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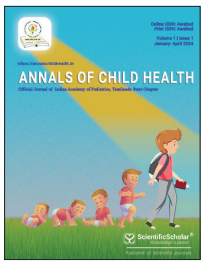

Original Article

Comparative Efficacy of Levetiracetam versus Phenobarbitone as First-Line Treatment for Neonatal Seizures

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ABSTRACT

Objectives: The study aimed to compare the efficacy and safety of levetiracetam versus phenobarbitone as first-line treatment for neonatal seizures.

Material and Methods: This randomized control trial was conducted from March 2018 to July 2018 at the special new born care unit, Coimbatore Medical College Hospital. Neonates admitted for seizures were randomly assigned to receive either levetiracetam or phenobarbitone as their initial anticonvulsant. Group A received levetiracetam starting at a dose of 10 mg/kg twice daily, escalating to 40 mg/kg twice daily if necessary. Group B received phenobarbitone, at a dose of 20 mg/kg slow IV infusion. Primary outcome included clinical seizure control and time taken for seizure control, while secondary outcomes measured included shock, apnea, respiratory failure, and mortality. Babies treated with anticonvulsants before admission were excluded from the study.

Results: Out of 68 neonates admitted, 52 were eligible for the study after excluding 16 pre-treated with anticonvulsants. Both groups consisted of 26 neonates each. Clinical seizure control was achieved in 53.8% of the levetiracetam group and 61.5% of the phenobarbitone group. Complications were included shock (11.5% with levetiracetam and 15.3% with phenobarbitone), apnea (0% with levetiracetam and 7.7% with phenobarbitone), and respiratory failure (7.75% in both groups). Mortality rates were identical at 11.5% for both groups. No significant difference in seizure control or complications was observed between the groups. Levetiracetam did not exhibit major side effects, indicating it can be considered a viable first-line drug for neonatal seizures. However, the small sample size necessitates larger trials for confirmation.

Conclusion: Levetiracetam and phenobarbitone demonstrated comparable efficacy and safety as first-line treatments for neonatal seizures. While levetiracetam showed promise with fewer side effects like apnea, further large scale, prospective randomized trials are required to establish definitive conclusions and optimize dosing strategies. This study contributes to the ongoing discussion on the best first-line anticonvulsant for neonatal seizures and suggests levetiracetam as a potential alternative to phenobarbitone.

Keywords: Neonatal seizures, Levetiracetam, Phenobarbitone, Primary outcome, Secondary outcome

INTRODUCTION

Neonatal seizures occur in 1–5/1000 live births with most seizure activity occurring in the first few days of life. The occurrence of seizure may be the first clinical indication of neurologic disorder.[1] Hypoxic–ischemic encephalopathy is the most common cause of neonatal seizures, accounting for 50–60%. Other causes are intracranial hemorrhage, central nervous system (CNS) infection, metabolic disorders, CNS malformations, and inborn errors of metabolism.

Clinical criteria for neonatal seizure diagnosis were historically subdivided into five categories: Focal clonic, multifocal clonic, tonic, myoclonic, and subtle seizures.[2,3]

It is important to note that generalized seizures are rare in neonates due to immature myelination of the nervous system. Neonatal seizures often have subtle manifestations such as ocular changes, tongue thrusting, cycling limb movements, apnea, or blood pressure fluctuations. Clonic seizures are more common and will usually begin in one extremity then migrate to an opposite extremity. Neonatal seizures some times are very difficult to control and refractory to treatment. Treatment with various antiepileptic drugs such as phenobarbitone and phenytoin during neonatal period impairs physiological maturation of synapses in neurons after the initial drug insult. There are many concerns for the short-term adverse effects of phenobarbital as well as long-term effect on neurocognitive development. Levetiracetam was found not to have effect on synaptic development. Levetiracetam is considered safe due to its linear pharmacokinetics, non-hepatic elimination, lack of protein binding, and no known interactions with other antiepileptic medications.[4] Levetiracetam is approved for usage in children above 4 years of age and adults by the US Food and Drug Administration but not for neonatal age group.[5,6] Randomized controlled trials (RCTs) for its usage in neonatal age group are lacking. Seizures account for about 1–2% of neonatal intensive care unit (NICU) admissions. Although there is agreement regarding the battery of diagnostic tests, the most appropriate anticonvulsant is still debatable. Phenobarbitone is the most commonly used drug for treatment of neonatal seizures, irrespective of the cause of the seizures. However, there is concern about its adverse effects on brain due to apoptosis and inhibition of brain growth resulting impairment of cognition and behavior. Moreover, repeated loading doses, especially with concomitant hypoxic liver injury in asphyxia, can potentially lead to unpredictable serum levels and exaggerated adverse effects. Hence, there is an urgent need for an alternative antiepileptic drug for treatment of neonatal seizures. Levetiracetam is a relatively new anticonvulsant. Experience in adults and older children have shown it to have good therapeutic index and efficacy in controlling seizures.

In vivo studies of animal models, reporting no neurotoxic side effects at therapeutic doses of levetiracetam, suggest its safety and potential in treating neonatal seizures. It appears that it has an anti-apoptotic effect, which eventuates in the reduction of cellular apoptotic processes in the hippocampus and cerebral cortex of treated patients.

As of now, there are insufficient literature data on the use of levetiracetam in NICU as an anticonvulsant drug for neonatal seizures, and little is known on its efficiency as first-line treatment in this age group.[7]

The controversies regarding the best first-line agent, second-line agent, dose, and duration still continue. Although mortality due to neonatal seizures has decreased from 40% to about 20% over the years, the prevalence of long term neurodevelopmental sequelae has remained almost remained unchanged at around 30%. This signifies that the treatment of neonatal seizures is still unclear and there is a potential for further improvement.

The aim of this study was to compare the efficacy and safety of levetiracetam with phenobarbitone as first-line treatment of neonatal seizures.

Aim

The aim of this study was to compare the efficacy of levetiracetam with phenobarbitone as a first-line drug in aborting clinical neonatal seizures.

MATERIAL AND METHODS

Neonates admitted in special new born care unit Coimbatore Medical College Hospital from March 2018 to July 2018 for seizures were randomized to receive either levetiracetam/phenobarbitone as first-line anticonvulsants. Consent was taken from babies parents before randomization. Random numbers are assigned from computer generated sequence. Neonates treated with levetiracetam were assigned as Group A and those treated with phenobarbitone was assigned as Group B. Levetiracetam was administered at a dose of 10 mg/kg twice daily with gradually increasing doses up to 40 mg/kg twice daily in case of non-responding to lower doses. Phenobarbitone was administered at a dose of 20 mg/kg slow IV infusion under cardiorespiratory monitoring. Babies which failed cumulative loading dose of 20 mg/kg levetiracetam or 30 mg/kg cumulative dose of phenobarbitone were treated by crossover technique. Babies treated with anticonvulsants before admission were excluded from the study. All seizures were initially treated as per unit protocol, that is, 2 mL/kg 10% dextrose if hypoglycemic [capillary blood glucose (CBG) <45 mg/dL] and 2 mL/kg of calcium gluconate before IV anticonvulsants along with supportive measures such as warmth, nasal oxygen, positioning, and oral suctioning if required. Clinical abortion of seizures was taken as a primary outcome. Separate monitoring sheet was maintained to document other outcome measures which include onset and duration of seizure control, hypotension, shock, apnea, coma, and respiratory failure[8].

Study design

Out of 68 neonates admitted for neonatal seizures, 52 were eligible for study.

Exclusion criteria: Sixteen babies were excluded as they were treated with anticonvulsants before admission.

Study design: Randomized control trial.

Among 52, 26 were given levetiracetam and assigned as Group A, 26 were given phenobarbitone and assigned as Group B.

Out of the 52 neonates studied, 26 each were given levetiracetam and phenobarbitone. The number of extreme preterm (<28 weeks), severe preterm (28–32 weeks), and moderate and late preterm (33–37 weeks) were comparable in both the groups. Predominantly term babies were admitted for neonatal seizures in both the groups [Table 1].

Babies belonging to the different weight categories were also comparable among the two groups. Predominant population of neonatal seizures were more than 2.5 kg [Table 2].

Among the 52 neonates, 39 were male babies and 13 were female babies. Both were equally distributed among the two groups [Table 3].

Among the neonates included, 37 were born at term and 15 were preterm.

Mean weight of babies who received levetiracetam was 2600 g ± 60 g and those who received phenobarbitone were 2650 g ± 55 g [Table 4].

Mean gestational age of neonates in levetiracetam group was 37 w ± 4 d and those in phenobarbitone group were 37 w ± 3 d [Table 4].

The mode of delivery was comparable in both groups.

RESULTS

Primary outcome

	Levetiracetam		Phenobarbitone	
	No.	%	No.	%
Clinical seizure control	14/26	53.8	16/26	61.5
Time taken for seizure control	5.5+0.5 min		5+0.5 min	

Clinical control of seizure activity and time taken for seizure control were the primary outcome of this study. Seizures were considered to be controlled if the baby was seizure free 24 h. After last seizure, 53.8% had clinical seizure control in levetiracetam group and 61.5% had seizure control in phenobarbitone group.

Secondary outcome

	Levetiracetam		Phenobarbitone	
	No.	%	No.	%
Shock	3	11.5	4	15.3
Apnea	0	0	2	7.7
Resp failure	2	7.7	2	7.7
Renal derangement	3	11.5	4	15.3
Mortality	3	11.5	3	11.5

We did not find significant difference in secondary outcomes (shock, respiratory failure, and mortality) between the two groups. Apnea was observed more in the phenobarbitone group.

Comparison between the two groups revealed that clinical seizure control attained with levetiracetam and phenobarbitone were 53.8% and 61.5%, respectively. Complications associated with levetiracetam and phenobarbitone such as shock were 11.5% and 15.3%, respectively, apnea was 0% and 7.7%, respectively, respiratory failure was 7.7% with both, and mortality was 11.5% with both. No neonate required second anticonvulsant therapy. There is no significant difference in seizure control and complications associated with levetiracetam and phenobarbitone. Regarding safety of levetiracetam, no major side effects were observed. Hence, levetiracetam can be used as first-line drug in place of phenobarbitone. However, the sample size is too small, and hence, a larger, prospective, and randomized trial should be conducted to confirm this result.

DISCUSSION

The present study demonstrated that levetiracetam is as good as phenobarbitone in controlling neonatal seizures. Furthermore, it took similar time in comparison with phenobarbitone in controlling clinical seizures. Same efficacy was observed when given as a first-line drug. We did not find any major side effects related to any of the drugs used. Levetiracetam has been reported to be a promising new drug for neonatal seizures. In two separate case series, Shoemaker and Rotenberg reported 80% seizure control in 10 infants aged 1 day–3 months, treated with oral levetiracetam for seizures refractory to phenobarbital, phenytoin, and benzodiazepines. A recently published case series of 22 neonates by Khan *et al*.[9] reported clinical control of seizures in 32%, in babies who had not responded to phenobarbitone. Similarly, Abend *et al*.[10] reported effective seizure control in 35% neonates. Most studies have used levetiracetam as second-line drug after phenobarbitone failure. Our study is one of the few studies to test levetiracetam as a first-line drug in treatment of neonatal seizures.

Our study does not report any significant difference on hemodynamic, cardiovascular, or renal status. Merhar *et al*.[7] also reported no change in vital sign or laboratory parameters with its use. Levetiracetam is reported to cause only minor side effects such as sedation, behavior abnormalities, and depression in older children and somnolence in neonates. Occasional reports of reversible thrombocytopenia and possible liver failure and anaphylactic shock due to levetiracetam have also been reported. Although levetiracetam has predominantly renal excretion, like us, other studies have also not reported derangements in renal parameters with its use. As apnea was encountered more in phenobarbitone group, in level 2 and level 1 centers, levetiracetam may play a promising role as first-line drug in controlling seizures.

Table 1: Gestation-wise distribution of neonatal seizures.

Weeks	Levetiracetam		Phenobarbitone	
	No.	%	No.	%
<28	1	3.8	0	-
28–32	1	3.8	2	7.6
33–37	6	23	5	19.2
>37	18	69.2	19	73
Total	26		26	

Table 2: Birthweight-wise distribution of neonatal seizures.

Weight	Levetiracetam	Phenobarbitone	%
<1.5 kg	1	-	4
1.6–2.5 kg	10	10	38
>2.5 kg	15	16	58

Table 3: Gender-wise distribution of neonatal seizures.

	Levetiracetam	Phenobarbitone	No.	%
Male	19	20	39	75
Female	7	6	13	25

The main strength of the study was that it is one of the few RCT's comparing levetiracetam and phenobarbitone in neonatal seizures, which demonstrates similar efficacy in controlling neonatal seizures. A limitation of this study is that drug level monitoring of the drugs could not be done. Hence, whether failure of a particular drug was due to inability to attain, therapeutic level could not be stated. This is especially so because dosing, therapeutic levels and pharmacokinetics of this drug in neonates is still not very clear. Furthermore, we did not do cerebral function or electroencephalogram monitoring and neurodevelopmental follow-up. Hence, electrical seizures could still be persisting despite clinical control of seizures. This could lead to demonstration of exaggerated efficacy of these drugs. However, this would be true for both the limbs of treatment.

In vivo studies of animal models, reporting no neurotoxic side effects at therapeutic doses of levetiracetam, suggest its safety and potential in treating neonatal seizures. It appears that it has an anti-apoptotic effect, which eventuates in the reduction of cellular apoptotic processes in the hippocampus and cerebral cortex of treated patients. To demonstrate these novel effects on growing brain, we need to do a long-term study on neurodevelopmental outcomes.

The present study shows equal efficacy of levetiracetam as phenobarbitone for neonatal seizures. However, more trials, with larger sample size are required. Role of higher first dose and repeated loading doses in non-responders to 1st dose also needs to be evaluated in further studies.

Table 4: Baseline characteristics among two groups.

	Levetiracetam	Phenobarbitone
Mean gestation	37±4 days	37±3 days
Mean birth wt.	2600±60 g	2650±55 g
Sex		
Male	19	20
Female	7	6
Mode of delivery		
NVD	16	17
LSCS	10	9
Antenatal brain malformation	2	1
Type of seizures		
Subtle seizures	18	16
Multifocal	4	4
Others	4	6
Hypoglycemia	4	5
Hypocalcemia	3	2
Meningitis	3	2
Intracranial bleed	1	0
HIE	15	17
Intrapartum drug	2	1
Outborn	8	10
Inborn	18	16
Comorbities:		
Shock	2	2
Respiratory failure	3	3

NVD: Normal vaginal delivery, LSCS: Lower-segment cesarean section, HIE: Hypoxic–ischemic encephalopathy

CONCLUSION

When used as a first-line drug for neonatal seizures, efficacy was comparable between levetiracetam and phenobarbitone in neonatal seizures.

What is already known

Phenobarbitone is often used as a first-line anticonvulsant in neonates with seizures. Levetiracetam has been tried for the treatment of seizures refractory to phenobarbitone in children and neonates.

What this study adds

When used as a first-line drug for neonatal seizures, efficacy was comparable between levetiracetam and phenobarbitone in neonatal seizures. The use of levetiracetam as first-line drug for neonatal seizure may be equally promising in control of neonatal seizures with lesser side effects.

Ethical approval

The research/study approved by the Institutional Review Board at Coimbatore Medical College Hospital, number 12/ February 14, 2018, dated February 14, 2018.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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