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Original Research Article

Efficacy of levetiracetam as the first line anti- epileptic drug in management of neonatal seizures

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ABSTRACT

Background: Neonatal seizure management has not changed much in the last 50 years. Neuronal apoptosis in animal models and cognitive impairment in human subjects has been reported with the use of Phenobarbitone. Levetiracetam is advantageous as it is effective, well tolerated and has least drug interactions.
Methods: This double blinded, randomized, parallel group, active controlled study was conducted among 66 neonates in the Neonatal intensive care unit of a tertiary care hospital for a period of 18 months. Neonates with seizures fulfilling the inclusion criteria were treated either with Phenobarbitone or Levetiracetam. Seizure control was defined as no seizure activity within 40 minutes of the administration of the first drug. Failure of first line agent was treated with Phenytoin. Neonates were observed for a period of 14 weeks for recurrence of seizure and any serious adverse effects.
Results: Effective seizure control was achieved in 64.7% neonates in Levetiracetam group as compared to 31.2% in Phenobarbitone group ($p < 0.05$). Early resumption of breast feeds within 6 hours of therapy was achieved in 73.5% neonates treated with Levetiracetam compared to 31.2% neonates treated with Phenobarbitone (p value = 0.001).
Conclusions: Levetiracetam is a promising alternative as first line Anti-epileptic drug in neonates with seizures. Prolonged sedation was the adverse effect noted to Phenobarbitone that made breast feeding and neuro- assessment difficult. No serious adverse effects were seen with Levetiracetam.

Keywords: Antiepileptic drug, Levetiracetam, Phenobarbitone, Neonate, Efficacy**,** Newborn seizures, Randomized controlled study

INTRODUCTION

Seizure in neonates is a common medical emergency. Several challenges are involved in the management of neonatal seizures right from making the diagnosis to that of identifying an appropriate treatment. Clinical and electroencephalographic manifestations vary with age group. Several factors adversely influence the management of neonatal seizures including environmental restrictions, diagnostic modalities and the adverse effect of the existing drugs.

The medical management protocols of treating seizures effectively remain vague and many to apply on the specific etiological spaces.[1] Not much change occurred in the management of neonatal seizures over the last 50 years. Very little information regarding adverse effects of phenobarbitone, the first drug used in the management of neonatal seizure is available in the literature.[2] Efficacy of

the first line and second line AED, Phenobarbitone or Phenytoin has been reported as 30 to 50 percent.[3] Several studies have demonstrated an increasing risk of neuronal apoptosis in animal models and cognitive impairment in human subjects with the use of phenobarbitone.[4] Prolonged sedation and adverse neuro developmental outcome has also been demonstrated. The sedative action of Phenobarbitone is long, which hinders with successful breast feeding.

The incidence of seizures is higher during the neonatal period than any other period of life. It is approximately 57.5 per thousand among low birth weight infants and around 2.8 per thousand in normal weight infants.[2] Levetiracetam is being increasingly used in certain neonatal tertiary care centres for the management of neonatal seizures. Studies have shown that Levetiracetam has favourable profile as it does not cause neuronal apoptosis in the animals.[4] Increase in the morbidity and mortality associated with seizures mandate the need for newer drugs with minimal complications and which improves the quality of life among these neonates.

Objectives of this study was to be carried out to evaluate the efficacy of Levetiracetam in terms of seizure control when used as the first line antiepileptic drug compared to Phenobarbitone.

METHODS

Study setting and participants

This double blinded randomized parallel group active controlled study was carried out in the neonatal intensive care unit of the tertiary teaching institution for a period of 18 months. All the neonates admitted during the study period with neonatal seizures were taken up for the study.

Sample size and sampling techniques

Based on published literature, the expected outcome with the Phenobarbitone was taken as 57% and with Levetiracetam, it was taken as 86%.[5,6] At the 95% confidence level limits and 80% power, the estimated sample size was calculated as 30 in each group. A total of 66 neonates took part in the study with 32 in the control group and 34 in experiment group. The participants were selected by systematic random sampling.

Selection criteria

Neonates admitted to the study setting with any of the following conditions were taken up for the study:

- Clinical seizures (Focal / Generalised clonic / tonic, myoclonic, subtle and spasms) with a consistent electro cortical signature.[1]
- Clinical seizures without consistent electro cortical signature.
- Documented EEG abnormality.
- Seizures in neonates secondary to hypoxic ischemic encephalopathy/ maternal drug withdrawal/ intracranial haemorrhage/ inborn errors of metabolism/ infections/ sepsis/ Kernicterus/ structural malformations.

Exclusion criteria

- Exclusive metabolic causes
- Serum creatinine greater than 1.2mg/dl
- Known pyridoxine dependant seizures
- Prior treatment with antiepileptic drugs.

Randomization

The study participants were divided into two groups. Allocation concealment was carried out using sequentially numbered sealed opaque envelopes. Subjects were allotted to either group-A or group-B randomly using table of random numbers.

Group- A: Received the standard treatment of care which is Phenobarbitone (Ampoules in the composition of 200 mg/ml or syrup in composition of 30 mg/5ml).

Group- B: This consisted of the experimental drug Levetiracetam (Ampoules in the composition of 100 mg/ml or syrup in composition of 100 mg/ml).

Blinding

This study was carried out as a double blind study. Parents/ Guardian of the subjects and the Principal investigator were blinded to the allotment of the participants in the study groups. Randomization was carried out by an external team who were not involved in the study.

Ethical approval and informed consent

Approval was obtained from Institutional Ethics Committee prior to the commencement of the study. Each parent was explained in detail about the study and informed consent was obtained from the parent/guardian of the neonates prior to commencement of data collection.

Data collection

Adequate history and necessary clinical examination were recorded in a structured interview schedule. The neonates were loaded with 20 mg/kg of intravenous drug-A or drug-B according to their respective allocation by the nursing staff and response was monitored by the principal investigator.

Response to the drug was considered as the cessation of seizures clinically within a time frame of 20 minutes from the initiation of the intravenous drug therapy. If the

seizures did not stop after 20 minutes, another 10mg/kg of the same drug was loaded and observed for a further period of 20 minutes. Cessation of seizures as observed clinically within this additional time frame was also considered as the response to the drug. If the episode did not cease within the total time frame of 40 minutes it was considered as treatment failure and intravenous phenytoin (20 mg/kg diluted in 20 ml of normal saline given in 20 minutes) was initiated in situation of failure of either of drug-A or drug- B. Crossing over with the other drug within the study was not done. In case of failure to respond to the second line agent, further plan was based on the existing protocol of management.

The maintenance dose of Phenobarbitone was 5 mg/kg/day given once daily and that for Levetiracetam was 20 mg/kg/day in two divided doses. These drugs were administered intravenously initially and then gradually shifted to oral route. All the neonates with treatment failure were managed with phenytoin initially and then maintenance dose of 5 mg/kg/ day was given.

The neonates were observed for five days in the ICU set up after initiation of AED. The patients were followed for the period of 14 weeks. Follow-up visits were undertaken to address any seizure after discharge, which was considered as treatment failure and was treated with phenytoin.

Lumbar puncture was done on all stable participants. MRI brain was done for those who had recurrent seizures, and events suggestive of hypoxic ischemic encephalopathy, structure brain malformation and bleed or IEM. AED was continued for a period of one month (if not stopped at discharge) and the subjects were re-assessed, and the drug tapered.

Data analysis

Data was entered and analysed using SPSS version 20. Descriptive parameters were expressed in percentages and means scores. Association with respect to efficacy and risk factors were analysed using Chi-square test. A p value <0.05 was considered statistically significant.

End point of the study

- Any subject with treatment failure either during acute phase or maintenance phase as observed by the principal investigator was considered as the end point.
- All the other subjects were followed for 14 weeks after the initiation of anti-epileptic therapy.
- Withdrawal was considered as end point, but treatment was given to those who back out from the study.
- Need for ventilator support or continued deterioration of the vitals.

RESULTS

This study was carried out among 32 neonates in Group A (Control) and 34 neonates in Group B (Experiment). Both the groups were similar in terms of the characteristics. Majority of the neonates in both the groups were >37 weeks old. Almost 68.8% of the neonates in Group A weighed over 2.5 kg while 76.5% of the neonates in group B weighed over 2.5 kg (Table 1).

Table 1: Background characteristics.

Characteristics	Group A		Group B	
	(N=32)	(%)	(N=34)	(%)
Age (in weeks)				
<28	0	(0.0)	0	(0.0)
28-34	1	(3.1)	1	(2.9)
35-37	4	(12.5)	1	(2.9)
>37	27	(84.4)	32	(94.2)
Gender				
Male	13	(40.6)	20	(58.8)
Female	19	(59.4)	14	(41.2)
Birth weight (in kg)				
< 1	0	0.0	0	0.0
1-1.499	2	(6.2)	1	(2.9)
1.5-2.499	8	(25.0)	7	(20.6)
>2.5	22	(68.8)	26	(76.5)

The antenatal risk factors for neonatal seizures are elaborated in Table 2. Pre-term neonates constituted about 15.6% among Group A and 5.9% among Group B participants. Gestational diabetes mellitus was a

predominant risk factor in Group A (18.8%) while hypertension was a predominant risk factor in Group B (14.7%). The association was statistically significant (p<0.05). About 43.8% of the participants in group A were delivered by caesarean section while 26.5% of the group B participants were delivered by caesarean section. Asphyxia was present in 50% of group A and 20.6% of group B participants. This difference was statistically significant (p<0.05).

Table 2: Antenatal risk factors.

Characteristics	Group A N (32)	(%)	Group B N(34)	(%)	p value
Gestational maturity					
Term	27	(84.4)	32	(94.1)	0.199
Preterm	5	(15.6)	2	(5.9)	
Maternal gravid status					
Primigravida	14	(43.8)	22	(64.7)	0.087
Multigravida	18	(56.2)	12	(35.3)	
Antenatal risk factors					
No risk factors	13	(40.6)	21	(61.8)	0.039*
Gestational diabetes	6	(18.8)	2	(5.9)	
Gestational hypertension	2	(6.2)	5	(14.7)	
PROM	4	(12.5)	2	(5.9)	
Thyroid disorders	0	0.0	1	(2.9)	
Seizure disorders	0	0.0	2	(5.9)	
Others	7	(21.9)	1	(2.9)	
Mode of delivery					
Normal delivery	17	(53.1)	24	(70.6)	0.329
Assisted vaginal delivery	1	(3.1)	1	(2.9)	
Caesarean section	14	(43.8)	9	(26.5)	
Association with asphyxia					
Yes	16	(50.0)	7	(20.6)	0.012*
No	16	(50.0)	27	(79.4)	

*statistically significant

Table 3: Characteristics of seizures.

Characteristics	Phenobarbitone N (32) (%)	Levetiracetam N(34) (%)	Chi sq	p value
Timing of onset of seizures				
Postnatal day1	10 (31.2)	5 (14.7)	6.341	0.096
Postnatal day 2-4	10 (31.2)	12 (35.3)		
Postnatal day 5-7	1 (3.1)	7 (20.6)		
Postnatal day>7 th day	11 (34.5)	10 (29.4)		
Number of episodes prior to initiation of AED				
1	12 (37.6)	14 (41.2)	3.875	0.423
2	10 (31.2)	14 (41.2)		
3	7 (21.9)	2 (5.8)		
4	1 (3.1)	2 (5.9)		
>/=5	2 (6.2)	2 (5.9)		
Average duration of seizure episode that demanded initiation of AED				
<3 mins	9 (28.1)	11 (32.4)	5.720	0.126
3-5 mins	7 (21.9)	15 (44.1)		
5-10 mins	14 (43.8)	7 (20.6)		
>10 mins	2 (6.2)	1 (2.9)		
Association of EEG abnormality				
EEG- Abnormal	1 (3.1)	10 (29.4)	12.451	0.002*
EEG- Normal	28 (93.8)	19 (55.9)		
EEG- Not done	1 (3.1)	5 (14.7)		
Imaging abnormalities				

Characteristics	Phenobarbitone N (32) (%)	Levetiracetam N(34) (%)	Chi sq	p value
HIE	18 (56.2)	12 (35.3)	5.525	0.355
Metabolic injury	0	3 (8.7)		
IVH	2 (6.2)	4 (11.8)		
Hematoma	1 (3.2)	2 (5.9)		
Normal imaging	10 (31.2)	11 (32.4)		
Imaging- Not done	1 (3.2)	2 (5.9)		
Etiological profile of neonates				
Idiopathic	5 (15.6)	11 (32.4)	7.348	0.119
HIE	20 (62.5)	13 (38.2)		
Metabolic	0	2 (5.9)		
Sepsis	4 (12.5)	2 (5.9)		
Vascular	3 (9.4)	6 (17.6)		

*statistically significant

The presentation of seizures was tonic in majority of the participants in both the groups, followed by clonic and spasms. However, most seizures in group B presented as a combination of all the types of seizures. (Figure 1) The seizure episode lasted for 5-10 minutes in 43.8% of the neonates in group A while it lasted for 3-5 minutes in 44.1% of the neonates in group B.

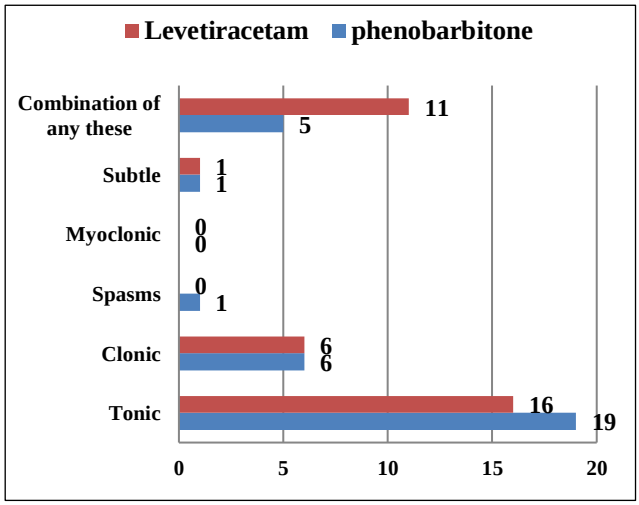

Figure 1: Types of seizures.

Abnormal EEG was present in 3.1% of the participants in Group A and 29.4% of the participants in Group B. The association was statistically significant (p<0.05). (Table 3).

DISCUSSION

Seizures in newborn cannot be seen as a one-time entity, considering the permanent neurological damage that it can create to the developing brain. Prompt diagnosis and appropriate intervention is needed to prevent damage to the developing brain. The essential differences between neonatal and adult brain determines the seizure threshold, response to AED, threshold for tolerating the adverse effects. And also, it is observed that the neonatal brain is more vulnerable to damage by an AED therapy.

In these study, the efficacy of the anti-convulsant medication was assessed by the time taken for control of seizure with the AED, requirement of second line AED, which indirectly quotes the failure of the first line AED, achievement of early breast feeds after AED administration and recurrence of seizure while the neonate is on AED therapy while being followed up for a period of 14 weeks. Effective seizure control within a period of 5 minutes was achieved in about 31.2% of the neonates in Phenobarbitone group as compared to 64.7% neonates in Levetiracetam group. This difference was statistically significant (p<0.05). Early resumption of breast feeds within six hours of AED therapy was achieved in 73.5% neonates treated with Levetiracetam as compared to only 31.2% neonates treated with Phenobarbitone. This was a statistically significant difference between the two groups (p<0.05). There was no recurrence in both the groups and no serious adverse effects were noted to Levetiracetam in these studies.

In practice, Phenobarbital remains the first line AED in neonatal seizures, although there is evidence that Phenobarbital itself may impair neuro-developmental outcome and induce neuronal apoptosis. Several studies have demonstrated adverse neurological outcome with Phenobarbital. Intrauterine exposure to Phenobarbital and Phenytoin is known to produce severe birth defects. Use of Phenobarbital in infancy is known to cause low IQ scores.[4]

A Retrospective study done involving 280 infants reported worse Bayley Scales of Infant Development (BSID) cognitive and motor scores with Phenobarbitone. These effects were less with Levetiracetam.[7] In various other studies, pronounced apoptotic neuro degeneration in neonatal rats was observed with Phenobarbital, phenytoin, valproate, Diazepam and Clonazepam within 24 hours of administration. But these effects were not observed with Topiramate or Levetiracetam.[8]

Painter et al, reported the efficacy of Phenobarbital as compared to Phenytoin in a randomized cross over study.[5] Seizure control in the Phenobarbital-treated group was found to be only 43% and, in the Phenytoin-treated group, seizure control was reported as 45%. A non-randomized study by Castro Conde et al, showed that, seizures persisted in 53% of the neonates who received phenobarbital/phenytoin.[9] A survey among 55 Paediatric neurologists in the USA found that 73% (40/55) recommended treatment of neonatal seizures with one or both of Levetiracetam and Topiramate.[10] Most Paediatricians in the country, invariably switch over to Levetiracetam for Neonatal seizures in case of failure of Phenobarbitone or Phenytoin although the results have not yet been sufficiently declared.

In a study conducted by Khan et al, 86% demonstrated immediate seizure cessation within the first hour with Levetiracetam.4 No serious side effects were reported in the study. A prospective feasibility study conducted by Ramantani et al, illustrated not only the efficacy, but also the safety of Levetiracetam in Neonatal seizures, including Preterms.4 Extensive Literature search revealed no serious adverse effects with Levetiracetam in Neonates, as quoted in different studies by Fuwentsches et al, Shoemaker M T and Rotenberg J S.[11,12] Rakshasbhuvankar et al, reported a significant seizure control of 80% with no serious adverse effects.[13] This proves Levetiracetam to be a promising alternative to Phenobarbitone as First line agent in Neonatal seizures.

Levetiracetam is the active, water-soluble S-enantiomer of racemic pyrrolidine acetamide. It works by a nonconventional mechanism, binding to the synaptic vesicle protein within the brain. The availability of an intravenous formulation, excellent oral bioavailability, lack of plasma protein binding, and CYP P450-independent metabolism make Levetiracetam an attractive antiepileptic agent for use in neonates. Doses reported in the neonatal population range from loading doses of 15 to 60 mg/kg and maintenance dosages of 30 mg/kg/day, which are similar to the dosages used in infants and older children.[14] However, the increased volume of distribution of levetiracetam reported in neonates, may indicate that neonates require a larger loading dosing than adults and older children.

CONCLUSION

Neonatal seizures, despite being one of the most common neonatal critical care problems, lack definite protocol in management lines. Phenobarbitone at present is being used as first-line agent in neonatal seizures worldwide despite its side effect profile. It is quite obvious from these study that Levetiracetam has been effective in control of neonatal seizures in this study by a fair margin of over 50% difference. Since this study has proved Levetiracetam to be effective as the first line agent in a tertiary care setting, it could serve the community by offering a safe, reliable, and relatively effective drug for neonates.

The limitation of this study is Since majority of the study participants were not delivered in this institution, there are high chances of under reporting of certain symptoms like asphyxia. The long-term outcomes and adverse effects of Levetiracetam were not analyzed in this study.

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