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ORIGINAL ARTICLE

Levetiracetam versus Phenobarbitone in Neonatal Seizures - An Open label Randomized Controlled Trial

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Abstract

Background: Phenobarbitone is the traditional first-line anticonvulsant for neonatal seizures, while levetiracetam, a newer anti-epileptic, has uncertain efficacy in comparison

Objective: To evaluate the efficacy and safety of levetiracetam versus phenobarbitone in term and preterm infants with clinically apparent seizures in a tertiary care neonatal setting, guiding safer, more effective neonatal seizure management

Methods: This study aimed to compare the efficacy and safety of levetiracetam (30 mg/kg/dose) and phenobarbitone (20 mg/kg/dose) in controlling neonatal seizures. An open-label, parallel randomized controlled trial (RCT) was conducted in a neonatal intensive care unit (NICU) in India

Results: Seizure cessation rates were 70% in the levetiracetam group and 66.6% in the phenobarbitone group, with no statistically significant difference ($P = 0.83$).

Conclusion: Levetiracetam and phenobarbitone demonstrated comparable efficacy and safety in managing neonatal seizures. Levetiracetam could be considered a viable alternative to phenobarbitone as a first-line treatment. Further studies are needed to confirm these findings, especially regarding levetiracetam's side effect profile.

Keywords: Neonatal seizures, Phenobarbitone, Levetiracetam, Efficacy, Neonatal intensive care unit

Introduction

Neonatal seizures are a prominent cause of morbidity and mortality, often indicating underlying neurological disturbances that can compromise vital functions like respiration and feeding. Left unmanaged, these seizures can lead to significant brain injury.[1] Evidence supporting the mechanisms of currently available anti-epileptic drugs (AEDs) remains limited.[2] Phenobarbitone, the widely accepted first-line treatment, controls fewer than half of EEG-confirmed neonatal seizures and has been linked to adverse neurodevelopmental outcomes, including cognitive impairments demonstrated in animal studies through neuronal apoptosis.[3] The limited efficacy and potential risks associated with phenobarbitone highlight the need for alternative therapies that are both potent and safer for the developing brain. Levetiracetam

(LEV) has emerged as a promising candidate. Retrospective data suggest that LEV is effective and safe in managing neonatal seizures, showing attributes of an "ideal" anticonvulsant, characterized by the absence of hepatic metabolism and drug drug interactions, which enhances its safety profile and minimizes potential side effects.[4,5] Moreover, LEV has not demonstrated additive cognitive impairment, making it theoretically superior to traditional agents like phenobarbitone.[5] These potential advantages of LEV are supported by clinical guidelines, such as a 2012 peer-reviewed treatment algorithm that recommends LEV based on its safety and efficacy profile.[6] Nonetheless, robust evidence from prospective studies remains limited.

This data gap underscores the need for a randomized controlled trial comparing LEV and phenobarbitone as first-line treatments for neonatal seizures. This study aims to evaluate the efficacy and safety of levetiracetam versus phenobarbitone in term and preterm infants with clinically apparent seizures in a tertiary care neonatal setting, guiding safer, more effective neonatal seizure management.

Materials and Methods

Ethics statement

The study protocol was approved by the Institutional Ethics Committee (90/2013) and also registered with CTRI (CTRI/2015/06/005849). Informed consent was obtained from parents of neonates prior to being enrolled in the study.

Study design and setting

This open labeled Phase II randomized controlled trial was conducted in a level 3 neonatal intensive care unit (NICU) of a tertiary care, medical college hospital in south India during the period from November 2013 to April 2015. This NICU acts as a referral unit for peripheral primary and secondary health care establishments in a catchment area of about 300 km^2 encompassing three South Indian states.

Inclusion criteria

Newborns over 28 weeks gestational age and weighing more than 1000 grams with neonatal seizures were included.

Exclusion criteria

Neonates with seizures from hypoglycemia or who had received anticonvulsants before admission were excluded.

Identification of subjects

A seizure was defined as abnormal movements persisting despite restraint, with altered sensorium or autonomic symptoms. Apnea was considered a seizure in term or late preterm neonates by exclusion. Seizures were classified by Volpe's types as subtle, clonic, tonic, or myoclonic.[1]

Infants at high risk of seizures due to conditions such as perinatal depression, sepsis with complications like shock, meningitis, suspected inborn errors of metabolism, cranial malformations and abnormal central nervous system examination were screened. Parents were approached for informed consent if criteria were met. A color-coded identifier on the baby's records and incubator served as a reminder of eligibility for randomization upon seizure occurrence.

Randomization, allocation concealment and blinding

Once seizures met study criteria, neonates were randomly allocated to the levetiracetam or phenobarbitone group using computer-generated numbers by a NICU consultant not directly involved in the study. Block randomization in 4 blocks of 10 with a 1:1 allocation ratio was used. Allocation was concealed in sequentially numbered, 40 opaque envelopes, ensuring the investigator was unblinded but the statistician remained blinded.

Sample size calculation, study outcomes and statistical analyses

To achieve a 50% superiority in seizure control within seven days in the levetiracetam group versus the phenobarbitone group, 16 neonates per group were required (90% power, 5% significance). Primary outcomes were seizure control within 24 hours and need for a second anticonvulsant, analyzed by Chi-square test. Parametric data were presented as means (standard deviation), and continuous variables were compared using Mann-Whitney U, Chi-square, or Fisher's exact test. Significance was defined as $P < 0.05$, and data were analyzed on an intention-to-treat basis using SPSS 16.0 software (SPSS Inc, Chicago, IL, USA).

Secondary outcomes included ventilation needs, duration of altered sensorium, EEG abnormalities after 7 days of AED initiation, and time to full feeds post-seizure onset.

Immediate management of seizures and enrollment

Before enrollment, neonates were stabilized, with hypoglycemia ruled out or treated with 2 ml/kg of 10% dextrose (IV), if glucose was <50 mg/dl when assessed

with glucometer. Babies with adequate glucose levels were randomized to levetiracetam or phenobarbitone.

To determine seizure etiology, a two-tier workup was done. First-tier tests included serum calcium, magnesium, electrolytes, complete blood count (CBC), quantitative C-reactive protein (CRP), blood culture, and lumbar puncture. The second tier included metabolic tests like ammonia, arterial blood gases (ABG), urine ketones, and tandem mass spectrometry (TMS). All subjects underwent a neurosonogram (NSG); computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed if clinically indicated.

Intervention

The levetiracetam group received IV levetiracetam (Levipil, Sun Pharmaceuticals) at 30 mg/kg, while the phenobarbitone group received IV phenobarbitone (Phenobarbitone, Abott Pharmaceuticals) at 20 mg/kg, similarly diluted with 10 ml of water for injection and administered over 15 minutes under aseptic conditions.[7] Participants were monitored for seizure cessation and autonomic stability, with recurrences treated by re-administering the same anticonvulsant at 10 mg/kg over 15 minutes.

Treatment for recurring seizures

For persistent seizures 12 hours after the initial levetiracetam dose, a second dose of 10 mg/kg was administered, followed by maintenance at 30 mg/kg/day. If seizures continued, this dose increased incrementally to a maximum of 50 mg/kg/day. In the phenobarbitone group, recurring seizures were treated with a second loading dose followed by IV phenytoin (Eptoin, Akums Pharmaceuticals) at 20 mg/kg if needed, in accordance with treatment guidelines.[8] For cases unresponsive to phenytoin, midazolam (Mezolam, Neon Laboratories) was used starting with a bolus of 0.15 mg/kg, followed by a drip adjusted up to 18 mcg/kg/min until seizure control was achieved. Resolution was considered achieved when the use of a second anticonvulsant was deemed unnecessary.

Maintenance anticonvulsants

The levetiracetam group received a maintenance dose of 20 mg/kg/day IV, transitioning to enteral dosing when feasible. The phenobarbitone group received 5 mg/kg/day IV, later given enterally. For neonates requiring phenytoin, maintenance was 5 mg/kg/day. After 48 hours without seizures, anticonvulsants were withdrawn in reverse order of their initiation, continuing monotherapy at discharge.

Monitoring

Neonates were monitored for adverse effects for 24 hours post-treatment, including respiratory rate, ventilator needs, arrhythmias, and changes in heart rate or blood pressure exceeding 10%. Serum phenobarbitone levels were checked in cases of depressed sensorium.[1] Recurrence of seizures was monitored for seven days, with EEG conducted on day seven and repeated at one and three months to guide treatment duration. The underlying etiology of seizures was treated as per unit protocol. Recurrence of seizures was monitored for seven days, with Electro encephalogram (EEG) conducted on day seven and repeated at one and three months to guide treatment duration.

Discharge and Follow Up

Discharge criteria included seizure-free status for at least three days, resolution of comorbidities, full enteral feeds, and adequate weight gain. Parents were counseled on follow-up at the Neonatal Follow-Up Clinic (NFC), with reminder calls by NFC staff. Follow-up assessments in the NFC tracked growth and development using the Amiel-Tison method for neuromotor assessment and developmental assessment scale for Indian infants (DASII) for developmental progress at 3, 6, 9, 12, and 15 months, determining motor and mental quotients (MoDQ and MeDQ).[9]

All neonates underwent hearing screening and were assessed for retinopathy of prematurity when indicated. Follow-up EEG was performed at one and three months, tapering off medications over 15 days if results were normal. Data was recorded in a predesigned proforma, with study protocols, equipment, and personnel unchanged throughout the study period.

Results

Demographic data

A total of 943 babies were admitted to our NICU during the study period. The trial flow of the study is shown in Figure 1.

The mean gestational ages of neonates were 36.90 ± 2.67 weeks in the LEV arm and 37.83 ± 1.82 weeks in the Phenobarbitone arm, with mean birth weights of 2655.25 ± 692.56 g and 2701.11 ± 592.55 g, respectively. Demographic data in Table 1 show comparable characteristics between the two arms. Clonic seizures were most common (42%), with 92.1% occurring within 6 hours of life. Hypoxic ischemic encephalopathy (55.3%) was the leading cause of seizures (Table 2).

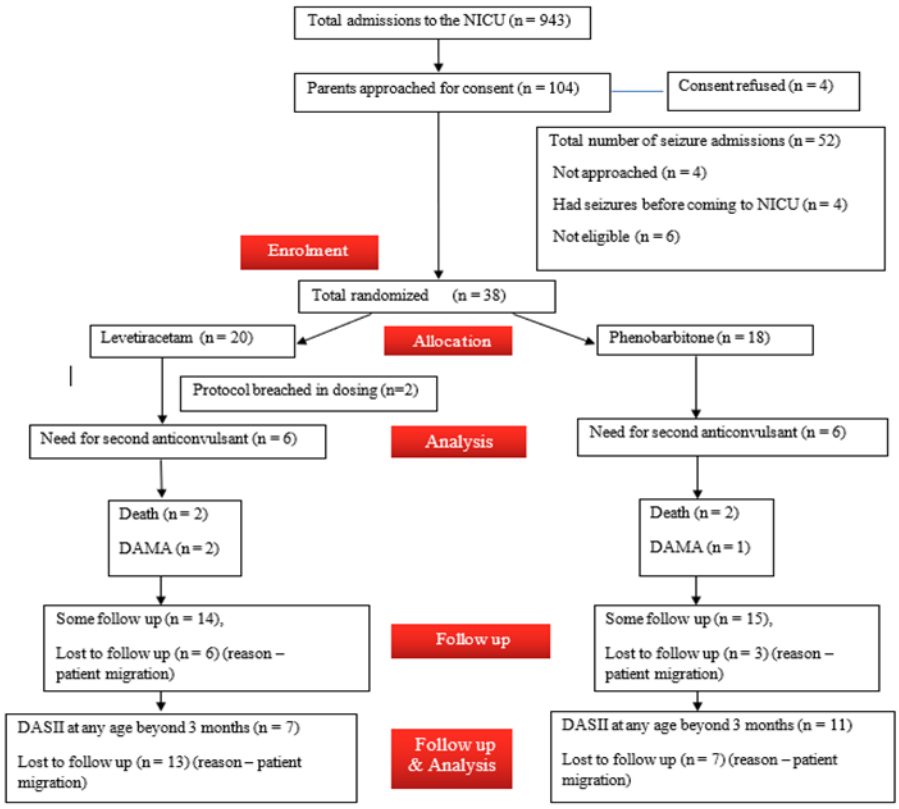

Figure I: Trial flow of the study.

Table 1: Demographic variables

Demographic variables	Levetiracetam group N (%)	Phenobarbitone group N (%)	*P* value
Maternal age (in years)	24.65 ± 4.83	25.60 ± 4.49	0.790$
Consanguinity	7 (35)	1 (5.6)	0.045*
Family history of seizures	2 (10)	3 (16.7)	0.653*
Nulliparous	12 (60)	11 (61.1)	0.944#
Intrapartum fever	2 (10)	1 (5.6)	1.000*
Maternal diabetes	3 (15)	2 (11.2)	
Mode of delivery: Normal/Forceps/Vacuum/Caesarean	9 (45)	7 (38.9)	
	1 (5)	1 (5.6)	
	10 (50)	10 (55.6)	
HIE II/III	10 (50)	10 (55.6)	
Therapeutic hypothermia	5 (25)	7 (38)	
Perinatal asphyxia	10 (50)	12 (60)	
Inborn	11(55)	9 (50)	0.758#
Male	18(90)	10(55.6)	0.027*
Gestational age Prematurity	36.90±2.673 10(50)	37.83±1.823 8(44.4)	0.222$ 0.732#
Weight (in grams)	2655.25±692.56	2701.11±592.55	0.829$
Length (in cm)	47.075±3.67	48.52±3.22	0.206$
Head circumference (in cm)	33.475±1.929	33.872±3.342	0.652$
AGA SGA	18(90) 2(10)	16(88.9) 2(11.1)	1.000*

*= Fisher Exact test., #= Chi Square test, $= Mean + 2SD

Table 2: Risk factors and co-morbidities for seizures.

Risk factor	Levetiracetam N (%)	Phenobarbitone N (%)	*P* value
NST: Category II Category III	5 4	4 1	0.580*
Resuscitation required Bag and mask Intubation (meconium) Intubation otherwise Chest compression	10 (50) 10 (50) 1 (5) 4 (20) 1 (5)	12 (66.7) 12 (66.7) 1 (5.6) 5 (27.8) 0 (0)	0.299# 0.299#
5 min APGAR≤4 5 min APGAR>4	3 (21.4) 14 (78.6)	3 (25) 12 (75)	1.000
Time required for APGAR to reach 7 <10 min: >10 min:	 10 (71.4) 4 (28.6)	 8 (66.7) 4 (33.3)	1.000
Perinatal asphyxia HIE II HIE III	10 (50) 10 (50) 0 (0)	12 (66.7) 11 (61.1) 1 (5.6)	0.299#
Therapeutic hypothermia	5 (41.7)	7 (58.3)	0.414#
Pneumonia	8 (40)	4 (22.2)	0.239*
Sepsis	6 (30)	3 (16.7)	0.454*
PPHN	4 (20)	3 (16.7)	1.000*
RDS	0	0	
Meningitis	0	2 (11.2)	0.218*
Shock	4 (20)	3 (16.7)	1.000*
DIC	4 (20)	6 (33.3)	0.468*
Anemia	7 (35)	3 (16.7)	0.278*
Neonatal jaundice	12 (60)	11 (61.1)	0.944#
Renal failure	6 (30)	7 (38.9)	0.734#
PDA	3 (15)	2 (11.2)	1.000*
Cardiac disease	6 (30)	5 (27.8)	1.000*
Congenital anomalies	8 (40)	4 (22.2)	0.239*
Number of antibiotics in each arm 2 antibiotics >2 antibiotics	 8 (40) 10 (50)	 3 (16.7) 7 (38.9)	0.043*
Phototherapy	10 (50)	9 (50)	1.000#
Blood products transfusion	3 (15)	1 (5.6)	
CRIB scores	2 (1 - 4)	1.5 (0 - 4)	0.504&

*= Fisher Exact test., # = Chi Square test, $= Mean + 2SD

Table 3: Outcome variables

Primary outcome	Levetiracetam N (%)	Phenobarbitone N (%)	*P* value (CI)
Need for second anticonvulsant (all cause seizures)	6 (30)	6 (33.3)	0.825# (- 0.32 - 0.26)
Need for second anticonvulsant (HIE Cause)	4 (40)	6 (60)	0.408* (- 0.56 - 0.22)
Need for second anticonvulsant (Causes other than HIE)	2 (25)	0	0.473* (- 0.05 - 0.55)
Loading doses One Two	 10 (50) 10 (50)	 11 (61.1) 7 (38.9)	0.492#
Need for Phenytoin	6 (30)	6 (33.3)	0.825# (- 0.32 - 0.26)
Need for Midazolam	1 (5)	2 (11.1)	0.595* (- 0.23 - 0.13)
Complete seizure control in time ≤24 hours >24 hours	 19(95) 1(5)	 16(88.9) 2(11.1)	 0.595 (-0.24 -0.11)*

*= Fisher Exact test., # = Chi Square test, $= Mean + 2SD

Table 4: Follow up outcomes

Follow up outcomes	Levetiracetam N (%)	Phenobarbitone N (%)	*P* value
Follow up (at least one visit at NFC)	14(70)	15(83.3)	0.454*
Follow up at 1 month	12(60)	14(77.8)	
			0.217*
EEG Abnormal	0	2(18.2)	1.000*
CNS examination Abnormal	11(91.7)	12(85.7)	
Tonal abnormality			
Normotonia	1(8.3)	1(7.1)	
Hypotonia	9(75)	9(64.3)	
Hypertonia	2(16.7)	4(28.6)	1.000*
Abnormal	11(91.7)	13(92.9)	
			1.000*
Neurodevelopmental delay	1(8.3)	1(7.1)	
Follow up at 3 months			
Recurrence of seizure at 3 months	0	1 (12.5)	1.000*
	0	1 (20)	0.455*
EEG Abnormal	6 (100)	4 (50)	0.085*
CNS examination Abnormal			
Tonal abnormality	0	4 (50)	
Normotonia	4 (66.7)	2 (25)	
Hypotonia	2 (33.3)	2 (25)	
Hypertonia	6 (100)	4 (50)	
Abnormal	0	2 (25)	0.473*
Neurodevelopmental delay			
DQ assessments at any age from 3 to 15 months			
Number of DQ assessments at any age from 3 months to 15 months	7(35)	11(61.1)	
Tonal abnormality	3(50)	4(42.9)	1.000
Any time motor DQ	93.5(90.9 - 100)	92(71.9 - 98.2)[&]	0.414
Any time mental DQ	100(90.3 - 100)	90.4(78.6 - 97.7)[&]	0.074
Combined DQ	96.7(91.9 - 99.15)	90.4(83.05 - 98.2)[&]	0.258

*= Fisher's exact test., & = median (interquartile range) Mann Whitney test.

Discussion

The efficacy of levetiracetam (LEV) in treating neonatal seizures, as demonstrated in this RCT, contrasts with a previous study by Perveen S *et al.,* which suggested LEV's inferiority.[10] Our findings, however, show similar efficacy and safety profiles between LEV and phenobarbitone, suggesting that LEV could be a potential first-line treatment. While LEV successfully controlled seizures in 70% of neonates within 24 hours, this rate was not statistically significant compared to phenobarbitone (66.7%). Both drugs, however, appear equally effective, though LEV may offer a better risk-benefit profile due to its relatively safer profile.

Observational studies have shown that LEV controls seizures in 35% to 50% of cases within 24 hours and up to 100% by 72 hours.[4,5,11] In contrast, this study found LEV's efficacy at 24 hours to be substantially higher (70%) than previous reports. Seizures resistant to LEV were mostly due to hypoxic-ischemic encephalopathy (HIE), a condition often unresponsive to single anticonvulsant therapy. This aligns with findings by Boylan *et al.,* who noted that seizures associated with abnormal EEG readings, such as those seen in HIE, are less responsive to phenobarbitone.[12] Another study comparing LEV and phenobarbitone for HIE-induced seizures found no significant difference in efficacy.[13]

LEV works through a novel mechanism involving the synaptic vesicle protein 2A, modulating neurotransmitter release. It is excreted by the kidneys, avoiding the liver, which is crucial for neonates since their liver is involved in bilirubin metabolism. Preliminary data

from animal studies suggest LEV has minimal untoward effects on the developing brain, in contrast to phenobarbitone, which is associated with potential long-term cognitive and motor impairments, including cerebral palsy.[14]

In our study, phenobarbitone toxicity was observed in 28% of neonates, and follow-up outcomes suggested worse results in the phenobarbitone group. Phenobarbitone operates through GABA-ergic agonism, which can paradoxically increase neuronal excitation in the developing brain, contributing to adverse outcomes, as seen in animal models.[15] The developmental quotient (DQ) assessed using the DASII was higher in the LEV group (96.7) compared to the phenobarbitone group (90.4), although this difference was not statistically significant as described by Maitre *et al.*[14]

Trials on anticonvulsants for neonatal seizures have used both EEG and clinical criteria to assess efficacy. The efficacy of phenobarbitone and phenytoin ranged from 29%-45% with EEG criteria and 14.5%-85% with clinical criteria.[12,16-18] However, EEG criteria have limitations, such as false positives and the inability to detect subtle neonatal seizures.[19,20] Using a 24-hour video EEG could address this, but it was not feasible in our setting due to resource constraints.

Despite the promising results for LEV, our study had limitations, including small sample size, inadequate follow-up, and the absence of electrographic criteria for seizure monitoring, which could have further corroborated our clinical observations. Future studies with larger sample sizes, EEG correlation, and extended follow-up are needed to substantiate these findings and potentially change clinical practices regarding first-line treatments for neonatal seizures.

Conclusion

Levetiracetam is an effective first-line anticonvulsant for neonatal seizures, offering comparable efficacy and safety to phenobarbitone, with a potentially more favorable long-term neurodevelopmental outcome.

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Conflict of interests

None

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