rat brain. No neurotoxic effect of Levetiracetam was found in the developing rat brain. A neuroprotective effect on hypoxic-ischemic brain injury in neonatal rats or rodent was confirmed by several studies [12]. So, the purpose of this study was to evaluate the clinical effectiveness and adverse effects of Levetiracetam and Phenobarbitone in the treatment of seizure in preterm neonate.

METHODOLOGY & MATERIALS

This open-label randomized controlled trial was conducted at Bangladesh Shishu Hospital and Institute from July 2020 to June 2022. Preterm neonates between 31st and less than 37 weeks of gestational age with convulsion due to perinatal asphyxia (stage II and III HIE) were included, while those with hypoglycemia, hypocalcemia, dyselectrolytemia, sepsis, major CNS malformations, or prior anticonvulsant use were excluded. After ethical approval and informed written consent from parents or guardians, neonates meeting criteria underwent randomization by lottery method using sealed envelopes. A sample size of 36 neonates was allocated to each group. The intervention group received intravenous Levetiracetam 20 mg/kg loading followed by 10 mg/kg/dose 12 hourly maintenance, while the control group received intravenous Phenobarbitone 20-40 mg/kg loading and 5 mg/kg/day in divided doses as maintenance. Seizure control was defined as complete cessation of convulsion without recurrence within 48 hours. If one drug failed, other anticonvulsants were added per institutional protocol. Primary outcome measures included time to seizure control, adverse effects within 2 hours of drug administration, duration of hospital stay, discharge with improvement, and need for more than one drug. Adverse effects such as desaturation, arrhythmias, somnolence, respiratory depression, and others were documented. Seizures were diagnosed clinically without continuous EEG monitoring. Data were collected using a structured questionnaire and analyzed using SPSS version 26.0. Categorical variables were compared using chi-square and Fisher's exact tests, while continuous variables were compared using unpaired t-test. A p-value less than 0.05 was considered statistically significant. Confidentiality of all patient information was maintained throughout the study.

RESULTS

Table I: Demographic characteristics of neonates (n=72)

Demographic characteristics	Group A (LEV) (n=36)	Group B (PHB) (n=36)	p-value
Gender			
Male	22 (61.1)	23 (63.9)	0.808[a]
Female	14 (38.9)	13 (36.1)	

Demographic characteristics	Group A (LEV) (n=36)	Group B (PHB) (n=36)	p-value
Gestational weeks	34.33±1.47	34.72±1.60	0.287[b]
Birth weight	2.09±0.33	2.16±0.31	0.360[b]
Mode of delivery			
Vaginal	32(88.9)	28(77.8)	0.209[c]
LUCS	4(11.1)	8(22.2)	
Antenatal checkup	16(44.4)	19(52.7)	0.479[a]
APGAR score			
at 1 min	5.33±1.84	5.50±1.54	0.678[b]
at 5 min	7.66 ± 1.29	8.66 ± 0.89	0.532
Age at admission			
<12 hrs	21(58.3)	18(50.0)	0.873[a]
12-24 hrs	6(16.7)	8(22.2)	
25-36 hrs	5(13.9)	5(13.9)	
37-48 hrs	3(8.3)	4(11.1)	
>48 hrs	1(2.8)	1(2.8)	
Age at onset of seizure			
<12 hrs	27(75.0)	23(63.9)	0.706[a]
12-24 hrs	6(16.7)	7(19.4)	
25-36 hrs	2(5.6)	4(11.1)	
37-48 hrs	1(2.8)	2(5.6)	

Data were expressed as frequency, percentage and mean±SD
a=p value reached from chi-square test
b=p value reached from unpaired t-test
c=p value reached from fisher exact test

Table I presents the demographic characteristics of the 72 studied neonates, comparing the Levetiracetam group (Group A, n=36) and the Phenobarbitone group (Group B, n=36). The two groups were statistically comparable with no significant differences in any baseline parameters. Male predominance was observed in both groups, comprising 61.1% (n=22) in Group A and 63.9% (n=23) in Group B (p=0.808). The mean gestational age was 34.33±1.47 weeks in Group A and 34.72±1.60 weeks in Group B (p=0.287), while mean birth weight was 2.09±0.33 kg and 2.16±0.31 kg respectively (p=0.360). Vaginal delivery was the predominant mode in both groups (88.9% vs 77.8%, p=0.209). The mean APGAR scores at 1 minute were 5.33±1.84 and 5.50±1.54 (p=0.678), and at 5 minutes were 7.66±1.29 and 8.66±0.89 (p=0.532) for Group A and B respectively. Most neonates presented with seizure onset within 12 hours of life (75.0% in Group A, 63.9% in Group B), and the majority were admitted to the hospital within the first 12 hours (58.3% vs 50.0%). Antenatal checkup history was documented in 44.4% of Group A and 52.7% of Group B neonates (p=0.479).

Table II: 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 ($\chi 2$) test
*= p-value significant

Table II shows, seizure control rate was significantly higher in group A compared to group B (p = .004). 27.78% and 55.6% neonates in group A and B respectively needed more than 1 drug to control seizure with significant difference (p value 0.004) between the groups. Seizure was significantly controlled within 12 hours in group A compared to group B.

Table III: Treatment outcome of neonates during hospital stay (n=72)

Treatment outcomes	Group A (LEV) (n=36) No. (%)	Group B (PHB) (n=36) No. (%)	p-value
Discharge	32(88.89)	29(80.56)	0.612
LAMA	3(8.33)	5(13.89)	
Expired	1(2.78)	2(5.56)	

p-value reached from chi square ($\chi 2$) test

Table III shows 88.89% neonates were discharged in group A (Levetiracetam) and 80.56% neonates in group B (Phenobarbitone).

Table IV: Duration of hospital stay of neonates (n=72)

No of days	Group A (LEV) (n=36) No. (%)	Group B (PHB) (n=36) No. (%)	p-value
<5 days	11(30.6)	9(25.0)	0.023*[a]
5-7 days	25(63.9)	15(41.7)	
8-10 days	2(5.6)	8(22.2)	
>10 days	0(0.0)	4(11.1)	
Total	36 (100.00)	36 (100.00)	
Mean±SD	5.31±2.34	7.69±5.31	0.016*[b]

a = p-value reached from chi square ($\chi 2$) test
b = p-value reached from unpaired t-test
*= p-value significant

Table IV shows shorter duration of hospital stay was significantly found in group A compared to group B (P = 0.016).

Table V: 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)	
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

Table V shows neonates in group B had significantly more adverse effects compared to group A (p value = 0.024).

DISCUSSION

The study was carried out in the Bangladesh shishu Hospital and institute, Dhaka, Bangladesh, from July 2020 to June 2022. This is the first randomized prospective clinical study of preterm neonate in Bangladesh that has compared between Levetiracetam and Phenobarbitone in neonatal convulsion due perinatal asphyxia.

Brain growth and development during the neonatal period are rapid with physiological maturation of synapses in neurons occurring during this time. Thus, protection and prevention of significant adverse effects upon the developing brain is critical in this period. Seizures remain a common problem in the neonatal period and prompt recognition and treatment may help prevent abnormal neurological outcome. Phenobarbital remains as the most frequently used antiepileptic drug for the treatment of neonatal seizures, although evidence exists that it causes neuronal apoptosis in animal models. Long-term adverse neurodevelopmental effects related to phenobarbital have also been demonstrated. Several other antiepileptic drugs are being researched and prescribed in children and neonates. Levetiracetam is increasingly being used as an antiepileptic drug in the neonatal period and is recognized as an antiepileptic drug with neuroprotective properties

In this study basic demographic data of newborn like age and sex were not significant and birth weight distribution was not significant.

Present study demonstrated that levetiracetam is better than phenobarbitone in controlling neonatal seizures due to perinatal asphyxia in preterm neonates.

Also, it takes shorter time than phenobarbitone in controlling clinical seizures. We did not find any major side effects related to any of the drugs used. Levetiracetam has been reported to be a promising new drug for neonatal seizures.

The efficacy of LEV has been earlier demonstrated in a study by Ramantani, *et al*., in which 30 (78%) out of 38 infants were seizure-free after receiving LEV [15]. In study by Khan, *et al.,*19 (86%) of the 22 neonates demonstrated seizure cessation within 1 hour of administration [16]. In a systematic review of the efficacy of LEV in neonatal seizures, complete or near complete seizure cessation was achieved in 37/48 (77%) who received LEV as first-line drug, and 24/52 (46%) of the ones with PB as first-line AED. These results show that LEV is as effective as PB in the control of neonatal seizures as a first-line agent.

In a study by Abend, *et al*., LEV was associated with seizure improvement within 24 hours in only 8 (35%) of 23 neonates [17]. The low response to LEV in this study could be due to the usage of LEV as first-line anti-epileptic drug in only one neonate in the study. Few other studies have documented good seizure control with LEV when it was used as a second- or third-line agent in control of neonatal seizures. The safety of LEV in neonates has also been documented in previous studies.

We used a loading dose of 20 mg /kg followed by maintenance dose of 10 mg/kg/day based on dose used in study by Gowda *et al.,* [1]. Though subsequent study on pharmecokinetics of levetiracetam were done using 40 mg/kg, Ramantani G *et al.,* have reported safety and efficacy of LEV with 60 mg/kg as well [15]. Higher dose may be required in neonates due to i) higher volume of distribution ii) greater than predicted clearance in first week of life iii) intractability of neonatal seizures in neonates and iv) safety demonstrated in childrens even with dose up to 275 mg/kg and up to 1800 mg/kg in animals (no death, organ failure or irreversible toxicities were noted). There is no clear dosing recommendations available in the literature where doses range from 10 to 100 mg/kg [15,18,19].

Sharpe CM et al demonstrated that 8 hourly dosing is required to ensure that 95% of infants maintain trough concentration >10 microgram/ml and above 20 microgram/ml for 1st 3 days when seizure frequency is maximum [20]. The 12 hourly dosing schedules used in our study was supported by a subsequent pharmacokinetic study, reported that 12 hourly interval is acceptable due to reduced renal clearance until the glomerular filtration matures over first few weeks [18].

Our study does not report any significant effect of levetiracetam on hemodynamic, cardiovascular or renal status. Levetiracetam is reported to cause only minor side effects like sedation, behavior abnormalities and depression in older children and somnolence in neonates. Occasional reports of reversible thrombocytopenia and possible liver failure and anaphylactic shock because of levetiracetam have also been reported. Though levetiracetam has predominantly renal excretion, like us, other studies has also not reported derangements in renal parameters with its use. Boylan GB et al had reported that only about 35% neonates with electrical seizures display clinical seizures [3]. In other two-third babies, clinical manifestations were unrecognized even by experienced neonatal staff. They therefore concluded that clinical diagnosis may not be enough in recognition and management of neonatal seizures.

The main strength of the study was that it is the first RCT on use of levetiracetam in preterm neonates, which demonstrates its efficacy and safety profile.

Kirmani *et al.,* in a retrospective study showed that thirty-two patients (age range, 2 months to 18 years) had received a levetiracetam load of 25-50mg/kg for status epilepticus [21]. There were 17 (53.1%) of males and 15 (46.8%) of females. Response to intravenous levetiracetam in all patients was favorable. Status epilepticus ceased clinically and electorgraphically. Eight-teen patients (56.5%) received intravenous levetiracetam after receiving fospenytoin and ativan with no response. No serious side effects were evident. Fifteen patients (46.8%) were discharged on levetircetam monotherapy and 9 (28.1%) received levetiracetam as adjunctive therapy after discharge from hospital.

Limitations of the study

The study has several limitations, including its single-centre design which may limit generalizability of the findings. Additionally, continuous EEG monitoring was not performed, potentially leading to underdetection of subclinical seizures. Furthermore, renal function tests were not conducted, which is relevant as Levetiracetam is primarily excreted renally and may require dose adjustment in neonates with impaired renal function.

CONCLUSION

This study showed that Levetiracetam is more effective and safer than Phenobarbitone for the treatment of seizure in preterm neonate due to perinatal asphyxia and reduces the hospital stay as well.

Financial support and sponsorship
No funding sources.

Conflicts of interest
There are no conflicts of interest.

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