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RESEARCH

Comparison between Phenobarbitone and Levetiracetam as the initial anticonvulsant in preterm neonatal seizures — a pilot randomized control trial in developing country setup

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Abstract

This study aimed to compare the efficacy and safety of intravenous Levetiracetam and Phenobarbitone in the treatment of seizures in preterm neonates. It was an open-labeled, parallel randomized controlled trial conducted in a tertiary Neonatal Intensive Care Unit, India. Total 48 preterm neonates (28–36^{+6} weeks) with clinical seizures were randomized to receive either Levetiracetam (LEV; 40 mg/kg, then 20 mg/kg) or Phenobarbitone (PB; 15 mg/kg, then 10 mg/kg) intravenously as first loading dose in ratio 1:1; second loading was given for persistent seizure. Efficacy was denoted by cessation of clinical seizures with first or second doses of the allotted antiepileptic, and remaining seizure-free for the next 24 h. The demographic characteristics of preterm neonates and seizure types were comparable between both groups. Clinical seizure was controlled in 19 (79%) neonates in LEV group and 17 (70%) neonates in PB group, RR 1.12 (95% CI: 0.80 to 1.55), $p = 0.504$. There was increased respiratory support in PB group 9 (38%) vs. 3 (13%) in LEV group, RR 3.0 (95% CI: 0.92 to 9.74), $p = 0.06$.

Conclusion: Levetiracetam and Phenobarbitone were equally efficacious for clinical neonatal seizure control, but increased respiratory support was found with Phenobarbitone use.

What is Known:

• *Preterm neonates are at higher risk of neonatal seizure and Phenobarbitone is commonly used as the first line antiepileptic drugs in treating them.*

What is New:

• *Levetiracetam found equally efficacious as Phenobarbitone for cessation of clinical seizures in preterm neonates, with less adverse effect.*

Keywords Neonatal seizure · Preterm · Levetiracetam · Phenobarbitone

Introduction

Seizure is the most common clinical manifestation of neurological insult in neonates. Preterm neonates are at higher risk of seizure in comparison to full-term neonates [1]. The burden of seizure in preterm neonates was around 57–132/1000 live births [2]. Presences of seizure in preterm neonates are associated with increased risk of late death and neurodevelopment impairment, i.e., cerebral palsy, developmental delay, epilepsy, and motor tone disabilities; hence, earliest control of seizure is essential in them [3].

Till now Phenobarbitone (PB) is commonly used as the first-line antiepileptic drugs in treating neonatal seizure including in both preterm and term neonates [4]. In animal model, neuronal apoptosis was associated with use of PB in neonatal rat brain [5]. There is some concern about both

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short-term adverse effect of PB, i.e., risks of respiratory depression and increase need of cardio-respiratory support, and in long-term impairment of neurodevelopment. Brain of preterm neonates are immature and in developing state, more vulnerable to adverse effects of PB. Hence, there is a need of an alternative efficacious antiepileptic drug (AED) with minimal adverse effects for management of neonatal seizure.

Recently the newer AED — Levetiracetam (LEV), permitted by the Food and Drug Administration (FDA) in 2012 for seizure management, is being increasingly used in management of neonatal seizure over the last decade. However, there are limited number of randomized control trials for head-to-head comparison of PB and LEV in neonates, with biphasic clinical outcomes [6–8]. In this context, the objective of the present study was to compare the efficacy and safety of PB vs. LEV in seizure control of preterm neonates.

Materials and methods

This was a non-blinded parallel randomized control trial, conducted in a tertiary-center neonatal unit of Odisha, India over a period of 21 months, February 2021 to October 2022. This study was initiated after approval of the Institute Ethical Committee and Clinical Trial Registry of India (CTRI). Informed written parental consent was taken prior to enrollment of study participants.

Randomization, group allocation

The randomization of the calculated sample size was done by Research Randomizer computer program generated into LEV and PB groups in ratio of 1:1. The allocation concealment of serial numbers was done in opaque-sealed envelope which was opened prior to enrollment of eligible participant.

Study population

All inborn preterm neonates (gestational age 28–36^{+6} weeks) with clinical seizure within 28 days of life during hospital stay were included. Extreme preterm neonates (gestational age < 28 weeks) were excluded from the study, considering higher risk of autonomic instability in them, may over- or under-diagnose the clinical seizure. Neonates with seizure secondary to hypoglycemia, dyselectrolytemia, and multiple congenital malformations were excluded. Preterm neonates with paroxysmal movement were identified by bedside nursing sisters and physicians on duty, and confirmed by senior physician. In absence of senior physician, all paroxysmal events were video recorded for 30 s by mobile phone and reconfirmed with virtual communication. Based on the pattern, the semiology of seizure was classified as either tonic, clonic, subtle, or myoclonic [2].

Intervention

Seizure management was as per-unit protocol. The patency of the airway, breathing, and circulation was assessed; intravenous calcium gluconate was given after assessment of random blood sugar by glucometer and blood samples were collected for serum electrolytes. After excluding hypoglycemia and giving injection calcium gluconate bolus, if seizure persisted, opaque sealed envelope was opened to receive either LEV or PB. One of the authors were always physically present during antiepileptic drug administration and monitored the adverse effect.

Injection LEV (Inj. Levipsy, Cipla Private India Limited) at 40 mg/kg was diluted in 10 ml normal saline and administered intravenously over 10 min under cardio-respiratory monitoring. Second loading dose of LEV at 20 mg/kg diluted in 5 ml NS was given if seizure persisted after 30 min of initiation of first loading dose. Neonates who responded to LEV after first or second loading dose were continued with maintenance dose at 20 mg/kg/dose twice daily after 24 h.

Injection Phenobarbitone (Inj. Fenobarb, Samarth Life Sciences Pvt., Ltd.) was administrated at a dose of 15 mg/kg diluted in 10 ml normal saline, given intravenously over 20 min. Second loading dose of 10 mg/kg of PB was given over 10 min in case of persisting seizure after 30 min of initiation of first loading dose. Neonates who responded to PB after first or second loading dose were continued with maintenance dose at 3–5 mg/kg/day in two divided doses after 24 h.

In either of the arms if seizure was not controlled with allocated AED, loading dose of alternative AED was given (PB at 15 mg/kg was given to neonates of LEV group similarly, LEV at 40 mg/kg to neonates of PB group).

Neonatal characteristics

Detailed maternal characteristics of study participants such as antenatal steroid, maternal hypothyroidism, premature rupture of membranes (PROM), diabetes mellitus (DM), and pregnancy-induced hypertension (PIH) were documented from maternal case records.

Neonatal gestational age was assessed from maternal last menstrual date, first trimester ultrasound, or by modified new Ballard scoring. Neonatal characteristics such as birth weight, mode of delivery, size at birth (small for gestational age [SGA]/appropriate for gestational age [AGA]), APGAR score at 5 min, and need of resuscitation (need of positive pressure ventilation [PPV] like bag and mask/tube, T-piece, chest compression, injection epinephrine) were documented. For neonates requiring PPV for > 1 min, umbilical cord arterial blood gas analysis was done.

Neonates with clinical seizure underwent sepsis evaluation (complete blood counts, C-reactive protein, blood culture) and cerebrospinal fluid (CSF) analysis (cell count, glucose, protein, and culture). Bedside neurosonogram was conducted within 24 h of seizure event by trained radiologist. The grading of intraventricular hemorrhage was labeled by Volpe's classification [9] and periventricular leukomalacia by De Vries et al. [10]. In case of refractory seizures second-line investigations like arterial blood gas, serum ammonia, serum lactate, liver function test (LFT), and metabolic screening were performed.

Neonates who presented with clinical signs and symptoms of sepsis, and supportive laboratory investigations with or without blood culture growth, were considered as cases of neonatal sepsis. Babies with CSF cell count > 30/cu.mm and/or protein > 150 mg/dl and/or glucose < 40 mg/dl were considered as meningitis. In neonates with APGAR score < 7 at 5 min, pH of umbilical cord blood or initial ABG within 1 h of age < 7 and base excess > − 16 and those who developed seizure within 48 h of life (could not be explained by other causes) were considered as hypoxic ischemic encephalopathy (HIE) cases.

Outcome variables

The primary outcome was cessation of clinical seizure and remaining seizure free for next 24 h with allotted AED, either with first or second loading dose.

The adverse events of AEDs were estimated within 4 h of their administration. The adverse events were apnea, increase in respiratory support (from noninvasive [NIV] to invasive mechanical ventilation or from room air/nasal prong to NIV or invasive mechanical ventilation), and hypotension (increase in dose or addition of another inotrope/vasopressor drug).

Statistical analysis

Sample size: In a previous study, the neonatal seizure cessation with PB and LEV were 80% and 28%, respectively [8]. Considering type-1 error 0.05, 90% power with allocation ratio of 1:1. the calculated sample size was 44, and considering 10% dropout final sample size was 48 with 24 in each arm. During registration of clinical trial, based on the study result of Gowda et al., the estimated sample size was 106 for this clinical trial [7]. This research was taken for postgraduate dissertation and conducted during COVID-19 pandemic; we had achieved a total of 48 sample size during student's study period, which is presented here as a pilot study.

The continuous variables were expressed as mean (SD) for normally distributed data, median (Q1, Q3) for skewness of data. Categorical variable was expressed as frequency (%). The comparisons of continuous variable between PB and LEV groups were analyzed by independent sample *t*-test/Mann–Whitney *U* test and chi-square and oblique fissure exact test for comparison of categorical variables. Intention to treat analysis was done. *P* value < 0.05 was considered to be statistically significant. The data was analyzed by using STAT 1.5 software.

Results

During the study period, total 64 preterm neonates had clinical seizure and 16 were excluded (hypoglycemia — 9, hypocalcemia — 4, and congenital malformation — 3). Total 48 preterm neonates were eligible for randomization, i.e., 24 assigned in the LEV group and 24 in PB group. Figure 1 depicts the flow diagram for the study participants.

Demographic characteristics of the neonates and their maternal characteristics were comparable between PB and LEV group (Table 1). The median (Q1, Q3) day of clinical seizure detected in LEV and PB groups were 2 (1,5) days and 1 (1,3) day, respectively, $p = 0.29$. Majority of clinical seizure onset was within first 3 days of age in both groups — 14 (60%) neonates in LEV group and 18 (75%) neonates in PB group; 6 (25%) neonates in LEV group and 3 (12.5%) neonates in PB group developed clinical seizure within 3–7 days, and rest 4 (15%) neonates in LEV group and 3 (12.5%) neonates of PB group developed clinical seizure after 7 days. The proportion of tonic, clonic, and subtle types of seizure in LEV group were 2 (8%), 13 (54%), and 9 (38%), respectively, whereas in PB group were 1 (4%), 12 (50%), and 11 (46%), respectively, $p = 0.75$. The proportion of neonates diagnosed as HIE, IVH, and meningitis in LEV group were 11 (46%), 7 (29%), and 2 (8%) respectively, whereas in PB group were 12 (50%), 6 (25%), and 3 (12.5%), respectively.

In this study, 14 (60%) out of 24 neonates had seizure controlled clinically with first loading dose of LEV and 5 (20%) more neonates stopped seizing after second loading dose. In PB group 12 (50%) out of 24 neonates had cessation of clinical seizure with first loading dose; another 5 (20%) neonates became seizure free with second loading dose of PB. Overall following first or second loading dose of AED, clinical seizure was controlled in 19 (79%) neonates in LEV group and 17 (70%) neonates in PB group, RR 1.12 (95% CI 0.80 to 1.55), $p = 0.504$.

Three out of five neonates in LEV group responded to PB and five out of seven neonates in PB group responded to LEV. Refractory seizures, in both LEV and PB groups, were documented in two neonates from each group.

The number of neonates developed apnea in LEV and PB groups were 5 (21%) and 4 (16%), respectively, $p = 0.71$. Total 3 (13%) neonates in LEV group and 9 (38%) neonates

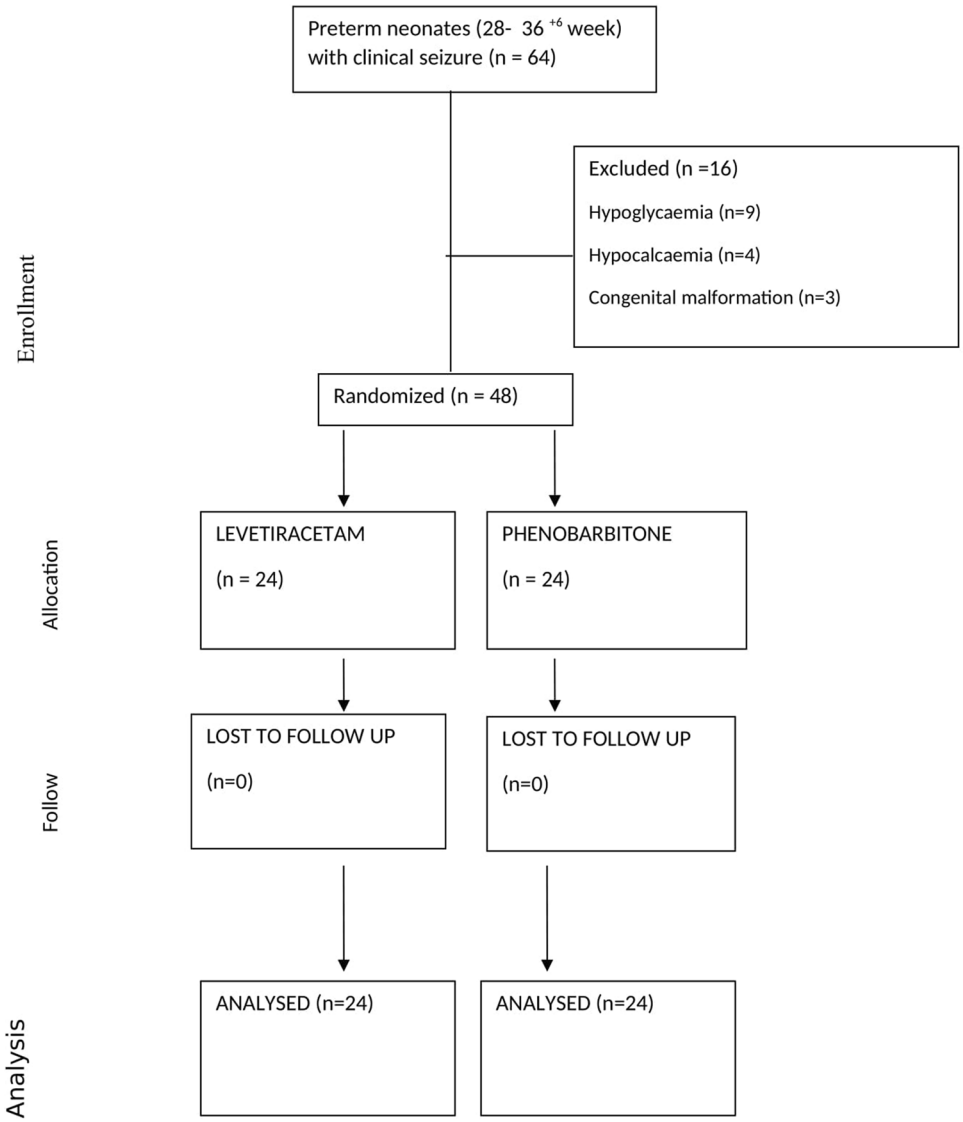

Fig. 1 The CONSORT flow diagram of study participants

in PB group required increased respiratory support, RR 3.0 (0.92 to 9.74), $p = 0.06$, and 4 (16%) neonates in LEV group and 3 (12%) in PB group had hypotension following AED administration, $p = 0.73$.

Discussion

In this prospective randomized control trial, the efficacy of LEV and PB for the control of clinical seizure in preterm neonates was first time studied. The efficacy of the LEV and PB were comparable in cessation of clinical seizure in the preterm neonates; however, more adverse effect was associated with PB in comparison to LEV. Around 50 percent of clinical seizure responded to initial loading dose of either PB or LEV, and nearly 70 percent of clinical seizure episodes were controlled after first or second loading dose in both arms of the study.

In previous studies comparing PB vs. LEV for neonatal seizure management, the efficacy of LEV was ranging from 23–86% vs. 34–86.7% with PB. In three previous studies, LEV was more efficacious than PB [6, 7, 11], whereas four studies showed equal efficacy between PB and LEV for seizure control [12–15] but two studies supported better efficacy of PB over LEV [8, 16]. In most of these RCTs, the seizure identification and response to AED were based on clinician observation except in Sharpe et al. where electroencephalography (EEG) was used for seizure management [8]. As EEG is the gold standard for management of neonatal seizure, the quality of evidence by Sharpe et al. was considered with least bias, with efficacy of PB and LEV being 80% and 28%, respectively. However, in a study by Painter et al. comparing the efficacy of the PB vs. phenytoin with EEG-based seizure management, the efficacy of PB was 43% [17], and similarly, in a video-EEG-based observational

Table 1 Comparison of baseline characteristics between both study groups

	Levetiracetam ($n=24$)	Phenobarbitone ($n=24$)	P value
Neonatal characteristics			
Gestational age (weeks)*	32.42 ± 3.43	33.66 ± 2.84	0.18
Birth weight (kg)*	1.66 ± 0.65	1.77 ± 0.50	0.51
Sex — male**	15 (62%)	16 (66%)	0.76
APGAR < 7 AT 5 min**	14 (60%)	13 (54%)	0.77
Vaginal delivery**	14 (60%)	12 (50%)	0.56
Resuscitation done — yes**	15 (62%)	17 (71%)	0.54
Inotrope requirement — yes**, [a]	4 (16%)	3 (12%)	0.68
Respiratory support — yes**, [a]	9 (37%)	11 (45%)	0.55
Maternal characteristics			
Antenatal steroid**	10 (40%)	7 (29%)	0.36
Hypothyroidism**	2 (8%)	1 (4%)	0.55
PPROM**	8 (33%)	4 (16%)	0.18
Gestational diabetes mellitus**	2 (8%)	1 (4%)	0.55
Pregnancy-induced hypertension**	1 (4%)	2 (8%)	0.55

*Mean ± SD

**n (%), *PPROM*-Preterm Premature Rupture of Membrane

[a]Prior to seizure onset

study by Boylan et al. 29% neonates had cessation of electrical seizure [18]. The variation in efficacy of PB and LEV in previous studies could be explained by variation in study participants (neonatal characteristics), drug dosing, etiology, and semiology of neonatal seizure. In two recent meta-analyses, LEV was equally efficacious with PB for management of neonatal seizure with minimal side effects similar to our study [19, 20].

In previous studies, most of the study participants were term neonates with limited number of preterm neonates. The initial loading dose of PB was 20 mg/kg in previous studies; in contrast, 15 mg/kg was used in this study aiming to reduce the adverse effect in preterm neonates. LEV was used in wide dosage range from 10 to 60 mg/kg in previous studies, whereas LEV was administered at dose of 40 mg/kg initial followed by second loading dose at 20 mg/kg in this study considering safety and better outcome observed with higher dose of LEV. We optimized the maximum dose of PB (25 mg/kg) and LEV (60 mg/kg) for preterm seizure management, considering both efficacy and adverse effect from previous clinical studies. As optimal dosing of PB for preterm neonates is not known, hence further lower loading dosing of PB at 10 mg/kg may be considered in future studies to get optimum clinical outcome with minimal adverse effect.

In previous studies increased adverse effects like apnea, hypotension, and increase in respiratory support were associated more with PB in comparison to LEV. Though we have noticed increased need of respiratory support in PB group in comparison to LEV, around 30–40% of neonates in both arms were in respiratory support prior to onset of seizure, mostly secondary to premature-related morbidity. It may have masked the real adverse effect of AED.

We acknowledged our study limitations: first the identification of seizure and clinical response were based on clinical decision, which has moderate agreement with electrographic seizure. Again, for both AED, it is known that sometimes clinical signs of seizures disappear, but electrographically the seizures persist. The long-term safety information as neurodevelopment follow-up of the patients was not available during writing of this manuscript. Again the evidence of study result is extrapolated from limited number sample size from a single center; hence, large-scale multicenter study is warranted.

Continuous video EEG or aEEG (amplitude integrated EEG) for 24 h is the gold standard for diagnosis and management of neonatal seizure, which are not available in neonatal units of low- to middle-income countries (LMIC). Again, interpretation of EEG in preterm neonates are complex and requires expertise of pediatric neurologist. Hence, the pediatrician of LMIC exclusively depend on clinical judgment to diagnose and treat neonatal seizure. Similarly, they are handicapped to manage the adverse effect of maximum dose of PB due to lack of adequate respiratory support and intensive care back up. In literature review of AED trials of neonatal seizure, electrographic seizures (seizure diagnosis by EEG or aEEG) were targeted in studies from high-income countries, whereas studies from LMIC were based on clinical seizures [21]. As the incidence, etiology, and management protocol of neonatal seizure in LMIC are different from high-income countries, the evidence generated in this AED trial for preterm neonates from a developing country setup

with local availability of infrastructure has its own clinical implication.

In conclusion, the efficacy of LEV for clinical seizure management in preterm neonates was comparable to PB with less adverse effects. Around two thirds of clinical seizure episodes in preterm neonates were controlled with administration of either PB or LEV. Hence, clinician may start using LEV as an alternative to PB as initial AED for seizure management in preterm neonates.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-023-04864-x.

Authors' contributions S. K. P.: conceptualization, study design, critical inputs to manuscript writing, and supervision. G. G.: data collection and writing the manuscript. S. S. B.: analysis and vital inputs to manuscript writing. S. K. S.: critical inputs to manuscript writing and supervision. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

Data availability The data that support the findings of this study are available and can be provided by the corresponding author, based upon reasonable request.

Declarations

Ethical approval The trial was approved by the Institutional Ethics Committee of the Kalinga Institute of Medical Sciences, KIIT University, Ethics number KIIT/KIMS/IEC/450/2020 on dated 3.11.2020. The trial was prospectively registered with the Clinical Trial Registry of India (CTRI), Number CTRI/2021/02/031290 on dated 15.02.2021, from which whole trial protocol can be assessed. The patient identity is not exposed in this study; hence, individual patient consent was not taken for publication.

Competing interests The authors declare no competing interests.

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