COMPARATIVE EFFICACY OF PHENOBARBITONE VERSUS LEVETIRACETAM IN THE INITIAL TREATMENT OF NEONATAL SEIZURE

KHAN TH[1], RAHMAN MM[2], BANERJEE M[3], UDDIN ZM[4], NAHARN[5], AKTHER M[6]

Abstracr:

Neonatal seizures are common in the first month of life and may impair neurodevelopmental outcome. Phenobarbitone (PB) currently represents the anti epileptic drug (AED) of choice, despite related to cognitive impairment in human subjects and limited efficacy. Intravenous levetiracetam is increasingly being used in the neonatal period to treat seizures. Presently, insufficient data about the efficacy and safety of intravenous levetriacetam in neonates, we have structured a randomized control trial with levetiracetam in the initial treatment of acute neonatal seizure.

Objective: *To find out the efficacy of levtiraracetam for controlling the convulsions in acute neonatal seizures compared to phenobarbitone.*

Methodology: *The study was a randomized control trial. A total of 100 neonates from 0 day to 28 days of age irrespective of sex with clinical presentation of neonatal seizures admitted in the special care baby unit (SCABU) of Dhaka Medical College Hospital were included in the study and were randomly assigned to either levetiracetam or Phenobarbitone group after matching inclusion and exclusion criteria. The outcome variables were seizure control, times taken to be seizure free, and hospital stay. Outcome was evaluated through routine monitoring up to 48 hours and followed up to discharge or death.*

Result: *The study groups were almost similar with respect to their demographic characteristics like age, sex and gestational age. According to maternal obstetric data i.e- antenatal care (ANC), modes of delivery in the both groups were statistically not significant. Seizures status was non-significant in both groups. The study demonstrated that controlling the seizure with levetiracetam & Phenobarbitone were 66.0% and 34.0% respectively. Length of the hospital stay was shorter in levetiracetam group. Eventually the phenobarbitone group required more than one drug to control seizures.. But immediate adverse effect was not significant in both groups.*

Conclusion: *The study concluded that levetiracetum significantly control the convulsion in comparison to phenobarbitone as first line antiepileptic drug in the initial treatment of acute neonatal seizures. Both the modalities of treatment were found to have no adverse effect.*

Key words: *(Efficacy, phenobarbitone,Levetiracetum,Neonatal seizure).*

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Introduction:

Neonatal seizures are the most frequent clinical manifestation of central nervous system dysfunction in the new born, with an incidence of 0.7 to 2.7 per 1000 live births. [1]Seizure in the newborn frequently signal significant brain pathology, such as hypoxic ischemic injury, stroke, intracranial inefection, hypoglycemia, inborn errors of metabolisom or brain maformations. Etiology significangly influences outcome. Newborn seizures correlate with higher mortality as well as motor or cognitive disability in survivors. [2]In this light effective therapeutic intervention addressing clinical seizures might significantly improve neurocognitive development as well as reduce morbidity and mortality.

1. Dr. Md. Tafazzal Hossain Khan, Associate professor, Department of Neonatology, Dhaka Medical College, Dhaka
2. Dr. Mohammed Mahfuzur Rahman, Consultant, pediatrics, National Medical College, Dhaka
3. Professor Dr. Manisha Banerjee, Professor and Head, Department of Neonatology, DMCH
4. Dr. Md Zahir Uddin, Assistant professor, Department of Neonatology, Dhaka Medical College, Dhaka
5. Dr. Nurun Nahar, Professor of pharmacology, MH Samorita Medical college, Dhaka
6. Dr. Mahfuza Akhter, OSD, DMCH, DGHS, Dhaka

Correspondence : Dr. Md. Tafazzal Hossain Khan, Associate professor, Department of neonatology, Dhaka Medical college, Dhaka, Email-tofa_dr@yahoo.com Mobile: 0171103151

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There are currently no evidence-based guidelines for evaluation and management of neonatal seizures available data indicate that phenobabitone (PB) remains the first line treatment for neonatal seizures. However there is known risk of cognative side effects in infants and toddlers.[3]conventional treatment Phenobarbital & phenytoin only achieves clinical control in 50%-60% of cases and is evenless effective in controlling most neonatal electrographic seizures.[4] on the other hand, there is increasing concern over the long time adverse effects of phenobarbitone and induce cognitive impairment in infants and toddlers. [5]in august 1999 a comparative study between Phenobarbital and phenytoin for the treatment of neonatal seizures shows Phenobarbital & phenytoin are equally but incompletely effective as anticonvulsants in neonates.[6] Other antiepileptic drugs like lidocaine, midazolam have serious side effects like impaired myocardial function, hypotension or arrhythmia[7].

Levetiracetam (LEV) is an effective and well tolerated antiepileptice drug currently licensed as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization. Prospective studies with small patients groups in infants and very young children reported similar results. There are hardly any reports of severe, life threatening side effects, with most frequently observed adverse effects include, irritability somnolence and behavioral problems. [8,9] a pilot study shows, four of the six patients remained seizure free during the study period of three months. In patient 2 there was a single seizure after 4 weeks, after which the levtiracetam dose was increased to 34 mg/kg/day. After 3month, five out of six patients were seizure free under monotherapy with levetiracetam.

In one prospective open-label trial of intravenous levetiractam in nenates with both partial and generalized seizures, 30 of 38 patients were seizure free at one week, and 27 remained seizure-free at 4 weeks.[11]an open multi center retrospective analysis has shown levetiracetam is a well tolerated new AED that may effectively improve seizure control as an add-on drug in resistant epilepsy in childhood with good tolerability.[12] Aretrospective study of acute neonatal seizures among preterm neonates demonstrated seizure cessation by 24 hrs in 82% patients.[13]A retrospective chort study have shown that increasing exposure to phenobarbitone is associated with worse outcomes at 2years of age and that levetiracetum may be associated with improved out comes compared with phenobarbitone.[14] A double blind placebo controlled trial of adjunctive levetiracetam in pediatric partial seizures has shown a reduction in partial onset seizure frequency per week and parcent reduction over placebo during the treatment period was 26.8%.[15]

In a retrospective study 100% neonates become seizure free Within 72 hours of treatment with levetiracetam. Moreover no immediate side effects were reported in the study.[18] Despite evidence from a rigorously conducted clinical trial that the administration of Phenobarbital or phenytoin was effective in less than 50% of cases.[4,20]

Despite the traditional treatment control of seizures in neonates still frustrating and challenging for the neonatologists. In view of the favorable pharmacological and clinical profile; this prospective randomized clinical trial can help to know the efficacy of levetiracetam over Phenobarbital in initial treatment of neonatal seizures.

Methodology:

It was a randomized control trial. The study was approved by the local ethical committee of Dhaka medical college and parents were asked for written informed consent. From the period of July 2013 to June 2014 both term and premature newborns with a gestational age more than 34 weeks to less than 42 weeks and a birth weight of more than 2000gm with neonatal seizures were enrolled. Patients were excluded when seizures had been caused by hypoglycemia, hypocalcaemia or dysel-ectrolytemia and sepsis. Patients also were not eligible for the study, if they had already received more than single loading doses of phenobabitone or medication with any other antiepileptic drugs (AEDs).After necessary

exclusion and inclusion criteria randomization was done by simple random method; i.e.by lottery method with replacement.

Study procedure:

Neonates attending at SCBU with seizures or admitted in SCBU develop seizure in DMCH was selected. Initial evaluation of the patient by history and clinical findings were recorded in the pre formed data sheet. Base line investigations like CBC, Blood grouping, Blood glucose S.Calcium, S.Electrolytes was sent. Intravenous loading dose (20mg/kg) of inj. Phenobarbital to control group and loading dose (50mg/kg) of inj. Levetiracetam to intervention group were given. If seizures recurred then 2nd& 3rd loading of Phenobarbital were given respectively as a dose 10mg/kg. Maintenance was be given as 5mg/kg/day 12 hourly for Phenobarbital and 10mg/kg/dose 8 hourly for levetircetam group. Decision regarding further for treatment in case of treatment failure was made on the basis of institutional treatment protocol. Patients were monitored round the clock and clinically examined and seizure frequency, antiepileptic medication and adverse events were documented. Study end point was up to 48 hours but if seizure was not controlled within 48 hours it was labeled as treatment failure. Seizures were diagnosed clinically. No continuous EEG monitoring was performed at time of diagnosis and enrolment.

Result:

The present randomized controlled trial was intended to compare outcome of two treatment modalities (inj. Levetiracetam = intervention group vs inj. Phenobarbitone=control group) in neonates with acute neonatal seizures. The main outcome variables were control of seizures and time required to control seizures. The findings obtained from data analysis are documented below.

Table –I shows basic demographic data of the neonates with seizure. Out of 50 neonates each of intervention group and control group, respectively, 30 (60%) and 37 (74%) were male and 20 (40%) and 13 (26%) were female. The sex distribution of neonates between groups was statistically not significant.

Table-I

Basicline demographic data of the neonates

Parameters	Intervention Group (n=50)(%)	Control Group (n=50)(%)	P value (X2 test)
Sex			
Male	30	(60.0)	37 (74.0)
Female	20 (40.0)	13 (26.0)	0.137
Gestational age (weeks)			
Premature (<37)	6 (12.0)	5 (10.0)	0.749
Full term(37-42)	44(88.0)	45 (90.0)	
Birth weight (gm)			
2000-<2500	8 (16.0)	9 (18.0)	0.790
2500-4000	42(84.0)	41(82.0)	
Breathing status of neonates delivered outside hospital			
	(n=26)	(n=14).	
Breathing status			
Within 1 minute	19 (79.2)	31(86.1)	0.480
Breathing<5 minutes	5 (20.8)	5 (13.9)	

Table-II

Comparison between inj. Levetiracetam and Inj. Phenobarbitone in controlling nenatal Seizures

Parameters	Intervention Group (n=50)%	Control Group (n=50)%	P value (X2 test)
Age on admission (hour)	No (%)	No (%)	
12	35 (70.0)	27 (540.0)	
>12-24	9 (18.0)	12 (24,0)	
>24-36	3 (6.0)	6 (12.0)	0.0.72
>36-48	2 (4.0)	4 (8,0)	
>48	1 (2.0)	1 (2.0)	
Age at onset of seizures(hours)			
< 12	38 (76.0)	32 (64.0)	
>12-24	8 (16.0)	10 (20,0)	
>24-36	1 (2.0)	7 (14.0)	0.101
>36-48	3 (6.0)	1 (2,0)	
Type of seizures			
Subtle	18 (36.0)	14 (28.0)	
Clonic	22 (44.0)	21 (42,0)	
Tonic	6 (12.0)	14(28.0)	0.137
Myoclonic	1(2.0)	1 (2,0)	

Table-II shows characteristics of neonates seizures. In intervention group and control group, respectively, age on admission after development of seizure was 12 hours in case 35 970%) and 27 (54%), >12-24 hours in case of 9 (18%) and 12 (24%),>24-36 hours in case of 3 (6%) and 6 (12%),>36-48 hours in case of 2(4%) and 4 (8%), and >48 hours in case of 1 (2%) each neonates. Statistically no variation was observed. Age on admission after development of seizure in case of maximum number of both intervention group (70%) and control group (54%) of neonates was within 12 hours.

Table-III

Comparison between inj. Levetiracetam and Inj. Phenobarbitone in controlling nenatal Seizures

Parameters	Intervention Group (n=50)%	Control Group (n=50)%	P value (X2 test)
Seizure Controlled			
Yes	33 (66.0)	19 (38.0)	0.005**
No	17 (34.0)	31 (62.0)	
More than one drug required to control seizure			
Yes	17(34.0)	31 (62.0)	0.005**
No	33 (66.0)	19 (36.0)	
Time required to control seizures (hours)			
12	40 (80.0)	25 (50.0)	
>12-24	6 (12.0)	12 (24,0)	
>24-36	2(4.0)	4(8.0)	0.030*
>36-48	1 (2.0)	6 (12,0)	
>48	1 (2.0)	3 (6.0)	

Most of the neonates of both intervention group (76%) and control group (64%) showed that age at onset of seizure was within 12 hours of birth . mean (±SD) age at onset of seizure was 8.97±11.93 (range 0.50-47.00) hours of intervention group and 11.35±11.21 (range 0.50-37.00) hours of control group of neonates. The mean difference was not statistically significant.

Type of seizure of intervention group and control group of neonates, respectively, was subtle in 18 (36%) and 14 (28%), clonic in 22 (24%) and 21 (42%), tonic in 6 (12%) and 14 (28%), clonic in 22 (44%) and 21 (42%), tonic in 6 (12%) and 14 (28%) and myoclonic in 4 (8%) and 1 (2%). Statistically no significant variation was observed .

Table-III. Showed status of treatment of neonatal seizure. Seizure of 33 (66%) neonates of intervention group was controlled with inj. Levetiracetam and 19 (38%) neonates of control group was controlled with inj. Phenobarbitone. Significantly neonatal seizure of higher number of neonates of intervention group (66%) was controlled with inj. Levetiracetam (P<0.01) compared to control with inj.Phenobarbitone). The rest of the neonates of intervention group, i.e.17 (34%0 and control group, i.e.31 (62%) required more than one drug to control their seizure (statistically significant, P<0.01).

Time required to control seizure of intervention group of neonates, in order of frequency, was 12 hours in 40 (80%), >12-24hours in 6(12%), >24-36 hour in 2(4%), >36-48 hours in 1 (2%) and >48 hours in 1 (2%). In control group, in order for frequency, was 12 hours in 25 (50%), >12-24 hours in 12 (24%), >36-48 hours in 6(12%), >24 hours in 4 (8%), and >48 hours in 3(6%). Most of the neonates of both intervention group and control group required. 12 hours to contol their seizure (80% and 50%). Statistically significant variation was observed (p<0.05). mean (±SD) time required to control seizure of intervention group of neonates as was 6.88±15.47 (range 0.33-93.00) hours and of control group of neonates as 19.41±17.35 (range 0.50-69.00) hours the mean difference was statistically significant (P<0.001).

Table-IV

Treatment outcome of neonates during hospital stay

Parameters	Intervention Group (n=50)%	Control Group (n=50)%	P value (X2 test)
Adverse Effect	No. (%)	No. (%)	
Yes	5 (100)	8 (16.0)	0.3.72
No	45 (90.0)	42 (84.0)	
Type of adverse effects			
Somnolence	3(60.0)	2(25)	
Irritability	2 (40.0)	2(40)	
Drowsiness	4 (50.0)	3(37)	
Lethargy	4 (50.0)	2(40)	
Treatment Outcome			
Discharged	37 (34.0)		36(72.0)
DORB	11 (22.0)	9 (18.0)	0.473
Expired	2(4.0)		5(10.0)
Hospital stay (days)			
<5	9 (18.0)	1 (2.0)	
5-7	29 (58.0)	18 (36.0)	
8-10	10 (20.0)	26(52.0)	0.001**
>10	2 (4.0)	5 (10.0)	

Table-IV. Showed treatment outcome of intervention group and control group of neonates. In intervention group and control group, respectively, adverse effect of drug was observed in 5 (10%) and 8(16%) neonates. Statistically no significant variation was observed.

Status of hospital stay for intervention group and control group of neonates, respectively, shows that 9 (18%) and 1 (2%) stayed for less than 5days, 29(58%) and 18(36%) stayed for 5-7days, 10days. Statistically the distribution was significant (P<0.01)

Discussion:

In this study basic demographic data of newborn like age and sex were not significant and birth weight distribution was not significant. Abend at al. study also shown no significant difference in male female distribution in both groups. [21]This study demonstrated range of birth weight was 2000-4000gm. But khan et all reported 2.803-4.627kg and 0.62 to 2.96 kg respectively. [13,18]Gestational age of neonates of this study was ranging from 35-42 weeks and 35-40 weeks in levetiracetam and phenobarbitone group respectively. Khan et al reported 37.5-41.2 weeks of gestation with means of 39.3±1.03 weeks which is nearly similar to this study.

The study demonstrated that controlling acute neonatal seizures in both pre term and term neonates were effective (66%) with levetircetam. Painteretal. Andboylan et al. demonstrated the efficacy in cessation of seizures among less than 50% of their patients treated with Phenobarbital and phenytoin.[4.6]khan etal. reported that intravenous lebetiracetam can be used for the management of acute neonatal seizures in neonates and cessation of neonatal seizures in 86% of patients [18]Abned et al. detected levetircetam was associated with a greater than 50% seizure reduction.

Out study used levetircetam as monotherapy for controlling the acute neonatal seizures. But ramanti et al, [11]khanet.al, [13]abned etal.[22]did not. They used concomitant phenobarbitone in acute seizure crisis upto two loading doses (10mg/kg) of phenobarbitone with routine lebetircetam.

In this study 50 patients got levetiracetam as first line anticonvulsant of which 33 had controlled seizure. During the study period there was non- significant adverse effects seen.no immediate and long term adverse effects were reported by several studies.[10,15,18,23]. Furwentsuches et al. have shown patients received LEV as monthrapy after titration period, initial treatment with PB may have contributed favourable outcome [10].This study reported only 10% and 16% adverse effects in levetiracetam and phenobarbitone group respectively, which was somnolence, irritability, drowsiness and lethargy but no cardio-pulmonary side effects were observed.

Levetiracetam continues to be used in varieties of clinical situations and sezureateiologies in neonates. Shoemaker and Rotenberg. [24]reported on the succesfull use of levetiracetam in neonates with varying seizure etiologies. In this study the primary seizure etiology was hypoxic ischemic encephalopathy but was also diverse and excluded metabolic such as hypoglycemia and hypocalcemia, dyselectoy* lytemia and sepsis. Other rare causes like CNS malformations, hypoma-gnesemia, IVH and pyroidixine dependency was not evaluated.

Previous studies done with levetircetam as anticonvulsant in neonatal seizures used phenobarbitone as rescue therapy concomitantly with LEV. But this study followed the institutional protocol, as after the first line with levetircetam or phenobarbitnone we used second line with fosphenytion and so on third line midazolam.

Kirmani et al. in a retrospective that thirty two patients (age range, 2 months to 18years) had received a levetiracetam load of 25-50mg/kg for status epilepticus. There were 17 (53.1% of males and 15 (46.8%ofemales. Response to intravenous levetiracetam in all patients was favorable. Status epilepticus ceased clinically and electorgraphically. Eight-teen patients (56.5%) received intravenous levetiracetam after receiving fospenytoin and ativan with no response. No serious side effects were evident. Fifteen patients (46.8%) were discharged on levetircetammonotherapy, and 9(28.1%) received levetiracetam as adjunctive therapy after discharge from hospital. [25]

Abend et al. in a retrospective cohort study found that 23 neonates received levetiracetam (11 males & 12 females), 88% were rendered seizure free. No serous cardiopulmonary adverse effect was identified [21].The present study reported about 90% were seizure free within 24hours without any serious side effects.

In the present study mean hospital stay was significantly reduced in levetiracetam group than phenobarbitone group. Most patients in levtiracetam group discharged within 7 days.

Finally it can be stated that despite the limitation of this controlled trial the findings are in agreement with other reported series and suggest that levetiracetam is safe and well tolerated when administered to all neonates both term and preterm. There is association with seizure reduction or termination within 24 hours of administration as first line antiepileptic medication .

Conclusion:

The study concluded that Levetiracetam significantly control the convulsion in comparison to Phenobarbitone and safe as first line antiepileptic drug in the initial treatment of acute neonatal seizures.

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