IJPSR (2025), Volume 16, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 February 2025; received in revised form, 19 February 2025; accepted, 21 February 2025; published 01 July 2025

RANDOMIZED CONTROLLED TRIAL BETWEEN LEVETIRACETAM AND PHENOBARBITONE IN THE TREATMENT OF NEONATAL SEIZURE DUE TO PERINATAL ASPHYXIA

Mayank Kumar, Chandan K. R. Abhishek * and Sujit Kumar

Department of Pediatrics, N. M. C. H, Patna - 800007, Bihar, India.

Keywords:

Phenobarbitone, Levetiracetam, AED, Seizure

Correspondence to Author:
Dr. Chandankr Abhishek

Senior Resident,
Department of Pediatrics,
N. M. C. H, Patna - 800007,
Bihar, India.

E-mail: imckabhishek@gmail.com

ABSTRACT: Background: Seizure occurs more frequently in neonatal period than in any other time of life. Estimated incidence of neonatal seizure varies according to case definition, method of ascertainment and definition of the neonatal period and ranges from 1 to 5 per 1000 live births. **Methodology:** Neonates admitted in Nicu, department of Paediatrics, Nalanda Medical College and Hospital, Patna in time period of Aug 2023- July 2024. Sample size was 100. For seizure control in neonates with active convulsion either levetiracetam or phenobarbitone was allocated to the randomization. Intravenous levetiracetam is given at a loading dose of 20 mg/kg. Maintenance is given at a dose of 10mg/kg 8 hourly. Intravenous phenobarbitone is given at a dose of 20mg/kg and 5mg/kg 12hrly of maintenance dose. **Results:** In levetiracetam Group, 23(46.0%) patients had1number of loading dose required, 14(28.0%) patients had 2 number of loading dose required and 13(26.0%) patient had 3number of loading dose required. In phenobarbitone Group, 28(56.0%) patients had 1number of loading dose required, 9(18.0%) patients had 2 number of loading dose required and 13(26.0%) patient had 3 number of loading dose required. **Conclusion:** Higher neonates were required only one loading dose of AED in phenobarbitone group compared to levetiracetam group .Majority patients needed 10 minute time period for termination of acute seizure in phenobarbitone group compared to levetiracetam group. Mortality rate was higher in phenobarbitone group compared to levetiracetam group.

INTRODUCTION: Seizure occurs more frequently in neonatal period than in any other time of life. Estimated incidence of neonatal seizure varies according to case definition, method of ascertainment and definition of the neonatal period and ranges from 1 to 5 per 1000 live births [1]. Common clinical seizure patterns include: Focal clonic seizure, focal tonic seizure, Myoclonic Seizure and Autonomic Seizure. Hypoxic- ischemic encephalopathy (HIE), is the most common cause of neonatal seizures, usually occurs within first 24 hours of life.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(7).2015-20

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(7).2015-20

It accounts for 50 - 75 % of neonatal seizures [2]. Perinatal stroke is the second most common cause of seizures in the newborn period accounting for up to 20% [3] of neonatal seizure. Intracranial hemorrhages are responsible for 10% to 15% of neonatal seizures. Acute metabolic disorders are rapidly remediable conditions, the focus of the initial investigations in neonatal seizure.

These include- Hypoglycaemia, Hypocalcaemia and Hypomagnesaemia. Malformations/ Structural lesions include 5% of neonatal seizures, caused by cerebral dysgenesis, can cause seizure from 1st day of life. Epilepsy syndrome includes 1% of the cases of seizures in the newborn period. At present phenobarbitone is the drug of choice for treatment of neonatal seizure which have some adverse effects on neurodevelopmental outcome in addition, the known risk of cognitive impairment of

phenobarbitone in infant and toddlers should be considered [4] Levetiracetam is a novel antiepileptic agent well tolerated in neonatal period. Levetiracetam is rapidly and completely absorbed after oral administration with lesser side effects [5]. Levetiracetam has not been found to increase neuronal apoptosis in animal models [6].

So, this study is intended to evaluate the efficacy of levetiracetam and phenobarbitone in neonatal seizure which may open a new frontier of neonatal seizure management and may help to tailor new guideline.

MATERIAL AND METHODS: Neonates admitted in neonatal intensive care unit, department of Paediatrics, Nalanda Medical College and Hospital, Patna in time period of Aug 2023- July 2024. Sample size was be 100. Sample size collected from patient admitted in neonatal intensive care unit presented with seizures due to perinatal asphyxia.

Study Design: Randomized controlled trial.

Inclusion Criteria: age group less than and equal to 28 days of life presenting with seizures due to perinatal asphyxia

Exclusion Criteria: Neonates with

A. Age group more than 28 days

B. Neonates with congenital malformation of the brain.

C. Neonates with C.N.S infections.

D. Neonates with acute metabolic disorders.

Methods of Study: For seizure control in neonates with active convulsion either levetiracetam or phenobarbitone was allocated to the randomization.

Intravenous levetiracetam is given at a loading dose of 20 mg/kg. Maintenance is given at a dose of 10mg/kg 8 hourly. Intravenous phenobarbitone is given at a dose of 20mg/kg and 5mg/kg 12hrly of maintenance dose.

Statistical Analysis: For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 29.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. p-value ≤ 0.05 was considered for statistically significant.

RESULTS AND OBSERVATION: In our study, 64(64.0%) patients had presented on day 1 of life, 27(27.0%) patients on day 2 of life, 6(6.0%) patients on day 3 of life and 3(3.0%) patient had on day 4 of life.

TABLE 1: DISTRIBUTION OF DAY OF LIFE

Day of life	Frequency	Percent
Day 1	64	64.0%
Day 2	27	27.0%
Day 3	6	6.0%
Day 4	3	3.0%
Total	100	100.0%

In our study, 13(13.0%) patients were PRETERM and 87(87.0%) patients were TERM.

TABLE 2: DISTRIBUTION OF TERM / PRETERM

T/PT	Frequency	Percent
P.T	13	13.0%
T	87	87.0%
Total	100	100.0%

TABLE 3: DISTRIBUTION OF PATIENTS IN RESPECTIVE GROUP BASED ON AED RECEIVED

Group	Frequency	Percent
Levetiracetam	50	50.0%
Phenobarbitone	50	50.0%
Total	100	100.0%

In our study, 50(50.0%) patients were on levetiracetam as 1st AED and 50(50.0%) patients were on phenobarbitone as 1st AED.

TABLE 4: DISTRIBUTION OF PATIENTS BASED ON NUMBERS OF LOADING DOSES REQUIRED

Number of loading dose required	Frequency	Percent
1	51	51.0%
2	23	23.0%
3	26	26.0%
Total	100	100.0%

In our study, 51(51.0%) patients had required only one loading dose of AED, 23(23.0%) patients had required two loading dose of AED and 26(26.0%) patients had required three loading dose of AED.

TABLE 5: DISTRIBUTION OF PATIENTS IN RESPECTIVE GROUP ON THE BASIS OF 2ND AED REQUIRED

2nd AED	Frequency	Percent
No	68	68.0%
yes, phenobarbitone	16	16.0%
yes, levetiracetam	16	16.0%
Total	100	100.0%

In our study, 16(16.0%) patients had 2nd AED phenobarbitone and 16(16.0%) patients had 2nd AED levetiracetam.

TABLE 6: DISTRIBUTION BASED ON MEAN SEIZURE FREE INTERVAL AFTER TERMINATION OF ACUTE SEIZURE IN MIN

	Number	Mean	SD	Minimum	Maximum	Median
Seizure Free Interval After Termination of Acute Seizure In Min	34	182.3529	304.5221	20.0000	1440.0000	60.0000

In above table showed that the mean seizure free interval after termination of acute seizure in mins (mean± SD) of patients was 182.3529 ± 304.5221.

TABLE 7: ASSOCIATION BETWEEN NUMBER OF LOADING DOSE REQUIRED: GROUP

	Group		
Number of Loading Dose Required	Levetiracetam	Phenobarbitone	Total
1	23	28	51
Row %	45.1	54.9	100.0
Col %	46.0	56.0	51.0
2	14	9	23
Row %	60.9	39.1	100.0
Col %	28.0	18.0	23.0
3	13	13	26
Row %	50.0	50.0	100.0
Col %	26.0	26.0	26.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

Chi-square value: 1.5772; p-value: 0.4545.

In levetiracetam Group, 23(46.0%) patients had1number of loading dose required, 14(28.0%) patients had 2 number of loading dose required and 13(26.0%) patient had 3 number of loading dose required. In phenobarbitone Group, 28(56.0%) patients had 1number of loading dose required, 9(18.0%) patients had 2number of loading dose required and 13(26.0%) patient had 3 number of loading dose required. Association of No of Loading Dose Required vs group was not statistically significant (p=0.4545).

TABLE 8: ASSOCIATION BETWEEN TIME PERIOD REQUIRED FOR TERMINATION OF ACUTE SEIZURE: PARTICULAR AED RECEIVED

	Group		
Time period required for termination of acute seizure	Levetiracetam	Phenobarbitone	Total
10 min	23	28	51
Row %	45.1	54.9	100.0
Col %	46.0	56.0	51.0
15 min	15	9	24
Row %	62.5	37.5	100.0
Col %	30.0	18.0	24.0
20 min	12	13	25
Row %	48.0	52.0	100.0
Col %	24.0	26.0	25.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

Chi-square value: 2.0302; p-value: 0.3624

In levetiracetam Group, 23(46.0%) patients had 10 mins time period required for termination of acute seizure, 15(30.0%) patients had 15 mins time period required for termination of acute seizure and 12(24.0%) patients had 20 mins time period required for termination of acute seizure. In phenobarbitone Group, 28(56.0%) patients had 10 min time period required for termination of acute seizure, 9(18.0%) patients had 15 min time period required for termination of acute seizure and 13(26.0%) patients had 20 min time period required for termination of acute seizure. Association of time period required for termination of acute seizurevs group was not statistically significant (p=0.3624).

TABLE 9: ASSOCIATION OF PATIENTS REQUIRED2ND AED AFTER 1STAED

	Group		
2nd AED	**Levetiracetam**	**Phenobarbitone**	**Total**
No	34	34	68
Row %	50.0	50.0	100.0
Col %	68.0	68.0	68.0
yes, phenobarbitone	16	0	16
Row %	100.0	0.0	100.0
Col %	32.0	0.0	16.0
yes, levetiracetam	0	16	16
Row %	0.0	100.0	100.0
Col %	0.0	32.0	16.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

Chi-square value: 32.0000; p-value :< 0.0001.

In levetiracetam Group, 16(32.0%) patients had 2nd AED phenobarbitone. In phenobarbitone Group, 16(32.0%) patientss had 2nd AED levetiracetam. Association of 2nd AEDvs group was statistically significant (p<0.0001).

TABLE 10: ASSOCIATION BETWEEN OUTCOME: GROUP RECEIVED PARTICULAR AED

	Group		
Outcome	**Levetiracetam**	**Phenobarbitone**	**Total**
death	9	10	19
Row %	47.4	52.6	100.0
Col %	18.0	20.0	19.0
discharged	41	40	81
Row %	50.6	49.4	100.0
Col %	82.0	80.0	81.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

Chi-square value: 0.0650; p-value: 0.7987, Odds Ratio: 0.8780 (0.3229, 2.3877).

In levetiracetam Group, 9(18.0%) patients were death and 41(82.0%) patients were discharged. In phenobarbitone Group, 10(20.0%) patients were death and 40(80.0%) patients were discharged. Association of Outcomevs group was not statistically significant (p=0.7987).

TABLE 11: MEAN NO OF LOADING DOSE REQUIRED FOR TERMINATION OF ACUTE SEIZURE: GROUP RECEIVED PARTICULAR AED

		Number	**Mean**	**SD**	**Minimum**	**Maximum**	**Median**	**p-value**
No of Loading	levetiracetam	50	1.8000	.8330	1.0000	3.0000	2.0000	0.5569
Dose Required	phenobarbitone	50	1.7000	.8631	1.0000	3.0000	1.0000	

In levetiracetam Group, the mean No of Loading Dose Required (mean± s.d.) was 1.8000 ± .8330. In phenobarbitone Group, the mean No of Loading Dose Required (mean± s.d.) was 1.7000± .8631. Difference of mean No of Loading Dose Required with Group was not statistically significant (p=0.5569).

DISCUSSION: In our study we found that majority of neonates were required [51(51.0%)] only one loading dose of AED, Compared to two loading dose AED in [23(23.0%)], and three loading dose AED [26(26.0%)]. we also found that more number of neonates were required only one loading dose in [28(56.0%)] phenobarbitone group compared to [23(46.0%)] levetiracetam group but this was not statistically significant (p=0.4545).

Prasath Ramachandran H *et al* [7](2020) found that the quest persists for an ideal newer antiepileptic drug (AED) with better efficacy and tolerability. Neonates with hypoglycemia, hypocalcemia, hypomagnesemia, inborn errors of metabolism, or those who received other AEDs prior to admission were excluded from the study. 20mg/kg Intravenous LEV was administered as first-line AED and graded up to 40mg/kg if seizures were not controlled in 2 h; thereafter, second-line AED was added. Only 36.2% (21/58) of the cases responded to LEV as first-line AED.

Our study showed that majority of neonates don't need [68(68.0%)] 2nd AED, and this was statistically significant (p<0.0001). In our study 16 % of levetiracetam group needed 2 AED. Meena J. *et al* [8] (2023) showed that this study compares the efficacy of levetiracetam with phenobarbital in early onset seizures in term, late preterm neonates. Efficacy was same in phenobarbital and LEV group. Adverse effects were lesser in LEV group. We found that in our study majority neonates were [81(81.0%)] alive compared to [19(19.0%)] mortality. Mortality rate were higher in [10(20.0%)] phenobarbitone group compared to [9(18.0%)] levetiracetam group. This was not statistically significant (p=0.7987). We found in levetiracetam group majority of neonates were 1 day old compared to phenobarbitone group but this was not statistically significant. In phenobarbitone group higher no. of neonates were term, compared to levetiracetam group but this was not statistically significant.

CONCLUSION: We found equal neonates were in both group levetiracetam and phenobarbitone. Higher neonates were required only one loading dose of AED in phenobarbitone group compared to levetiracetam group but this was not statistically significant.

Majority patients needed 10 minute time period for termination of acute seizure in phenobarbitone group compared to levetiracetam group which was not statistically significant. Mortality rate was higher in phenobarbitone group compared to levetiracetam group. This was not statistically significant. Majority of neonates required additional doses inlevetiracetam group compared to phenobarbitone group but this was not statistically significant.

Limitations of the Study: In spite of every sincere effort my study has lacunae.

The notable short comings of this study are:

1. The sample size was very small. Only 100 cases are not sufficient for this kind of study.
2. The study has been done in a single centre.
3. The study was carried out in a tertiary care hospital, so hospital bias cannot be ruled out.

ACKNOWLEDGEMENT: The authors would like to thank Pediatrics department of N.M.C.H, Patna for their kind support during experimentation.

Financial Disclosure: The authors hereby declare that the present study has not received financial support of any sort.

CONFLICT OF INTEREST: None

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How to cite this article:
Kumar M, Abhishek CKR and Kumar S: Randomized controlled trial between levetiracetam and phenobarbitone in the treatment of neonatal seizure due to perinatal asphyxia. Int J Pharm Sci & Res 2025; 16(7): 2015-20. doi: 10.13040/IJPSR.0975-8232.16(7).2015-20.