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Comparison of Levetiracetam and Phenobarbital for Treating Neonatal Seizures Associated with Hypoxic-Ischemic Encephalopathy

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ABSTRACT

***Objective*:** To compare the effectiveness of Levetiracetam and Phenobarbital for treating neonatal seizures associated with hypoxic-ischemic encephalopathy.

***Study Design*:** Quasi-experimental study.

***Place and Duration of the Study*:** Department of Neonatology, The Children's Hospital and Institute of Child Health, Multan Pakistan, from Mar to Nov 2021.

***Methodology*:** A total of 132 term neonates of both genders, with birth weight above 1800 grams, presenting within 24 hours of life, with clinical or electric seizures onset secondary to perinatal hypoxia and requiring resuscitation at birth, were included. The neonates were allocated to either Phenobarbital or LEV Group. The efficacy was labelled "yes" if a neonate showed cessation of seizures after the 1st or 2nd dose of the drug and remained seizure-free for the next 24 hours.

***Results*:** Out of 132 neonates, 77(58.3%) were male. The mean age was 8.92±4.22 hours. The mean birth weight was 2.29±0.28 kg, ranging between 1.9 and 3 kg. The mean gestational age was 37.67±0.91 weeks. Cessation of seizures occurred among 43(65.2%) neonates in the PB-Group in comparison to 54(81.8%) in the LEV-Group (p=0.030). Mortality was reported in 7(5.3%) neonates (4 in the PB-Group and 3 in the LEV-Group).

***Conclusion*:** The LEV was found to be more effective than PB as a first-line treatment agent for neonatal seizure associated with hypoxic-ischemic encephalopathy. Therefore, the LEV can be considered a good and safe alternative to PB for treating NS.

Keywords: Hypoxic-ischemic encephalopathy, Levetiracetam, Neonatal seizures, Phenobarbital, Seizures.

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INTRODUCTION

Neonatal seizure (NS) is known to be a commonly presented emergency among children. Around 1/3rd of NS, cases are attributed to Hypoxic-Ischemic Encephalopathy (HIE) and are estimated to affect between 1.5 to 26.5 per 1,000 live births.[1-3] Phenobarbital (PB) and phenytoin are the most frequently chosen anti-convulsant agents for NS following rectification of hypoglycemia and hypocalcaemia. The PB is perceived to have acceptable central nervous system penetration, less protein binding and very good effectiveness in the treatment of NS.[4] On the other hand, some researchers have reported irregularities of maturation of synapses and enhanced neuronal apoptosis with long-term usage of PB.[5]

Levetiracetam (LEV) is endorsed by the "Central Drug Standard Control Organization (CDSCO)" and "Food and Drug Administration (FDA)" as an adjunctive treatment option in partial-onset seizure among infants aged above one month. Although off-label LEV has also been used in the management of NS. [6] A study comparing the efficacy of PB and LEV in neonatal HIE found that PB was ineffective in 61% (n=32) neonates, but when those 32 neonates were further given LEV, 27 reported cessation of seizures.[7] Another research reported improved EEG among 69% of NS cases using LEV compared to 89% with PB (p=0.36).[8]

As only a few studies have been conducted to evaluate the efficacy of LEV against other most commonly adopted first treatment options like PB for treating NS because of HIE, the current study was planned to compare the effectiveness of LEV and PB for treating NS associated with HIE. As of now, controversy exists about whether LEV can be endorsed for routine use in NS associated with HIE; the present study was expected to provide some helpful information about the potential utilization of LEV as a possible alternative to PB in the management of NS.

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METHODOLOGY

The quasi-experimental study was conducted at the Neonatology Department, "The Children's Hospital and Institute of Child Health, Multan Pakistan", from March to November 2021. Approval from Institutional Ethical Committee (Letter #13/13, dated:17-01-2021) was acquired. Taking the ratio of sample size 1:1, the efficacy of LEV as 69% and PB as 89% in NS, the sample size was calculated.[8]

Inclusion Criteria: Term neonates (gestational age between 27 to 42 weeks) of either gender, with birth weight above 1800 grams, presenting within 24 hours of life, with clinical or electric seizures onset secondary to perinatal hypoxia and requiring resuscitation at birth, were included.

Exclusion Criteria: Neonates who had used any kind of anti-epileptic drugs, neonates with hypoglycemia, hypocalcaemia, or hypomagnesaemia, neonates with congenital malformations or congenital heart diseases were not included.

Informed and written consents were acquired from parents/guardians. An electroencephalogram was used to confirm the inclusion criteria if there was confusion about the clinical diagnosis of NS. A seizure lasting > 3 minutes or > 2 seizures lasting > 20 seconds within a one-hour period was considered as fulfilment of inclusion criteria about the presence of NS. Perinatal hypoxia was described as an APGAR score less than or equal to 6 at 5 minutes.[9] In each child, appropriateness of airway, breathing and circulation were ensured, and blood glucose and ionic calcium levels were evaluated. If seizures persisted even after correcting hypoglycemia and hypocalcaemia, the neonate was considered for this study if he/she fulfilled the inclusion/exclusion criteria. A total of 132 neonates (66 in each group) were non-randomly allocated to either PB-Group (20 mg per kg) or LEV-Group (20 mg per kg) as per the treating physician's discretion (Figure).

The LEV was diluted in normal saline up to a concentration of 20 mg/mL and given IV as 1 mg/kg/min. In the case of seizure cessation, LEV was maintained at 20 mg/kg/day in 2 divided doses. In case of continuation of seizures, another loading dose of LEV (20 mg/kg) was given. The PB (20 mg/kg) was diluted in 1:10 normal saline and administered 1 mg/kg/min IV. In case of seizures cessation, PB was continued at 5 mg/kg/day in 2 divided doses as maintenance. Another loading dose of 10 mg/kg of PB was administered among cases who failed to respond. The efficacy was perceived as "yes" if a neonate showed cessation of seizures after 1stor second dose of the drug and remained seizure-free for the next 24 hours. If seizures persisted after treatment with both study drugs, patients exited the study protocol and received additional treatment according to institutional protocols. Adverse events were noted in both study groups. Termination of seizure was labelled in the absence of abnormal movement /eyeball deviation/nystagmus, no change in heart rate, no change in respiration/saturation, and autonomic dysfunction.[9]

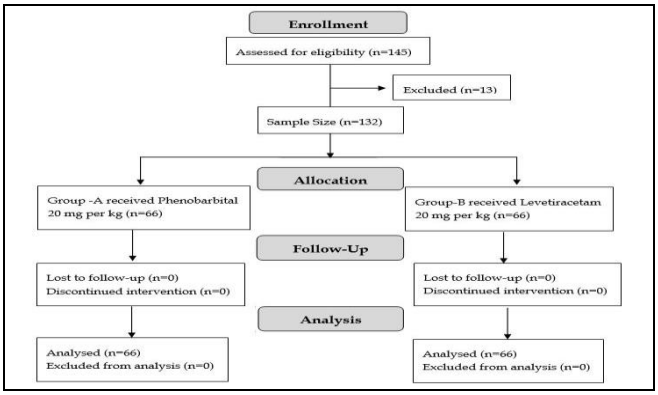

Figure: Patient Flow Diagram (n=132)

All study data was recorded on a pre-designed proforma while analysis was performed on Statistical Package for Social Sciences (SPSS) version 26.0. Qualitative data was represented as frequencies and percentages. Mean and standard deviation were calculated for quantitative data. The chi-square test was applied, considering *p*-value of <0.05 as significant.

RESULTS

Out of 132 neonates, 77(58.3%) were male. Overall, the mean age at the time of presentation in the neonatal emergency was 8.92±4.22 hours, ranging between 1 and 20 hours. The mean birth weight was 2.29±0.28 kg, ranging between 1.9 and 3 kg. The mean gestational age was 37.67±0.91 weeks (Table-I).

Cessation of seizures was noted among 97(73.5%) neonates. Table-II compares efficacy between both study groups, and it was seen that cessation of seizures occurred among 43(65.2%) neonates in the PB-Group in comparison to 54(81.8%) in the LEV-Group (p=0.030). No adverse events were observed in 122 (93.2%) neonates. Table-III details various adverse events noted in both study groups following treatment strategies. All the adverse events were managed according to standard institutional protocols. Mortality

was reported in 7 neonates (4 in the Phenobarbital-Group and 3 in the Levetiracetam-Group).

Table-I: Characteristics Between Neonates of Both Study Groups (n=132)

Characteristics		Phenobarbital -Group(n=66)	Levetiracetam –Group (n=66)	*p*-value
Gender	Male	37(56.1%)	40(60.6%)	0.596
	Female	29(43.9%)	26(39.4%)	
Age in hours	<8	41(62.1%)	37(56.1%)	0.478
	>8	25((37.9%)	29(43.9%)	
Gestational Age in weeks	<38	59(89.4%)	56(84.8%)	0.435
	>38	7(10.6%)	10(15.2%)	
Birth Weight in kg	<2.5	48(85.7%)	47(71.2%)	0.846
	>2.5	18(14.3%)	19(28.8%)	
Mode of Delivery	Vaginal Delivery	25(37.9%)	29(43.9%)	0.479
	Cesarean Section	41(62.1%)	37(56.1%)	

Table-II: Comparison of Efficacy in Between Both Study Groups (n=132)

Efficacy	Phenobarbital-Group (n=66)	Levetiracetam-Group (n=66)	*p*-value
Yes	43(65.2%)	54(81.8%)	0.030
No	23(34.8%)	12(18.2%)	

Table-III: Adverse Events in Neonates of Both Study Groups(n=132)

Adverse Events	Phenobarbital-Group (n=66)	Levetiracetam-Group (n=66)	*p*-value
Bradycardia	2(3.0%)	1(1.5%)	0.209
Hypotension	4(6.1%)	-	
Need for Mechanical Ventilation	1(1.5%)	1(1.5%)	
None	59(89.4%)	64(97.0%)	

DISCUSSION

Although most of the neonates with seizures have good prognoses, 20-30 % of reported cases are generally considered to be challenging to treat and are prone to have poor prognoses or long-term neurological sequelae like cerebral palsy, intellectual deficiency and epilepsy.[10]

The present study is the first comparative study comparing PB and LEV for treating NS secondary to hypoxic-ischemic encephalopathy. In this study, we noted that cessation of seizures occurred among 65.2% of neonates in the Phenobarbital Group in comparison to 81.8% in the Levetiracetam Group, and the significance was statistically significant (p=0.030). A study reported 44% of the total study cases with NS to have HIE as the leading cause of seizure, while 86% of neonates using LEV showed cessation of seizure. No seizures occurred in the next 24 hours.[9] It was also noted that 16/19 neonates who did not respond to 2 doses of PB also responded to a single dose of 20 mg/kg of Levetiracetam. A systemic review noted Levetiracetam as 1st line drug, resulting in near-complete cessation of seizures in 77% of the neonates. In comparison, phenobarbital was the 1st line drug in 46% of the neonates for the treatment of neonatal seizures. [11] These findings highlight that Levetiracetam can be considered at least as effective as phenobarbital if not more effective, for the treatment of NS. On the contrary, Abend and colleagues found Levetiracetam to have efficacy in neonatal seizure in just 35% of neonates, but the researchers did not use Levetiracetam as 1st line choice (except in one case).[12] Some other studies have also highlighted Levetiracetam as a good 2nd line or 3rdline treatment agent for the control of neonatal seizures.[11,13] Khan *et al.*, in a recently published local trial, found Levetiracetam to be effective in 88.4% of cases of neonatal seizures, while 41.3% of neonates had seizures secondary to hypoxic-ischemic encephalopathy in their study. Some other studies have highlighted Levetiracetam as a good choice anti-epileptic drug among preterm neonates with seizures as well.[14] The findings of the LEVNEONAT-1 trial are expected to soon that will unveil some of the significant benefits/drawbacks of LEV as 1st line treatment for NS in the context of HIE.[15]

Phenobarbital is the 1st line anti-epileptic drug but has side effects like hypotension and respiratory depression. The literature reports the efficacy of phenobarbital in controlling neonatal seizures among 43-80% of newborns, while some neonates still require 2nd or 3rd-line anti-epileptic drugs.[16,17] The LEV is a relatively newer anti-epileptic drug that the FDA approved for clinical anti-epileptic treatment in 2012. However, it is generally used as 2nd line drug for the treatment of neonatal seizures, and literature reports the efficacy of LEV between 35-86%.[12,18] Researchers have confirmed that Levetiracetam has neuro-protective effects and does not cause neuronal apoptosis, unlike phenobarbital.[19]

LIMITATIONS OF THE STUDY

Being a resource-limited setting, the unavailability of electroencephalographic monitoring and documentation for the cessation of seizure activity was another area for improvement in this study.

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CONCLUSION

The LEV was found to be more effective than PB as a first-line treatment agent for NS associated with HIE. Therefore, the LEV can be considered a good and safe alternative to PB for the treatment of NS.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MKS & ARM: Data acquisition, data analysis, critical review, approval of the final version to be published.

NF & MAR: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AA & AN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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