ORIGINAL RESEARCH

Comparative study of phenobarbitone and levetiracetam as first line anticonvulsant in neonatal seizures treatment

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ABSTRACT

Background: Seizures are the foremost common manifestation of neurological insult during the time of life. There are not any evidence-based guidelines for the pharmacologic treatment of neonatal seizures and management is highly variable. Hence this study was conducted with the target to match the efficacy and adverse effects of levetiracetam and phenobarbitone used for treatment of neonatal seizures.**Methods:** Open labelled, randomized controlled trial done in Special new-born care unit (SNCU) on 80 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 change over to other drug occurred if the seizures persisted even after second dose of same drug. **Results:** Seizures stopped in 35(87.5%) and 23(57.5%) neonates in Levetiracetam and Phenobarbitone group, respectively(P value= 0.0047). 9 neonates had adverse reactions in the phenobarbitone group (hypotension in 4, bradycardia in 2 and requirement of mechanical ventilation in 3 neonates) while none had any adverse reaction in Levetiracatam group. **Conclusions:** Levetiracetam achieves better control than Phenobarbitone for neonatal seizures when used as first-line antiepileptic drug and is not associated with adverse drug reactions.

Key words: Neonate, convulsions,phenobarbitone,levetriacetam

INTRODUCTION

Seizures are the foremost common manifestation of neurological insult during the time of life. Etiology and presentation of neonatal seizures are different from the youngsters and adults[1]. The most common explanation for symptomatic neonatal seizures is hypoxic /ischemic encephalopathy (HIE) which affects approximately 1-2/100 live births[2,3]. There are not any evidence-based guidelines for the pharmacologic treatment of neonatal seizures and management is highly variable. Phenobarbitone (PB) is considered the mainstay for neonatal seizures treatment. The efficacy of PB in the complete resolution of seizures varies between 33 and 77%[4]. Phenobarbitone can cause neuronal apoptosis *in vitro* and have highly variable pharmacokinetics in neonates[5,6,7]. Levetiracetam (LEV) may have a far better safety profile since it doesn't cause neuronal apoptosis in infant rodents[8]. 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[9,10]. Literature concerning use of levetiracetam in neonatal seizures is restrictedand there's a scarcity of randomized controlled trials. Hence this study was conducted with the target to match the efficacy and adverse effects of LEV and PB used for treatment of neonatal seizures.

METHODS

The present study was carried out at MGM medical college Indore for a period of 1 year. After review of

synopsis of our research, approval by ethical committee and talking written informed consent from the parents, the neonates with seizures were included in the study population.

SOURCE OF DATA

All patients attending Dept. of Paediatrics, M.Y Hospital, Indore and Chacha Nehru BalChikitsalayaEvamAnusandhan Kendra,Indore. Neonates (age 0-28 d) with clinical seizures were enrolled in the study[11]. The sample size required for this study was calculated as 80(40 in levertiracetam group, 40 in phenobarbitone group and 22 received both phenobarbitone and levertiracetam) 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%)[12,1].

AIMS AND OBJECTIVES

To compare the efficacy and safety of intravenous Levetiracetam and Phenobarbitone in the treatment of neonatal seizures.

STUDY DESIGN

Randomized controlled trial.

INCLUSION CRITERIA

- Newborn born at term gestational age (>37 weeks),Gestational age was assessed by new Ballard score.
- Neonates (age 0-28 d) with clinical seizures were enrolled in the study.

EXCLUSION CRITERIA

- Preterm neonates.
- Neonates with hypoglycemia, hypocalcemia, hypomagnesemia.
- Neonates received anticonvulsants prior to admission.
- Neonates with major congenital malformations.
- Parents gave negative consent were excluded.

Clinical data, type of seizure and administration of antiepileptic drug including Clinical details, seizure types and antiepileptic administration, including the sequence of drugs, dosage, timing and duration of treatment was recorded. Investigations included blood glucose, serum calcium, magnesium, electrolytes, complete blood counts, C reactive protein, liver function tests, renal function tests, arterial blood gas, cranial ultrasonography, whenever required to find out the cause for seizures. Neonates with clinical seizures were randomly assigned to receive either phenobarbitone (PB) or levetiracetam (LEV) with a 1:1 allocation as per a computer-generated randomization schedule and using sequentially numbered, opaque and sealed envelopes. Clinician who is not a part of study opened the envelope when an eligible neonate was enrolled. After ensuring patency of the airway, breathing and circulation, blood sugar and serum calcium level were performed. After correcting hypoglycemia and hypocalcemia, if a seizurestill persisted, randomized neonates received either intravenous bolus of LEV (20 mg/ kg) or PB (20 mg/kg). The exact volume determined by the dosing (mg/kg) and patient weight. On termination of seizure LEV was given in maintenance in two divided doses at 20mg/kg/day. On continuation of seizure, another loading of LEV (20 mg/kg) was given, and on persistence of seizure, patient was given loading of PB in a dose of 20mg/kg (1:10 dilution) intravenously slowly. On termination of seizure, PB was continued in a maintenance dosed of 5mg/kg/day. If seizure persisted, again a loading dose of PB with 10mg/kg was givenand if there was persistence of seizure after two loading doses then patient was switched 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. 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.

STATISTICAL ANALYSIS

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. Logistic regression analysis were applied and odds ratio was calculated. 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

A total of 120 babies with clinical seizures were assessed for eligibility during the study period; 40 were excluded and 40 neonates were randomized to each group (i.e. LEV and PB group) (Figure 1). Baseline charactersics of both groups were comparable(Table I). The commonest etiology for seizures was hypoxic-ischemic encephalopathy (HIE). Focal clonic seizures constituted the most common type of seizure in the study subjects.

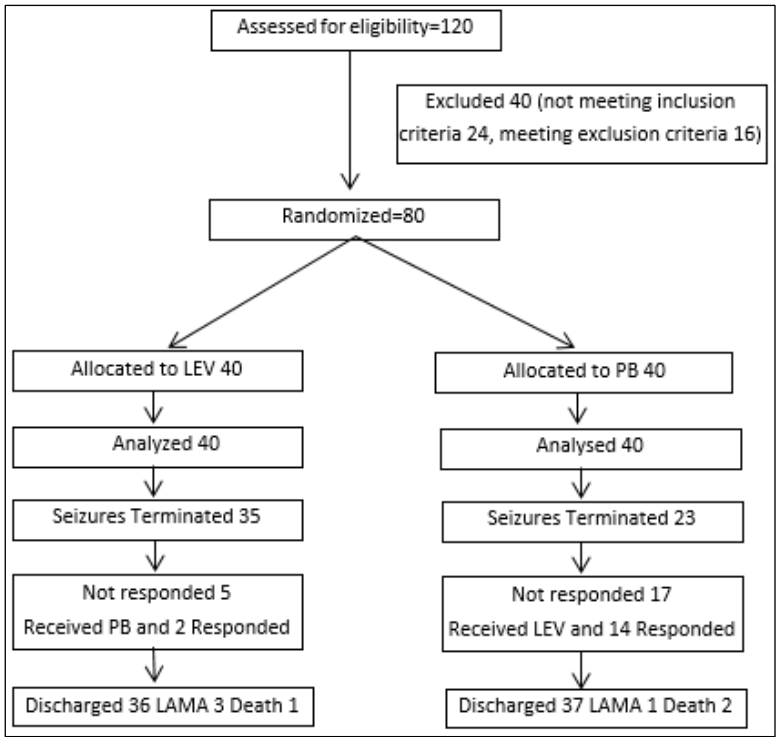

Fig1:Flow chart of study subject

Table 1: Base line characteristics of study subjects

Characteristics	Levetiracetam (N=40)	Phenobarbitone (N=40)	P value
Age (d), mean(SD)	9.8(8.50)	8(8.33)	0.323
Female, n (%)	18(45)	14(35)	0.494
Female, n(%)	22(55)	26(65)	
Mode of delivery, n (%)			
Vaginal	31(77.5)	35(87.5)	0.23
Caesarian	9(22.5)	5((12.5)	
Gestation, n (%)			
Term	32(80)	33(84)	0.77
Birth weight (kg)	2.67+-0.69	2.57+-0.63	
Maternal age	26.07+-3.11	27.92+-5.05	0.504
Etiology of seizures, n (%)			0.06
HIE	17(42.5)	18(45)	
Neonatal sepsis/Meningitis	14(35)	12(30)	
Intracranial hemorrhage	1(2.5)	3(7.5)	
Unknown	7(17.5)	6(15)	

Table 2shows following first dose of drug, seizures stopped in 35 (87.5%) neonates in LEV group and 23(57.5%) neonates in PB group. In the LEV group, there was a cessation of clinical seizures (and remaining seizure free at 24 h) in 35 (87.5%), and in the PB group, it was 23(57.5%) after one or two doses (P value 0.0047). Seizure control was better (RR 1.5217; 95% CI (1.13 2.03) in the LEV group. A total of 9 adverse events were observed in the PB group and none in LEV group. Various adverse events noted in the PB group were; hypotension in 4 neonates, bradycardia in 2 neonates and requirement of mechanical ventilation in 3 neonates.Out of the 5 neonates who did not respond to LEV, 2 responded to PB. Among the 17 neonates who did not respond to PB, 14 showed seizure cessation with LEV. In the LEV group, 36 were discharged, 3 left against medical advice (LAMA), and 1 death. In the PB group, 37 neonates were discharged and 1 LAMAand 2 death.

Table 2: Various outcome of patients after drug administration

	Levetiracetam (N=40)	Phenobarbitone (N=40)	P value
Seizure free for 24 hrs receiving one or two dose	35(87.5%)	23(57.5%)	0.0047
Seizure free after receiving other group drug	2(40%)	14(82%)	0.06
Adverse reaction			
Hypotension	0(0%)	4(10%)	0.04
Bradycardia	0(0%)	2(5%)	0.15
Mechanical ventilation	0(0%)	3(7.5%)	0.07
Outcome			
Discharged	36(90%)	37(92.5)	0.69
LAMA	3(7.5%)	1(2.5)	0.30
Death	1((2.5%)	2(5%)	0.5

DISCUSSION

In this study, higher and better anticonvulsant efficacy and safety of LEV was documentedin comparison to PB as a first-line antiepileptic drug used in management in neonatal seizures. A greater percentage of neonates had a cessation of seizures in LEV group as compared to PB group. No adverse drug reactions were noted in the neonates who received LEV in the present study whereas, 9 of the neonates in the PB group developed adverse drug reactions but it was difficult to determine whether it was mainly due to seizure or due to the drug.The efficacy of LEV has been in advanced demonstrated and verified in a study by Ramantani, *et al*.[13]30 (78%) out of 38 after receiving LEV were seizure free. In study by Khan, *et al*.[14] 19 (86%) of the 22 neonates demonstrated seizure cessation within 1 hour of administration. In a systematic scientific 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 [10]. These results positively display that LEV is at least as effective as PB in the control of neonatal seizures when used as a first-line agent. However, in a study by Abend, *et al*.[15], LEV was associated with seizure improvement within 24 hours in only 8 (35%) of 23 neonates. Few other studies[10,16], have documented better 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[13,15,16,17].

LIMITATIONS OF THE STUDY

The limitation of this study was that electroencephalographic monitoring was not performed 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 thisstudy for such settings is reasonable.

CONCLUSION

It was concluded from this study that levetiracetam is an effective and safer alternative to phenobarbitone in the management of neonatal seizures, as a first-line AED.

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DECLARATIONS

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Conflict of interest: None

Ethical approval: Approved by institutional ethical committee.

REFERENCES

1. Thibeault-Eybalin MP, Lortie A, Carmant L. Neonatal seizures: Do they damage the brain? Pediatr Neurol. 2009;40:175-80.https://doi.org/10.1016/j.pediatrneurol.2008.10.026
2. Ronen GM, Penney S, Andrews W. The epidemiology of clinical neonatal seizures in Newfoundland: a population based study. J Pediatr. 1999;134:71.https://doi.org/10.1016/S0022-3476(99)70374-4
3. 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.https://doi.org/10.1093/oxfordjournals.aje.a010079
4. Van Rooij LG, Hellström-Westas L, DeVries LS. Treatment of neonatal seizures. Semin Fetal Neonatal Med. 2013;18:209-15.https://doi.org/10.1016/j.siny.2013.01.001
5. 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;37:8590.https://doi.org/10.1016/j.pediatrneurol.2007.04.003
6. Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord. 2007;9:353-

412.https://icnapedia.org/guidelines/open/18077226.pdf
7. 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. DOI: 10.1056/NEJM199908123410704
8. 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.https://doi.org/10.1016/j.expneurol.2005.01.006
9. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: A review. J PediatrPharmacolTher. 2015;20:76-89.https://doi.org/10.5863/1551-6776-20.2.76
10. McHugh DC, Lancaster S, Manganas LN. A systematic review of the efficacy of levetiracetam in neonatal seizures. Neuropediatrics. 2018;49:12-17. DOI: 10.1055/s-0037-1608653
11. Han JY, Moon CJ, Youn YA, Sung IK, Lee IG. Efficacy of Levetiracetam for neonatal seizures in preterm infants. BMC Pediatr. 2018;18:131. https://doi.org/10.1186/s12887-018-1103-1
12. 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.https://fn.bmj.com/content/86/3/F165.abstract
13. 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.https://doi.org/10.1016/j.ejpn.2010.10.003
14. 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.https://doi.org/10.1016/j.pediatrneurol.2010.11.005
15. Abend NS, Gutierrez-ColinaAM, Monk HM, Dlugos DJ, Clancy RR. Levetiracetam for treatment of neonatal seizures. J Child Neurol. 2011;26:465-70.https://doi.org/10.1177/0883073810384263
16. Rakshasbhuvankar A, Rao S, Kohan R, Simmer K, Nagarajan L, J ClinNeurosci. 2013;20:1165-7.https://doi.org/10.1016/j.jocn.2012.08.014
17. Koppelstäetter A, Buhrer C, Kaindl AM. Treating neonates with levetiracetam: A survey among German university hospitals. KlinPediatr. 2011;223:450-2. DOI: 10.1055/s-0031-1287822.