RESEARCH PAPER

Levetiracetam *versus* Phenobarbitone in Neonatal Seizures – *A Randomized Controlled Trial*

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Received: April 01, 2018; Initial review: August 20, 2018; Accepted: June 20, 2019.

Objective: To compare the efficacy and safety of intravenous Levetiracetam and Phenobarbitone in the treatment of neonatal seizures. **Design:** Open labelled, Randomized controlled trial. **Setting:** Level III Neonatal Intensive Care Unit (NICU). **Participants:** 100 neonates (0-28 days) with clinical seizures. **Intervention:** If seizures persisted even after correction of hypoglycemia and hypocalcemia, participants were randomized to receive either Levetiracetam (20 mg/kg) or Phenobarbitone (20 mg/kg) intravenously. The dose of same drug was repeated if seizures persisted (20 mg/kg of Levetiracetam or 10 mg/kg of Phenobarbitone) and changeover to other drug occurred if the seizures persisted even after second dose of same drug. **Main outcome measures:** Cessation of seizures with one or two doses of the first drug, and remaining seizure-free for the next 24 hours. **Results:** Seizures stoped in 43 (86%) and 31 (62%) neonates in Levetiracetam and Phenobarbitone group, respectively (RR 0.37; 95%CI 0.17, 0.80, P<0.01). 10 neonates had adverse reactions in the phenobarbitone group (hypotension in 5, bradycardia in 3 and requirement of mechanical ventilation in 2 neonates) while none had any adverse reaction in Levetiracatam group. **Conclusion:** Levetiracetam achieves better control than Phenobarbitone for neonatal seizures when used as first-line antiepileptic drug, and is not associated with adverse drug reactions.

Keywords: *Antiepileptic drugs, Convulsions, Management, Neonate, Outcome.*

Trial Registration: Clinical Trial Registry of India (CTRI/2018/04/013161).

Seizures are the most common manifestation of neurological insult during the neonatal period [1]. Etiology and presentation of neonatal seizures are different from the children and adults. The most common cause of symptomatic neonatal seizures is hypoxic/ischemic encephalopathy (HIE) which affects approximately 1-2/100 live births [2,3]. There are no evidence-based guidelines for the pharmacologic treatment of neonatal seizures and management is highly variable. Phenobarbitone (PB) is the mainstay for neonatal seizures treatment. The efficacy of PB in the complete resolution of seizures varies between 33 and 77% [4]. Phenobarbitone can cause neuronal apoptosis in vitro and have highly variable pharmacokinetics in neonates [5-7].

Levetiracetam (LEV) may have a better safety profile since it does not cause neuronal apoptosis in infant rodents [8]. A recent review on the use of LEV in neonatal seizures revealed that complete or near complete seizure cessation was achieved in 77% of LEV, compared to 46% in PB group [9,10]. Literature pertaining to use of levetiracetam in neonatal seizures is limited, and there is a lack of randomized controlled trials. Hence we conducted this study with the objective to compare the efficacy and adverse effects of LEV and PB in the treatment of neonatal seizures.

Accompanying Editorial: Pages 639-40.

METHODS

This randomized controlled trial was conducted in the level III NICU of a tertiary-care center over a period of 18 months (November 2014 to April 2016). Outborn neonates (age 0-28 d) with clinical seizures were enrolled in the study. Neonatal seizures were clinically defined as abnormal, stereotyped and paroxysmal dysfunction in the central nervous system (CNS), occurring within the first 28 days after birth in full-term infants or before 48 weeks of gestational age in preterm infants [11]. Neonates with hypoglycemia, hypocalcemia, hypomagnesemia, those who received anticonvulsants prior to enrolment, and those with major congenital malformations *e.g.*, congenital heart defects, neural tube malformations, diaphragmatic hernia, choanal atresia, esophageal atresia, tracheoesophageal

fistula, omphalocele, gastroschisis, intestinal obstruction and imperforate anus) were excluded.

Clinical details, seizure types and antiepileptic administration, including the sequence of drugs, dosage, timing and duration of therapy were recorded. Investigations included blood glucose, serum calcium, magnesium, electrolytes, complete blood counts, C-reactive protein, liver function tests, renal function tests, arterial blood gas, lactate, ammonia, cranial ultrasonography, Imaging of brain, Electroencephalo-graphy (EEG), and metabolic and genetic testing, whenever required to find out the cause for seizures.

Neonates with clinical seizures were randomly assigned to receive either PB or LEV with a 1:1 allocation as per a computer-generated randomization schedule and using sequentially numbered, opaque and sealed envelopes. When an eligible neonate was eligible to be enrolled, the envelope was opened by a clinician who was not part of the study.

After ensuring patency of the airway, breathing and circulation, blood sugar and ionic calcium level were performed. If seizures persisted even after correction of hypoglycemia and hypocalcemia, neonates were randomized for intervention to receive either LEV (20 mg/kg) or PB (20 mg/kg) intravenously. Levetiracetam was 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, LEV was continued as maintenance at 20 mg/kg/day in two divided doses. If seizures continued, another loading dose of LEV (20 mg/kg) was injected, and if seizures still persisted, patient was switched over to PB. PB was administered in the dose of 20 mg/kg diluted in 1:10 normal saline given intravenously slowly at the rate of 1 mg/kg/min under cardiorespiratory monitoring; if seizures were terminated, it was continued at 5 mg/kg/day in two divided doses as maintenance. Another loading dose of 10 mg/kg of PB was administered in neonates who failed to respond, and if seizures still persisted after two loading doses, patient was switched over to LEV.

The proportion of patients achieving cessation of seizures following the first or second dose of the drug (PB or LEV), and those remaining seizure-free for next 24 hours was considered as the primary outcome. Secondary outcome measure was the proportion of patients experiencing adverse events. Termination of seizure was defined clinically if there were no abnormal movement/eyeball deviation/nystagmus, no change in heart rate, no change in respiration/saturation and autonomic dysfunction. Adverse effects occurring within two hours of drug administration, including desaturation, reduced respiratory rate, increased ventilator support requirement, arrhythmias, blood pressure, or heart rate fluctuations by more than 10% compared to the previous 2 hours, or if vasopressors were initiated or increased, were recorded. Increased ventilator requirement was considered, if requirement of tidal volume more than 6 mL/kg on volume controlled-ventilator, peak inspiratory pressure (PIP) more than 22 cm H_2O in preterm and 23 cm H_2O in term, and mean airway pressure (MAP) of more than 12 cmH_2O on a pressure-controlled ventilator.

Informed consent was obtained from the parents on pre-structured proforma as soon as possible after assessing for eligibility. The study was approved by the institutional ethics committee of Indira Gandhi Institute of Child Health, Bangalore. The sample size required for this study was calculated as 100 (50 in each group) with 95% two-sided significance (α), 80% power, 1:1 randomization and a drop out of 15% assuming a difference in proportion of outcomes between the groups as 31% (LEV 77% and PB 46%) [12,13].

Statistical analyses: Continous variables were compared between the two groups using independent samples t-test. Termination of seizures at 24 hours and occurrence of adverse events were compared by Chi-square test. Effect size and its 95% CI were computed for the primary and secondary outcomes. *P* value of less than 0.05 was considered as significant. The analyses were carried out using the Statistical Package for Social Sciences (SPSS) 20.0 software.

RESULTS

A total of 122 babies with clinical seizures were assessed for eligibility during the study period; 22 were excluded and 50 neonates were randomized to each group (***Fig.* 1**). Baseline characteristics were comparable in the two groups (***Table* I**). The commonest etiology for seizures was hypoxic-ischemic encephalopathy (HIE). Focal clonic seizures constituted the most common type of seizure in the study population.

Following first dose of drug, seizures stopped in 30 (60%) neonates in LEV group, and 25 (50%) neonates in PB group. In the LEV group, there was a cessation of clinical seizures (and remaining seizure free at 24 h) in 43 (86%), and in the PB group, it was 31 (62%) after one or two doses ($P<0.001$). Seizure control was better (RR 0.37; 95% CI (0.17, 0.80) in the LEV group.

A total of 10 adverse events were observed in the PB group and none in LEV group. Various adverse events noted in the PB group were; hypotension in 5 neonates, bradycardia in 3 neonates and requirement of mechanical ventilation in 2 neonates.

TABLE I COMPARISON OF BASELINE CHARACTERISTICS OF THE STUDY GROUPS

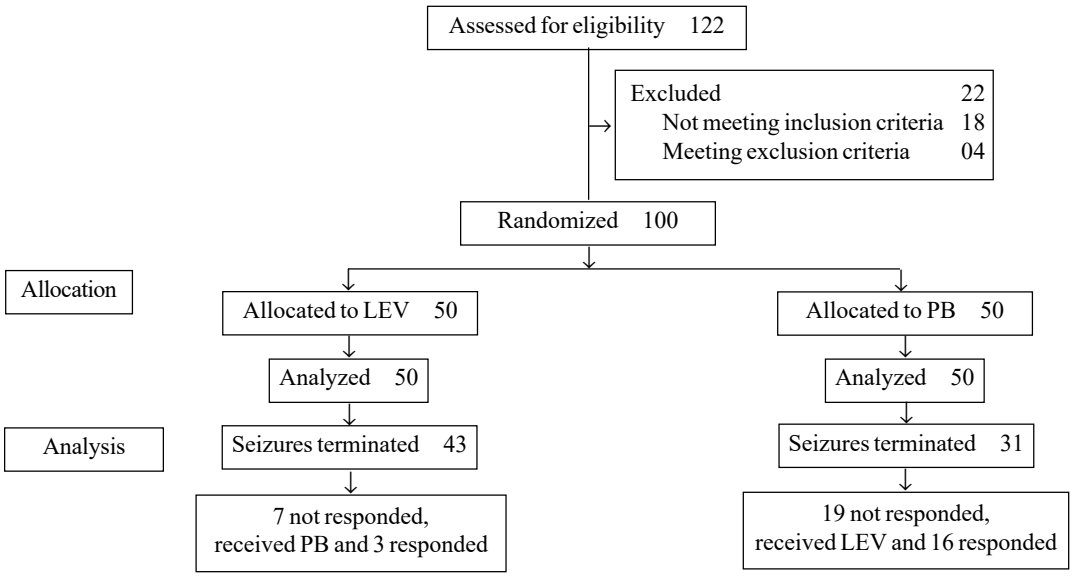
Characteristics	*Levetiracetam (n=50)*	*Phenobarbitone (n=50)*
Age (d), mean (SD)	9.8 (8.50)	8 (8.33)
Male, *n* (%)	28 (56)	28 (56)
Mode of delivery, *n* (%)		
Vaginal	35 (70)	36 (72)
Caesarian	15 (30)	14 (28)
Gestation, *n* (%)		
Term	40 (80)	42 (84)
Preterm	10 (20)	08 (16)
Birth weight (kg) , mean (SD)	2.56 (0.64)	2.73 (0.64)
Etiology of seizures, *n* (%)		
HIE	20 (40)	24 (48)
Neonatal sepsis/Meningitis	18 (36)	15 (30)
Intracranial hemorrhage	3 (6)	2 (4)
Benign neonatal epilepsy syndrome	2 (4)	1 (2)
Malignant neonatal epilepsy syndrome	1 (2)	1 (2)
Cortical malformation	1 (2)	1 (2)
IEM	1 (2)	2 (4)
Unknown	4 (8)	4 (8)

HIE: *Hypoxic ischemic encephalopathy,* IEM: Inborn *errors of metabolism.*

Three out of the seven neonates who did not respond to LEV, responded to PB. Among the 19 neonates who did not respond to PB, 16 showed seizure cessation with LEV. In the LEV group, 47 were discharged, two left against medical advice, and one died. In the PB group, 46 neonates were discharged and four left against medical advice.

DISCUSSION

In the present study, we documented better anticonvulsant efficacy and safety of LEV in comparison to PB as a first-line antiepileptic drug in neonatal seizures. A higher proportion of neonates had a cessation of seizures in LEV group as compared to PB group. There were no adverse drug reactions noted in the neonates who received LEV in the present study whereas, 10 of the neonates in the PB group developed adverse drug reactions. The efficacy of LEV has been earlier demonstrated in a study by Ramantani, *et al*. [13] , in which 30 (78%) out of 38 infants were seizure-free after receiving LEV. In study by Khan, *et al*. [14], 19 (86%) of the 22 neonates demonstrated seizure cessation within 1 hour of administration. 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 [10]. These results show that LEV is at least as effective as PB in the control of neonatal seizures as a first-line agent. However, in a



PB: Phenobarbitone; LEV: Levetiracetam

FIG. 1 *Flow of participants in the study.*

WHAT IS ALREADY KNOWN?

- Phenobarbitone currently represents the antiepileptic drug of choice in the management of neonatal seizures.

WHAT THIS STUDY ADDS?

- Levetiracetam is an effective and safer alternative to phenobarbitone as a first line drug in the management of neonatal seizures.

study by Abend, *et al*. [15], LEV was associated with seizure improvement within 24 hours in only 8 (35%) of 23 neonates. 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 [10,16] 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 [13,15-17].

The limitation of our study was that we did not perform electroencephalographic monitoring to document cessation of seizure activity. However, in most of the neonatal units, especially with limited resources, clinical control of seizures is usually the only guide to treatment. Thus, despite this limitation, the generalizability of our study for such settings is reasonable. Lack of long-term follow-up and inability to perform therapeutic drug levels of PB and LEV were the other limitations of the present study. The sample size of our study was also inadequate for the outcomes related to various adverse effects.

We conclude that levetiracetam is an effective and safer alternative to phenobarbitone in the management of neonatal seizures, as a first-line AED.

Contributors: VR: conceptualization of study, and critical inputs to manuscript for important intellectual content; AR: data collection and writing the manuscript; NS and NB: data collection and analysis, and critical inputs to manuscript writing; AB: supervision of the work and revision of manuscript.
Funding: None; *Competing interests*: None stated.

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