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Efficacy of Levetiracetam as first-line treatment in neonatal seizure

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Abstract
Background: *Appropriate treatment of neonatal seizures is important in reducing long-term neurologic disabilities. In our NICU, the first-line anti-seizure medication for the treatment of neonatal seizures is phenobarbitone (PB).The purpose of this study is to evaluate the efficacy of levetiracetam (LEV) as 1stline treatment in neonatal seizures.*
Materials and Methods: *This study was conducted in neonates admitted in Neonatal Intensive Care Unit of Patna Medical College and Hospital, Patna, Bihar from July 2017 to December 2017. 20 neonates with clinical convulsions were enrolled in the study and received IV LEV at standard doses.*
Results: *65 % of neonates responded to IVLEV treatment, at the end of 1stweek. Other neonates required additional anticonvulsant therapy like phenobarbitone, phenytoin. No major side-effects of LEV were noted.*
Conclusions: *LEV is effective as 1stline treatment in neonatal seizures.*
Keywords: *Efficiency and safety, levetiracetam, neonatal seizures, prospective study.*

Introduction

Seizures occur often in neonates adversely affecting the neuro developmental outcome. In India incidence of neonatal seizures varies from 0.5 to 0.8%in term babies. Neonatal seizures have varied presentations such as ocular changes, tongue thrusting, cycling limb movements, apnoea, or blood pressure fluctuations (Subtle seizures). Clonic seizures are more common, it can be focal clonic or (random) multifocalclonic i.e. usually begin in one extremity and spreadsrandomly.[1]

Prolonged seizures are associated with poor neurodevelopmental outcome.[2,3,4] So, prompt treatment of neonatal seizures is important in reducing long-term neurologic disabilities. In a standard NICU protocol, phenobarbitone (PB) is the first-line anti-seizure drugto treat neonatal seizures,thoughit has efficacy of around 50% only. Phenobarbital has many acute side effects like hypotension, sedation and respiratory suppression. Phenobarbital on long use is found to be associated with cognitive impairment.[4],[5]

These drugs, are widely used in Neonatal Intensive Care Units (NICUs), is derived from adult studies and there is not much studies to support their use compared to new generation drugs. Studies in rat models showed that

phenobarbital and phenytoin caused neuronal apoptosis, when administered to premature babies.[6,7,8]

LEV is a relatively new and wide spectrum anti-seizure drug which acts through synaptic vesicle glycoprotein 2A (SV2A).[7] LEV has a better pharmacokinetic and safety profile than other antiepileptic drug in neonates.[8, 9] LEV is found to be having an anti-apoptotic effect in the hippocampus and cerebral cortex of treated patients.[11]

Levetiracetam has been used in some western countries since over a decade to control neonatal seizures with good outcome, without any complications. LEV has been used as add on drug to control neonatal seizures in up to 30-50% cases after failure with Inj. Phenobarbital 40 mg/kg, plus inj. Phosphenytoin.[4]

The aim of this study was to evaluate the efficacy of LEV as first-line treatment in neonatal seizures, using a standard protocol, if LEV resistant seizure, additional antiepileptic was added.

Material and Methods

We performed a prospective observational study on preterm and term infants, affected by neonatal seizures, requiring anticonvulsant treatment. Neonates were recruited from Neonatal Intensive Care Unit of Patna Medical College and Hospital, Patna, Bihar from July 2017 to December 2017. We randomly included all preterm and term neonates having signs and/or symptoms of the seizure. We diagnosed neonatal seizure clinically as bed side EEG was not available

All patients with known major neurologic diseases and/or syndromes, metabolic causes (e.g., hypocalcemia and/or hypoglycemia), were excluded from the study.

LEV (40 mg/kg) was mixed with normal saline and initially loaded over 30 min; after initial loading, LEV (30 mg/kg) was administered thrice per day. For Neonates who continued to have seizures after LEV administration, additional loading of LEV 20 mg/kg was done, total dose upto 60 mg/kg was given. In those with LEV resistant seizure, infusion of PB (IV, 20 mg/kg) was used as the second anti-seizure medication, and phenytoin (IV, 20 mg/kg), midazolam (IV continuous infusion, 0.1–0.3 mg/kg/h), or valproic acid (IV, 10–15 mg/kg) was used as the third anti-seizure medications.

At baseline, the following data were collected: Patients' demographic data, familial and personal historical records, signs and/or symptoms description, inclusion and exclusion criteria evaluation, blood routine texts, cerebral ultrasound scan. The safety was evaluated by the presence of side effects and blood routine tests with evaluation of renal and kidney functions.

Informed consent was obtained from all patients' parents before the onset of therapy.

Result

The sample population included 20 neonates, of whom 15 were born on term, whereas 5 were preterm (2 were born at 35th, and 3 at 36th gestational weeks). Mean weight of patients was estimated 2712.60 g (SD: ±960.32). The mean head circumference was 33.61 ± 1.60 SD.

Table 1: Demographic detail of patients

Sex	Male	12 (60%)
	Female	8 (40%)
Gestation age	Mean	37± 1.8
Birth weight	Mean	2712.60 g (±960.32)

Among included patients, 15 (75%) were born by cesarean section and 5 by vaginal delivery. In general, positive perinatal history of the sample included meconium aspiration syndrome (33.2% of cases), respiratory distress (40%), perinatal asphyxia in 44%. Mean Apgar index at 1st min was 5.290(±3.50 SD), and 6.82 (±3.10 SD) at 5thmin. Mean onset of symptoms was 3.3 ± 1.2 days and symptoms for which LEV was started included subtle seizure (33.5%), focal seizures (16.5%), generalized tonic-clonic seizures (50%).

LEV was administrated intravenously (IV) as the first-line anti-seizure medication and Phenobarbitone (PB) was used as the second anti-seizure medication (Table 2). Overall, seizures terminated in 13 of 20 of the neonates (65%) after

receiving LEV, and no additional anti-seizure medications were required (Table 2). Seven infants (35%) required additional anti-seizure medications during LEV treatment. Seizure cessation was achieved 5 infants (25%) after administration of both LEV and PB. The remaining 2 infants (10%) continued with seizures until a third line anti-seizure medication (phenytoin, midazolam, or valproic acid) were administered. No major side effects were noted with LEV.

Table 2: Response of neonatal seizures to anti-seizure medications (*N* =20)

Drug	Seizure responded
Levetiracetam	65 %
Levetiracetam + Phenobarbital	25 %
Levetiracetam + Phenobarbital + other anti-seizure medications	10 %

Discussion

In this study, we found that LEV as 1st line agent was effective in most of neonates and safe in the resolution of neonatal seizures. In baseline data, male sex was found predominant in comparison to female in both groups. It is probably due the social custom of our country where still male offspring is more preferred and taken care of by the parents and family members.

Neonatal seizures are neurological emergencies and must be treated promptly since prolonged seizures can worsen neuronal injury in the immature brain and can lead to later neurodevelopmental disabilities or post-neonatal epilepsy.[2] We have only few antiepileptic drugs for neonatal seizure like PB, phenytoin, and benzodiazepines and these are not very effective in controlling seizures in neonates, and phenobarbital causes cognitive impairment in infants [11]

Khan *et al*. reported in 22 neonates after failure of phenobarbital therapy, 35% patients responded to LEV.[10]In a retrospective study by Abend *et al.*[11]LEV was given in 23 term neonates affected by neonatal seizures with pathologic EEG, Seizures resolution was observed in 8/23 neonates after 24 h of treatment and in other four patients between 24 and 72 h. Ramantani *et al.*[14] published a study on the use of LEV as first-line treatment in 38 on term and preterm neonates; LEV was safely administered both to on term and preterm babies, but was not efficient in controlling sizure, when administered alone and phenobarbital was required in more than 50% of the patients.

Maitre *et al.*[5] did a retrospective study to evaluate the neurodevelopmental progression of 280 neonates treated with phenobarbital and LEV. An increased neurotoxicity and altered neuromotor development was found in phenobarbital-treated patients. But, they found a reduction of neuronal apoptosis and a better neuromotor outcome in the LEV treated group. In this study, LEV was used as adjunctive therapy, on a second-line choice.

Yau *et al.*[15] treated 6 neonates with LEV in neonates and had control of seizures in about 75% of neonates within 72 h from the onset of treatment. All neonates received a first dose of phenobarbital before being treated with LEV, No side effects were observed.

A pilot study by Perveen et al,[16] with 60 patients (30 in LEV and 30 in phenobarbital group), found that LEV was effective in only 23.3% as comparing with phenobarbital which was effective in 86.7% neonates. Kirmani et al[17]retrospectively reviewed neonates treated with 10-50 mg/kg loading of levetiracetam for seizure found86% seizure control within one hour and 100% within72 hours.

Conclusion

Our results suggest that LEV is a potentially good option as the first-line anti-seizure antiepileptic for treating neonatal seizures.

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