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Original Research Article

Phenobarbitone versus levetiracetam in neonatal seizures

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ABSTRACT

Background: There is increasing evidence that neonatal seizures have an adverse effect on neurodevelopmental progression and it may predispose to cognitive, behavioral or epileptic complications later in life. The objective of this study was to compare the efficacy of phenobarbitone and levetiracetam for the treatment of neonatal seizures in term and late preterm neonates. The study was aimed to know the efficacy of phenobarbitone (PB) in comparison with levetiracetam (LEV) in controlling neonatal seizures.
Methods: This was a randomized controlled trial where data of the babies with seizures weighing more than 2 kg who were admitted in NICU of Muzaffarnagar Medical College was collected and analysed for intervention to either phenobarbitone or levetiracetam.
Results: Clinically apparent seizures were controlled in only 65.38% neonates assigned to receive levetiracetam as compared to 76.92% neonates assigned to receive phenobarbitone.
Conclusions: LEV although lesser effective than PB with very fewer side effects is found to be a good alternative in controlling neonatal seizures.

Keywords: Levetiracetam, Neonatal seizures, Phenobarbitone

INTRODUCTION

There is increasing evidence that neonatal seizures have an adverse effect on neurodevelopmental progression and it may predispose to cognitive, behavioral or epileptic complications later in life. The incidence of neonatal seizures ranges from 1 to 5:1000 live births.[1] Hypoxic Ischemic Encephalopathy (HIE) due to asphyxia is the most common cause of seizure activity in neonatal population accounting for approximately two-thirds of neonatal seizures.[2,3] The main line of treatment irrespective of the cause of neonatal seizures is phenobarbitone. But there is a concern about its adverse effects on brain due to apoptosis and inhibition of brain growth resulting in impairment of cognition and behaviour.[4]

Therefore, due to these reasons, there have been a great interest in the use of new anticonvulsant like Levetiracetam. LEV is a relatively new and wide septrum anti-seizure medication with favorable pharmacokinetics and safety profile.

LEV is designed to act through synaptic vesicle glycoprotein 2A (SV2A), which is a protein believed to be involved in the release of neurotransmitters.[5] LEV has a unique mechanism of action, novel structure and very favorable pharmacokinetic and safety profile in neonates.[6,7] However, there are insufficient data available on the efficacy and safety of LEV in neonatal seizures. So, authors undertook this study to compare the efficacy of phenobarbitone (PB) and levetiracetam (LEV) in the treatment of clinically apparent neonatal seizures.

METHODS

Authors performed a randomized controlled study in Muzaffarnagar Medical College, Muzaffarnagar from

March 2019 to January 2020. Infants were eligible for inclusion if they met the following criteria.

Inclusion criteria

- Term and near-term babies
- >2 kg admitted in NICU
- Seizures occurring within 48 hours of birth with the most likely cause due to HIE.[8]

Exclusion criteria

- Neonates already on ventilator support or electrolyte imbalance i.e., hypoglycemia, hypocalcemia and hyponatremia
- Prior history of anti-epileptic drug administration.

Randomized controlled trial was conducted over 72 patients and their clinical history, seizure type was recorded.

Investigations such as complete blood count, sepsis screen, blood glucose, liver function test, kidney function test, serum electrolytes were conducted.

Neonates with clinical seizures were randomly assigned to receive either PB/LEV based on computer generated randomized schedule. After ensuring patency of airway, breathing and circulation, all investigations were performed. After clearing the exclusion criteria, neonates were randomized for intervention to receive either LEV (20 mg/kg) or PB (20 mg/kg) I/V. LEV was diluted in normal saline to achieve a concentration of 2 mg/ml and given slowly over 20 minutes.

If seizures were terminated, LEV was continued as a maintenance at 15 mg/kg/day daily in two divided doses. If seizures continued, another loading dose of LEV (20 mg/kg) was injected and if seizures still persisted, patient was switched over to PB. PB was administered in a dose of 20 mg/kg diluted ten times with normal saline given I/V slowly at a rate of 1 mg/kg/min slowly over 20 minutes under cardiorespiratory monitoring. If seizures were terminated, PB was continued as maintenance at 5 mg/kg/day in two divided doses. Another loading dose of 10 mg/kg of PB was given who failed to respond and if seizures still persisted after two loading doses, patient was switched over to LEV.

The number of patients achieving seizure control after first and second loading dose of the drug i.e., PB or LEV and remaining seizure free for next 24 hours was considered as primary outcome. Number of patients having adverse effects occurring within 2 hours of drug administration was considered as secondary outcome.

Seizure control was defined clinically if there was no abnormal movement, nystagmus or deviation of eyeballs, no autonomic dysfunction, no change in respiration, heart rate and saturation. Adverse drug reactions included decrease in respiratory rate, arrhythmias, change of heart rate, blood pressure or desaturation. Informed consent was obtained from the parents on pre-structured performa. The study was approved by institutional ethics committee of Muzaffarnagar Medical College.

Statistical analysis

It was done using intention to treat analysis on SPSS 10. Analysis of continuous data with normal distribution was analysed by student t test and non-normally distributed data by Mann-Whitney U test. Categorical data was analysed by chi-square test and Fischer exact where applicable.

RESULTS

A total of 72 babies were taken with clinically apparent seizures and they were analyzed during study period. 20 were excluded due to various reasons and rest 52 were enrolled in the study.

A total 26 babies were randomized to LEV and 26 babies were randomized to PB and baseline characteristics of both the groups were comparable (Table 1).

Table 1: Baseline characteristics of the 2 groups.

	LEV group (n=26)	PB (n=26)
Weight (kg)	2.62	2.68
Gestational age (weeks)	37.22	38.13
Mode of delivery		
Normal	18	16
LSCS	8	10
Gender (%)		
Male	15	13
Female	11	13
Perinatal asphyxia	18	20
Positive sepsis screen	4	5

Table 2: Outcome variable.

	LEV group (n=26)	PB (n=26)	p value
Primary variable		20 (76.92%)	
Seizure control with primary drug	17 (65.38%)		0.35
Seizure control with secondary drug	4 (15.38%)	5 (19.23%)	0.04
Adverse events	22 (84.62%)	24 (92.31%)	
Decrease respiration rate/apnoea	5	8	0.3
Decrease heart rate	4	5	0.1
Arrythmias	3	6	0.27
Decrease blood pressure	4	9	0.10
Desaturation	4	8	0.18

Clinically apparent seizures were controlled in 17 of the 26 (65.38%) neonates assigned to receive levetiracetam as compared to 20 of the 26 (76.92%) neonates assigned to receive phenobarbitone (Table 2).

Similarly, the side effects profile of each of the drugs were almost comparable 22 (84.62%) neonates with LEV and 24 (92.31%) neonates on PB.

DISCUSSION

Present study revealed that LEV is not as efficacious as PB in controlling neonatal seizures both in term and near-term neonates. It is found that PB was superior than LEV both when used as primary drug or after its usage as secondary drug. However, there was not huge difference in the side effect profile in both the groups of drugs being used. But it can be said that LEV is found to be a new anticonvulsant and good alternative to PB in controlling neonatal seizures.

As there are many studies that are showing that LEV is the new generation anticonvulsant that is being used. In a study done by Ramantani et al, in which it was found that 30 (78%) out of 38 infants were seizure free after receiving LEV.[9] In a study by Khan et al, 19 (86%) of the 22 neonates demonstrated seizure cessation within 1 hour of administration of LEV.[10]

However, in a study done by Abend et al LEV was associated with seizure improvement within 24 hours in only 8 (35%) of 23 neonates.[11] Similarly, there are few other studies, showing good seizure control with LEV when it was used as second or third line agent in controlling seizures.[12,13] Shoemaker and Rotenberg also reported 80% seizure control in 10 infants aged 1 day to 3 months treatment with oral LEV for seizures refractory to phenobarbitone, phenytoin and benzodiazepines.[14,15]

There was not enough data on the pharmacokinetics of LEV at the time of onset of this trial. Authors used a loading dose of 20 mg/kg each followed by a maintenance dose of 15 mg/kg/day for LEV and 5 mg/kg/day for PB in two divided doses in comparison to study done by Rottenberg MT et al, that used a much higher dose of 60 mg/kg with maintenance dose of 30 mg/kg.[15]

There is subsequent study on the pharmacokinetics of LEV using 40 mg/kg, Ramantani et al reported safety and efficacy of LEV with 60 mg/kg as well.[9,16]

This study does not report much side effects of LEV on haemodynamic, cardiovascular as well as on renal status in comparison to study done by Merher SL et al.[15] LEV is reported to cause only minor side effects like sedation, behavior abnormalities and depression in older children and somnolence in neonates.[17] Occasional reports of reversible thrombocytopenia and possible liver failure and anaphylactic shock because of LEV has also been reported.[18-20]

But the limitation of this study was that authors did not perform electroencephalographic monitoring to document cessation of seizure activity. Another limitation was lack of long-term follow-up and inability to perform therapeutic drug levels of PB and LEV.

CONCLUSION

LEV although lesser effective than PB with fewer side effects is found to be a good alternative in controlling neonatal seizures.

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