Levetiracetam versus Phenobarbitone for Acute Seizure Control in Neonates

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ABSTRACT

Introduction: Neonatal seizures or neonatal convulsions are epileptic fits occurring from birth to the end of the neonatal period. Hypoxic/ischemic encephalopathy (HIE) is the commonest cause. Apart from Group B streptococcus and E coli, the nonbacterial causes include intrauterine toxoplasmosis, cytomegalovirus, herpes simplex, coxsackie infection etc. Malformations of cortical development frequently present with early life seizures. We aimed to compare efficacy of levetiracetam versus phenobarbitone for acute seizure control in neonate and to observe for any immediate adverse effects due to administration of these drugs.

Material and methods: This was an open-label randomized enrolled study conducted over a period of two years in the department of pediatrics SKIMS Srinagar. Patients were randomly assigned to two groups PB group and LEV group and lab parameters CNS examination and EEG done to evaluate efficacy at certain points of time in future follow up.

Results: The primary outcome measure in our study was the clinical cessation of seizure activity and secondary outcome measures comprised immediate adverse effects including variations in cardio respiratory parameters. Both of the study drugs were equally effective in controlling the seizures in neonates acutely. There was no significant difference in the two groups in various vital parameters heart rate, CRT, spO_2 and respiratory rate recorded at regular intervals at acute stage ($p>0.05$).

Conclusion: Levetiracetam is an attractive treatment option in neonatal seizures.

Keywords: Seizures, LEV, PB

INTRODUCTION

Neonatal seizures or neonatal convulsions are epileptic fits occurring from birth to the end of the neonatal period are an important example of an age-specific seizure syndrome. Neonatal seizures are the most frequent clinical manifestation of central nervous system dysfunction in the newborn, with an incidence of 1.5-3.5/1000 in term newborns and10-130/1000 in preterm newborns.[1]

Etiology

Seizures in the newborn frequently signal significant brain pathology, such as hypoxic ischemic injury, stroke, intracranial infection, hypoglycemia, inborn errors of metabolism, or brain malformations. Etiology significantly influences outcome. The most common cause of symptomatic neonatal seizures is hypoxic/ischemic encephalopathy (HIE), which affects approximately 1–2/1000 live births.[2,3] In the case of HIE, these seizures carry with them a risk of long-term epilepsy and neurological/ cognitive deficits.[4,5] The next most common causes of neonatal seizures are infectious etiologies and malformations of cortical development. Metabolic disturbances responsible for neonatal seizures include hypoglycemia, hypocalcemia, hypomagnesemia, and abnormalities of other electrolytes and amino acids. Other less common causes of neonatal seizures include benign familial neonatal convulsions, an autosomal dominant disorder that presents within the first week of life and is associated with subsequent normal development.[6-8]

Clinical Manifestations

Neonatal seizures, as with any other type of seizure, are paroxysmal, repetitive and stereotypical events. They are usually clinically subtle, inconspicuous and difficult to recognize from the normal behaviors of the inter-ictal periods or physiological phenomena. There is no recognizable post-ictal state. Generalized tonic clonic seizures (GTCS) are exceptional. The most widely used scheme is by Volpez[9] of five main types of neonatal seizure.

- Subtle seizures (50%)
- Tonic seizures (5%)
- Clonic seizures (25%)
- Myoclonic seizures (20%)
- Non-paroxysmal repetitive behaviors

Diagnosis

Neonatal seizures can be difficult to diagnose as there are often no clinical correlates of the electrographic seizures, a phenomenon called electroclinical dissociation.[10] A recent study revealed that approximately 80% of EEG documented seizures were not accompanied by observable clinical seizures.[11] Hence, EEG is essential for diagnosis and for assessing treatment efficacy in this.

Brain Imaging

Cranial ultrasonography, brain imaging with X-ray

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computed tomography (CT) scan and preferably magnetic resonance imaging (MRI)[12] should be used for the detection of structural abnormalities such as malformations of cortical development, intracranial hemorrhage, hydrocephalus and cerebral infarction.

Electroencephalography

The neonatal EEG is probably one of the best and most useful of EEG applications. Polygraphic studies with simultaneous video–EEG recording are essential.[13] Suspected clonic movements have the highest yield of 44% but this is only 17% for 'subtle' movements[14]

Management

Neonatal seizures require urgent treatment to *prevent brain injury.*

Give anticonvulsant medication *only after adequate ventilation and perfusion have been established and the blood glucose concentration has been measured*.

Seizures with hypoglycemia or hypoxia are detrimental to the brain!

1. *Ensure adequate ventilation and perfusion.*
2. *Correct metabolic disturbances.*
3. *Begin anticonvulsant therapy*.

The most common anticonvulsant used initially in the newborn period for seizure treatment is intravenous PB[15] although there are many concerns regarding the short-term adverse effects of PB as well as long-term effect on neurocognitive development. Conventional treatment (Phenobarbital and phenytoin) only achieves clinical control in 50%-80% of cases and is even less effective in controlling most neonatal electroencephalographic seizures.[16] On the other hand, there is increasing concern over the long time adverse effects of phenobarbital, since it was shown to increase neuronal apoptosis in animal models[17] and induce cognitive impairment in infants and toddlers.[18] Newer AEDs, including levetiracetam, oxcarbazepine, and topiramate, are increasingly used to treat neonatal seizures.[19,20] Unlike other AEDs, levetiracetam (LEV) has shown improved neurodevelopment outcomes and lack of neurodegenerative effects in early animal studies, making LEV an attractive treatment option in neonatal seizures

Levetiracetam

LEV, a novel anticonvulsant drug with a non-conventional mechanism of action, is well studied as an adjunctive therapy for partial epilepsy. Given the safety profile of this medication as well as its linear pharmacokinetics (half-life of 7 h)[21] rapid absorption (30 min), non-hepatic elimination and favorable efficacy in children,[22] it is empirically considered a viable alternative for seizure treatment in all pediatric age groups, including infants and neonates.[23]

Study aimed to compare efficacy of levetiracetam versus phenobarbitone for acute seizure control in neonates and to bserve for any immediate adverse effects due to administration of these drugs.

MATERIAL AND METHODS

This was an open-label randomized enrolled study conducted over a period of two years in the department of pediatrics SKIMS Srinagar. Proper clearance was taken from IEC before the beginning of study. A total of 76 neonates were enrolled in the study with 40 patients as cases and 36 patients as controls. Patients were enrolled only after written ascent from the care takers/ parents. Randomization was done by computer generated random numbers.

Inclusion criteria

1. Age up to 28 days
2. Actively convulsing patients

Exclusion criteria

1. Age more than 28 days
2. Lack of informed ascent.
3. Seizures due to acute metabolic disorder like Hypoglycemia, Hypocalcemia, hypomagnesaemia and hyponatremia.
4. Subtle seizures.

Consort

As discussed above all patients who were enrolled in the study were divided into case group and control group based on computer generated random numbers. Forty patients were included in case group (levetiracetam group) and 36 in control group (phenobarbitone group). All patients who developed/ presented with seizures were shifted to level III NICU. Patients were investigated and monitored as per uniform protocol. IV access was established. After taking care of ABC of the patients, blood samples for septic workup, blood sugar, serum calcium, serum magnesium and electrolytes were taken. Metabolic derangements (hypoglycemia, hypocalcemia, hypomagnesaemia) were swiftly ruled out and patients were given either of the two drugs, as decided by the already computer-generated randomization. Patients were closely monitored for any adverse effect during the infusion of the drug like SpO2, pulse, B.P, CFT and RR.

Levetiracetam group- received iv levetiracetam loading dose (30mg/kg) IV over 20mins, followed by two half loading doses of 15mg/kg each if needed (a total of 60 mg/kg), followed by maintenance 10mg/kg IV administered twice daily, increased by 10mg/kg over 3 days up to 30mg/kg. while a further increase up to 45-60mg/kg was performed at the end of first week of treatment in case of persistent seizures. Additional loading doses of 30mg/kg/dose were given as acute intervention during the first 3 days of LEV titration

Phenobarbitone group - received iv phenobarbitone loading 20mg/kg over 20 mins followed by maintenance 5mg/kg/day in 2 divided doses as prophylaxis.

Once the patients in both the groups were able to tolerate orals, maintenance drugs were given orally. In most cases, this coincided with the initiation of oral feeding after an initial period of full parenteral nutrition.

The dose adjustment was done as indicated or withdrawn depending upon the neurological examination of the neonate or EEG findings at the end of 3 months. The study ended regularly at 3 months of age. The patients were followed

regularly in our OPD with daily visits in the first 4 days followed by visits at days 7, 15, 30, and 90 after start of LEV/ PB treatment. Patients were clinically examined, and seizure frequency, antiepileptic medication, and adverse events were documented at every visit. Additional examinations were performed during rapid LEV titration in the first week and later, in the case of seizure recurrence.

The CNS examination was graded as normal, mildly abnormal, moderately abnormal and severely abnormal.

Normal: normal alertness for age;

Mildly abnormal: hypertonia, hyperexcitability;

Moderately abnormal: hypotonia/ hypertonia, decreased muscle movements, lethargy;

Severely abnormal: flaccid, inactive and coma Normal: normal muscle tone, active muscle movements,

Conventional EEG was performed at the end of 3 months, a decision regarding further treatment was considered on an individual basis. EEG reporting was done by the neurologists of department of neurology of SKIMS Srinagar. Cerebral ultrasound was performed in all infants in the first 48 h. findings were graded as

Normal: no pathology;

Moderately abnormal: IVH I/II, mild ventriculomegaly, periventricular echo densities;

Severely abnormal: IVH III/IV, cystic PVL, malformation

Laboratory tests including complete blood count, hepatic and renal function parameters were performed weekly during the first four weeks and at all further visits. The classification of patients as seizure free was based on clinical observation (lack of suspicious clinical events) on day 7 and also with conventional EEG recordings on day 90.

Monitoring

Pulse rate, respiratory rate, blood sugar, oxygen saturation, were monitored for a 24 our period every 30 minutes for 1 hour, then hourly for 3 hours, and then every 2 hourly for 12 hours, and then every 4 hourly until 24 hours had passed. Patients were also monitored for development of any adverse effect and recurrence of seizures.

RESULTS

The observed data was entered in the computer to analyze with the help of MS, Excel, and SPSS version 15 for windows. The primary outcome measure is presented as mean and SD and statistically significant difference was evaluated using one-way ANOVA. A p value of < 0.05 was considered as significant and a p- value less than 0.001 ($p< 0.001$) as highly significant.

The mean gestational age of neonates in LEV group was 36.225 while as the mean gestational age of neonates in Phenobarbitone group was 36.8333 and the difference was statistically insignificant (p-value =.564).

The mean birth weight of neonates in LEV group was 2.55kgs while as the mean birth weight of neonates in Phenobarbitone group was 2.7 kgs and the difference was statistically insignificant (p-value =.072).

In LEV group 40% of neonates were delivered by LSCS and 60% were delivered through normal vaginal delivery where as 25% and 75% of neonates were delivered through LSCS and normal vaginal delivery respectively. The difference is statistically insignificant (p value= 0-164).

In LEV group 45% of neonates were male and 55% were female whereas in PB group 55.6% and38% of neonate's males and females respectively. The difference is statistically insignificant (p value= .358).

The mean Apgar score of neonates in LEV group was 5.15 while as the mean Apgar score of neonates in Phenobarbitone group was 5.5833 and the difference was statistically insignificant (p-value =0.265).

70% of patients in LEV group had HIE2 at the time of admission where as 63.9% of patients in Phenobarbitone group had HIE2. The difference was statistically insignificant (p –value=0.571).

17.5% of patients in LEV group had HIE III at the time of admission where as 16.7% of patients in Phenobarbitone group had HIE III. The difference was statistically insignificant (p –value=0.923).

12.5% of patients in LEV group had sepsis at the time of admission where as 11.1% of patients in Phenobarbitone group had sepsis. The difference was statistically insignificant (p –value=0.852).

55% of patients in LEV group developed seizures with in first 48 hours of life whereas 50% of patients in phenobarbitone group developed seizures within first 48 hours of life. The difference was statistically insignificant (p-value= 0.663).

In Levetiracetam group focal clonic, multifocal clonic, focal tonic, generalized tonic and myoclonic seizures were present in 15%,27.5%,12.5%,30%and 15% respectively whereas In Phenobarbitone group focal clonic, multifocal clonic, focal tonic, generalized tonic and myoclonic seizures were present in 13.9%, 27.8%, 16.7%, 30.6% and 11.1% respectively. The difference was statistically insignificant (p value = 0.977).

The mean basal heart rate in Levetiracetam group was 160.7 whereas the mean basal heart rate in Phenobarbitone group was 160.25 and the difference was statistically insignificant (p-value=0.638).

The mean heart rate at 30 mins.in Levetiracetam group was 146.47 whereas the mean heart rate at 30 mins. in Phenobarbitone group was 146.28 and the difference was statistically insignificant (p-value=0.865).

The mean heart rate at 60 mins.in Levetiracetam group was 125.87 whereas the mean heart rate at 60 mins. in Phenobarbitone group was 125.58 and the difference was statistically insignificant (p-value=0. 0.552).

The mean basal respiratory rate in Levetiracetam group was 61.77 whereas the mean respiratory rate in Phenobarbitone group was 62.2 and the difference was statistically insignificant (p-value=0. 0.609).

The mean respiratory rate at 30 mins in Levetiracetam group was 54.5 whereas the mean respiratory rate at 30 mins. in Phenobarbitone group was 54.52 and the difference was statistically insignificant (p-value=0.738).

The mean respiratory rate at 60 mins.in Levetiracetam group was 44.05 whereas the mean respiratory rate at 60 mins. in Phenobarbitone group was 44.1389 and the difference was

statistically insignificant (p-value=0.692).
The mean basal SpO_2 in Levetiracetam group was 91.52 whereas the mean SpO2in Phenobarbitone group was 91.02 and the difference was statistically insignificant (p-value=0.464).
The mean SpO_2 at 30 mins. in LEV group was 94.47 whereas the mean SpO2 at 30 mins.in Phenobarbitone group was 94.22 and the difference was statistically insignificant (p-value=0.867).
The mean SpO_2 at 60 mins. in LEV group was 97.37 whereas the mean spo2 at 60 mins.in Phenobarbitone group was 97.19 and the difference was statistically insignificant (p-value=0.226).
In LEV group 22.5% of patients had normal CNS examination where as 25% of patients in Phenobarbitone group had normal examination. 20%, 47.5% and 10% of patients in LEV group had mildly abnormal, moderately abnormal and severely abnormal CNS examination respectively whereas. 25%, 41.7% and 8.3% of patients in Phenobarbitone group had mildly abnormal, moderately abnormal and severely abnormal CNS examination respectively. The difference was statistically insignificant (p-value=0.927).
12.5% of the patients in LEV group had IVH on USG within 48 hours of seizure episode whereas 11.1% of the patients in PB group had IVH on USG within 48 hours of seizure episode. The difference was statistically insignificant (P-value=0.852).
72.5% of the patients in LEV group had PH < 7.2 at the time of seizure episode whereas 63.9% of the patients in PB group had PH < 7.2 at the time of seizure episode. The difference was statistically insignificant (P-value=0.42).
72.5% of the patients in LEV group had base deficit > 12 at the time of seizure episode whereas 63.9% of the patients in PB group had base deficit > 12 at the time of seizure episode. The difference was statistically insignificant (P-value=0.42).
85% of the patients in LEV group got their seizure primarily controlled by levetiracetam where as 86.1% of the patients in PB group got their seizure primarily controlled by Phenobarbitone. The difference was statistically insignificant. (P-value 0.891).
Seizures in 1 out of 40 patients (2.5%) in levetiracetam group and 1 out of 36 patients (2.8%) were not controlled with levetiracetam and phenobarbitone respectively. They required some other drug (Cross Over) for seizure control. The mean seizure control time in LEV group was 1.5875 whereas the mean seizure control time in PB group was 1.6458 mins and the difference were statistically insignificant (P-value=0.940).
90% of the patients in LEV group where free of seizures on day 30 whereas 89.5% of the patients in PB group where seizure free on day 30. And the difference was statistically insignificant (P-value=0.875). The mean hemoglobin level in LEV and PB groups were 13.4 and 13.26 respectively and the difference was statistically insignificant (P-value=0.974)
The mean Total Leucocyte Count in LEV and PB groups were 12.81 and 12.15 thousand respectively and the difference was statistically insignificant (P-value=0.129). The mean platelet Count in LEV and PB groups were 246.87 lakhs and 260.89 lakhs respectively and the difference was statistically insignificant (P-value=0.231).
The mean calcium level in LEV and PB groups were 8.95 mgs and 8.78mgs respectively and the difference was statistically insignificant (P-value=0.432).
The mean magnesium level in LEV and PB groups were 1.93 mgs and 1.94 mgs respectively and the difference was statistically insignificant (P-value=0.555). The mean sodium level in LEV and PB groups were 149.92 mmol and 148.41 mmol respectively and the difference was statistically insignificant (P-value=0.824).
The mean blood sugar level in LEV and PB groups were 83.8 mgs and 83.444 mgs respectively and the difference was statistically insignificant (P-value=0.939).10% of the patients in LEV group had abnormal LFT whereas 11.1% of the patients in PB group had abnormal LFT. And the difference was statistically insignificant (P-value=0.875).
10% of the patients in LEV group had abnormal KFT whereas 8.3% of the patients in PB group had abnormal KFT. And the difference was statistically insignificant (P-value=0.802).
In LEV group death occurred in 10% of the patients while in hospital whereas in PB group death occurred in 8.3% of the patients. And the difference was statistically insignificant (P-value=0.802).
In LEV group death had occurred in 1% of the patients at 3 months whereas in PB group death had occurred in 5.6% of the patients. And the difference was statistically insignificant (P-value=0.495).
22% of the patients in LEV group had abnormal CNS examination at the time of discharge whereas 22.2% of the patients in PB group had abnormal CNS examination at the time of discharge. And the difference was statistically insignificant (P-value=0.977).
7.5% of the patients in LEV group had abnormal CNS examination at three months whereas 11.1% of the patients in PB group had abnormal CNS examination at three months. And the difference was statistically insignificant (P-value=0.587).
5% of the patients in LEV group had abnormal CNS examination at 6 months whereas 8.3% of the patients in PB group had abnormal CNS examination at 6 months. And the difference was statistically insignificant (P-value=0.558).
In LEV group 55%, 20% and 15% of the patients received treatment for a period of 1 month, 2 months and for more than 3 months respectively whereas in LEV group 50%, 25% and 16.7% of the patients received treatment for a period of 1 month, 2 months and for more than 3 months respectively. And the difference was statistically insignificant (P-value=0.942).
Abnormal EEG was present in 10% of the patients in LEV group and 11.1% of the patients in PB group after 3 months. And the difference was statistically insignificant (P-value=0.875).
Epilepsy was present in 15% of the patients in LEV group and 11.1% of the patients in PB group after 6 months. And the difference was statistically insignificant (P-value=0.514).

DISCUSSION

Neonatal seizures are epileptic fits occurring from birth to the end of neonatal period The cause of neonatal seizures vary as do the duration and frequency, and the distinction between epileptic and non-epileptic event in neonates is often difficult to demonstrate.[24] On the other hand, current data from human studies suggest that neonatal seizures affect the developing brain with long term adverse effects on cognition, learning and seizure threshold.[25,26] Repeated seizures may be deleterious to the brain even without disturbances of ventilation or perfusion by increasing central nervous system metabolic demand and causing release of excitatory amino acids such as glutamate.[27]

The most common anticonvulsant used initially in the newborn period for seizures treatment is phenobarbitone[15], although there are many concerns regarding the short-term adverse effects of phenobarbitone as well as long term effects on neuro-cognitive development.[28] A more recent study shows that phenobarbitone causes apoptotic neuro-degeneration in developing brain.[16]

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. Studies have shown that it does not cause neuronal apoptosis in the immature brain and also has neuro-protective effect.[29-34]

Though, there are cases series, small trials, including some recent ones on use of Levetiracetam in neonatal seizures in neonates, there are no randomized controlled trials.[35-38] We therefore designed a trial with the objective to compare the efficacy of levetiracetam and phenobarbitone in the treatment of clinically apparent neonatal seizures.

A total of 76 patients were enrolled in study group.40 patients received levetiracetam while 36 patients received phenobarbitone for the acute control of seizures.

In our study, the mean gestational age was 36.2±2.9 weeks in levetiracetam group and 36.8±3.5 weeks in phenobarbitone group with a statistically insignificant p value (p=.564). In a similar study conducted by Parveen et al[39], the mean gestational age in the two groups was 38.29±1.03 and 38.43±1.10 weeks respectively (P>0.05).

The mean birth weight was 2.5±0.38 kgs in levetiracetam group and 2.7±0.6 kgs in phenobarbitone group with a statistically insignificant p value (p=0.72). In a similar study conducted by Parveen et al[39], the mean birth weight was 2.78±o.33 and 2.9±0.3 kgs respectively in the two groups (p>0.05).

60% patients in the levetiracetam group and 75% patients in phenobarbitone group were delivered by Normal vaginal delivery with a statistically insignificant p value (p=0.164). Similar results were obtained by Praveen et al[39] in their study.

45% patients in levetiracetam group and 55.6% patients in phenobarbitone group were males with a statistically insignificant p value (p=0.356). In a similar study conducted by Parveen et al[39], 63% patients in levetiracetam group and 73% patients in phenobarbitone group were males (p>0.05).

The mean Apgar score at 5 min was 5.1±1.5 in levetiracetam group and 5.58±1.6 in phenobarbitone group and the difference was statistically insignificant (p=0.265). Similar results were obtained by Praveen et al[39] in their study.

70% patients in levetiracetam group, while 63.9% patients in phenobarbitone group had HIE2 with a statistically insignificant p value(p=0.571). In a similar study conducted by Parveen et al[39], 80%patients in Levetiracetam group and 83.3% patients in phenobarbitone group had HIE2 (p>0.05).

17.5% patients in Levetiracetam group and 16.7%patients in phenobarbitone group had HIE3 with a statistically Insignificant p value (p=0.923). In a similar study conducted by Parveen et al[39], 20% patients in levetiracetam group and 16.6% patients in phenobarbitone group had HIE3(p>0.05)

12.5% patients in levetiracetam group and 11.1% patients in phenobarbitone group had sepsis at the time of admission with a statistically insignificant p value (p=0.852). In a similar study conducted by Parveen et al[39], 10% patients in levetiracetam group and 6.6% patients in phenobarbitone group had sepsis at the time of admission (p>0.05).

In our study, 55% patients in levetiracetam group and 50% patients in phenobarbitone group developed seizures with 48 hours of life and the difference was statistically insignificant (p=0.663). Similar results were obtained by Ramantani et al[19] in their study.

In our study, focal cloic, multifocal clonic, focal tonic, generalized tonic and myoclonic seizures were presents in 15%, 27.5%, 12.5%, 30%and 15% respectively in levetiracetam group and 13.9%, 27.8%, 16.7% 30.6%and 11.1%respectivelly in phenobarbitone group and the difference was statistically insignificant in the two groups (p=0.977). Similar results were obtained by Ramantani et al[19] in their study.

In our study, the mean basal heart rate, heart rate at 30 min and 60 min was 160.7±6.8,146±5.15 and 125.8±4.96 beats per minute respectively in levetiracetam group and 160.2± 6.67,146.27±5.3,125.5±4.58 beats per min respectively in phenobarbitone group and the difference was statistically insignificant (p>0.05).

The mean basal respiratory rate, at 30 min. and 60 min. was 61.7 ±3.9, 54.5±3.3, 44±2.56 per min respectively in levetiracetam group and 62.2 ±3.8,54.5±3.2,44.13±2.46 per min respectively in phenobarbitone group and the difference was statistically insignificant (p>0.05).

In our study, the arterial pH at admission was <7.2 in 72.5% patients in levetiracetam group and 63.9% patients in phenobarbitone group and the difference was statistically insignificant (p=0.42). In a similar study by Praveen et al[39], 63.3% patients in levetiracetam group and 56.6% patients in phenobarbitone group had pH<7.0(P>0.05).

72.5% patients in levetiracetam group and 63.9% patients in phenobarbitone group had base deficit <12 at admission with a statistically insignificant p value (p=0.42). Similar results were obtained by Praveen et al[39] in their study.

In our study, neurological examination at admission was normal, mildly abnormal, moderately abnormal and severely abnormal in 22.5%,20%,47.5% and 10% patients respectively in levetiracetam group and 25%,25%,41.7%and

8.3% patients respectively in phenobarbitone group and the difference was statistically insignificant (p=0.927). Similar results were obtained by Ramantania et al[19] in their study.

12.5% patients in levetiracetam group and 11.1% in phenobarbitone group had IVH and the difference was statistically insignificant (p=0.852).

In our study, 85% patients in levetiracetam group and 86.1% patients in phenobarbitone group got their seizures controlled primarily with levetiracetam and phenobarbitone respectively with a statistically insignificant p value (p=0.891).

97.5% patients in levetiracetam group and 97.2% patients in phenobarbitone group got their seizures controlled after cross over with a statistically insignificant p value (p=0.94).

The mean duration in hours for acute control of seizures was 1.58±1.14 hours in levetiracetam group and 1.64±1.08 hours in phenobarbitone group and the difference was statistically insignificant(p=0.940).

80% patients in levetiracetam group and 80.6% patients in phenobarbitone group were seizure free on day 7 and the difference was statistically insignificant (p=0.952)

90% patients in levetiracetam group and 88.9% patients in phenobarbitone group were seizure free at one month and the difference was statistically insignificant(p=0.875)

The mean hemoglobin, TLC and platelet count was 13.4±1.6, 12.8±3.1 and 246.8±86 respectively in levetiracetam group and 13.26±1.62, 12.15±3.96 and 260±76 in phenobarbitone group and difference was statistically insignificant (p>0.05).

Mean serum calcium, magnesium, sodium and blood sugar at admission was 8.9±0.8, 1.93±0.26, 149±10.5 and 83.8±14.04 respectively in levetiracetam group and 8.7±0.7, 1.94±0.246, 148.4±10.3 and 83.44±13.08 respectively in phenobarbitone group and the difference was statistically insignificant (p>0.05).

10% patients in levetiracetam group and 11.1% patients in phenobarbitone group had abnormal LFT (P= 0.875), while10% patients in levetiracetam group and 8.3% patients in phenobarbitone group had abnormal KFT after treatment and the difference was statistically insignificant (p=0.802).

10% patients in levetiracetam group and 8.3% patients in phenobarbitone group died in hospital and the difference was statistically insignificant (p=0.802). In a similar study conducted by Praveen et al[39], 13.3% patients in levetiracetam group and 6.6% patients died in hospital with a statistically insignificant p value (p= 0.67)

22.5% patients in levetiracetam group and 22.2% in phenobarbitone group had abnormal neurological examination at discharge and the difference was statistically insignificant (p=0.977). In a similar study by Praveen et al[39], 38.4% patients in levetiracetam group and 21.4% patients in phenobarbitone group had abnormal neurological examination at discharge (p=0.23).

7.5% patients in levetiracetam group and 11.1% patients in phenobarbitone group had abnormal CNS examination at 3 months and the difference was statistically insignificant (p=0.587). Similar results were obtained by Praveen et al[39] in their study (p=0.22)

5% patients in levetiracetam group and 8.3% patients in phenobarbitone group had abnormal CNS examination at 6 months and the difference was statistically insignificant (p=0.558). Similar results were obtained by Praveen et al[39] in their study (p=0.40).

CONCLUSION

The primary outcome measure in our study was the clinical cessation of seizure activity and secondary outcome measures comprised immediate adverse effects including variations in cardio respiratory parameters.

Taking into consideration, the improved neuro-developmental outcomes and lack of neuro-degenerative effects of levetiracetam as compared to other AEDs, pharmacokinetic profile of Levetiracetam (not liver metabolized, excreted unchanged in urine,with no drug -drug interactions) as seen in the earlier studies and the equal efficacy of levetiracetam in controlling the neonatal seizures acutely as compared to phenobarbitone in our study, makes levetiracetam and attractive treatment option in neonatal seizures.

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