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Research Article

Phenobarbitone Versus Levetiracetam: A Qualified Approach to Initial Neonatal Seizure Management

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Abstract

Background: Seizures in newborns are frequent throughout the first month of life and might affect their neurodevelopment. Despite its limited effectiveness and association with cognitive impairment in human subjects, phenobarbitone (PB) is presently the preferred anti-epileptic medication (AED). The use of intravenous levetiracetam to treat seizures in neonates is growing. We have designed a randomized control study using levetiracetam in the initial treatment of acute newborn seizures since there is currently inadequate information on the safety and effectiveness of intravenous levetiracetam in neonates. The objective of the research was to determine if levetiracetam is more applicable than phenobarbitone at reducing convulsions in acute newborn seizures. The procedure of the research was conducted as a randomized control trial. After meeting the inclusion and exclusion criteria, 100 neonates, ages 0 to 28 days of any sex who were admitted to the special care baby unit (SCABU) of Dhaka Medical College Hospital and had a clinical presentation of neonatal seizures were randomly assigned to levetiracetam (Intervention Phenobarbitone; Control Group = 50). Seizures, the amount of time it took to be seizure-free, and the length of hospital stay were the outcome factors. Regular monitoring was conducted for 48 hours and continued until discharge or death. The outcome of the research was conducted as a randomized control trial. After meeting the inclusion and exclusion criteria, 100 neonates, ages 0 to 28 days of any sex who were admitted to the special care baby unit (SCABU) of Dhaka Medical College Hospital and had a clinical presentation of neonatal seizures were randomly assigned to levetiracetam (Intervention Phenobarbitone; Control Group = 50). Seizures, the amount of time it took to be seizure-free, and the length of hospital stay were the outcome factors. Regular monitoring was conducted for 48 hours and continued until discharge or death. In conclusion, the study found that when used as a first-line antiepileptic medication to treat acute newborn seizures, levetiracetam dramatically reduces convulsions when compared to phenobarbitone. It was discovered that none of the therapy techniques had any negative effects.

Keywords

Neonatal Seizures, Phenobarbitone Treatment, Levetiracetam in Neonates, Neonatal Seizure Management, Seizure Control in Neonates, Neonatal Anticonvulsants

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1. Introduction

With an incidence of 0.7 to 2.7 per 1000 live births, neonatal seizures are the most common clinical sign of central nervous system dysfunction in newborns. A newborn's seizure often indicates serious brain illness, including intracranial infection, hypoglycemia, stroke, hypoxia ischemic damage, inborn metabolic abnormalities, or brain deformities. Etiology has a big impact on the result. Seizures in newborns are associated with increased mortality and cognitive or motor impairment in survivors [1]. Given this, clinical seizures may benefit greatly from successful treatment strategies that lower morbidity and mortality while also enhancing neurocognitive development. Phenobarbitone (PB) is still the first-line therapy for newborn seizures, according to the data available, although there are presently no evidence-based guidelines for the evaluation and management of these convulsions [2]. However, babies and toddlers are known to be at risk for cognitive adverse effects traditional therapy Only 50% to 60% of instances are clinically controlled by phenobarbital and phenytoin, and they are much less successful in managing the majority of newborn electrographic seizures [3, 4]. However, the long-term negative consequences of phenobarbitone, which can cause cognitive impairment in newborns and toddlers, are causing growing worry [5]. A comparison of phenobarbital and phenytoin for the treatment of newborn seizures conducted in August 1999 revealed that both medications are similarly, but not entirely, effective as anticonvulsants in neonates [6]. Serious adverse effects include arrhythmia, hypotension, and decreased cardiac function with other antiepileptic medications including lidocaine and midazolam.

Currently approved as an adjuvant therapy for partial onset seizures with or without subsequent generalization, levetiracetam (LEV) is a well-tolerated and efficient antiepileptic medication. Similar findings were seen in prospective trials involving small patient groups in newborns and very young children. The most common adverse effects include irritation, somnolence, and behavioral issues; there are very few instances of serious, life-threatening side effects. During the three-month research period, four out of the six participants in a pilot study stayed seizure-free. After four weeks, patient 2 experienced a single seizure; thus, the dosage of levetiracetam was raised to 34 mg/kg/day. Five of the six patients were seizure-free after three months of levetiracetam treatment [7].

Thirty out of thirty-eight patients who received intravenous levetiracetam in a prospective open-label study for both partial and generalized seizures were seizure-free after one week, and twenty-seven of them were still seizure-free at four weeks. Levetiracetam is a well-tolerated novel AED that may successfully enhance seizure control as an add-on medication in children with refractory epilepsy with high tolerability, according to an open multicenter retrospective research. 82% of patients in a retrospective study of acute newborn seizures in preterm neonates reported that their seizures had stopped within 24 hours [8, 13]. According to a retrospective cohort research, levetiracetam may be linked to better results when compared to phenobarbitone, whereas increased exposure to the drug is linked to worse outcomes at age two In a double-blind, placebo-controlled study, levetiracetam was found to reduce the frequency of partial onset seizures in children by 26.8% throughout the course of the treatment period, as well as the frequency of partial seizures each week [14, 15].

Within 72 hours of starting levetiracetam medication, 100% of newborns in a retrospective trial stop having seizures. Furthermore, the research did not reveal any acute negative effects.18 even though a well-conducted clinical research showed that less than 50% of patients responded well to phenobarbital or phenytoin treatment [8, 20].

Even with conventional therapy, neonatologists still find it difficult and frustrating to manage seizures in newborns. This prospective randomized clinical study can assist in determining the effectiveness of levetiracetam over phenobarbital in the initial treatment of newborn seizures due to its good pharmacological and clinical characteristics [9, 10].

2. Method and Materials

2.1. Study Place

A randomized control trial was used. The Dhaka Medical College's local ethics committee accepted the trial, and parents were requested to provide written informed permission. Mature and preterm neonates with a gestational age of more than 34 weeks to fewer than 42 weeks, a birth weight of more than 2000 grams, and neonatal seizures were enrolled between July 2013 and June 2014. Patients who experienced seizures due to hypoglycemia, hypocalcemia, dyselectrolytemia, or sepsis were excluded. Patients who had previously had more than one loading dose of phenobarbitone or therapy with any other antiepileptic medications (AEDs) were not eligible to participate in the trial.

2.2. Sampling Procedure

Randomization was carried out using a simple random approach, i.e., the lottery method with replacement, following the requisite exclusion and fulfillment of the inclusion conditions.

2.3. Study Procedure

Seizures in DMCH were chosen from among neonates who were hospitalized to SCBU or who attended SCBU with seizures. The patient's history and clinical results were documented on the pre-made data sheet at the initial exam. Sam-

ples were sent in for baseline tests such as CBC, blood grouping, blood glucose, serum calcium, and serum electrolytes. The control group received an intravenous loading dose of phenobarbital (20 mg/kg), while the intervention group received a loading dose of levetiracetam (50 mg/kg). The second and third loadings of phenobarbital, each at a dosage of 10 mg/kg, were administered if seizures returned and Maintenance will be administered as 10 mg/kg/dose 8 hours per day for the levetiracetam group and 5 mg/kg/day 12 hours per day for the phenobarbital group. The institutional treatment protocol served as the foundation for the decision about further treatment in the event that therapy failed. Patients received clinical examinations, round-the-clock monitoring, and documentation of adverse events, antiepileptic medication, and seizure frequency. The study ended after 48 hours, but if the seizure was not under control in that time, it was considered a therapeutic failure. Clinical diagnoses were made for seizures. At the time of diagnosis and enrollment, no ongoing EEG monitoring was done.

3. Result

The goal of the current randomized controlled experiment was to examine the effects of two treatment modalities on neonates with acute neonatal seizures (injection of levetiracetam = intervention group vs. injection of phenobarbitone = control group). Control of seizures and the amount of time needed to control seizures were the primary outcome factors. The results of the data analysis are listed below.

Table 1. *Primitive demographic data of the neonates.*

Parameters	**Intervention Group (n=50)%**	**Control Group (n=50)%**	**P value (X^2 test)**
Sex			
Male	30 (60.0)	37 (74.0)	0.137 (%)
Female	20 (40.0)	13 (26.0)	
Gestational age (weeks)	**NO. (%)**	**NO. (%)**	**P value (X^2 test)**
Premature (<37)	6 (12.0)	5 (10.0)	0.749
Full-term (37-42)	44 (88.0)	45 (90.0)	
Mean ±SD	38.00±1.43	38.06±1.11	0.815
Parameters	**Intervention Group (n=50)%**	**Control Group (n=50)%**	**P value (X^2 test)**
Birth Weight	NO. (%)	NO. (%)	
2000- <2500	8 (16.0)	9 (18.0)	0.790
2500-4000	42 (84.0)	41 (82.0)	
Mean ±SD	2776.00±267.50	2750.20±345.48	0.677
Range	2300.03-3200.0	2000.0-3400.0	

Apgar score for neonates delivered in hospital	
(n=26)	**(n=14).**
No. (%)	**No. (%)**
26 (100.0)	14 (100.0)

Breathing status of neonates delivered outside hospital			
Parameters	**(n=26)** **No. (%)**	**(n=14)** **No. (%)**	**P value (X^2 test)**
No breathing Within 1 minute	19 (79.2)	31 (86.1)	0.480
Breathing within1 minute	5 (20.8)	5 (13.9)	

Table 1: Illustrating the basic demographic information about the newborns with seizures. 13 (26%) and 20 (40%) of the 50 neonates in the control group and 30 (60%) and 37 (74%) in the intervention group were female. There was no statistically significant difference in the neonatal sex distribution between the groups.

According to the neonatal gestational age status of the intervention group and control group, respectively, 6 (12%) and 5 (10%) babies were born before 37 weeks, while 44 (88%) and 45 (90%) babies were born between 37 and 42 weeks. There was no statistically significant difference between the groups. The neonates in the intervention group and control group had mean (±SD) gestational ages of 38.00±1.43 (range 35–42) and 38.06±1.11 (range 35–40) weeks, respectively. Additionally, there was no statistically significant difference in the mean gestational age between the groups.

8 (16%) and 9 (18%) neonates in the intervention group and 42 (84%) and 41 (82%) neonates in the control group were born weighing 2000–<2500g and 2500–4000g, respectively (statistically not significant). The intervention group's mean (±SD) birth weight was 2776.00±267.50 (range 2300-3200) g, whereas the control group's was 2750.20±3.45.48 (range 2000-3400) g. There was no statistically significant difference in the mean.

Within one minute of delivery, the Apgar score of all 14 (100%) neonates in the control group and all 26 (100%) neonates in the intervention group who were delivered to the hospital was < 7. In the case of 19 (79.2%) of the intervention group and 31 (86.1%) of the control group of neonates born outside of a hospital, the breathing status of 24 intervention group and 36 control group neonates revealed that only 5 (20.8%) of the intervention group and 5 (13.9%) of the control group breathed within 1 minute of birth (statistically no significant).

Table 2. *A comparison of Inj. Levetiracetam and Inj. Phenobarbitone in the management of neonatal seizures.*

Parameters	**Intervention Group (n=50)%**	**Control Group (n=50)%**	**P value (X^2 test)**
Age on admission (hour)	No (%)	No (%)	
12	35 (70.0)	27 (54.0)	
>12-24	9 (18.0)	12 (24.0)	0.72
>24-36	3 (6.0)	6 (12.0)	
>36-48	2 (4.0)	4 (8.0)	
>48	1 (2.0)	1 (2.0)	
Age at onset (hour)	No. (%)	No (%)	
12	38 (76.0)	32 (64.0)	
>12-24	8 (16.0)	10 (20.0)	0.101
>24-36	1 (2.0)	7 (14.0)	
>36-48	3 (6.0)	1 (2.0)	
Type of seizure	No. (%)	No (%)	
Subtle	18 (36.0)	14 (28.0)	0.137
Clonic	22 (44.0)	21 (42.0)	
Tonic	6 (12.0)	14 (28.0)	

Parameters	Intervention Group (n=50)%	Control Group (n=50)%	P value (X^2 test)
Myoclonic	1 (2.0)	1 (2.0)	

Table 2: Features of seizures in newborns are given in the table 2. Age at admission following seizure onset was 12 hours for 35 (70%) and 27 (54%), >12-24 hours for 9 (18%) and 12 (24%), >24-36 hours for 3 (6%) and 6 (12%), >36-48 hours for 2 (4%), and 4 (8%), and >48 hours for 1 (2%) neonates in each intervention group and control group, respectively. There was no statistically significant variance. The intervention group's mean (±SD) age at admission after the onset of a seizure was 10.10±12.69 (range 0.50-49.00) hours, whereas the control group's was 15.00±14.22 (range 0.50-56.00) hours. There was no statistically significant mean difference. Maximum age of admission following seizure onset for both the intervention group (70%) and control group (54%) of neonates was within 12 hours..

Age at onset of neonates seizure of intervention group and control group of neonates, respectively, was 12 hours in case of 38 (76%) and 32 (64%), >12-24 hours in case of 8 (16%) and 10 (20%), >24-36 hours in case of 1 (2%) and 7 (14%) and >36-48 hours in case of 3 (6%) and 1 (2%) neonates. Statistically no significant variation was observed. The majority of newborns in the intervention group (66%) and control group (64%), respectively, demonstrated that the age at which seizures began was within 12 hours after delivery. The intervention group's mean (±SD) age at seizure start was 8.97±11.93 (range 0.50-47.00) hours, whereas the control group's was 11.35±11.21 (range 0.50-37.00) hours. There was no statistically significant difference in the mean.

The neonatal intervention group experienced subtle seizures in 18 (36%) and 14 (28%), clonic seizures in 22 (24%) and 21 (42%), tonic seizures in 6 (12%) and 14 (28%), clonic seizures in 22 (44%) and 21 (42%), tonic seizures in 6 (12%) and 14 (28%), and myoclonic seizures in 4 (8%) and 1 (2%). There was no statistically significant variance found. Both the therapeutic group 44% and the control group 42% had clonic seizures often.

Table 3. *Comparison between inj. Levetiracetam and Inj. Phenobarbitone in controlling neonatal Seizures.*

Parameters	Intervention Group (n=50)% No (%)	Control Group (n=50)% No (%)	P value (X^2 test)
Seizure Controlled			
Yes	33 (66.0)	19 (38.0)	0.005**
No	17 (34.0)	31 (62.0)	
More than one drug required To Control seizure			
Yes	17 (34.0)	31 (62.0)	0.005**
No	33 (66.0)	19 (38.0)	
Time required to control Seizure (hour)			
12	40 (80.0)	25 (50.0)	
>12-24	6 (12.0)	12 (24.0)	0.030*
>24-36	2 (4.0)	4 (8.0)	
>36-48	1 (2.0)	6 (12.0)	
>48	1 (2.0)	3 (6.0)	
Mean ±SD	6.88±15.47	19.41±17.35	0.0001***
Range	0.33-93.00	0.50-69.00	

The status of newborn seizure therapy is displayed in Table 3. Levetiracetam was used to treat the seizures of 33 (66%) of

the intervention group's newborns, whereas phenobarbitone was used to treat 19 (38%) of the control group's neonates. Levetiracetam injection significantly reduced newborn seizures in a larger percentage of the intervention group's neonates 66% than phenobarbitone injection did (P<0.01). The remaining neonates in the intervention group, namely 17 (34%), and the control group, specifically 31 (62%), needed several medications to manage their seizures (statistically significant, P<0.01).

12 hours in 40 (80%), >12-24 hours in 6 (12%), >24-36 hours in 2 (4%), >36-48 hours in 1 (2%) and >48 hours in 1 (2%), in that order, was the amount of time needed to control seizures in the neonatal intervention group. 12 hours in 25 (50%), >12-24 hours in 12 (24%), >36-48 HOURS IN 6 (12%), >24 hours in 4 (8%), and >48 hours in 3 (6%), were the frequencies in the control group. The majority of the newborns in the control and intervention groups were needed. Control their seizure (80% and 50%) for 12 hours. Variation was statistically substantial (p<0.05). The intervention group's mean (±SD) seizure control time was 6.88±15.47 (range 0.33-93.00) hours, whereas the control group's was 19.41±17.35 (range 0.50-69.00) hours.

Table 4. *Treatment outcome of neonates during hospital stay.*

Parameters	**Intervention Group (n=50)%** **No. (%)**	**Control Group (n=50)%** **No. (%)**	**P value (X^2 test)**
Adverse Effect			
Yes	5 (100)	8 (16.0)	0.372
No	45 (90.0)	42 (84.0)	
Type of adverse effects	NO. (%)	NO. (%)	
Somnolence	3 (60.0)		
Irritability	2 (40.0)		
Drowsiness		4 (50.0)	
Lethargy		4 (50.0)	
Treatment Outcome			
Discharged with Advice	37 (34.0)	36 (72.0)	
Left against	11 (22.0)	9 (18.0)	0.473
Medical Advice Expired	2 (4.0)	5 (10.0)	
Hospital stay (days)			
<5	9 (18.0)	1 (2.0)	
5-7	29 (58.0)	18 (36.0)	0.001**
8-10	10 (20.0)	26 (52.0)	
>10	2 (4.0)	5 (10.0)	
Mean ± SD	6.22±2.20	8.10 ±2.17	0.0001
Range	2.00-12.00	4.00-1200	

Table 4 displays the treatment results for the neonatal intervention group and control group. 5 (10%) and 8 (16%) neonates in the intervention group and control group, respectively, had negative medication effects. There was no statistically significant variance found. 2 (40%) and 3(60%) of the 5 infants in the intervention group exhibited irritability and somnolence, whereas 4 (50%) of the 8 neonates in the control group displayed lethargy and sleepiness..

11 (22%) and 9 (18%) neonates in the intervention group and control group, respectively, departed against medical advice, 2 (4%) and 5 (19%) expired, while 37 (74%) and 36 (72%) neonates were discharged with advice. Notably, there was no discernible variance.

9 (18%) and 1(2%) of the neonates in the intervention group and control group, respectively, were in the hospital for fewer than five days, whereas 29 (58%) and 18 (36%) stayed

for five to seven (5-7 days) days. The distribution was statistically significant (P<0.01). Neonatal in the intervention group needed to stay in the hospital for 5-7 days (58.8%), but those in the control group needed to stay for eight to ten days (52%). The neonates in the intervention group spent an average (±SD) of 6.22±2.20 (range 2-12) days in the hospital. The average length of hospitalization was considerably greater (P<0.001) in the case of control group neonates.

4. Discussion

Both the birth weight distribution and the sex distribution of the newborns in this investigation proved to be non-significant. The distribution of males and females in the two groups did not differ significantly, according to Abend et al.'s study. 21 This study showed that the birth weight ranged from 2000 to 4000 grams. 0.62 to 2.96 kg and 2.803-4.627 kg, respectively, were reported by Buty Khan et al. [11, 12]. The neonates in this trial ranged in gestational age between 35 and 42 weeks for the levetiracetam group and between 35 and 40 weeks for the phenobarbitone group. This research is almost identical to Khan et al.'s report of 37.5-41.2 weeks of gestation with averages of 39.3±1.03 weeks.

The study showed that levetiracetam was an effective (66%) treatment for acute newborn seizures in both term and preterm neonates. Painteretal. Andboylan et al. showed that phenobarbital and phenytoin were effective in stopping seizures in fewer than half of their patients.4.6 Khan et al. Levetiracetam administered intravenously has been shown to be effective in treating acute neonatal seizures in infants and to stop them in 86% of cases. According to 18 Abned et al., levetiracetam was linked to a decrease in seizures of more than 50% [16, 17].

Levetiracetam was employed as a monotherapy in our investigation to manage acute newborn seizures. However, 13abned et al. 22, 11khanet. al, and Ramanti et al. did not. In acute seizure crises, they utilized phenobarbitone along with regular levetiracetam up to two loading doses (10 mg/kg) [18, 19].

33 of the 50 patients in this trial who received levetiracetam as a first-line anticonvulsant experienced controlled seizures. During the study period, no significant negative effects were observed. Several investigations found no negative effects, either short-term or long-term.10, 15, 18, and 23. According to Furwentsuches et al., patients who took LEV as a monotherapy following the titration phase may have benefited from initial PB therapy. 10. This study found that the levetiracetam and phenobarbitone groups had somnolence, irritability, sleepiness, and lethargy at rates of only 10% and 16%, respectively, with no cardiovascular side effects [21, 22].

Levetiracetam is still used to treat a range of clinical conditions and neonatal seizure etiologies. Levetiracetam was successfully used in newborns with different seizure etiologies, according to Shoemaker and Rotenberg's study from 24. Although hypoxic ischemic encephalopathy was the main cause of seizures in this research, other possible causes included metabolic conditions such sepsis, dyselectrolytemia, and hypoglycemia and hypocalcemia. There was no evaluation of other uncommon causes, such as pyridoxine dependence, hypomagnesemia, IVH, and CNS abnormalities [23].

In earlier research, phenobarbitone was utilized as a rescue medication in conjunction with levetiracetam (LEV) as an anticonvulsant for newborn seizures. However, this trial adhered to the institutional protocol, using midazolam on the third line and Fosphenytoin on the second line following the first line of levetiracetam or phenobarbitone [24].

In a retrospective, Kirmani et al. reported that thirty-two patients, ranging in age from two months to eighteen years, had been treated for status epilepticus with a levetiracetam load of 25–50 mg/kg. There were fifteen (46.8%) girls and seventeen (53.1%) men. Every patient responded well to intravenous levetiracetam. Both clinically and electrographically, status epilepticus stopped. Levetiracetam was administered intravenously to eighteen patients (56.5%) who had not responded to ativan and fosphenytoin. There were no obvious severe negative effects. Nine patients (28.1%) got levetiracetam as an adjuvant medication after being released from the hospital, whereas fifteen patients (46.8%) were discharged on levetiracetam monotherapy [25].

In a retrospective cohort trial, Abend et al. discovered that 88% of the 23 newborns (11 males and 12 females) who received levetiracetam were seizure-free. There were no serious cardiopulmonary side effects found 21. According to the current study, 90% of participants experienced no seizures within 24 hours and experienced no severe adverse effects.

In this experiment, the mean hospital stay for the levetiracetam group was significantly lower than that of the phenobarbitone group. Most patients in the levetiracetam group were discharged within seven days.

5. Conclusion

The results of this controlled study, despite its limitations, are consistent with other published research and demonstrate that levetiracetam is safe and well tolerated when given to all babies, term and preterm. This first-line antiepileptic drug is linked to a decrease in seizures or their cessation within 24 hours after administration.

Abbreviations

No such Abbreviation.

Author Contributions

Mohammed Mahfuzur Rahman is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The author declares no conflicts of Interest.

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