Efficacy of levetiracetam in neonatal seizures, a prospective open label comparative study

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Abstract
Objective: This study compares the efficacy of levetiracetam with phenobarbital in early onset seizures in term, late preterm neonates.

Setting: Prospective randomized, open label comparative study

Participants: 78 terms, and late preterm neonates admitted in NICU with neonatal seizures.

Intervention: Neonates with seizures, were randomized into 2 groups to receive levetiracetam or phenobarbital as 1st line anti consultant in each group.

Results: As 1st line anti epileptic drug (AED) levetiracetam (LEV) was effective in 16 patients (41%), and phenobarbital was effective in 19 patients (48.7%), where P value was not significant. But mortality was more in phenobarbital group with death of 10 patients (25.6%), and in LEV group death was only in 3 patients (7.7%) statistically significant (P value of 0.033).

Conclusion: Levetiracetam and phenobarbital attained seizure control in less than 50% patients, both were equally effective, levetiracetam as 1st line anticonvulsant in early neonatal seizures leads to early seizure control and less mortality than use of phenobarbital.

Keywords: Levetiracetam, Neonatal Seizures.

Introduction
Seizures occur often in neonates adversely affecting the neurodevelopmental 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) multifocal clonic i.e., usually begin in one extremity and spreads randomly.1

Since years the preferred agent for treatment of neonatal seizures has been phenobarbital, followed by phenytoin or fosphenytoin, and then benzodiazepines. The evidence for treatment with these agents was made out from data in adults and children. Single drug is often ineffective for seizure cessation in neonates.2 Painter et al in his study of neonatal seizures opined that attaining seizure control is better predictor of outcome than the anti epileptic drug used.2

Decreased efficacy and adverse neurodevelopmental outcomes of traditional therapies have generated an interest in the use of levetiracetam (LEV) for the treatment of neonatal seizures. LEV lacks neurotoxic effects at all given doses (5, 10, 25, 50, and 100 mg/kg per dose, similar to doses used in humans in 7-day-old rats), making LEV an attractive treatment option.2

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 40mg/kg.4

Bittigau et al5 studied the effects of multiple AEDs in animal models at relevant human doses. Study revealed that phenobarbital caused neuronal apoptosis in the brains of rats at therapeutic serum concentrations of 25 to 35 mcg/mL, which is within the usual therapeutic window of 15 to 40 mcg/mL used in clinical practice. Phenytoin triggered apoptotic neurodegeneration starting at a dose of 20 mg/kg or a plasma concentration of 10 to 15 mcg/mL; however, its toxicity was found to be dose dependent, unlike phenobarbital and diazepam. Such plasma concentrations are easily attained in human infants with seizures in an acute setting and in the course of long-term antiepileptic treatment with phenobarbital.5

Painter et al2 reported phenobarbital and phenytoin relieved seizures in only 43% and 45% of neonates, respectively, when used as the primary agent and up to 62% of the time in combined therapy.

Hence there is need to try LEV as First line drug for NS instead of third/ add on drug. LEV is found safe in NS, its efficacy when used alone is documented, but efficacy is not confirmed in large group. Once confirmed in the large scale trials, use of phenobarbital and phenytoin can be minimized and respiratory depression, and other significant side effects of those can be avoided. Even in 2006 when studies supporting LEV use were few, a survey conducted among pediatric neurologists showed that 47% suggested LEV off-label for neonatal seizure treatment.5
NIH sponsoring ongoing multicentre study, on LEV as 1st line AED in neonatal seizures, expected to be completed and submitted by end of December 2017. 

Methods
A prospective study involving late pre term (34 weeks to 36 weeks completed GA) and term neonates admitted in NICU with convulsions at Shri B. M. Patil Medical College, Hospital & Research Centre, Vijayapur, and Karnataka. Ethical Clearance was taken from institutional Ethical committee.

Open labelled but randomized study was done, by randomly allotting the case or control through use of sealed envelope.

78 newborns with clinically confirmed seizures were included in this study. Study was done over a span of 1 ½ years from February 2016 to July 2017.

After taking written informed consent from the parents and fulfilling inclusion and exclusion criteria, the neonates were included in the study. All babies were hemodynamically stabilized and nursed in thermo neutral environment. Securing IV access and collecting blood for investigations was done.

Data Analysis
Determination of sample size (n):
With anticipated mean difference of seizure cessation time between two study groups as 12.3 hours and anticipated standard deviation as 18.4 hours, the minimum sample size per group is 37 with 80% power and 5% level of significance.

Total sample size = (37 x 2) = 74.

Formula used:

\[ n = \left( Z_\alpha + Z_\beta \right) ^2 \times 2SD^2 \]

MD = anticipated mean difference.

SD = anticipated standard deviation.

Statistical Analysis
All characteristics will be summarized descriptively. For continuous variables, the summary statistics of N, arithmetic mean (referred to as mean), Standard Deviation (SD) will be used. For categorical data, the number and percentage will be used in data summaries.

A chi-square (\( \chi^2 \)) test will be employed to determine the significance of differences between groups for categorical data. For continuous data, the differences of the analysis variables will be tested with the t-test. p-value & It:0.05 would be considered to be statistically significant.

Selection Criteria
Inclusion Criteria:
The study includes

1. Neonates with seizures admitted in NICU at Shri B. M. Patil Medical College Hospital sand Research Centre.
2. Neonates with gestational age of 34 completed weeks or more, with neonatal seizures of varied aetiology.

Exclusion Criteria:
The study will exclude
1. Neonates with multiple severe congenital anomalies.
2. Mother on anti-convulsants
3. Neonates treated with anti convulsions elsewhere.

Inclusion Criteria

2. Neonates were randomly allotted into 2 groups, 
A) LEV group, where LEV was used as 1st line and phenobarbital used as 2nd line.
B) Phenobarbital group, where phenobarbital was used as 1st line and levetiracetam as 2nd line.

All neonates were checked for hypoglycaemia, and were given IV calcium gluconate and IM 50% magnesium sulphate as per the standard protocol, to rule out hypocalcaemia seizures. If seizures continue despite correction of hypocalcaemia, then AED were given as per group protocol.

In LEV group levetiracetam with a loading dose of 50mg/kg was given over 15 minutes, if there was no response in 15 minutes, additional dose of LEV 20mg/kg was administered intravenously. Maximum total loading dose of 70mg/kg was given.

If seizures were still uncontrolled, phenobarbital was administered as second drug with loading dose of 20mg/kg intravenously over 15 minutes, if uncontrolled in next 15 minutes additional doses of phenobarbital 10 mg/kg every 15 minutes were administered intravenously till seizure control or till a dose of 40mg/kg reached.

Results
A total number of 78 newborns with clinically evident seizures were enrolled with 39 in each group. In both groups, parameters Sex distribution (P-value: 0.624), birth weight (P-value: 0.329), GA, mean APGAR score at 1st minute and 5th minute, means GRBS (P-value: 0.258), mean serum calcium (P-value: 0.961), mean time of onset of convulsion (P-value: 0.496) are comparable and shown in Table 1. Both the groups had same severity as P values are not significant.

APGAR score at 5th minute is 6.1 in LEV Group and 6.2 in phenobarbital Group. Seizure pattern in LEV Group is clonic type and in phenobarbital Group subtle seizures, indicating severity of seizure more in LEV Group. Sixteen patients responded to LEV therapy alone (41%), and nineteen patients responded to phenobarbital alone (48.7%) with P value 0.495 is not significant. After failure of LEV therapy as 1st line AED in 23 patients (59%), 14 patients (35.9%) responded to phenobarbital. In phenobarbital group 19 patients (48.7%) responded to Phenobarbital therapy, 6
patients (15.4%) responded to LEV as 2nd AED, details shown in Table 2.

Table 1: Comparison of patient characteristics in levetiracetam and henobarbital group

<table>
<thead>
<tr>
<th></th>
<th>LEV Group (n=39)</th>
<th>Phenobarbital Group (n=39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution</td>
<td>M-28, F-11</td>
<td>M-26, F-13</td>
<td>0.624</td>
</tr>
<tr>
<td>Mean Birth weight</td>
<td>2.7 kilograms(0.4)</td>
<td>2.8 kilograms(0.4)</td>
<td>0.329</td>
</tr>
<tr>
<td>Mean GA</td>
<td>39.3 weeks(1.3)</td>
<td>39.3 weeks(1.4)</td>
<td>-</td>
</tr>
<tr>
<td>Mean APGAR score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st minute</td>
<td>4(1.5)</td>
<td>4(1.6)</td>
<td>0.987</td>
</tr>
<tr>
<td>5th minute</td>
<td>6.1(1.5)</td>
<td>6.2(1.5)</td>
<td>0.827</td>
</tr>
<tr>
<td>Mean GRBS</td>
<td>103.4(24.7)</td>
<td>109.5(23)</td>
<td>0.258</td>
</tr>
<tr>
<td>Mean se.Ca++</td>
<td>9.8(1)</td>
<td>9.8(0.8)</td>
<td>0.961</td>
</tr>
<tr>
<td>Mean time of onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of convulsion</td>
<td>13.8 hours (21.3)</td>
<td>10.9 hours (14.7)</td>
<td>0.496</td>
</tr>
<tr>
<td>Most common type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of convulsion</td>
<td>Clonic (46.2%)</td>
<td>Subtle (48.7%)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

Values in mean (SD)

Table 2: Comparing seizure control by levetiracetam versus phenobarbital

<table>
<thead>
<tr>
<th></th>
<th>LEV Group 39</th>
<th>PHENOBARBITOL Group 39</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to 1st line</td>
<td>16(41%) (LEV)</td>
<td>19(48.7%) (Phenobarbital)</td>
<td>0.495</td>
</tr>
<tr>
<td>AED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response of 2nd AED</td>
<td>14(35.9%) (Phenobarbital)</td>
<td>6(15.4%) (LEV)</td>
<td>0.038*</td>
</tr>
<tr>
<td>Mean Time taken to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>attain seizure control</td>
<td>10.2 hours (13.3)</td>
<td>16 hours (15.6)</td>
<td>0.084</td>
</tr>
<tr>
<td>after onset of seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>29</td>
<td>0.033</td>
</tr>
<tr>
<td>discharged (seizure free)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths</td>
<td>3</td>
<td>10</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Values in mean(SD)

Discussion

Our present study demonstrates that LEV is as efficacious as phenobarbital in controlling NS as 1st line AED. It also has early seizure control than phenobarbital. It also proves that LEV is safer than phenobarbital as mortality in LEV group is significantly less than phenobarbital group (P value is 0.033, significant). Even when LEV group babies were more severely asphyxiated than phenobarbitone group. No major side effects were found after administration of LEV.

In a retrospective study by Abend et al where in 23 neonates levetiracetam given as first line (17%), second line (61%) and as a third line(22%) with a dose range of 10-80 mg/kg/day, noticed seizure improvement within 24 hours in 35%,with termination in 88%. They found that levetiracetam was effective and has shown seizure reduction 35% (8 of 23). In a study by khan et al in 22 neonates after failure of phenobarbitol therapy, 35% patients responded to LEV 2nd line therapy.

In a retrospective study performed by Maitre et al, DAYC scoring at 12 months of age, BSID scoring at 24 months was done, and evaluated neuro developmental outcomes at 2 years of age after 280 infants with NS who got treated with phenobarbital and LEV. They have received a median cumulative dose of 360mg/kg of LEV and 60 mg/kg of phenobarbital. Seizure severity was similar in both group of patients which was EEG documented. DAYC scoring was done in 62% of patients for cognitive, communication and motor status, and they found that both phenobarbitol and LEV were associated with decreased motor scores. At the age of 24 months BSID scores were reported, and the results were significant in both groups. Phenobarbitol had decrease of 8 point cognitive score and a decrease of 9 point motor score for every 100mg/kg of phenobarbital, but LEV for every 300mg/kg demonstrated decrease of 2.2 and 2.6 points respectively. There was also a decrease in BSID communication scores with both LEV and phenobarbitol use, but the authors felt it was less significant. Out of 159 surviving patients at 2 years of age, authors found that with every 100mg/kg increase of phenobarbitol dosage, patients had 2.3 fold increases in risk of developing cerebral palsy by 2 years of age, but same association was not found between cerebral palsy and LEV. Hence phenobarbitol has neurotoxicity and poor neurodevelopment outcomes as documented in animal models and also proves that LEV has less neuronal apoptosis and improved outcomes.
A pilot study by Perveen et al.\textsuperscript{11} 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. Not waiting for adequate period (at least 15 min. after end of LEV infusion), may be the possible reason behind poor seizure control with LEV as 1\textsuperscript{st} line drug, in Perveen study.

\textbf{Conclusion}

Levetiracetam is effective as 1\textsuperscript{st} line anti epileptic drug in controlling neonatal seizures, and also its use leads to better outcome in terms of mortality and morbidity (early seizure control).

\textbf{Limitations of Study}: EEG and video correlation of seizure was not possible. Long term follow-up for neurodevelopment outcome was not done. Sample size is adequate but small.

Current knowledge about Neonatal seizure management is that “To use Inj. Phenobarbitone 20 mg/kg loading dose, another 10 mg/kg as second loading dose is given. Inj. Phosphenytoin also can given as Loading dose 20 mg/kg.

Phenobarbital and fosphenytoin are found to be neurotoxic in animal models and use of them as 1\textsuperscript{st} line AED in NS may lead to poorer neurodevelopment outcome

What our study contributes to the knowledge about Anti-convulsions in Newborns?

LEV can be used as 1\textsuperscript{st} line AED in Neonatal Seizures, it is nearly as efficacious as phenobarbital, and it’s use will lead to lesser morbidity and mortality.

\textbf{References}

7. NIH ongoing study details: http://grantome.com/grant/NIH/R01-FD004147-03.