## Research Article

# A randomized controlled trial on comparison of phenobarbitone and levetiracetam for the treatment of neonatal seizures: pilot study

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## ABSTRACT

**Background:** 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, resulting in impairment of cognition and behaviour, and liver. So there is an urgent need for an alternative antiepileptic drug for treatment of neonatal seizures. Levetiracetam is a relatively new anticonvulsant. There are no randomized controlled trials about its use in neonates. This trial was designed with the objective to compare the efficacy of levetiracetam and phenobarbitone in the treatment of clinically apparent neonatal seizures in term and late preterm neonates.
**Methods:** The study was designed as an open label randomized controlled trial. Study population included babies of >2 kg admitted in Neonatal Intensive Care Unit within 48 hours of birth with neonatal seizures due to perinatal asphyxia. If seizures persisted even after correction of hypoglycemia and hypocalcaemia, babies were randomized for intervention to either levetiracetam or phenobarbitone.
**Results:** Clinically apparent seizures were controlled in only 23.3% neonates assigned to receive levetiracetam as compared to 86.7% neonates assigned to receive phenobarbitone (p<0.001).
**Conclusions:** Present study demonstrated that levetiracetam is not as good as phenobarbitone in controlling neonatal seizures due to perinatal asphyxia in term and near term neonates. Also, it takes longer time than phenobarbitone in controlling clinical seizures. Superiority of phenobarbitone was observed both when given as a first line drug and after cross over.

**Keywords**: Neonatal seizures, Phenobarbitone, Levetiracetam

## INTRODUCTION

Seizures account for about 1-2% of neonatal ICU admissions. Though there is agreement regarding the battery of diagnostic tests, the most appropriate anticonvulsant is still debatable.[1-4] Perinatal asphyxia is the commonest cause of neonatal seizure worldwide. 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 behaviour.[5] Moreover, repeated loading doses, especially with concomitant hypoxic liver injury in asphyxia can potentially lead to unpredictable serum levels and exaggerated adverse effects. So 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.[6-10.] Animal studies have shown that it does not cause neuronal apoptosis in the immature brain and it also has neuro-protective effect.[11]

Though, there are case series, small trials, including some recent ones on use of levetiracetam in neonatal seizures in term and preterm infants, there are no randomized controlled trials.[12-19] We therefore designed a trial with the objective to compare the efficacy of levetiracetam and phenobarbitone in the treatment of clinically apparent neonatal seizures in term and late preterm neonates.

## METHODS

The study was designed as an open label randomized controlled trial in a government hospital in North India, from July 2014 to December 2015. Study population included babies of >2 kg admitted in NICU within 48 hours of birth with neonatal seizures due to perinatal asphyxia with clinical features of HIE.

For the purpose of inclusion in study, the following movements were considered as seizures:

- Subtle seizure manifested as eye movements (roving, blinking, fluttering, rolling, gaze fixation or nystagmus) sucking, smacking, chewing and tongue protrusions, swimming, pedalling, bicycling, thrashing or struggling movements and rarely apnea
- Tonic seizures in which there is sustained contraction of group of muscle either axial or limb
- Clonic seizures like rhythmic jerky movement of muscle
- Myoclonic seizures like rapid, single or arrhythmic repetitive jerky movement affecting limb or whole body.

Perinatal asphyxia was defined as:

- APGAR score <5 at 5 minute in deliveries in hospital attended by pediatrician or
- Babies born hospital with delayed onset of cry after 3 min of birth in deliveries not attended by doctor or at home.

The babies were excluded if he had any of the following at admission:

1. anticonvulsant prior to admission,
2. serum creatinine greater than 2 mg/dl,
3. major congenital malformations,
4. refractory shock, or
5. need for assisted ventilation at admission.

### *Method of randomization, allocation concealment and blinding*

Randomization was done using computer generated numbers. Labelled slips were put in serially numbered opaque and sealed envelopes. They were opened when an eligible baby was enrolled by an independent worker, not worked in the study.

The team members managing the babies were aware of the treatment allocation. However, the EEG technician and neurologist were unaware of the treatment limb allocation. Before enrollment, written informed consent was obtained from parents on a pre-structured proforma. The trial was approved by institutional ethics committee.

After ensuring patency of airway, breathing and circulation, an intravenous cannula was secured and blood sugar and ionic serum calcium level were done. If seizures persisted even after correction of hypoglycemia and hypocalcaemia, babies were randomized for intervention to either levetiracetam or phenobarbitone (Figure 1).
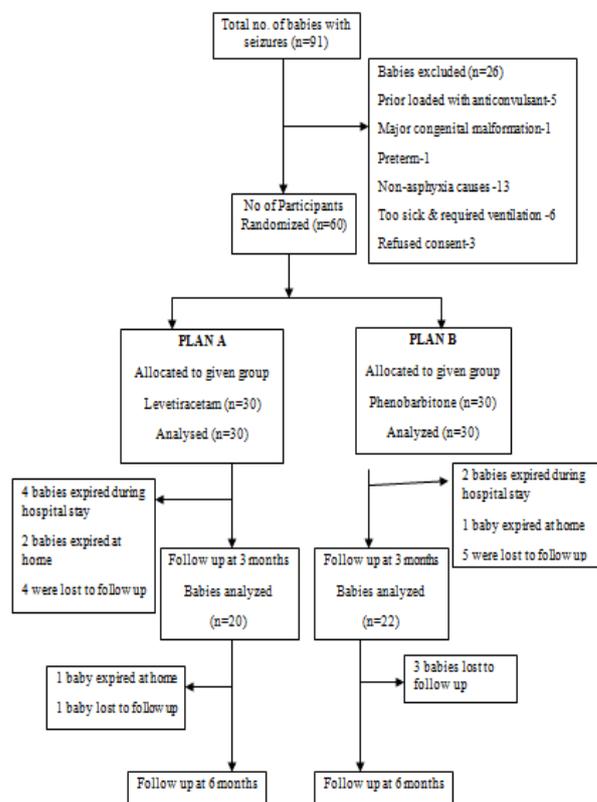


**Figure 1: Flowchart of participants in trial.**

### *Group 1*

Babies were loaded with IV levetiracetam in dose of 60mg/kg diluted in 30 ml normal saline given slowly over 15-20 min, under cardio respiratory system monitoring. If seizures were controlled, maintenance was continued (15mg/kg/day q 12 hr) for 5 days. If seizures persisted after the loading dose of levetiracetam, babies crossed over to receive IV phenobarbitone, followed by maintenance (5 mg/kg/day q 12 hr) for 5 days (Figure 2).
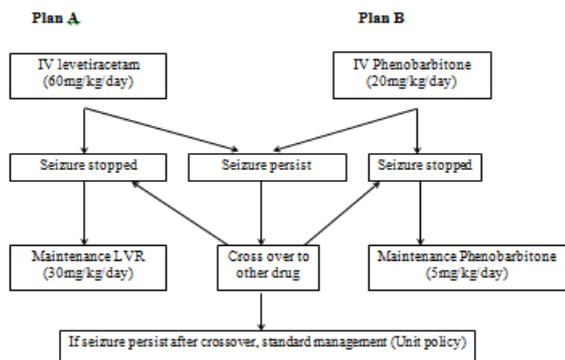
**Figure 2: Study protocol.**

### Group 2

Babies were loaded with IV phenobarbitone in dose of 20mg/kg diluted in 1:10 of distilled water given slowly at the rate of 1mg/kg/min under strict cardiorespiratory monitoring. If seizures persisted, the babies were crossed over to treatment with IV levetiracetam. If seizures were controlled then they were kept on maintenance dose of both drugs.

If seizures persisted despite crossover, the babies were treated as per unit policy. Complete blood count, liver function test and kidney function tests were done at admission, at 5 days and when indicated. EEG was recorded within 48-72 hours of control of all clinical seizures and baby was hemodynamically stable.

Once the baby was seizure free for 5 days, anticonvulsants were abruptly stopped in the same order as they were started except phenobarbitone. Phenobarbitone was stopped last if neurological examination was normal and EEG demonstrated no electrical seizures. If neurological examination or EEG was not normal then phenobarbitone was continued at discharge, as per unit protocol.

Neurological examination was done in all babies at discharge. It included examinations of overall activity, response to stimuli, ability to suck and swallow, active and passive tone of neck and trunk muscles and neonatal reflexes (Moro's, traction, and habituation). Examination at 3 months and 6 months of age on follow up was done by Amiel Tison method. Achievement of milestones like social smile and recognition of mother, ability to turn over, neonatal reflexes (Moro's, grasp) head circumference growth and persistence of seizures were also evaluated.

For those babies who could not come for follow up, telephonic interview of parents and/or local doctor was undertaken. They were asked about age specific developmental milestones, persistence of seizures and over all perception of parents about the baby. At 6 months, baby was labelled abnormal if the baby was not able to hold objects, not hold neck, not able to turn over or recognize mother or track faces.

As levetiracetam is a relatively new drug, an institutional drug monitoring committee was formulated. It reviewed all babies receiving levetiracetam. Any worsening of hemodynamic and respiratory status within 2 hours of administration of the drug was looked for. All mortalities were reviewed the next day in a departmental meeting and the cause of death was determined. It was specifically reviewed if the mortality could have been due to any of the anticonvulsant drug.

### Outcome variables

Clinical control of seizure activity was the primary outcome variable of this study. Seizures were considered to be controlled if the baby was seizures free 24 hrs after last seizures.

Secondary outcomes were safety profile of levetiracetam, electrical seizures after control of clinical seizure, time taken to control seizures, and neurological examination till 6 months.

A prior study at institute had demonstrated 72% efficacy of phenobarbitone in clinical control of seizures.[24] To detect difference in efficacy of 30% with 5% error and 80% power, 30 babies in each group were needed.

### Statistical analysis

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

### RESULTS

A total of 91 babies with clinically apparent seizures were screened during the study period. Thirty-one were excluded due to various reasons and rest 60 babies were enrolled in this study (Figure 1). Thirty babies were randomized to levetiracetam group and 30 to phenobarbitone group (Figure 2). Baseline characteristics were comparable in the two groups (Table 1).

Clinically apparent seizures were controlled in only 7 of the 30 (23.3%) neonates assigned to receive levetiracetam as compared to 26 of the 30 (86.7%) neonates assigned to receive phenobarbitone (p<0.001) (Table 2). Relative risk (95%Confidence Interval) for seizure control was 0.27 (0.09- 0.63), in favour of phenobarbitone.

One baby with HIE stage 3 developed apnoea 2 hours after levetiracetam administration and required mechanical ventilation. The baby ultimately died at 62 hours of life. During hospital stay, 6 (10%) babies with

HIE III expired after a mean of 52 hours. None of these mortalities were within 4 hours of drug administration so were probably not related to drugs. Serum levels of drugs could not be done.

**Table 1: Baseline characteristics of the 2 groups.**

|  | Levetiracetam group (n=30) | Phenobarbitone group (n=30) | P Value |
|---|---|---|---|
| Gestational age*(weeks) | 38.29 (1.03) | 38.43 (1.10) | >0.05 |
| Weight*(kg) | 2.78 (0.33) | 2.90 (0.310) | >0.05 |
| Male | 19 (63.3) | 22 (73.3) | >0.05 |
| Intramural deliveries | 11(36.7) | 13 (43.3) | >0.05 |
| HIE stage two | 24 (80) | 25 (83.3) | >0.05 |
| HIE stage three | 6(20) | 5 (16.6) | >0.05 |
| Duration of hospital stay* (days) | 7.7 (4.56) | 8.9(4.91) | >0.05 |
| Need of boluses and inotropic | 15 (50) | 10 (30) | >0.05 |
| Sepsis Screen positive | 3/30 (10) | 2/30 (6.6) | >0.05 |
| ph< 7.0 at admission | 19/30 (63.3) | 17/30 (56.6) | >0.05 |
| Base deficit >12 | 20/30 (66.6) | 18/30(60) | >0.05 |

Values indicate Mean (SD)*OR number (%)

At the time of discharge, 16/54 (29.8%) were neurologically abnormal with no difference in the 2 groups (Table 2). Of these neurologically abnormal babies, 12/16 (75%) had HIE stage 3 and 4/16 (25%) had HIE stage 2 at admission.

**Table 2: Outcomes in the 2 groups.**

|  | Levetiracetam group (n=30) | Phenobarbitone group (n=30) | p value |
|---|---|---|---|
| **Seizures controlled (with primary drug)** | 7/30 (23.3) | 26/30 (86.7) | <0.001 |
| **Seizures controlled after cross over** | 26/30 (86.6) | 29/30 (96.7) | 0.001 |
| **Time of complete control of seizures*(hours)** | 3.6 (5) | 1.27 (2.9) | <0.05 |
| **Electrical seizures after clinical control** | 7/21 (33.3) | 4/26 (15.3) | >0.05 |
| **Abnormal liver function** | 3/30 (10) | 4/30 (13.3) | >0.05 |
| **Abnormal kidney function** | 4/30 (13.3) | 2/30 (6) | >0.05 |
| Mortality at discharge | 4/30 (13.33) | 2/30 (6.6) | 0.67 |
| 3 Months | 2/20 (10) | 1/22 (4.54) | 0.59 |
| 6 Months | 1/18 (5.5) | 0/19 (0) | 0.48 |
| **Abnormal neurological outcome** |  |  |  |
| Discharge | 10/26 (38.46) | 6/28 (21.4) | 0.23 |
| 3 Months | 5/20 (25) | 2/22 (9.09) | 0.22 |
| 6 Months | 4/18 (22.22) | 2/19 (10.5) | 0.40 |

## DISCUSSION

Present study demonstrated that levetiracetam is not as good as phenobarbitone in controlling neonatal seizures due to perinatal asphyxia in term and near term neonates. Also, it takes longer time than phenobarbitone in controlling clinical seizures. Superiority of phenobarbitone was observed both when given as a first line drug and after cross over. We did not find any major side effects related to any of the drugs used. Occurrence of electrical seizures after clinical control of seizure was similar in the two groups. 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 to 3 months, treated with oral levetiracetam for seizures refractory to phenobarbital, phenytoin and benzodiazepines.[12,13] Furwentsches A et al did

prospective pilot feasibility study of oral levetiracetam for 3 days on newborns with seizures but they permitted additional treatment with single daily doses of phenobarbitone.[17] So, which drug contributed more to this seizure control would be difficult to say. A recently published case series of 22 neonates by Khan O et al reported clinical control of seizures in 32%, in babies who had not responded to phenobarbitone.[21] Similarly, Abend NS et al reported effective seizure control in 35 % neonates.[22] Most studies have used levetiracetam as second line drug after phenobarbitone failure. Our study is the first study to test levetiracetam as a first line drug in treatment of neonatal seizures.

There was not enough data on pharmacokinetics of levetiracetam at time of onset of our trial. We used a loading dose of 60 mg /kg followed by maintenance dose of 30 mg/kg/day based on dose used in study by Rottenberg MT et al.[12] Though subsequent study on pharmecokinetics of levetiracetam were done using 40 mg/kg, Ramantani G et al have reported safety and efficacy of LVR with 60 mg/kg as well.[15,23,24] Higher dose may be required in neonates due to i) higher volume of distribution ii) greater than predicted clearance in first week of life iii) intractability of neonatal seizures in neonates and iv) safety demonstrated in childrens even with dose up to 275 mg/kg and up to 1800 mg/kg in animals (no death, organ failure or irreversible toxicities were noted).[19,25,26]

Sharpe CM et al demonstrated that 8 hourly dosing is required to ensure that 95% of infants maintain trough concentration >10microgram/ml and above 20 microgram/ml for 1st 3 days when seizure frequency is maximum. The 12 hourly dosing schedule used in our study was supported by a subsequent pharmacokinetic study by Merher SL et al who reported that 12 hourly interval is acceptable due to reduced renal clearance until the glomerular filtration matures over first few weeks.[15]

Our study does not report any significant effect of levetiracetam on hemodynamic, cardiovascular or renal status. Merher SL et al also reported no change in vital sign or laboratory parameters with its use.[15] Levetiracetam is reported to cause only minor side effects like sedation, behavior abnormalities and depression in older children and somnolence in neonates.[20] Occasional reports of reversible thrombocytopenia and possible liver failure and anaphylactic shock because of levetiracetam have also been reported.[27-29] Though levetiracetam has predominantly renal excretion, like us, other studies has also not reported derangements in renal parameters with its use. Boylan GB et al had reported that only about 35% neonates with electrical seizures display clinical seizures.[3] In other two-third babies, clinical manifestations were unrecognized even by experienced neonatal staff. They therefore concluded that clinical diagnosis may not be enough in recognition and management of neonatal seizures. So, the superior efficacy of phenobarbitone in our study could be because of underestimation of electrical seizures. However, only a few neonatal centers are equipped with cerebral function monitors and EEG monitoring. In most of these units, clinical control of seizures is the only guide to treatment. Thus the generalisability of our study for such centres is reasonable.

The main strength of the study was that it is the first RCT on use of levetiracetam in neonates, which demonstrates its safety profile and follow up till 6 months of age. A limitation of this study is that drug level monitoring of the drugs could not be done. So, whether failure of levetiracetam 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. Also, we did not do cerebral function or continuous EEG monitoring. So electrical seizures could still be persisting despite clinical control of seizures. This could lead to demonstration of exaggerated efficacy of these drugs. But this would be true for both the limbs of treatment.

Present study further established the utility of phenobarbitone as a good drug for neonatal seizures. Our previous study had demonstrated that phenobarbitone is superior to phenytoin as well[28]. However, more trials, with larger sample size are required. Further studies are required to evaluate role of LVR in neonatal seizure both as first line and 2nd line therapy. Role of higher first dose and repeated loading doses in non-responders to 1st dose also needs to be evaluated in further studies. More studies on pharmacokinetics with larger sample size are also required.

## CONCLUSION

When used as a first line drug for neonatal seizures, efficacy of levetiracetam is lesser than phenobarbitone in term or near term neonates with perinatal asphyxia and HIE.

***What is already known:*** Phenobarbitone is often ineffective as a first line anticonvulsant in neonates with seizures in whom the background EEG is significantly abnormal. Levetiracetam has been tried for the treatment of seizures refractory to phenobarbitone in children and neonates.

***What this study adds:*** It shows that phenobarbitone is more efficacious than levetiracetam in control of clinical seizures in term or near term neonates with perinatal asphyxia. Use of levetiracetam as first line drug for neonatal seizure leads to delay in control of neonatal seizures

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