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A Randomized Controlled Trial of Levetiracetam vs Phenobarbitone in The Treatment of Neonatal Seizures

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Abstract

Background: Seizures are the most common manifestations of neurological insult during the neonatal period. Neonatal seizures place the neonate at an increased risk for neurologic impairment, developmental delay, and even death. The objective of the study was to compare the efficacy of levetiracetam versus phenobarbitone in the treatment of neonatal seizures.

Methods: A randomized controlled trial was conducted in neonatal intensive care unit (NICU), at tertiary care hospital, Udaipur, Rajasthan, over a period of January 2020 to August 2021, after obtaining permission from ethical committee of the institute. Total 36 neonates (age 0-28 d) with clinical seizures were included in the study. These were divided into two groups by simple randomization. Levetiracetam was given in one group while phenobarbitone was given to another group intravenously. The proportion of patients achieving cessation of seizures following the first or second dose of the drug (PB or LEV) and those who remained seizure-free for the next 24 hours was considered as the primary outcome. The proportion of patients experiencing adverse events was the measure of secondary outcome.

Results: Among 18 neonates in each group, cessation of clinical seizure was observed in 15 (83.33%) neonates in the levetiracetam group, and 12 (66.67%) neonates in the phenobarbitone group**.** The mean duration of NICU stay in the levetiracetam group was 7± 0.82 days and in the phenobarbitone group, it was 11±1 days, which was statistically significant (p value<0.001). In phenobarbitone group, adverse effects e.g. respiratory abnormalities, hypotension and requirement of vasopressor support were higher than in levetiracetam group, which were statistically significant. (p value <0.02)

Conclusions: Levetiracetam may be a safer and effective alternative to phenobarbitone in the treatment of neonatal seizures, as a first-line anti-epileptic drug. The overall rates of adverse events are low and mild in severity, suggesting a fairly safe profile for levetiracetam.

Keywords: Antiepileptic drugs, Seizures, Management, Neonate, Outcome

Introduction:

Seizures are the most common manifestations of neurological insult during the neonatal period.[1] Neonatal seizure place the neonate at an increased risk for neurologic impairment, developmental delay, and even death.[2] Compared with seizures at older ages, neonatal seizures are different in etiology, semiology, electroencephalographic signatures and can be refractory to antiepileptic drugs that are effective in other age group populations.

The risk of seizures is higher in the neonatal period. The etiology and presentation of seizures in the neonatal period are varied from child and adult. The most common etiology of symptomatic seizures is hypoxic- ischemic encephalopathy, which affects approximately 1-2 /100 live births.[3]

The next most common causes are infectious etiologies: common bacterial infections are Group B streptococcus and E.coli. Nonbacterial causes include: Intrauterine toxoplasmosis, cytomegalovirus (TORCHes) infections. Other includes cerebrovascular disorders, including arterial and venous stroke, intracerebral hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage also frequently present with clinical seizures. Inborn error of metabolisms can also represent with seizures in the first days of life such as hyperglycinemia, type 2 glutaric aciduria, urea cycle disorders and other metabolic disorders.

Historically, the primary treatment option for neonatal seizures has been phenobarbitone, followed by phenytoin or fosphenytoin.[4] Common adverse effects of phenobarbitone are hypotension, hypothermia, sedation, poor feeding, respiratory depression and developmental delay. Continuous monitoring is required in neonates with hepatic and renal impairment and with respiratory failure.

Levetiracetam, a novel agent, may have a better safety profile because it does not cause apoptosis in the nervous system in infant rodents according to experimental studies.[5,8,9] It possesses a more desirable pharmacokinetic profile for use in neonates due to its linear time-dependent kinetics, reduced protein binding, and renal-dependent clearance. [6,7] When looking at long-term effects in neonates treated for seizures, phenobarbitone exposure was associated with worsening neurodevelopmental outcomes, which were not seen when compared to the results obtained with levetiracetam and continuous monitoring is not required with levetiracetam.[10]

Literature pertaining to the use of LEV in neonatal seizures is limited also there is a lack of randomized controlled trials. Despite some studies and levetiracetam's favorable pharmacokinetic and safety profile, use of levetiracetam as a first-line drug for neonatal seizures is not well accepted.[11] Additionally; current guidelines for neonatal seizure management either do not list levetiracetam as an option or only list it as a second-line agent. So the primary objective of this study is to evaluate the effectiveness of levetiracetam as a first-line treatment for the treatment of neonatal seizures.

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 the PB group.[12]

Methods:

This was a randomized controlled trial, conducted in neonatal intensive care unit (NICU), at tertiary care hospital, Udaipur, Rajasthan, over a period of January 2020 to August 2021, after obtaining permission from ethical committee of the institute. Neonates (age 0-28 d) with clinical seizures were included in the study. Neonatal seizures were clinically defined as abnormal, stereotyped and paroxysmal dysfunction in the central nervous system, occurring within the first 28 days after birth. Neonates with metabolic disturbances include hypoglycemia, hypocalcaemia, hypomagnesaemia, those who received anticonvulsants prior to enrollment, those with major congenital malformations e.g., congenital heart defects, neural tube malformations, diaphragmatic hernia, choanal atresia, esophageal atresia, tracheoesophageal fistula, omphalocele, gastroschisis, imperforated anus) were excluded.

Neonates were divided into two groups. Neonates having clinical seizures were randomly divided to receive either phenobarbitone or levetiracetam with a 1:1 allocation as per a computer-generated randomization and using sequentially numbered, opaque and sealed envelopes. When a neonate was eligible to be enrolled, clinician who was not part of the study opened the envelope. The study was single blinded, Investigator and statistician were aware of the drug, being given to the patient.

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

Blood sugar and ionic calcium level were performed after ensuring patency of the airway, breathing and circulation. Neonates were randomized for intervention to receive either LEV (20 mg/ kg) or PB (20 mg/kg) intravenously, if seizures persisted even

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after correction of hypoglycemia and hypocalcaemia. Levetiracetam was given in dilution in normal saline to achieve a concentration of 20 mg/ml and administered intravenously at a rate of 1 mg/ kg/min under cardiac and respiratory monitoring. If seizures terminated, levetiracetam 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, the patient was switched over to PB. Phenobarbitone was given in the dose of 20 mg/kg diluted in 1: 10 normal saline, intravenously slowly at the rate of 1 mg/kg/min under cardiac and respiratory monitoring. If seizures were terminated, it was given 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 even after two loading doses, the neonate 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 who remained seizure-free for the next 24 hours was considered as the primary outcome. The proportion of patients experiencing adverse events was the measure of secondary outcome. Clinically if there were no abnormal movement/ eyeball deviation or nystagmus, no change in heart rate, no change in respiration/saturation and autonomic dysfunction was defined as the termination of seizure. Adverse effects - desaturation, decreased respiratory rate, increased ventilation requirement, arrhythmias, blood pressure, or heart rate fluctuations by > 10% compared to previous 2 hours, or if vasopressors were initiated or increased, etc. were recorded within two hours of drug administration.

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 Research Ethics Board of Geetanjali Medical College and Hospital (GMCH), Udaipur (Ref: GU/HREC/EC/2019/1756). The sample size required for this study was 36 (18 in each group) with 95% confidence level and 80% power of study, which was decided on the basis of incidences in the previous studies.

Statistical Analysis:

The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analyzed and statistically evaluated using SPSS-PC-20 version. Quantitative data were expressed in mean, standard deviation and differences between two comparable groups were tested by student's t-test (unpaired) while quantitative data were expressed in percentage. Statistical differences between the proportions were tested by chi-square or Fisher's exact test. p- value less than 0.05 was considered statistically significant.

Results:

A total of 36 neonates were enrolled in this study. The demographic and anthropometric data in both groups were shown. Both groups were comparable in term of mean age, weight and gender. No significant difference was observed between both groups.

Table 1: Comparison of demographic and anthropometric data in both groups

	LEV Group (n=18)		**PB Group (n=18)**		p value
Age (days)	**Mean**	**SD**	**Mean**	**SD**	0.9701
	4.5	3.12	4.72	2.95	
Weight (grams)	2809.94	513.28	2732.67	487.14	0.6471
Gestational age (weeks)	37.09	2.08	36.89	2.04	0.9921
	Number	**%**	**Number**	**%**	
Male	13	72.22	14	77.78	0.7003

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Female	5	27.78	4	22.22	

Baseline characteristics were comparable in the two groups.

The commonest etiology for seizures was hypoxic-ischemic encephalopathy (HIE). Focal clonic seizures constituted the most common type of seizure in the study population.

Table 2: Comparison of baseline characteristics of the study groups

Mode of delivery	**LEV Group (n=18)**	**PB Group (n=18)**
	Number (%)	**Number (%)**
Lower segment caesarean section	10 (55.56)	8 (44.44)
Vaginal delivery	8 (44.44)	10 (55.56)
Etiologies of seizures	**Number (%)**	**Number (%)**
Hypoxic ischemic encephalopathy	9 (50.00)	8 (44.44)
Sepsis	5 (27.78)	7 (38.89)
Benign neonatal epilepsy syndrome	1 (5.56)	0 (0.00)
Intracranial hemorrhage	2 (11.11)	1 (5.56)
Inborn errors of metabolism	0 (0.00)	1 (5.56)
Unknown	1 (5.56)	1 (5.56)

Among 18 neonates in each group, following the first dose of the drug, seizures stopped in 12 (66.67%) neonates in the levetiracetam group, and 9 (50.00%) neonates in the phenobarbitone group. Among 18 neonates in each group, following the 1 or 2 doses of the same drug, cessation of clinical seizure was observed in 15 (83.33%) neonates in the levetiracetam group, and 12 (66.67%) neonates in the phenobarbitone group**.**

Table 3: Distribution of neonates according to the cessation of clinical seizure after one/two doses of the drug

Cessation of clinical seizure after 1or 2 doses of the drugs	**LEV Group (n=18)**		**PB Group (n=18)**		p value
	Number	**%**	**Number**	**%**	
Yes	15	83.33	12	66.67	0.2551
Recurrence of clinical seizure	3	16.67	6	33.33	
Total	18	100	18	100	

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Recurrence of seizure [after 1or 2 doses of the drugs] was observed in 3 (16.67%) neonates in the levetiracetam group, and 6 (33.33%) neonates in the phenobarbitone group, which required the administration of another antiepileptic drug.

3 neonates who did not respond to two loading doses of levetiracetam, 2 neonates responded after the administration of phenobarbitone while 6 neonates who did not respond to two loading doses of phenobarbitone, 4 neonates achieved cessation of seizure after the administration of levetiracetam.

Mean seizure free interval (hours) [In case of recurrence of seizure] suggested that in the levetiracetam group it was higher e.g. 3.83± 0.35 hours and in the phenobarbitone group, it was 1.93± 0.17 hours, which was statistically significant

.

Table 4: Distribution of neonates according to adverse effects following the administration of drugs

Adverse effects	**LEV Group (n=18)**	**PB Group (n=18)**	p value
	Number (%)	**Number (%)**	
Bradycardia*	1 (5.56)	5 (27.78)	0.0778
Respiratory abnormality#	2 (11.11)	7 (38.89)	0.0139
Hypotension+	1 (5.56)	7 (38.89)	0.0177
Sedation	1 (5.56)	5 (27.78)	0.0778
Vasopressor support	1 (5.56)	7 (38.89)	0.0177
Ventilation requirement=	1 (5.56)	5 (27.78)	0.0778
O_2 requirement	4 (22.22)	8 (44.44)	0.1594

This table shows the various adverse effects following the administration of drugs. A statistically significant difference was observed in respiratory abnormality, hypotension and vasopressor support.

* <100/min

#central apneas, desaturation, reduced respiratory rate, a requirement of oxygen supplementations or ventilation support

+blood pressure fluctuations by more than 10% compared to the previous 2 hours

=requirement of tidal volume more than 6 mL/kg on volume controlled-ventilator, peak inspiratory pressure (PIP) more than 22 cm H2O in preterm and 23 cm H2O, mean airway pressure (MAP) of more than 12 cmH2O on a pressure-controlled ventilator.

Mean time of introduction of feeds after cessation of seizure in LEV group was 22.78± 1.86 hours and in PB group, it was higher (35.39± 5.35 hours), which was statistically significant. (p value <0.05)

Out of 18 neonates in each group, the mean duration of NICU stay in the levetiracetam group was 7± 0.82 days and in the phenobarbitone group, it was 11±1 days, which was statistically significant. (p value <0.05)

Discussion:

Neonatal seizure is one of the important neurological emergencies requiring immediate medical care. Therefore it is important to early recognition, determine the cause and treat it appropriately. It is defined clinically as a paroxysmal alteration in neurologic function, i.e., motor, behavior and/or autonomic function.

LEV was effective in resolving neonatal seizures and was more safely administered in the current study. Most of the studies have seen the efficacy of levetiracetam either separately or compared with other drugs in adults. We found limited evidence regarding the best pharmacologic treatment for neonatal seizures but were able to devise a treatment algorithm from available data.

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In present study, mean age, weight and gender were comparable in both groups. (p value= 0.9701, 0.6471, 0.7003 respectively.) In the present study, we documented better anticonvulsant efficacy and safety of LEV in comparison to PB as a first line anticonvulsant drug in the treatment of neonatal seizures. After administration of the first dose of the drug, seizures stopped in 12 (66.67%) neonates in the levetiracetam group, and 9 (50.00%) neonates in the phenobarbitone group in our study. Following the 1 or 2 doses of the same drug, cessation of clinical seizure was observed in 15 (83.33%) neonates in the levetiracetam group, and 12 (66.67%) neonates in the phenobarbitone group**.** Both groups were comparable and no statistically significant difference was observed (p value>0.05).

However, seizure stoppage was observed in 28 of the 42 (66.6%) neonates of the LEV group and 31 of 38 (81.5%) neonates receiving PB after the first dose (p>0.05) in the study by *Prakash A* et al. [13] Similar to our study, *Gowda V K* et al observed that after giving the first dose of a drug, seizures stopped in 60% of neonates in LEV group, and 50% of neonates in PB group while 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 of the same drug. [14] Seizure cessation was seen in 35% of neonates within 24 hours, including termination in 88% and reduction by >50% in 12% neonates according to a study by *Abend N* et al. [15] *Ramantani* et al published that 30 (78%) out of 38 infants were seizure-free after receiving LEV. [17] *Raffaele Falsaperla* et al observed that all the patients who responded to the treatment with the levetiracetam showed a variable duration of cessation of seizure from 24 hours to 15 days (mean duration of seizure cessation: 96±110.95 hours). [16] *Kreimer A* et al concluded that 83% had seizure control with levetiracetam monotherapy or combination therapy of levetiracetam plus fosphenytoin or phenobarbitone.[18]

In the present study, 3 neonates who did not respond to 2 loading doses of levetiracetam, 2 neonates achieved seizure termination after administration of phenobarbitone while 6 neonates who did not respond to 2 loading doses of phenobarbitone, 4 neonates responded after administration of levetiracetam (p value >0.05). Similar to our study, *Gowda V K* et al published that among 50 in each group, 3 neonates out of the 7 who did not respond to LEV loading doses, responded to PB while out of the 19 neonates who did not respond to PB, 16 showed seizure cessation after administration of LEV.[14]

We observed higher side effects in the phenobarbitone group e.g. bradycardia (27.78%), hypotension (38.89%), respiratory depression (38.89%), sedation (27.78%), ventilation and oxygen requirements than in the levetiracetam group. A statistically significant difference (p value <0.05) was observed in respiratory abnormality, hypotension and vasopressor support. In our study, intergroup comparison in heart rate, respiratory rate, systolic and diastolic blood pressures revealed that phenobarbitone had suppression effects on vital parameters and was statistically significant at 15 min and 30 min, whereas no such significant effects on cardiorespiratory parameters were reported in the levetiracetam group.

Maitre et al published a retrospective study to evaluate the neurodevelopmental progression of 28 neonates treated with phenobarbital and LEV concluded that increased exposure to PB was associated with the poor neurodevelopmental outcome than with LEV.[19] Short term side effects (cardiac and respiratory depression and sedation) were noted in 52.6% of neonates in PB group whereas 7.1% of babies in LEV group (p<0.05) and long term developmental and neuromotor complications were more in the PB group than LEV group (p<0.05) at 1 year of age in the study by *Prakash A* et al.[13] *Raffaele Falsaperla* et al published that after administration of LEV, 50% of the cases had lethargy and feeding difficulty, and in two cases had minor hypertransaminasemia however, all improved after the modifications of LEV doses.[16] *Khan* et al did a study on 22 neonates on treatment with LEV; however no significant side effects were reported by them. The study by *Gowda V K* et al noticed neonates had adverse effects in the phenobarbitone group (hypotension in 5 neonates, bradycardia in 3, and requirement of mechanical ventilation in 2) whereas none had any adverse reaction in the levetiracetam group.[14]

The limitation of our study was that we could not perform electroencephalographic monitoring to document the cessation of seizure activity. Lack of long-term follow-up and inability to perform

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therapeutic drug monitoring of levetiracetam and phenobarbitone were the other limitations of the present study. The sample size of our study was also small for the outcomes related to various adverse effects.

Conclusion:

Levetiracetam may be a safer and effective alternative to phenobarbitone in the treatment of neonatal seizures, as a first-line anti-epileptic drug. However, we need further clinical studies with a large sample size to further define the efficacy of levetiracetam in the treatment of neonatal seizures. The results support the overall conclusion that LEV is comparable in its efficacy to PB for treating neonatal seizures. The overall rates of adverse events are low and mild in severity, suggesting a fairly safe profile for LEV in an actual clinical context.

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Tables:

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Sepsis	5 (27.78)	7 (38.89)
Benign neonatal epilepsy syndrome	1 (5.56)	0 (0.00)
Intracranial hemorrhage	2 (11.11)	1 (5.56)
Inborn errors of metabolism	0 (0.00)	1 (5.56)
Unknown	1 (5.56)	1 (5.56)

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