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A STUDY ON LEVETIRACETAM VERSUS PHENOBARBITONE IN NEONATAL SEIZURES IN A TERTIARY CARE CENTRE IN EASTERN BIHAR.

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ABSTRACT

Objective: Neonatal seizures poses a serious medical challenge. Acute repetitive seizures leads to frequent emergency room visits and hospital admissions. Delay of treatment may lead to resistance to the first-line anticonvulsant therapies. To compare the efficacy and safety of intravenous Levetiracetam and Phenobarbitone in the treatment of neonatal seizures.

Methods: Open labelled, Randomized controlled trial. **Setting:** level III Neonatal Intensive Care Unit (NICU) of a tertiary-care center at Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar over a period of 12 months from July 2020 to June 2021. 200 neonates (0-28 days) with clinical seizures. If seizures persisted even after correction of hypoglycemia and hypocalcemia, participants were randomized to receive either Levetiracetam (20 mg/kg) or Phenobarbitone (20 mg/kg) intravenously. The dose of same drug was repeated if seizures persisted (20 mg/kg of Levetiracetam or 10 mg/kg of Phenobarbitone) and changeover to other drug occurred if the seizures persisted even after second dose of same drug. **Main outcome measures:** Cessation of seizures with one or two doses of the first drug, and remaining seizure-free for the next 24 hours.

Results: Seizures stoped in 86 (86%) and 62 (62%) neonates in Levetiracetam and Phenobarbitone group, respectively (RR 0.37; 95%CI 0.17, 0.80, P<0.01). 20 neonates had adverse reactions in the phenobarbitone group (hypotension in 10, bradycardia in 6 and requirement of mechanical ventilation in 4 neonates) while none had any adverse reaction in Levetiracatam group.

Conclusion: Levetiracetam achieves better control than Phenobarbitone for neonatal seizures when used as first-line antiepileptic drug, and is not associated with adverse drug reactions. However, larger prospective, randomized, blind comparison trials between phenobarbitone and levetiracetam would provide more information regarding the use of this newer agent in acute management of neonatal seizures.

KEYWORDS : Antiepileptic drugs, Neonate, Convulsions, Management, Outcome.

INTRODUCTION:

Neonatal seizures can be refractory to conventional antiepileptic drugs (AEDs) [1,2], and recently, newer-generation drugs have been considered for off-label use and/or clinical trials for this indication. Levetiracetam ((*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide; LEV) is a newer AED with more than a 10-y history of US Food and Drug Administration approval for use as adjunctive therapy for partial epilepsy and is efficacious and safe as monotherapy in adult and pediatric epilepsy syndromes [3,4]. Phenobarbital and phenytoin have been the mainstay treatment modalities for neonatal seizures. Studies have revealed these agents control seizures in less than half of neonates, can cause neuronal apoptosis in vitro, and have highly variable pharmacokinetics in neonates. In contrast, there have been no reports of levetiracetam causing these neurotoxic effects. Due to its favorable side effect and pharmacokinetic profiles and positive efficacy outcomes in neonatal studies to date, there is great interest in the use of levetiracetam for neonatal seizures. Seizures are the most common manifestation of neurological insult during the neonatal period [5]. Etiology and presentation of neonatal seizures are different from the children and adults. The most common cause of symptomatic neonatal seizures is hypoxic/ischemic encephalopathy (HIE) which affects approximately 1-2/100 live births [6,7]. There are no evidence-based guidelines for the pharmacologic treatment of neonatal seizures and management is highly variable. Phenobarbitone (PB) is the mainstay for neonatal seizures treatment. The efficacy of PB in the complete resolution of seizures varies between 33 and 77% [8]. Phenobarbitone can cause neuronal apoptosis in vitro and have highly variable pharmacokinetics in neonates [9-11].

Levetiracetam (LEV) may have a better safety profile since it does not cause neuronal apoptosis in infant rodents [12]. A recent review on the use of LEV in neonatal seizures revealed that complete or near complete seizure cessation was achieved in 77% of LEV, compared to 46% in PB group [13,14]. Literature pertaining to use of levetiracetam in neonatal seizures is limited, and there is a lack of randomized controlled trials. Hence we conducted this study with the objective to compare the efficacy and adverse effects of LEV and PB in the treatment of neonatal seizures.

METHODS:

This randomized controlled trial was conducted in the level III NICU of a tertiary-care center at Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar over a period of 12 months from July 2020 to June 2021. Outborn neonates (age 0-28 d) with clinical seizures were enrolled in the study. Neonatal seizures were clinically defined as abnormal, stereotyped and paroxysmal dysfunction in the central nervous system (CNS), occurring within the first 28 days after birth in full-term infants or before 48 weeks of gestational age in preterm infants [15]. Neonates with hypoglycemia, hypocalcemia, hypomagnesemia, those who received anticonvulsants prior to enrolment, and those with major congenital malformations *e.g.*, congenital heart defects, neural tube malformations, diaphragmatic hernia, choanal atresia, esophageal atresia, tracheoesophageal fistula, omphalocele, gastroschisis, intestinal obstruction and imperforate anus) were excluded.

Clinical details, seizure types and antiepileptic administration, including the sequence of drugs, dosage, timing and duration of therapy were recorded. Investigations included blood glucose, serum calcium, magnesium, electrolytes, complete blood counts, C- reactive protein, liver function tests, renal function tests, arterial blood gas, lactate, ammonia, cranial ultrasono-graphy, Imaging of brain, Electroencephalo-graphy (EEG), and metabolic and genetic testing, whenever required to find out the cause for seizures.

Neonates with clinical seizures were randomly assigned to receive either PB or LEV with a 1:1 allocation as per a computer-generated randomization schedule and using sequentially numbered, opaque and sealed envelopes. When an eligible neonate was eligible to be enrolled, the envelope was opened by a clinician who was not part of the study.

After ensuring patency of the airway, breathing and circulation, blood sugar and ionic calcium level were performed. If seizures persisted even after correction of hypoglycemia and hypocalcemia, neonates were randomized for intervention to receive either LEV (20 mg/kg) or PB (20 mg/kg) intravenously. Levetiracetam was diluted in normal saline to achieve a concentration of 20 mg/mL and administered intravenously at a rate of 1 mg/kg/min under cardiorespiratory monitoring. If seizures terminated, LEV was continued as maintenance at 20 mg/kg/day 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 the dose of 20 mg/kg diluted in 1: 10 normal saline given intravenously slowly at the rate of 1 mg/kg/min under

cardiorespiratory monitoring; if seizures were terminated, it was continued at 5 mg/kg/day in two divided doses as maintenance. Another loading dose of 10 mg/kg of PB was administered in neonates who failed to respond, and if seizures still persisted after two loading doses, patient was switched over to LEV.

The proportion of patients achieving cessation of seizures following the first or second dose of the drug (PB or LEV), and those remaining seizure-free for next 24 hours was considered as the primary outcome. Secondary outcome measure was the proportion of patients experiencing adverse events. Termination of seizure was defined clinically if there were no abnormal movement/eyeball deviation/ nystagmus, no change in heart rate, no change in respiration/saturation and autonomic dysfunction. Adverse effects occurring within two hours of drug administration, including desaturation, reduced respiratory rate, increased ventilator support requirement, arrhythmias, blood pressure, or heart rate fluctuations by more than 10% compared to the previous 2 hours, or if vasopressors were initiated or increased, were recorded. Increased ventilator requirement was considered, if requirement of tidal volume more than 6 mL/kg on volume controlled-ventilator, peak inspiratory pressure (PIP) more than 22 cm H2O in preterm and 23 cm H2O in term, and mean airway pressure (MAP) of more than 12 cmH2O on a pressure-controlled ventilator.

Informed consent was obtained from the parents on pre-structured proforma as soon as possible after assessing for eligibility. The study was approved by the institutional ethics committee of Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar. The sample size required for this study was calculated as 200 (100 in each group) with 95% two-sided significance (□), 80% power, 1:1 randomization and a drop out of 15% assuming a difference in proportion of outcomes between the groups as 31% (LEV 77% and PB 46%) [16,17].

***Statistical analyses*:** In the present study, Continuous variables were compared between the two groups using independent samples t-test. Termination of seizures at 24 hours and occurrence of adverse events were compared by Chi-square test. Effect size and its 95% CI were computed for the primary and secondary outcomes. *P* value of less than 0.05 was considered as significant. The analyses were carried out using the Statistical Package for Social Sciences (SPSS) 20.0 software.

RESULTS:

In the present study, a total of 244 babies with clinical seizures were assessed for eligibility during the study period; 44 were excluded and 100 neonates were randomized to each group. Baseline characteristics were comparable in the two groups. The commonest etiology for seizures was hypoxic-ischemic encephalopathy (HIE). Focal clonic seizures constituted the most common type of seizure in the study population.

Table 1:comparison Of Baseline Characteristics Of The Study Groups

Characteristics	Levetiracetam	Phenobarbitone
	(n=100)	(n=100)
Age (d), mean (SD)	9.8 (8.50)	8 (8.33)
Male, n (%)	56 (56)	56(56)
Mode of delivery, n (%)		
Vaginal	70 (70)	72 (72)
Caesarian	30 (30)	28 (28)
Gestation, n (%)		
Term	80(80)	84(84)
Preterm	20(20)	16 (16)
Birth weight (kg) , mean (SD)	2.56 (0.64)	2.73 (0.64)
Etiology of seizures, n (%)		
HIE	40 (40)	48 (48)
Neonatal sepsis/Meningitis	36 (36)	30 (30)
Intracranial haemorrhage	6 (6)	4 (4)
Benign neonatal epilepsy syndrome	4 (4)	2 (2)
Malignant neonatal epilepsy syndrome	2 (2)	2 (2)
Cortical malformation	2 (2)	2 (2)
IEM	2 (2)	4 (4)
Unknown	8 (8)	8 (8)

HIE: Hypoxic ischemic encephalopathy, IEM: Inborn errors of metabolism.

Following first dose of drug, seizures stopped in 60 (60%) neonates in LEV group, and 50 (50%) neonates in PB group. In the LEV group, there was a cessation of clinical seizures (and remaining seizure free at 24 h) in 86 (86%), and in the PB group, it was 62 (62%) after one or two doses (P<0.001). Seizure control was better (RR 0.37; 95% CI (0.17, 0.80) in the LEV group.

A total of 20 adverse events were observed in the PB group and none in LEV group. Various adverse events noted in the PB group were; hypotension in 10 neonates, bradycardia in 6 neonates and requirement of mechanical ventilation in 4 neonates.

6 out of the 14 neonates who did not respond to LEV, responded to PB. Among the 38 neonates who did not respond to PB, 32 showed seizure cessation with LEV. In the LEV group, 94 were discharged, four left against medical advice, and two died. In the PB group, 92 neonates were discharged and 8 left against medical advice.

DISCUSSION:

This study aims to obtain essential data regarding the efficacy and safety of LEV in this vulnerable and under researched population. In the present study, we documented better anticonvulsant efficacy and safety of LEV in comparison to PB as a first-line antiepileptic drug in neonatal seizures. A higher proportion of neonates had a cessation of seizures in LEV group as compared to PB group. There were no adverse drug reactions noted in the neonates who received LEV in the present study whereas, 20 of the neonates in the PB group developed adverse drug reactions. The efficacy of LEV has been earlier demonstrated in a study by Ramantani, *et al*. [17], in which 30 (78%) out of 38 infants were seizure-free after receiving LEV. In study by Khan, *et al*. [18], 19 (86%) of the 22 neonates demonstrated seizure cessation within 1 hour of administration. In a systematic review of the efficacy of LEV in neonatal seizures, complete or near-complete seizure cessation was achieved in 37/48 (77%) who received LEV as first-line drug, and 24/52 (46%) of the ones with PB as first-line AED [14]. These results show that LEV is at least as effective as PB in the control of neonatal seizures as a first-line agent. However, in a study by Abend, *et al*. [19], LEV was associated with seizure improvement within 24 hours in only 8 (35%) of 23 neonates. The low response to LEV in this study could be due to the usage of LEV as first-line anti-epileptic drug in only one neonate in the study. Few other studies [14,20] have documented good seizure control with LEV when it was used as a second- or third-line agent in control of neonatal seizures. The safety of LEV in neonates has also been documented in previous studies [17,19-21]. Li et al. demonstrated that levetiracetam is a safe and effective treatment for infants and children in an observational, prospective study, Li et al. prospectively analyzed 120 patients (39.3% female, 61.7% male) with epilepsy receiving mono or combination therapy with levetiracetam that were 1 month-old and younger. [22] In an another study, Michaelides et al. concluded that i.v LEV was very well tolerated in their neonatal population [23].

The limitation of our study was that we did not perform electroencephalographic monitoring to document cessation of seizure activity. However, in most of the neonatal units, especially with limited resources, clinical control of seizures is usually the only guide to treatment. Thus, despite this limitation, the generalizability of our study for such settings is reasonable. Lack of long-term follow-up and inability to perform therapeutic drug levels of PB and LEV were the other limitations of the present study. The sample size of our study was also inadequate for the outcomes related to various adverse effects.

CONCLUSION:

Levetiracetam can be a good and safe choice for treatment of neonatal seizures in comparison to Phenobarbitone as a first line AED in management of neonatal seizures. Levetiracetam has shown to have promising anti-epileptic properties for the management of neonatal seizure with better efficacy and less or no side effects. There is a need to conduct more randomized controlled trials seeking the role of LEV in the acute management of neonatal seizures and also for assessing its neuro protective role and neuro developmental outcome in these neonates. Prospective double blind controlled studies are needed in the future.

REFERENCES

1. Silverstein FS, Jensen FE . Neonatal seizures. Ann Neurol 2007;62:112–20.
2. Sankar R, Painter MJ . Neonatal seizures: after all these years we still love what doesn't work. Neurology 2005;64:776–7.
3. Glauser TA, Ayala R, Elterman RD, et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology 2006;66:1654–60.

4. Khurana DS, Kothare SV, Valencia I, Melvin JJ, Legido A . Levetiracetam monotherapy in children with epilepsy. Pediatr Neurol 2007;36:227–30.
5. Thibeault-Eybalin MP, Lortie A, Carmant L. Neonatal seizures: Do they damage the brain? Pediatr Neurol. 2009;40:175-80.
6. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population-based study. J Pediatr. 1999;134:71.
7. Saliba RM, Annegers JF, Walker DK, Tyson JE, Mizrahi EM. Incidence of neonatal seizures in Harris County, Texas, 1992-1994. Am J Epidemiol. 1999; 150:763.
8. Van Rooij LG, Hellström-Westas L, deVries LS. Treatment of neonatal seizures. Semin Fetal Neonatal Med. 2013;18:209-15.
9. Bartha AI, Shen J, Katz KH, Mischel RE, Yap KR, Ivacko JA, et al. Neonatal seizures: multicenter variability in current treatment practices. Pediatr Neurol. 2007;37:85-90.
10. Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord. 2007;9:353-412.
11. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999;341:485-9.
12. Manthey D, Asimiadou S, Stefovska V, Kaindl AM, Fassbender J, Ikonomidou C, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp Neurol. 2005;193:497e503.
13. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: A review.□ J Pediatr Pharmacol Ther. 2015;20:76-89.
14. McHugh DC, Lancaster S, Manganas LN. A systematic review of the efficacy of levetiracetam in neonatal seizures. Neuropediatrics. 2018;49:12-17.
15. Han JY, Moon CJ, Youn YA, Sung IK, Lee IG. Efficacy of Levetiracetam for neonatal seizures in preterm infants. BMC Pediatr. 2018;18:131.
16. Boylan GB, Rennie JM, Pressler RM, Wilson G, Morton M, Binnie CD. Phenobarbitone, neonatal seizures, and video EEG. Arch Dis Child Fetal Neonatal Ed. 2002;86:165-70.
17. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: Safety and efficacy in neonatal seizures.□Eur J Paediatr Neurol.□2011;15:1-7.□
18. Khan O, Chang E, Cipriani C, Wright C, Crisp E, Kirmani B. Use of intravenous levetiracetam for management of acute seizures in neonates.□ Pediatr Neurol.□2011;44:265-9.
19. Abend NS, Gutierrez-Colina AM, Monk HM, Dlugos DJ, Clancy RR. Levetiracetam for treatment of neonatal seizures.□J Child Neurol.□2011;26:465-70.
20. Rakshasbhuvankar A, Rao S,□ Kohan R,□ Simmer K,□ Nagarajan L, J Clin Neurosci.□2013;20:1165-7.
21. Koppelstätetter A, Buhrer C, Kaindl AM. Treating neonates with levetiracetam: A survey among German university hospitals. Klin Pediatr. 2011;223:450-2.
22. Li J, Xiao N, Chen S. Efficacy and tolerability of levetiracetam in children with epilepsy. Brain Dev (2011) 33:145–5110.1016/j.braindev.2010.03.002 [PubMed] [CrossRef] [Google Scholar]
23. Michaelides C, Thibert RL, Shapiro MJ, Kinirons P, John T, Manchharama D, et al. Tolerability and dosing experience of intravenous levetiracetam in children and infants. Epilepsy Res (2008) 81:143–710.1016/j.eplepsyres.2008.05.004 [PubMed] [CrossRef] [Google Scholar]