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SAFETY AND EFFICACY OF LEVETIRACETAM OVER PHENOBARBITONE IN CASE OF NEONATAL SEIZURES: A RANDOMISED CONTROL TRIAL

Neonatology

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ABSTRACT

Background: Neonatal seizures are one of the significant morbidity and preventable cause of neonatal mortality. Phenobarbitone was the preferred antiepileptic drug for the control of neonatal seizures. In our study, we aimed to determine and compare the safety and efficacy of Levetiracetam over Phenobarbitone in neonatal seizures in a Randomised control trial. Also comparison in terms of control of Neonatal seizures, prevention of recurrence of seizures, and reduction of adverse effects. **Methodology:** A total of 80 cases were enrolled in both groups as per inclusion and exclusion criteria and is a randomized double-blinded study and the allocation of samples in each group will be done by random lottery method. Thompson score was taken as a baseline before administering the drug and serial monitoring was done for consecutive five days. All the baseline parameters are documented and monitored among both groups. **Results:** The primary outcomes of the study, included control of seizures, recurrence of seizures, the requirement of ventilatory support, intravenous fluids, ionotropic support, and serial trends in Thompson score. The secondary outcomes are days of ventilation requirement, days of ventilatory support, EEG changes, and outcomes in the form of discharge and death are compared among two groups, and statistical significance was compared. The incidence of encephalopathy was higher in the Levetiracetam group than in the Phenobarbitone group. A cohort of 80 neonates in our study had neonatal seizures requiring AED. 67% of neonates in the Levetiracetam group had control of seizures and 50% of neonates in the Phenobarbitone group had control of seizures. Their seizure control in both groups was compared by using the chi-square test and found to be statistically significant. The number of Neonates discharged is more in the levetiracetam group than in the Phenobarbitone group. **Conclusions:** Levetiracetam is an effective and safer alternative to Phenobarbitone as a first-line drug in managing neonatal seizures.

KEYWORDS

Neonatal seizures, Encephalopathy, Levetiracetam, Thompsons Score

BACKGROUND:

Neonatal seizures are one of the significant morbidity and preventable cause of neonatal mortality. Neonatal seizures are involuntary jerky movements caused by abnormal electrical impulses in the brain due to an imbalance between excitatory and inhibitory processes in the immature brain i.e Increase activity of excitatory neurotransmitter (Glutamine) over inhibitory neurotransmitter (GABA) which results in autonomic disturbance in the brain which leads to the generation of neonatal seizures.(1)

Phenobarbitone (PB) is the drug of choice in neonatal seizures which enhances GABA-related inhibition. It may also inhibit excitatory amino acid transmission and block voltage-activated calcium currents. Its half-life is longer in premature infants. When administered in recommended doses it has side effects like respiratory depression, depressed level of consciousness, hypotension, and hypotonia. (2)Phenobarbitone induces hepatic metabolism and is therefore associated with a large number of drug interactions. Despite being most used, various trials have shown limitations of phenobarbitone in control of seizures in the neonatal period. Moreover, there are concerns regarding its adverse effects on the brain.

Levetiracetam (LEV) is the active, water-soluble S-enantiomer of racemic pyrrolidine acetamide. It acts by binding to the synaptic vesicle protein within the brain and involves a reduction in presynaptic neurotransmitter release by binding to a synaptic vesicle glycoprotein (SV2A), with the greatest effect in rapidly discharging neurons. The other mechanism of action of LEV involves inhibiting the release of calcium from intraneuronal stores, selective inhibition of N-type calcium channels, the opposition of allosteric inhibition of GABA- and glycine-gated currents, and inhibition of excessive synchronized activity between neurons. Two-thirds of drugs are excreted renally. Stimulation of the presynaptic SV2A by LEV may inhibit the neurotransmitter release without affecting normal neurotransmission. It is absorbed very rapidly and has a reported absolute oral bioavailability of 100% which makes it a very efficient drug for the management of neonatal seizures with minimal Side effects.(3)

By considering all these advantages of Levetiracetam over Phenobarbitone and various studies and trials we have tried as an alternative drug in the management of neonatal seizures.

AIMS AND OBJECTIVES :

This study was to determine and compare the safety and efficacy of Levetiracetam over Phenobarbitone in neonatal seizures in a Randomised control trial. Comparison in terms of control of Neonatal seizures, prevention of recurrence of seizures, and reduction of adverse effects (Secondary outcomes)

METHODOLOGY:

It's a randomized control study and we took a sample size of 80 infants with neonatal seizures requiring antiepileptic drug administration for our randomized control trial who are admitted in extramural and intramural NICU of Baroda medical college, Vadodara during our study period, with 40 samples in each arm (Phenobarbitone and Levetiracetam) and study population. We considered the patient for enrollment and drug administration. Written informed consent would be taken before enrolment. A septic screen and routine blood investigations was sent for all enrolled patients. Randomization will be done by random lottery chit method with the help of the resident duty doctor. Before enrollment exclusion criteria were enlisted and enrolled as per inclusion criteria.

Inclusion Criteria:

Any case of neonatal seizures with any of the following risk factors : Term infants ,Perinatal asphyxia ,APGAR Score <5 , Meconium stained liquor ,Early-onset sepsis and Late-onset sepsis (Meningitis) , Birth weight >2.0kg , Hypoxemic ischemic encephalopathy , Intraventricular or Intracranial Hemorrhage.

Exclusion Criteria :

Preterm infants, Inborn errors of metabolism , Metabolic causes like hypoglycemia, hypocalcemia ,Major Congenital anomalies ,Neural tube disorders. Thompson score was taken as a baseline before administering the drug and serial monitoring was done for consecutive five days. All the baseline parameters are documented and monitored among both groups.

RESULTS:

A total of 80 patients were enrolled and randomized into two groups. Both groups were comparable with the baseline characteristics The average gestational age of the infants was 57 were AFD and 23 were SFD. The results of primary and secondary outcomes are compared.

The primary outcomes of the study included control of seizures, recurrence, the requirement of ventilatory support, intravenous fluids, ionotropic support, and trends in Thompson score.

Table:1-Comparison Of Thompson Scoring At Various Days Among Both Groups:

Days	Levetiracetam		Phenobarbitone		Mann-Whitney U test	p-value
	Median	IQR	Median	IQR		
Day 1	10	7-13	13	10-16	6.18	0.01
Day 2	8	6-13	12	10-16	9.93	0.001
Day 3	6	3-9	13.5	8-15	20.36	<0.001
Day 4	3	3-6	10	7-15	17.45	<0.001
Day 5	2	1-4	10	5-14	14.04	0.0002

The above table shows the comparison of Thompson's score in both groups on each day. The statistical difference was calculated through the Mann-Whitney U test and was statistically significant(p:0.001) for all the days. The Median Thompson score was less among the levetiracetam group as compared to the phenobarbitone group

The phase IIb study by **Sharpe C et al. Department of Paediatric Neurology, Starship Children's Health, Auckland, New Zealand in 2020,** revealed greater efficacy of 20 to 40 mg/kg of phenobarbital than 40 to 60 mg/kg of levetiracetam. More adverse events occurred with phenobarbital. Higher dose studies of levetiracetam are warranted but more definitive studies with long-term outcome measures were recommended. There was a 2% death in the phenobarbital group and a 3% death in the levetiracetam group during the study with over 3% death.(4)

The efficacy of LEV has been earlier demonstrated in a **study by Ramantani, et al.Department of Pediatric Neurology, University Children's Hospital Dresden GERMANY,** in which 30 (78%) out of 38 infants were seizure-free after receiving LEV.(5)

The secondary outcomes are days of ventilation, days of ventilatory support, EEG changes, and outcomes in the form of discharge and death are compared among two groups and statistical significance is noted.

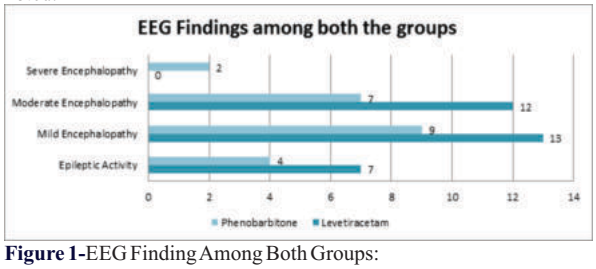


Figure 1-EEG Finding Among Both Groups:

EEG findings among neonates revealed that the majority of the patients had encephalopathy followed by an epileptic activity. The higher incidence of encephalopathy in levetiracetam had been attributed to neonatal hypoxia, sepsis, pyogenic meningitis, etc

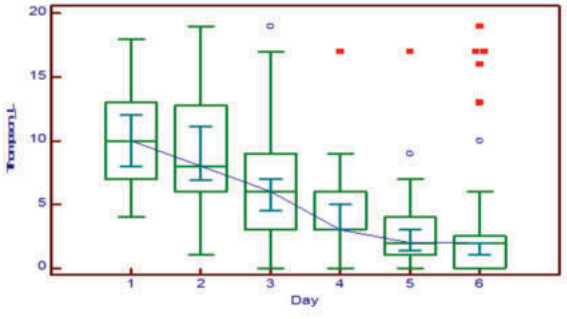


Figure 2- Comparison Of Thompson Scoring At Various Days Among Patients Given Levetiracetam:

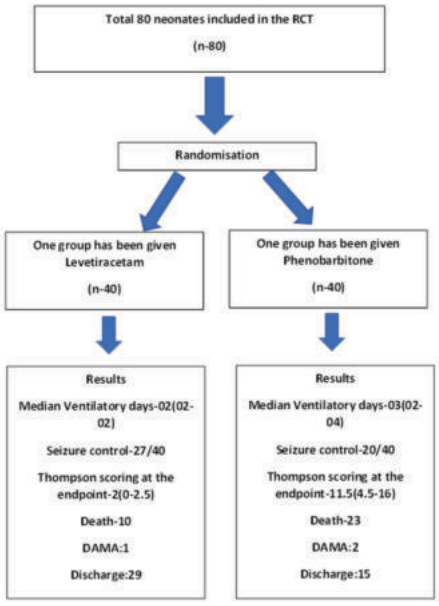
The study by **Bhawani D. et. Al Department of Paediatrics, Hindu Rao Hospital, Delhi, India.** in 2016 on 145 post-asphyxiated full-term babies with low-Apgar scores Thompson's score allows a very precise description of infants by assigning a numeric score rather than 'mild', 'moderate', or 'severe and there is no requirement for an Electroencephalogram which is beneficial.(6)

Table No.2: Comparison Of Significant Parameters In Both Groups

Comparative Parameters		Leviteracetam		Phenobarbitone		Chi-square	p-value
		Number	Percentage	Number	Percentage		
Seizure control	Yes	27	67	20	50	19.35	0.0001
	No	13	33	20	50		
Mean ventilatory days		2	2-3	3	2-5	0.04*	
Ionotropic support		18	45%	23	57%		
Thompson endpoint		2	1-2.5	11.5	4.5-16	22.76	0.0001
Outcome	Discharge	28	35%	15	18.75%	21.01	0.0001
	Death	12	15%	23	31.25%		

The above table shows a comparison of all parameters like control of seizures, mean ventilatory days, ionotropic support, Thompson score endpoint, and outcome parameters including death and discharge

FLOW-CHART SUMMARY FOR RESULTS:



CONCLUSION & RECOMMENDATION :

In the current study, Levetiracetam was efficient and safe in the early cessation of neonatal seizures. The proportion of neonates obtaining complete seizure or near-complete cessation was higher in neonates who received Levetiracetam than in the phenobarbitone group and also decreased the risk probability for adverse events and we observed a significant reduction in the mean number of days of hospital stay and the number of ventilator-required days in the levetiracetam group than in the phenobarbitone group. The number of neonates discharged in the case of Levetiracetam is higher than those in the phenobarbitone group. The THOMPSON scoring system used in this study is highly predictive of neonatal outcomes & neurological status in terms of early morbidity.

By all these parameters, we conclude that Levetiracetam is an effective and safer alternative to phenobarbitone as a first-line drug in managing neonatal seizures.

LIMITATIONS OF OUR STUDY

Our study had a small sample size. Hence, more studies over a more extended period and including a more significant number of subjects are required to validate these results and know whether other outcome parameters are significantly better when Levetiracetam is preferred as a drug for neonatal seizures.

Encephalopathy was higher in the case of neonates who received

Levetiracetam as a drug for neonatal seizure, which needs further evaluation. These findings could be attributed to severe perinatal asphyxia, early onset of sepsis, pyogenic meningitis .etc rather than the adverse effect of anti-seizure medication.

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