International Journal of Contemporary Pediatrics
Bhasin D et al. Int J Contemp Pediatr. 2025 Apr;12(4):615-620
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20250767

Original Research Article

A comparative study on the efficacy and safety of intravenous levetiracetam and phenobarbitone in the treatment of neonatal seizures

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Received: 17 February 2025
Accepted: 12 March 2025

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ABSTRACT

Background: Seizures are the most common manifestation of neurological insult during the neonatal period with a significant risk of mortality and subsequent neurological disability. Phenobarbitone has been the mainstay of treatment for decades despite its limited efficacy and potential adverse effects. Levetiracetam being a newer antiepileptic with favorable pharmacological and clinical profile and better neurodevelopmental outcomes may be used as an alternative first line antiepileptic. This study compares the efficacy and safety of intravenous levetiracetam and phenobarbitone in the treatment of neonatal seizures.
Methods: Prospective randomized controlled trial conducted at level 3 Neonatal Intensive Care Unit including 150 neonates 0-28 days with clinical seizures randomized to receive either intravenous Levetiracetam or Phenobarbitone as first line antiepileptic. Cessation of seizures for 24 hours duration after drug administration is considered as primary outcome measure.
Results: Seizure control was noted in 53.3% neonates in phenobarbitone group, which was significantly higher as compared levetiracetam (21.3%, $p<0.05$) after first loading. A significantly higher percentage of neonates in levetiracetam group required further doses and another drug (25.3%). Adverse effects and requirement of mechanical ventilation was significantly higher in patients of phenobarbitone group (22.7%) ($p<0.05$). However neurological outcomes measured by HINE score did not show significant difference between the groups($p>0.05$).
Conclusions: Phenobarbitone is found to be more efficacious than levetiracetam as a first line antiepileptic in terms of seizure control while levetiracetam requires more frequent dosing but with better safety profile and survival rates. Thus, levetiracetam can be considered as an alternative in treatment of neonatal seizures.

Keywords: Antiepileptic, Hammersmith infant neurological examination score, Levetiracetam, Neonatal seizure, Phenobarbitone

INTRODUCTION

Seizures are the most common manifestation of neurological insult during the neonatal period, with reported incidences ranging from 1.5 to 5.5 per 1000 live births in full-term infants and 57.5 to 132 per 1000 live births in preterm infants. The most common etiology being hypoxic ischemic encephalopathy.[1] The timely identification and appropriate management of neonatal seizures are crucial in minimizing the negative impact on the developing brain. Despite the urgency, there remains significant debate regarding the optimal management of neonatal seizures. Phenobarbital (PB) continues to be the first-line antiepileptic with its efficacy ranging from 33% to 77%.[2-4] However, phenobarbital is associated with acute side effects such as hypotension, bradycardia, respiratory depression and sedation and chronic exposure may lead to decreased cognitive function. Levetiracetam (LEV), a newer antiepileptic drug approved by the FDA in 2012 for clinical use, is currently used as a second-line therapy in management of neonatal seizures, with seizure control rates reported between 35% and 86%.[5-8] Due to its favorable efficacy, high safety profile and beneficial pharmacokinetic characteristics, LEV has seen increasing

use in the treatment of neonatal seizures.[9-10] As a result, there is potential for LEV to replace PB as the first-line drug for neonatal seizure management.[4-5] However, numerous previous studies have examined LEV as a second-line antiepileptic therapy and the evidence supporting its use as a first-line drug for neonatal seizures remains inconclusive.[11-12]

This prospective randomized clinical trial aims to compare the efficacy and safety of levetiracetam versus phenobarbital in the initial treatment of neonatal seizures, with the goal of improving outcomes for affected infants.

METHODS

Study design

This prospective randomized controlled trial was conducted in the Level 3 NICU of tertiary care centre over period of twelve months. The study involved 150 neonates aged 0-28 days, diagnosed with clinical seizures. The neonates were randomly assigned to receive either Levetiracetam or Phenobarbitone as the first-line antiepileptic drug.

Inclusion criteria

Inborn and out born neonates (age 0-28 d) with seizures diagnosed by clinical criteria/signs or by electroencephalogram (EEG).

Exclusion criteria

Age>28 days. Neonates with hypoglycaemia, hypocalcaemia, hypomagnesemia and dyselectrolytemias. Neonates who received anticonvulsants prior to enrolment, neonates with major congenital malformations (congenital heart defects, neural tube malformations, diaphragmatic hernia, choanal atresia, esophageal atresia, tracheoesophageal fistula, omphalocele, gastroschisis, intestinal obstruction and imperforate anus).

Informed written consent was obtained from the parents or guardian of every neonate who enrolled for study.

Neonates with clinical seizures were randomly assigned to receive either intravenous PB or LEV with 1:1 allocation using sequentially numbered opaque and sealed envelope. Neonates received infusion over 15 minutes of either levetiracetam at 20 mg/kg or Phenobarbital at 20 mg/kg, with an additional 15 minutes allowed for the medication to produce effect. If seizures persisted or reoccurred even after 15 minutes of the first infusion, an additional dose of the same treatment type was given. Patients who had received levetiracetam at 20 mg/kg received an additional 10 mg/kg infusion over 15 minutes and patients who had received phenobarbitone at 20 mg/kg received an additional 10 mg/kg infusion over 15 minutes. If seizures still persisted or recurred after dose escalation up to 40 mg/dl of levetiracetam or phenobarbital, the patient were treated with additional drug according to institutional protocols (Figure 1).

Outcome measures

Cessation of seizures was defined as the disappearance of clinical seizures (e.g., no abnormal gaze or eye movement, tongue extension, apnoea, clonus, tonic or convulsive movements, etc).

Primary outcome measure

Neonates with seizure cessation when given levetiracetam (20-40 mg/kg) as first line compared to phenobarbitone (20-40 mg/kg) for 24 hours.

Secondary outcome measure

Dose escalation component-number of babies with seizure control at 40 mg/kg as compared to 20 mg/kg loading for both drugs Evaluation of adverse effects including hypotension, respiratory depression, bradycardia in both the groups

Neurological assessment of the infant at 3-month,6 month and 12 months. Neurological development was assessed on follow up using Hammersmith infant neurological examination (HINE) proforma.[13] It includes 26 items that assess five subsections: cranial nerve function, posture, movements, tone and reflexes. Each item can be scored from 0-3, 3 being considered as optimal giving a maximum score of 78. Global scores are reported as optimal if they are equal or above 57 at 3 months and 63 at 6-12 months of age. Lower scores are associated with poorer neurodevelopmental outcome. HINE scoring of<57 at 3 months has 96% sensitivity 87% specificity, 6-12 months score <63, 90% predictive value. <40 score at any age predicts severe cerebral palsy.

The information collected regarding all the selected cases was recorded in a Master chart in Microsoft Excel spread sheet. Data analyses was carried out using the recent most version of statistical Package for Social Sciences (SPSS) software. A ‘p’ value less than 0.05 will be considered as significant.

RESULTS

The study was conducted on a total of 150 neonates with clinical seizure. The flow of patients is described in the (Figure 2). Baseline characteristics were comparable in the two groups. The commonest Etiology for the seizure was hypoxic ischemic encephalopathy (Table 1). Seizure control was noted in 21.3% neonates in levetiracetam group, which was significantly lower as compared to neonates receiving phenobarbitone (53.3%, $p<0.05$) after first loading (Table 2). Requirement of further loadings and other drug was also found to be significantly higher in Levetiracetam group (25.3%) as compared to phenobarbitone group (10.7%, $p<0.05$).

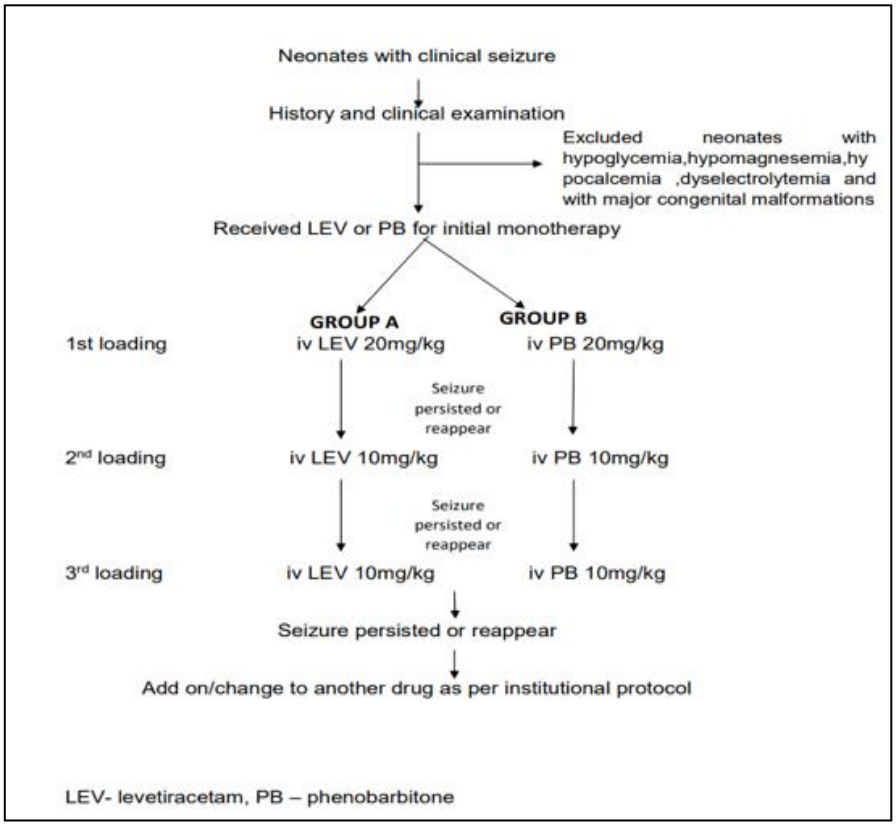

Figure 1: Plan of action.

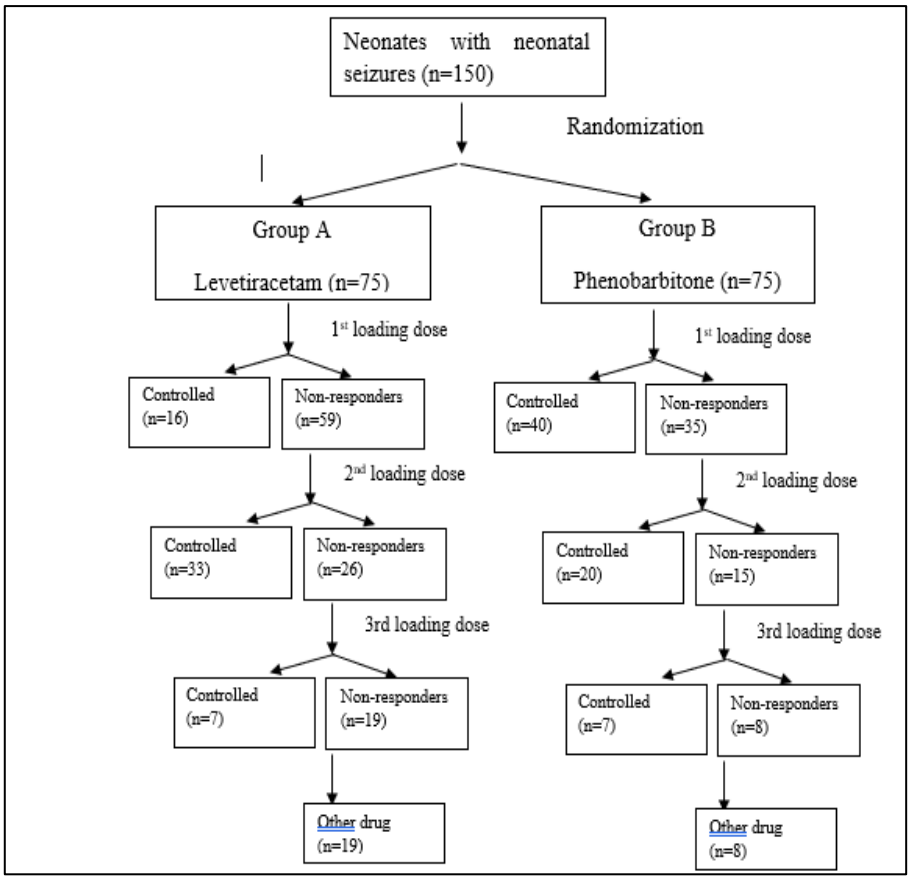

Figure 2: Flow of neonates in our study.

Adverse effects were reported in 5.3% cases in levetiracetam group and 25.3% cases in phenobarbitone group (Table 3). In phenobarbitone group, respiratory depression was the most frequently observed adverse effect documented in 13.3% cases, followed by bradycardia in 4% cases, Respiratory depression with hypotension and bradycardia in 4% cases, hypotension in 2.7% cases and Respiratory depression with hypotension in 1.3% cases.

Table 1: Comparison of baseline variables between two groups.

Baseline variables		Group				χ^2	P value
		Levetiracetam (n=75)		Phenobarbitone (n=75)			
		N	%	N	%		
Gender	Male	39	52.0	49	65.3	2.75	0.097
	Female	36	48.0	26	34.7		
Birth weight (in kg)	<1	0	0.0	0	0.0	0.35	0.554
	1-1.5	0	0.0	0	0.0		
	1.5-2.5	15	20.0	18	24.0		
	>2.5	60	80.0	57	76.0		
	Mean±SD	2.78±0.49		2.73±0.489			
Inborn/Outborn	Inborn	44	58.7	39	52.0	0.674	0.412
	Outborn	31	41.3	36	48.0		
Term/Preterm	Preterm	11	14.7	15	20.0	0.744	0.388
	Term	64	85.3	60	80.0		
Mode of delivery	NVD	54	72.0	58	77.3	0.564	0.453
	LSCS	21	28.0	17	22.7		
Diagnosis	HIE	46	61.3	53	70.7	1.54	0.464
	Sepsis	27	36.0	20	26.7		
	Others	2	2.7	2	2.7		

Table 2: Comparison of requirement of loading doses and other drugs between the groups.

Number of doses		Group				χ^2	P value
		Levetiracetam (n=75)		Phenobarbitone (n=75)			
		N	%	N	%		
1st loading dose	No	0	0.0	0	0.0	NA	NA
	Yes	75	100.0	75	100.0		
2nd loading dose	No	16	21.3	40	53.3	16.41	0.001
	Yes	59	78.7	35	46.7		
3rd loading dose	No	49	65.3	60	80.0	4.06	0.044
	Yes	26	34.7	15	20.0		
Requirement of other drug	No	56	74.7	67	89.3	5.47	0.019
	Yes	19	25.3	8	10.7		

Table 3: Comparison of adverse effects between two groups.

Adverse effect	Group			
	Levetiracetam (n=75)		Phenobarbitone (n=75)	
	N	%	N	%
None	71	94.7	56	74.7
Bradycardia	0	0.0	3	4.0
Hypotension	0	0.0	2	2.7
Respiratory depression	4	5.3	10	13.3
Respiratory depression, hypotension	0	0.0	1	1.3
Respiratory depression, Hypotension, Bradycardia	0	0.0	3	4.0
χ^2	13.34			
P value	0.02			

Table 4: Comparison of need for mechanical ventilation between the groups.

Mechanical ventilation	Group			
	Levetiracetam (n=75)		Phenobarbitone (n=75)	
	N	%	N	%
No	71	94.7	58	77.3
Yes	4	5.3	17	22.7
χ^2	9.36			
P value	0.002			

Table 5: Comparison of outcome between two groups.

Outcome	Group			
	Levetiracetam (n=75)		Phenobarbitone (n=75)	
	N	%	N	%
Discharge	72	96.0	64	85.3
Expired	3	4.0	11	14.7
χ^2	5.042			
P value	0.025			

Table 6: Comparison of HINE score between two groups stratified by diagnosis.

Diagnosis	HINE score		Group				χ^2	P value
			Levetiracetam		Phenobarbitone			
			N	%	N	%		
HIE	3 months	Suboptimal	18	42.9	14	40.0	0.064	0.80
		Optimal	24	57.1	21	60.0		
	6 months	Suboptimal	16	51.6	15	50.0	0.016	0.90
		Optimal	15	48.4	15	50.0		
	12 months	Suboptimal	10	50.0	6	42.9	0.169	0.68
		Optimal	10	50.0	8	57.1		
Sepsis	3 months	Suboptimal	2	9.5	0	0	0.063	0.80
		Optimal	19	90.5	17	100.0		
	6 months	Suboptimal	2	14.3	1	7.1	0.37	0.51
		Optimal	12	85.7	13	92.9		
	12 months	Suboptimal	2	28.6	0	0	2.64	0.10
		Optimal	5	71.4	8	100.0		
Other	3 months	Suboptimal	1	50.0	0	0	0.75	0.39
		Optimal	1	50.0	1	100.0		
	6 months	Suboptimal	1	100.0	0	0	NA	NA
		Optimal	0	0	0	0		
	12 months	Suboptimal	1	100.0	0	0	NA	NA
		Optimal	0	0	0	0		

Mechanical ventilation was required in 5.3% cases in levetiracetam group; however, requirement for mechanical ventilation was significantly higher in patients of phenobarbitone group (22.7%, $p<0.05$) (Table 4). Mortality rate was 4% in levetiracetam group as compared to 14.7% in phenobarbitone group (Table 5). The observed difference in HINE score among two groups at 3 months, 6 months and 12 months was statistically not significant ($p>0.05$) (Table 6).

DISCUSSION

This prospective randomized controlled trial aimed to compare the efficacy and safety of intravenous levetiracetam vs phenobarbitone in the treatment of neonatal seizures. Phenobarbitone demonstrated a higher efficacy in seizure control (53.3%) as compared to levetiracetam (21.3%) as first line antiepileptic. Levetiracetam required more frequent dosing to achieve the same level of seizure control as phenobarbitone. Studies by Pervez et al, (2018) and Prakash et al, (2019)

also found phenobarbitone to have a higher initial efficacy as compared to levetiracetam.[14,15] Levetiracetam exhibited a more favorable safety profile with significantly lesser adverse effects (5.3%) compared to phenobarbitone. Respiratory depression was observed in 13.3% of cases, bradycardia occurred in 4% of neonates and hypotension was noted in 2.7% of cases in the phenobarbitone group. 22.7% of neonates in the phenobarbital group required mechanical ventilation, whereas only 5.3% in the levetiracetam group needed such support ($p<0.002$). This significant difference highlights the better safety profile of levetiracetam concerning respiratory function. At the 3 months follow-up, the mean HINE score in the Levetiracetam group was 61.15±7.244, while in those receiving Phenobarbitone, it was slightly higher at 62.02±8.452. However, the difference was not statistically significant ($p=0.486$). In the Levetiracetam group, 67.7% of neonates had an optimal HINE score, compared to 73.6% in those receiving Phenobarbitone, indicating that both drugs had a similar impact on early neurological outcomes, study showed no significant difference among the two groups at 3, 6 and 12-months follow-ups.

CONCLUSION

The outcome of this study suggests that while phenobarbitone remains a potent option for initial seizure control, levetiracetam's favourable safety profile and comparable long-term neurological outcomes make it an attractive alternative. Levetiracetam can be particularly beneficial in neonates at more risk of adverse effects from phenobarbitone. Further studies with larger sample sizes and longer follow up periods are necessary to validate these findings and to explore the potential of higher dose levetiracetam protocols. In future levetiracetam can be considered as the first line antiepileptic drug but with an initial higher loading dose as compared to phenobarbitone although more studies are required to support the fact. Clinicians should consider these findings when selecting an appropriate treatment regimen for neonatal seizures, balancing the immediate need for seizure cessation with the long-term safety and developmental outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Bhasin D, Sethi A, Chaurasiya OS, Chhabra K. A comparative study on the efficacy and safety of intravenous levetiracetam and phenobarbitone in the treatment of neonatal seizures. Int J Contemp Pediatr 2025;12:615-20.