“RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF LEVETIRACETAM VERSUS PHENOBARBITAL AS FIRST LINE THERAPY FOR NEONATAL SEIZURES.”

BY

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I hereby declare that this dissertation/thesis entitled **"RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF LEVETIRACETAM VERSUS PHENOBARBITAL AS FIRST LINE THERAPY FOR NEONATAL SEIZURES."** is a bonafide and genuine research work carried out by me under the guidance of **Dr.R.H.GOBBUR** **M.D.**, Professor, Department of Pediatrics, Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapur.

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LIST IF ABBREVIATIONS USED

LEV	-	Levetiracetam
AED	-	Anti Epileptic Drug
NICU	-	Neonatal Intensive Care Unit
HIE	-	Hypoxic Ischemic Encephalopathy
NS	-	Neonatal Seizures
EEG	-	Electroencephalography
NNPD	-	National Neonatal-Perinatal Database
IEM	-	Inborn Errors of Metabolism
CSF	-	Cerebro Spinal Fluid
SAH	-	Sub Arachnoid Hemorrhage
IVH	-	Intra Ventricular Hemorrhage
NMDA	-	N-Methyl-D-aspartate
AMPA	-	Amino methyl phosphonic acid
GABA	-	Gamma-Aminobutyric acid
CYP2C9	-	cytochrome P450 enzyme
I V	-	Intra Venous
I M	-	Intra Muscular
DAYC	-	Developmental Assessment of Young Children
BSID	-	Bayley Scale of Infant Development
FDA	-	Food and Drug Administration
SV2a	-	Synaptic Vesicle protein 2
SCR	-	Sub Coastal Retractions
ICR	-	Inter Coastal Retractions

CFT	-	Capillary Filling Time
mg	-	milligram
BA	-	Birth Asphyxia
MSAF	-	Meconium Stained Amniotic Fluid
TMSAF	-	Thick Meconium Stained Amniotic Fluid
AGA	-	Appropriate for Gestational Age
SGA	-	Small for Gestational Age

ABSTRACT

INTRODUCTION:

Seizures occurs more frequently in neonates than in older child and may adversely affect the neuro developmental outcome. Since decades Phenobarbital has remained the AED of choice, even though seizure control is not up to the mark, it also causes further damage to the immature brain due to neonatal apoptosis, a potential risk with Phenobarbital. Levetiracetam is newer AED with least side effects when used in children and adults which is increasingly being used in neonates for NS, without knowing its efficacy in neonates.

OBJECTIVES:

The purpose of this study is to compare the efficacy of Levetiracetam with Phenobarbital in early onset seizures in term, late preterm & low birth weight neonates admitted in NICU.

MATERIAL AND METHODS:

Sample for the study are all term, late preterm & low birth weight neonates admitted in NICU with neonatal seizures at Shri B. M. Patil Medical College, Hospital & Research Center, Bijapur. Neonates were randomly allotted into 2 groups. In Group-A, LEV was used as 1st line AED, and in Group-B Phenobarbital was used as 1st line AED.

RESULTS:

A total of 78 patients with clinically confirmed NS were randomly allotted into 2 groups with 39 patients in each group. In LEV group, it was effective in 16

patients(41%), and in Phenobarbital group, it was effective in19 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%) with significant P value of 0.033.

CONCLUSION:

LEV and Phenobarbital as 1st line AED controls NS in less than 50% patients, both being equally effective. However LEV use may lead to lesser mortality and early seizure control than Phenobarbital. Larger study may confirm our findings.

KEY WORDS: Levetiracetam, Phenobarbital, Neonatal Seizures

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INTRODUCTION

Seizures occurs more frequently in neonates than in older child and may adversely affect the neuro developmental outcome. In India incidence of neonatal seizures varies from 0.5 to 0.8% in term babies. Generalized seizures do not occur in neonates due to immature myelination of the nervous system. Neonatal seizures have varied presentations such as ocular changes, tongue thrusting, cycling limb movements, apnea, 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 to other extremity[1].

Since years the preferred agent for treatment of neonatal seizures has been Phenobarbital, followed by phenytoin or phosphenytoin, and then benzodiazepines. The evidence for treatment with these agents was made out from data in adults and children. These drugs alone are not adequate to attain 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 neurodevelopment 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[3].

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. fosphenytoin 40mg/kg.

Bittigau et al[4] studied the effects of multiple AEDs in animal models at relevant human doses. Study results 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 to15 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[4].

Hence there is need to try LEV as First line drug instead of third/ add on drug. Safety of LEV is never disputed , its efficacy when used alone is documented , but efficacy is not confirmed in large group. When that is confirmed in the largescale trials, then many unnecessary use of phenobarbital and phenytoin can be stopped, and respiratory depression, and other significant side effects of those can be avoided. Even though there were lack of studies supporting LEV use in 2007, a survey conducted among pediatric neurologists showed that 47% suggested LEV off-label for neonatal seizure treatment[5].

AIMS AND OBJECTIVES

OBJECTIVES OF STUDY:

To compare the efficacy of Levetiracetam with Phenobarbital in early onset seizures in term, late preterm & low birth weight neonates admitted in NICU.

REVIEW OF LITERATURE

Neonatal seizures are never idiopathic[6]. Hypoxic-ischemic encephalopathy (HIE) due to asphyxia[7] is the leading cause of seizures in the neonates, accounting for approximately two-thirds of neonatal seizures[8]. HIE seizures are generally self-limiting, stopping by 48-72 hours[9] and therefore, proving efficacy of agents in treatment of these seizures is difficult. Other causes of seizures include metabolic disturbances, cerebrovascular disease, sepsis, and congenital malformations[6,9].

Neonatal seizures(NS) which occurs in first 28 days of life, are the most distinctive and frequent clinical manifestations of neurological dysfunction in newborns. Even though mortality due to NS has reduced to half from 40% to 20%, morbidity like neurological impairment/ epilepsy disorders in later life has remained unchanged, which accounts for around 30%[10].

Definition of Neonatal Seizures:

Clinically seizure is defined as paroxysmal alteration in neurological functions, like motor, behaviour and autonomic functions. Definition also includes[11]:

1. Epileptic seizures: phenomena with corresponding EEG seizure activity, e.g: clonic seizures
2. Non epileptic seizures: clinical seizures without EEG activity,
   e.g: subtle and generalized tonic seizures.

EPIDEMIOLOGY:

According to National Neonatal Perinatal Database(NNPD: 2002-03), data from 18 tertiary centers across country was collected, and incidence was found to be 1.03% of live births[12]. Incidence was found to be indirectly proportional to birth

weight and gestational age, i.e preterm babies(2.08%) has twice the incidence of term babies (0.84%), while very low birth weight infants had more than 4 fold higher incidence(3.61%)[13].

CLASSIFICATION OF NEONATAL SEIZURES:[12]

There are four types of NS:

1. **Subtle seizures**: they occur most commonly in premature than in full term neonates, manifestations include transient deviation of eyes, nystagmus, mouthing, blinking, abnormal extremity movements like rowing, swimming, bicycling, pedalling, stepping and fluctuations in heart rate, hypertension episodes and apnea.
2. **Clonic seizures**: they are rhythmic movements of muscle groups, can be focal or multifocal. Multifocal clonic seizures includes several body parts and are migratory in nature. In neonatal period, bilateral, symmetric and synchronous clonic seizures are uncommon presumably due to decreased connectivity and incomplete myelination at this age. They are commonly associated with EEG changes. They have frequency of 1-3 jerks per second.
3. **Tonic seizures**: they can be focal or generalized, in which later are more common. It manifests like persistent posture of limbs or trunk or neck in asymmetric way, often associated with horizontal eye deviation. It resembles decerebrate or decorticate posturing and usually EEG changes are not seen.
4. **Myoclonic jerks**: they are divided into focal, multifocal, generalized types and can be distinguished from clonic seizures by the rapidity of jerks(<50 msec) and by their lack of rhythmicity. Common changes seen in EEG are burst suppression pattern, focal sharp waves and hypsarrhythmia.

Focal clonic seizures has best prognosis and myoclonic seizures carry the worst prognosis.

TABLE 1. Classification of Neonatal Seizures[14]:

Seizure type	Clinical manifestations
Subtle	Swimming movements Pedalling movements Stepping movements Ocular movements Lingual-buccal-oral movements Autonomic dysfunction
Clonic	Rhythmic, slow jerky movements They can be Focal or multifocal May involves facial, extremity, or axial structures
Tonic	Focal or generalized Asymmetric position of trunk/neck Sustained posturing of limbs
Myoclonic	isolated and rapid jerky movements Involves limbs or trunk Generalized, multifocal, or focal

COMMON CAUSES OF NEONATAL SEIZURES[12,15-18]:

Most common causes of NS are hypoxic ischemic encephalopathy(HIE), metabolic disturbances like hypocalcemia, hypoglycaemia, hypomagnesemia and meningitis

1. **Hypoxic ischemic encephalopathy(HIE):** HIE secondary to birth asphyxia is the commonest cause of NS, which accounts for 50-65% of NS and manifests mostly within first 12 hours of life. Problems like intracranial hemorrhage, hypocalcemia, hypoglycaemia may coexist in neonates with perinatal asphyxia. Subtle seizures are the most common type of seizures following HIE.
2. **Metabolic changes**: Most commonly they include hypoglycaemia, hypocalcemia, hypomagnesemia and rarely pyridoxine dependency and inborn error of metabolism(IEM).
3. **Infections**: meningitis should always be excluded in all neonates with seizures. They account for 5-10%of NS. Meningitis secondary to intrauterine infections like TORCH(particularly herpes simplex encephalitis) and syphilis may also presents as NS.
4. **Vascular events**: they include intracranial bleed and ischemic stroke which accounts for 10-20% of NS. Mainly three types of haemorrhages are seen i.e, subarachnoid hemorrhage, subdural hemorrhage, germinal matrix-intraventricular hemorrhage. Seizures occurring in term normal babyon day 2-3 of life is often due to subarachnoid hemorrhage. Most seizures due to intracranial hemorrhage occurs between 2-7 days of life.
5. **Brain malformations**: cerebral dysgenesis and neuronal migration disorders are rare causes of NS, which accounts for 5-10%.

6. **Miscellaneous**: these causes include polycythemia, maternal narcotic withdrawal, drug toxicity(e.g. theophylline, doxapram), local anesthetic injection into scalp and phacomatosis(tuberous sclerosis, incontinentia pigmenti). Benign idiopathic neonatal convulsions manifests with multifocal clonic seizures on 5^{th} day of life which may be related to low zinc levels in CSF fluid.

NS due to SAH and late onset hypocalcemia carries good prognosis for long term neurodevelopmental outcome, where as seizures due to hypoglycaemia, cerebral formations and meningitis have adverse outcome.

TABLE 2. Causes of Neonatal Seizures[14]:

ETIOLOGY	TERM INFANTS	PRETERM INFANTS	OUTCOME
HIE	Most common	Common	Variable
IVH (severe)	Uncommon	Common	Poor
SAH (severe)	Common	Uncommon	Good
Hypoglycemia	Common	Common	Variable
Hypocalcemia	Uncommon	Uncommon	Good
Intracranial infection	Common	Common	Variable
Cerebral dysgenesis	Common	Common	Poor
Drug withdrawal	Uncommon	Uncommon	Variable

TABLE 3. Correlation of Timing and Etiology of Neonatal Seizures[14]

ETIOLOGY	MOST COMMON TIME OF ONSET		
	BIRTH TO 2Days	Days 3 TO 7	Days 7 TO 10
HIE	X		
Hypoglycemia	X		
Anaesthetic injection	X		
Intracranial hemorrhage	X	X	
Hypocalcemia	X (early)		X (late)
IEM		X	
Intracranial infection		X	
Drug withdrawal		X	
Cerebral dysgenesis	X	X	X
Neonatal epilepsy syndromes		X	X

PATHOPHYSIOLOGY OF NS[15-18]:

The neonatal brain which is immature has lots of differences from the mature brain that makes it more excitable and more likely to develop seizures. Based mostly on animal studies, these are delay in Na^+, k^+ adenosine triphosphate maturation, increased NMDA, AMPA receptor density. In addition, the specific types of receptors that are increased are those that are permeable to calcium, which contributes to increased excitability and to long term consequences associated with seizures.

Another difference is delay in the development of inhibitory GABAergic transmission, in fact GABA has excitatory function in immature brain, as chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus opening of chloride channels results in depolarizing the cell and not hyperpolarizing it in immature brain.

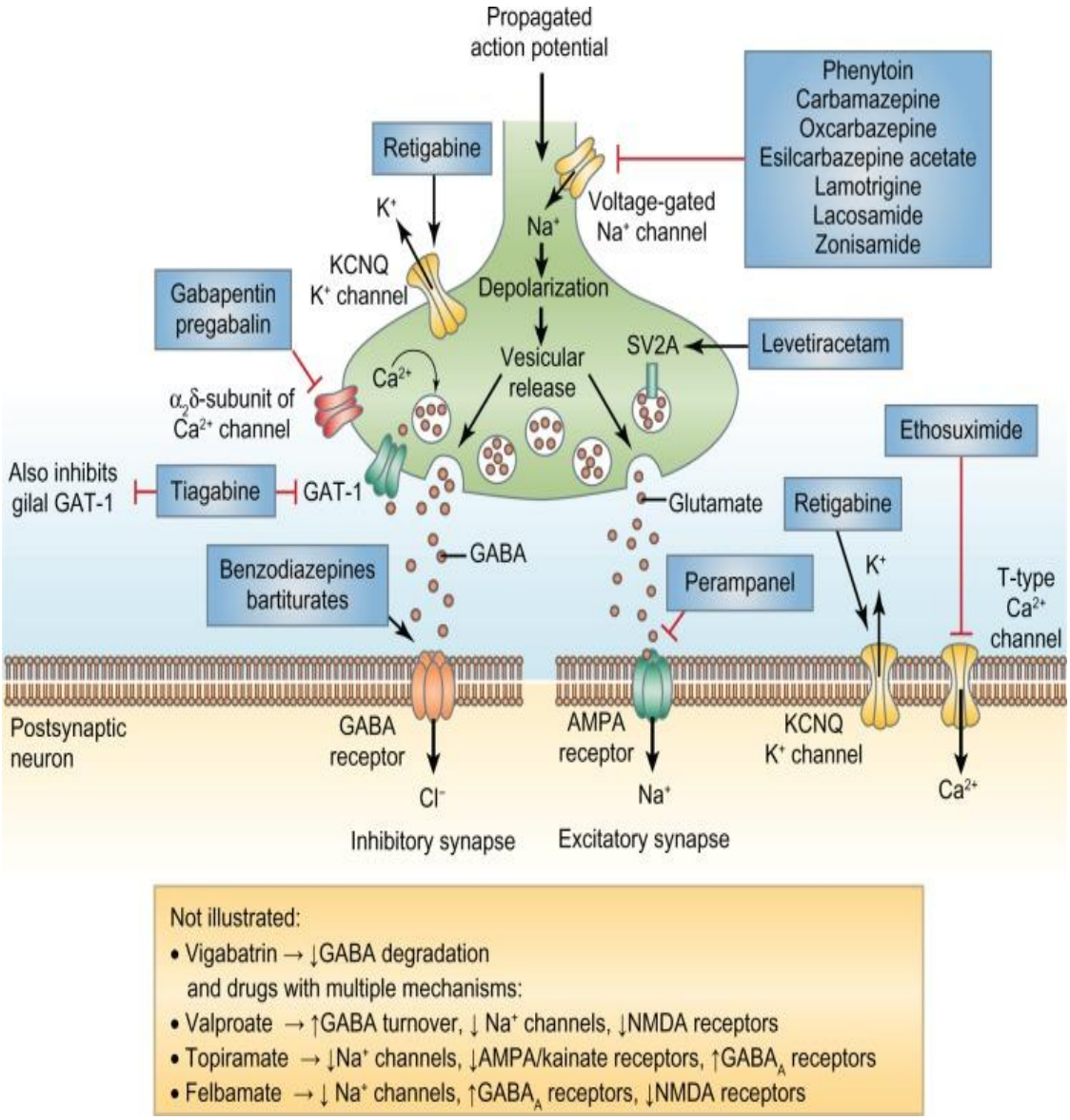
Although it is susceptible to developing seizures, the immature brain appears to be more resistant to the deleterious effects of seizures than mature brain, as a result of increases in calcium binding proteins that buffer injury related increases in calcium, increased extracellular space, decreased levels of second messenger inositol triphosphate, and immature brains ability to tolerate hypoxic conditions by resorting to anaerobic energy metabolism.

STANDARD ANTICONVULSANT THERAPY PROTOCOL IN NICU:

The most preferred drug for treatment of NS is Phenobarbital, followed by phenytoin or fosphenytoin and benzodiazepines. There was no adequate evidence for treatment with these agents in neonates, treatment data from adults and children was extrapolated for neonates. Eventhough phenytoin is preferred anti epileptic agent in pediatric and adult age group, there are lot of difficulties associated with this drug like dosing and monitoring in neonatal population. Challenges with phenytoin dosing in neonatal age group include reduced protein binding which is 60%-90% , compared to adults which is more than 90% albumin bounded[19]. Phenytoin also has competitive binding with bilirubin, endogenous corticosteroids, free fatty acids which results in increased free drug concentration or increased free bilirubin and kernicterus[19]. As newborns has low serum albumin concentrations compared to that of adults which may lead to free drug concentration[19-21]. Due to incomplete maturation of CYP2C9 enzyme in new borns and immature saturable metabolism, half life of phenytoin is prolonged from 8 hours to 20 hours in term neonates and to 75 hours in preterm infants[22,23].

Even though Phenobarbital is considered as drug of choice in NS, a decreased response may be expected as the targeted inhibitory GABA receptors are underexpressed in neonatal brains. Immature GABA receptors overexpress the α_4 subunit compared to α_1 in adults, which has been shown to reduce responsiveness of Phenobarbital and benzodiazepine therapy. The reason for limited efficacy of Phenobarbital and benzodiazepines in NS might be also due to altered responsiveness of immature neonatal brain, like GABA activation by an agonist leading to efflux of chloride due to high intracellular concentrations, which may cause depolarization of membrane resulting in neuronal firing[24].

FIGURE 1: Mechanism of action of various anti epileptic drugs:



Not illustrated:

- Vigabatrin → ↓GABA degradation

and drugs with multiple mechanisms:

- Valproate → ↑GABA turnover, ↓ Na^+ channels, ↓NMDA receptors
- Topiramate → ↓Na^+ channels, ↓AMPA/kainate receptors, ↑$GABA_A$ receptors
- Felbamate → ↓ Na^+ channels, ↑$GABA_A$ receptors, ↓NMDA receptors

TABLE 4. Acute Treatment of Neonatal Seizures[14]

● Ensure respiration
● Ensure cardiac support
● If hypoglycemic: give glucose 10% solution: 2 mL/kg IV followed by continuous glucose infusion rate at 5 to 7 mg/kg per minute
● In view of hypocalcemia: —Calcium gluconate 5% solution: 4 mL/kg IV — Magnesium sulfate 50% solution: 0.2 mL/kg IM —Pyridoxine 50 to 100 mg IV
● if still seizures persists, then treatment with AED: —Phenobarbital loading dose: 20 mg/kg IV; additional doses: 5 mg/ kg IV (10 to 15 min) to maximum of 20 mg/kg —Phenytoin 20 mg/kg (1 mg/kg per minute) —Lorazepam 0.05 to 0.10 mg/kg IV.

Abend et al[25] in a restrospective study on 23 neonates who had electroencephalographically confirmed seizures, Levetiracetam was given as first line(17%), second line(61%) and as a third line(22%) with a dose range of 10-80 mg/kg/day. They have noticed seizure improvement within 24 hours in 35%,with termination in 88%, seizure reduction of more than 50% was seen in 12%. They have concluded that Levetiracetam was effective and has shown seizure reduction in 35% (8 of 23), including seizure termination in 7.

In a study by Khan et al[26], intravenous Levetiracetam was used for NS as second line drug after failure of Phenobarbital therapy. A total of 22 newborns with

neonatal seizures were studied with HIE being cause of NS in 55%, that is 12 0f 22. Before starting intravenous LEV therapy, 72% were treated with 1 AED, 9 % were treated with 2 AED and 5% were treated with 3 AED. Due to failure of Phenobarbital therapy 68% patients have received LEV with a loading dose of 50 mg/kg followed by 50 mg/kg/day of maintenance therapy in 2 divided doses. After loading dose of LEV, 7 of 22 neonates had complete seizure control at 1 hour, and at 72 hours 100% had complete seizure sessation. All patients were discharged home with only oral LEV, except 9% who were discharged along with an additional oral AED. Very minimal side effects were noted in this study. This study proves that LEV is safe and efficient in NS.

In a prospective study by Ramantani et al[27], LEV was used as a first line anti epileptic therapy in 38 preterm and term infants with NS due to varied etiology but HIE being most common cause. LEV was used with an initial dose of 10mg/kg, twice daily, and reached a maximum dose of 30 mg/kg/day with a dosage increase of 10mg/kg/day over next 3 days. If NS were persistent dosage was further increased up to 60/mg/kg/day. Two doses of Phenobarbital was allowed during LEV dose titration for prolonged or repetitive breakthrough seizures. At the end of first week, 30 neonates remained seizure free, but at the end of 1 month 3 infants had seizure recurrence, and 1 extremely premature infant had required Phenobarbital, so 27 patients remained seizure free at the end of 1 month. Authors have concluded that, LEV was safe in NS, but may not achieve seizure control as monotherapy, as they have used Phenobarbital adjunctive therapy in more than 50% of study population. They also opined that higher loading dose of LEV would have reduced the usage of Phenobarbital for breakthrough seizures and would have achieved early seizure control.

In a retrospective study performed by Maitre et al[28], Developmental Assessment of Young Children (DAYC) score was done at 12 months of age, Bayley Scales of Infant Development(BSID) score at 24 months, and evaluated neuro developmental outcomes at 2 years of age after 280 infants with NS who got treated with Phenobarbital and LEV. A total of 141 patients were treated with both Phenobarbital and LEV, 33 patients received only LEV, and 106 neonates received only Phenobarbital. Doses were calculated as a cumulative dose in mg/kg, which they have received throughout the hospital stay. 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 Phenobarbital and LEV were associated with decreased motor scores. At the age of 24 months BSID scores were reported, and the results were significantly different in both groups. Phenobarbital 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 Phenobarbital 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 Phenobarbital dosage, patients had 2.3 fold increase in risk of developing cerebral palsy by 2 years of age, but same association was not found between cerebral palsy and LEV. Hence this study supports that Phenobarbital has neuro toxicity and poor neurodevelopmental outcomes as documented in animal models and also proves that LEV has less or no neuronal apoptosis and improved outcomes.

Painter et al[29] 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.

Hmaimess et al[30] demonstrated the efficacy of LEV in a neonate with malignant migrating partial seizures refractory to phenytoin, clonazepam, Phenobarbital, and lamotrigine. The patient received an initial dose of LEV, 10 mg/kg/day, which was increased to 30 mg/kg/day without adverse effects. Within 8 days, LEV therapy resulted in improvement in clinical status and decreased seizure activity confirmed via EEG recordings[30].

Shoemaker et al[31] discussed the use of LEV in 3 infants (2 days to 3 months of age) for whom conventional AED therapy had failed. Patients were treated with LEV dosages ranging from 30 to 60 mg/kg/day divided into 2 to 3 doses daily. Despite the fact that all 3 patients' seizures had different causes (infarction, hydrocephalus, and meningitis), each neonate was safely and effectively treated with LEV as adjunct therapy without adverse effects.

In a retrospective study done by Yau et al[32], which was done on 12 neonates with 6 male and 6 female babies, and major cause of NS being HIE, all neonates were initially treated with Phenobarbital followed by the use of LEV. In 58% and 75% of neonates they achieved seizure freedom both clinically and electrographically at 24 hours and 72 hrs respectively after adding LEV. They have not noticed any serious adverse effects.

A total of 16 neonates with convulsions were enrolled in a prospective study by Raffaele et al[33]. All patients were initially treated with LEV 10 mg/kg/dose twice a day, if seizures persisted dose escalation was done till 40 mg/kg twice daily, with an

increment LEV dose not more than 10 mg/kg/dose. They have also used Phenobarbital in cases which were resistant to LEV. All patients have responded to the LEV treatment without the need for second antiepileptic therapy. They have attained seizure resolution period with mean hours of 96 ± 110.95. No major side effects were observed in their study.

Perveen et al[34] , in their prospective study with comparision between LEV and Phenobarbital has found that LEV was not as good as Phenobarbital in control of NS, and they also found that LEV took longer time than Phenobarbital to attain seizure control. A total of 60 newborns with clinically proven NS were enrolled, 30 babies were randomized to LEV group and 30 to Phenobarbital group. They used I.V LEV with loading dose of 60mg/kg and I.V Phenobarbital with 20mg/kg. In this study 23.3% neonates who were assigned to LEV group attained seizure control alone with LEV, and in Phenobarbital group seizures got controlled in 86.7%. They conclude that Phenobarbital is more efficacious than LEV in controlling seizures in preterm and term babies with perinatal asphyxia. They also found that LEV as first line therapy for NS lead to delayed control of NS.

LEVETIRACETAM:

Levetiracetam was approved by US Food and Drug Administration(FDA) in November 1999 only for use in adult patients with seizures but not in pediatric or neonatal age group. In 2012 FDA approved LEV for use in partial onset seizures in infants and children one month of age and older[30]. Levetiracetam has several advantages over other commonly used anti epileptic drugs as mentioned below…

ADVANTAGES OF LEVETIRACETAM(LEV) AS COMPILED IN REVIEW ARTICLE BY 2015[35]:

1. Levetiracetam is pyrrolidine derivative antiepileptic that binds to synaptic vesicle protein SV2a, which is expressed throughout the brain, which impedes neurotransmitter release and vesicle transport within the neuron. SV2a receptor is important in both partial and generalized seizures, which is targeted uniquely by LEV and, therefore provides a novel mechanism of action for neonatal patients. As SV2a if found in all areas of brain, it can treat partial seizures that arise in various regions of brain, as seen in neonatal seizures[36].

2. LEV exhibits high bioavailability(>95%), quickly reaches peak and steady state concentrations in 1.3 hours, and display linear time dependent kinetics[37].

3. LEV undergoes minimal hepatic metabolism, resulting in fewer drug – drug interactions[37,38].

4. LEV has lower protein binding (~10%), resulting in less serum drug variability in neonates[37,38].

5. Sixty six percent of drug is eliminated in urine and clearance is dependent on renal function (no role of premature liver) [37-40].

6. Manthley et al demonstrated that LEV lacked neurotoxic effects at all studied doses like 5, 10, 25, 50, and 100mg/kg per dose in 7 day old rats, which is similar to doses in humans[40].

7. LEV appeared to exert disease modifying effect on hypoxic ischemic seizures that may potentially attenuate seizures later in life[41].

8. LEV doesn't cause neuronal apoptosis in hypoxic ischemic encephalopathy[41].

9. Due to limited side effects like headache(24%), pyrexia(22%), upper respiratory tract infection(21%) and less drug interactions of LEV, routine monitoring is not necessary[42].

Innovations and breakthroughs[32]:

Yau MLY et al in their study opined that LEV could be safely administered in sick neonates and its efficacy might be limited in those with most severe hypoxic ischemic encephalopathy. The experience from literature review also supports the relative safety of the drug. They concluded that LEV is a relatively safe and feasible treatment option for neonatal seizures.

MATERIALS AND METHODS

Source of data:

Sample for the study are all term, late preterm & low birth weight neonates admitted in NICU at Shri B. M. Patil Medical College, Hospital & Research Center, Bijapur.

Prospective study involving late preterm and term neonates with seizures admitted in NICU. A total of 78 cases of neonatal seizures were studied in a span of 1 1/2 year.

Method of collection of Data (including sampling procedures if any)

After taking written informed consent from the parents and fulfilling inclusion and exclusion criteria, the neonates were included in the study.

Method of study:

A prospective study involving late preterm and term neonates admitted in NICU.

Period of study – 1 1/2 year

INITIAL STABILIZATION OF SEIZURES:

Baby was looked for Airway, Breathing, Circulation.

AIRWAY: By checking oxygen saturation with pulseoximeter.

BREATHING: looked for pattern of breathing, subcoastal retractions(SCR), intercoastal retractions(ICR), xiphoid retractions and nasal flaring.

CIRCULATION: capillary filling time(CFT) was checked.

All neonates were nursed in thermoneutral environment, airway, breathing , circulation was ensured. securing IV access and collecting blood for investigations like RBS and serum calcium levels was done.

Initially oxygen supplementation, ventilator support, ionotropic support was provided as per the need. **If glucostix shows hypoglycaemia(<40mg/dl), 2ml/kg 10% dextrose was given as bolus followed by a continuous infusion of 6-8mg/kg/min. if hypoglycaemia excluded as a cause of convulsions, neonates have received 2ml/kg of 10% calcium gluconate IV over 10 minutes under cardiac monitoring. If seizures continue despite correction of hypocalcaemia, 0.25ml/kg of 50% magnesium sulphate was given intramuscularly.**

Then the neonates were randomly allotted alternatively in to Group 1 or Group 2.

IN GROUP 1: Levetiracetam is administered as 1st drug, Phenobarbital as 2nd drug.

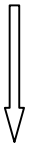
In Group 1:Levetiracetam with a loading dose of 50mg/kg was given over 15minutes, if there was no response in 15minutes, additional dose of LEV 20mg/kg was administered intravenously. Maximum total loading dose of 70mg/kg was given.

If seizures were still uncontrolled, Phenobarbital was administered as second drug with loading dose of 20mg/kg intravenously over 20 minutes, if uncontrolled in 15 minutes additional doses of Phenobarbital10 mg/kg every 15 minutes was administered intravenously till seizure controls or till a total dose of 40mg/kg of Phenobarbital reaches.

GROUP 1:

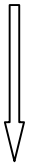
1ST LINE: **LEV 50mg/kg**(LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside



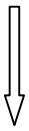
LEV 20mg/kg(MINI LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside



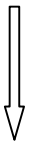
2ND LINE: **PHENOBARBITAL 20mg/kg**(LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside



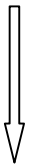
PHENOBARBITAL 10mg/kg (1ST MINI LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside



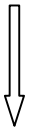
PHENOBARBITAL 10mg/kg (2ND MINI LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside



3RD LINE: **FOSPHENYTOIN 20mg/kg** (LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside



FOSPHENYTOIN 10mg/kg (MINI LOADING DOSE)

IN GROUP 2: Phenobarbital was administered as 1st drug , and LEV as 2nd drug.

In Group2: Phenobarbital was administered as 1st line with loading dose of 20mg/kg intravenously over 20 minutes. If seizures were uncontrolled in 15 minutes additional doses of Phenobarbital 10 mg/kg every 15 minutes was administered intravenously till seizure controls or till a Maximum dose of 40mg/kg of Phenobarbital reached.

If seizures were still uncontrolled, LEV was administered as a 2nd Drug with a loading dose of 50mg/kg was given over 15minutes. If there was no response in 15minutes, additional dose of LEV 20mg/kg was administered intravenously for a total dose of 70mg/kg of LEV .

If seizure control requires two drugs, then both of these drugs were continued as maintenance dose for a minimum of one week seizure control period.

As a third line of anti epileptic treatment fosphenytoin was given with a loading dose of 20mg/kg and mini loading dose of 10mg/kg. If still seizure control was not attained, then midazolam infusion at the rate of 0.1 to 0.4 mg/kg/hour was given, with respiratory monitoring.

GROUP 2:

1ST LINE: **PHENOBARBITAL 20mg/kg**(LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside

⇩

PHENOBARBITAL 10mg/kg (1ST MINI LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside

⇩

PHENOBARBITAL 10mg/kg (2ND MINI LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside

⇩

2ND LINE: **LEV 50mg/kg**(LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside

⇩

LEV 20mg/kg(MINI LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside

⇩

3RD LINE: **FOSPHENYTOIN 20mg/kg** (LOADING DOSE)

Observe for 15 mins, if seizures doesn't subside

⇩

FOSPHENYTOIN 10mg/kg (MINI LOADING DOSE)

IN BOTH GROUPS – MAINTENANCE DOSE was continued for 1 week.

LEV- 20mg/kg/day.

Phenobarbital- 3-5mg/kg/day.

If still seizures were persistent in spite of 3 AED, then midazolam infusion was given at the dosage of 0.1 mg/kg/hour.

Time for seizure control, that is from the time of onset of seizure to the time of cessation of seizures was noted in both the groups.

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:

$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 \text{ X } 2SD^2}{MD^2}$$

Where Z_{α} = statistic at the level of significance = 95%.

Z_{β} = Z value at β level of significance = 80%.

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 (χ^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<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 & Research Center.
2. Neonates with birth weight of >1500gms, with neonatal seizures of varied etiology.

Exclusion criteria:

The study will exclude

1. Neonates with multiple severe congenital anomalies.
2. Mother on anti convulsions.
3. Neonates treated with anti epileptics elsewhere.

Duration of study: 1 ½ year(1-Jan-2016 to 1-Jun-2017).

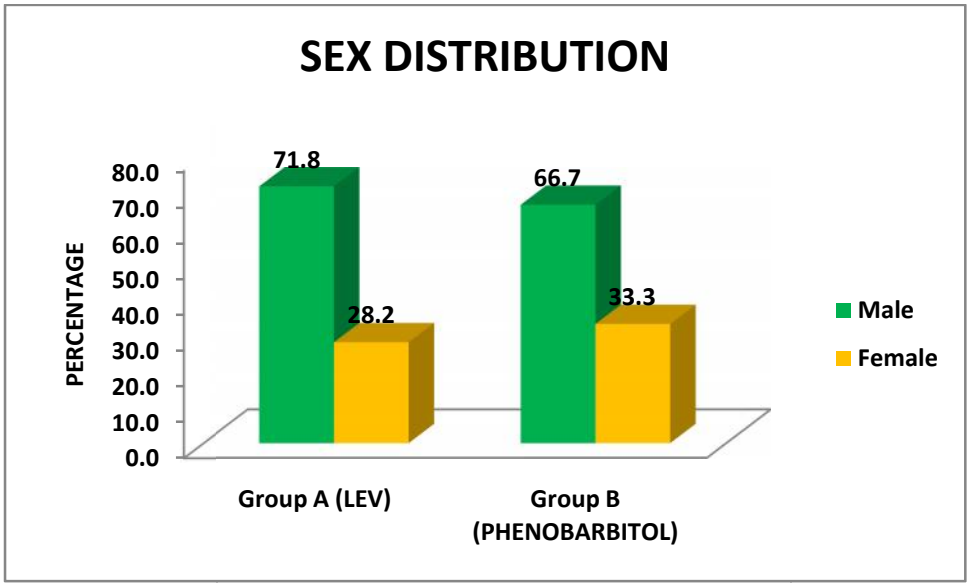
RESULTS

A total of 78 neonates with clinically proven convulsions were enrolled in this study and randomly they were assigned to LEV(group 1) group and Phenobarbital(group 2) group respectively. Sex distribution in both groups is almost same with p value of 0.624 which is not so significant. Details are seen in following table and figure.

TABLE 5: DISTRIBUTION OF SEX BETWEEN STUDY GROUPS

SEX	Group A (LEV)		Group B (PHENOBARBITOL)		p value
	N	%	N	%	
Male	28	71.8	26	66.7	0.624
Female	11	28.2	13	33.3	
Total	39	100.0	39	100.0	

FIGURE 2: DISTRIBUTION OF SEX BETWEEN STUDY GROUPS

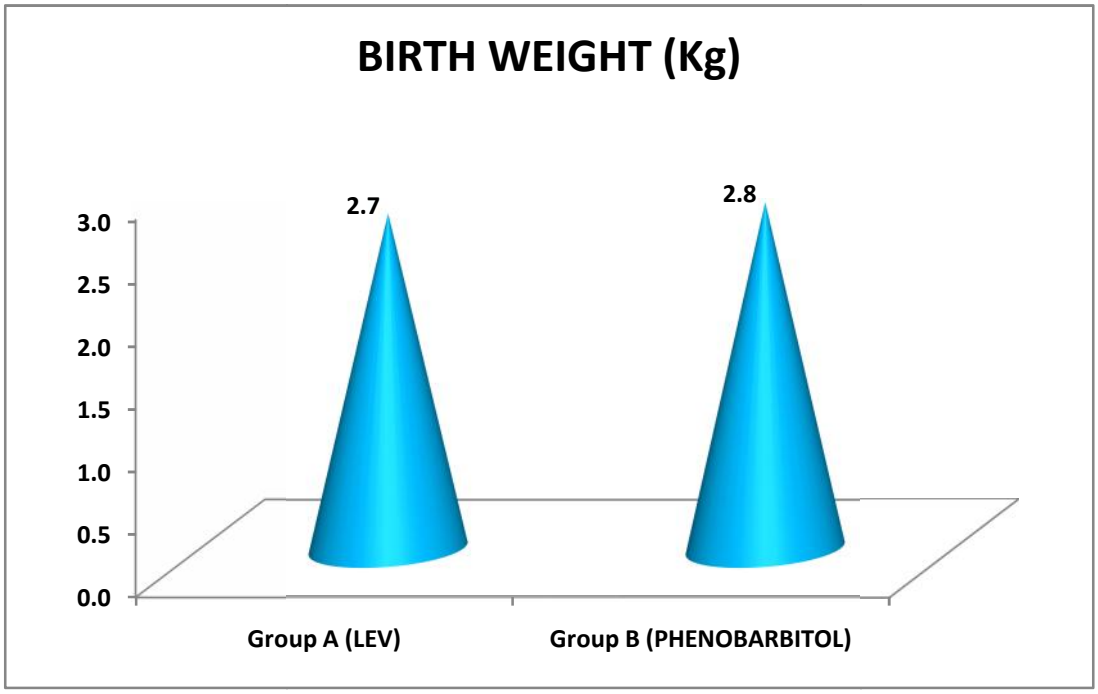


Mean Birth weight in both Group-A and Group-B is 2.7 and 2.8 kilograms respectively with a p value of 0.329

TABLE 6: COMPARISON OF MEAN BIRTH WEIGHT BETWEEN STUDY GROUPS

Parameters	**Group A (LEV)**		**Group B (PHENOBARBITOL)**		**p value**
	Mean	**SD**	**Mean**	**SD**	
BIRTH WEIGHT (Kg)	2.7	0.4	2.8	0.4	0.329

FIGURE 3:COMPARISON OF MEAN WEIGHT BETWEEN STUDYGROUPS

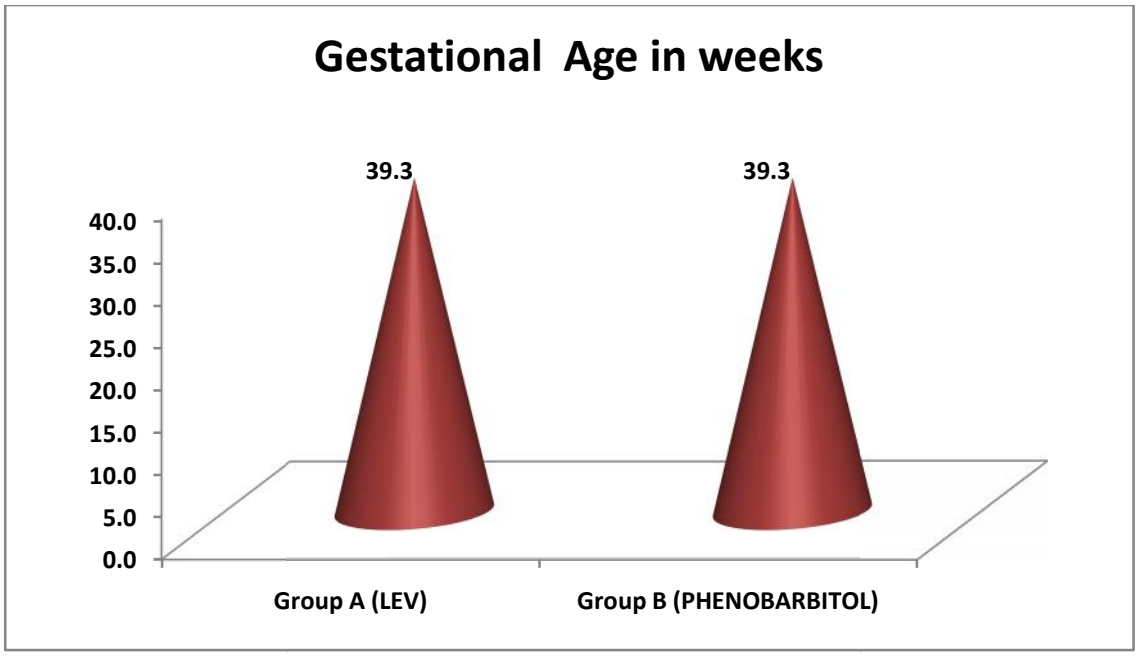


Mean GA in both groups is 39.3 weeks.

TABLE 7: COMPARISON OF MEAN GESTATIONAL AGE BETWEEN STUDY GROUPS

Parameters	Group A (LEV)		Group B (PHENOBARBITOL)		p value
	Mean	SD	Mean	SD	
G A in weeks	39.3	1.3	39.3	1.4	-

FIGURE 4: COMPARISON OF MEAN GESTATIONAL AGE BETWEEN STUDY GROUPS

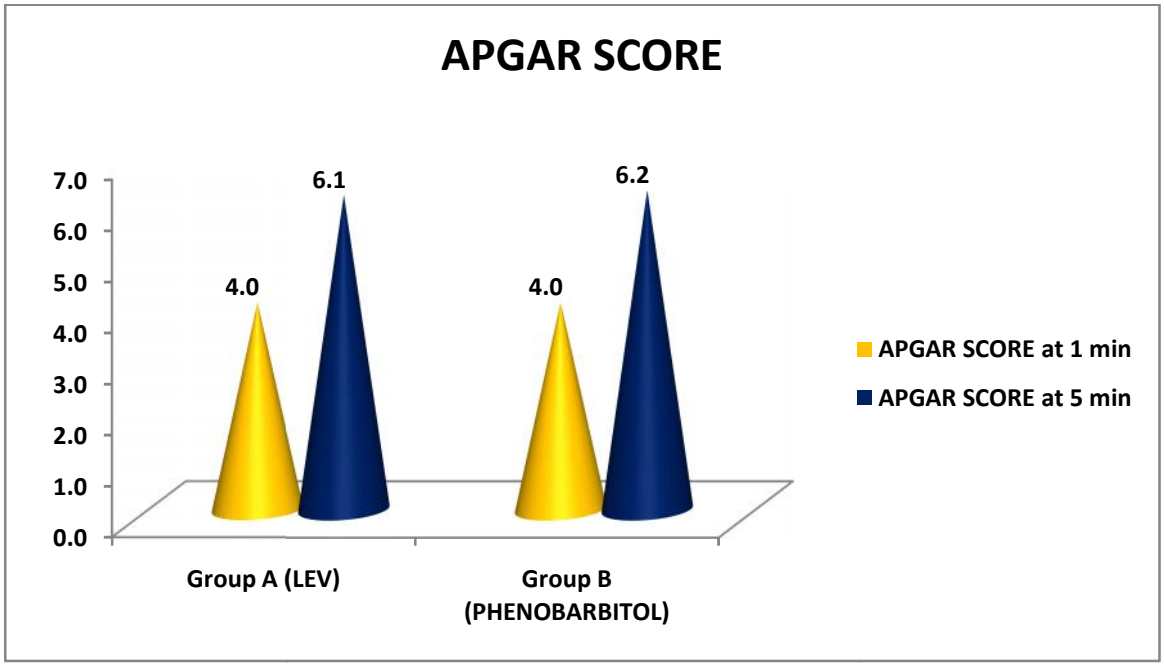


Mean APGAR score at 1st minute is 4/10 in both groups, at 5th minute it is 6.1/10 in Group-A and 6.2/10 in Group-B, which indicates severity of NS are same in both the groups, in fact even though P-value is not significant NS in Group-A are slightly severe with 6.1/10 at 5th minute.

TABLE 8: COMPARISON OF MEAN APGAR SCORE BETWEEN STUDY GROUPS

Parameters	Group A (LEV)		Group B (PHENOBARBITOL)		p value
	Mean	SD	Mean	SD	
APGAR SCORE at 1 min	4.0	1.5	4.0	1.6	0.987
APGAR SCORE at 5 min	6.1	1.5	6.2	1.5	0.827

FIGURE 5: COMPARISON OF MEAN APGAR SCORE BETWEEN STUDY GROUPS

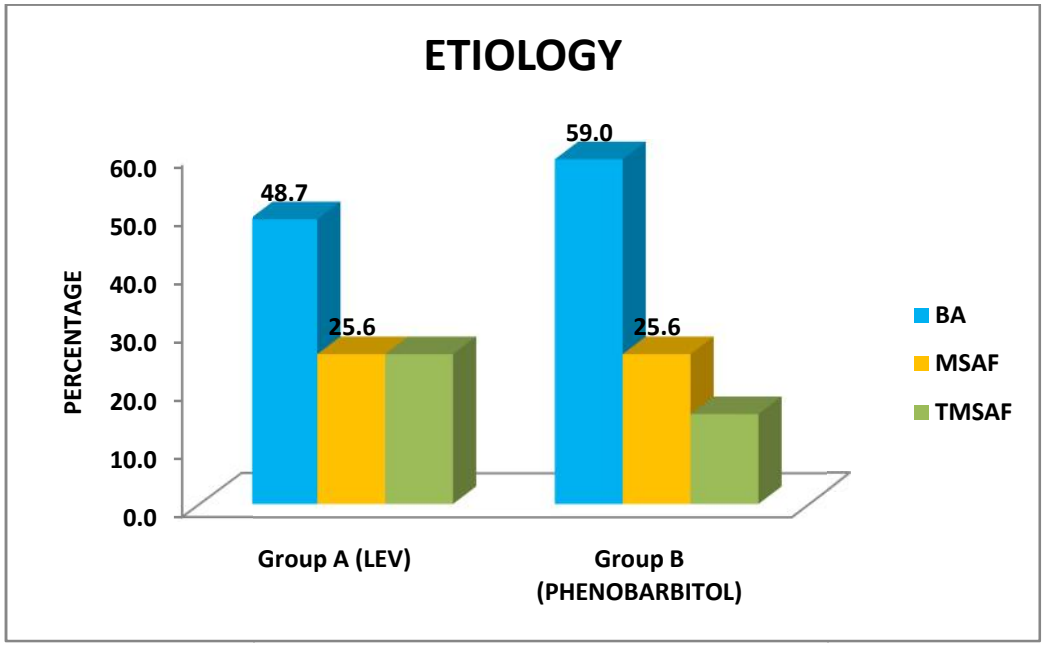


Neonates who presented with NS due to metabolic or syndromic causes were excluded. Only those neonates who had Birth Asphyxia, Meconium Stained Amniotic Fluid , Thick Meconium Stained Amniotic Fluid were included.

TABLE 9: DISTRIBUTION OF ETIOLOGY BETWEEN STUDY GROUPS

ETIOLOGY	Group A (LEV)		Group B (PHENOBARBITOL)		p value
	N	%	N	%	
BA	19	48.7	23	59.0	0.501
MSAF	10	25.6	10	25.6	
TMSAF	10	25.6	6	15.4	
Total	39	100.0	39	100.0	

FIGURE 6: DISTRIBUTION OF ETIOLOGY BETWEEN STUDY GROUPS



Most common type of seizure in Group-A is clonic type, whereas in Group-B it is subtle seizures.

TABLE 10: TYPE OF CONVULSION BETWEEN STUDY GROUPS

TYPE OF CONVULSION	Group A (LEV)		Group B (PHENOBARBITOL)		P value
	N	%	N	%	
CLONIC	18	46.2	14	35.9	0.419
FOCAL CLONIC	3	7.7	3	7.7	
G C	2	5.1	0	0.0	
MULTI FOCAL CLONIC	1	2.6	1	2.6	
SUBTLE	15	38.5	19	48.7	
TONIC	0	0.0	2	5.1	
Total	39	100.0	39	100.0	

FIGURE 7: TYPE OF CONVULSION BETWEEN STUDY GROUPS

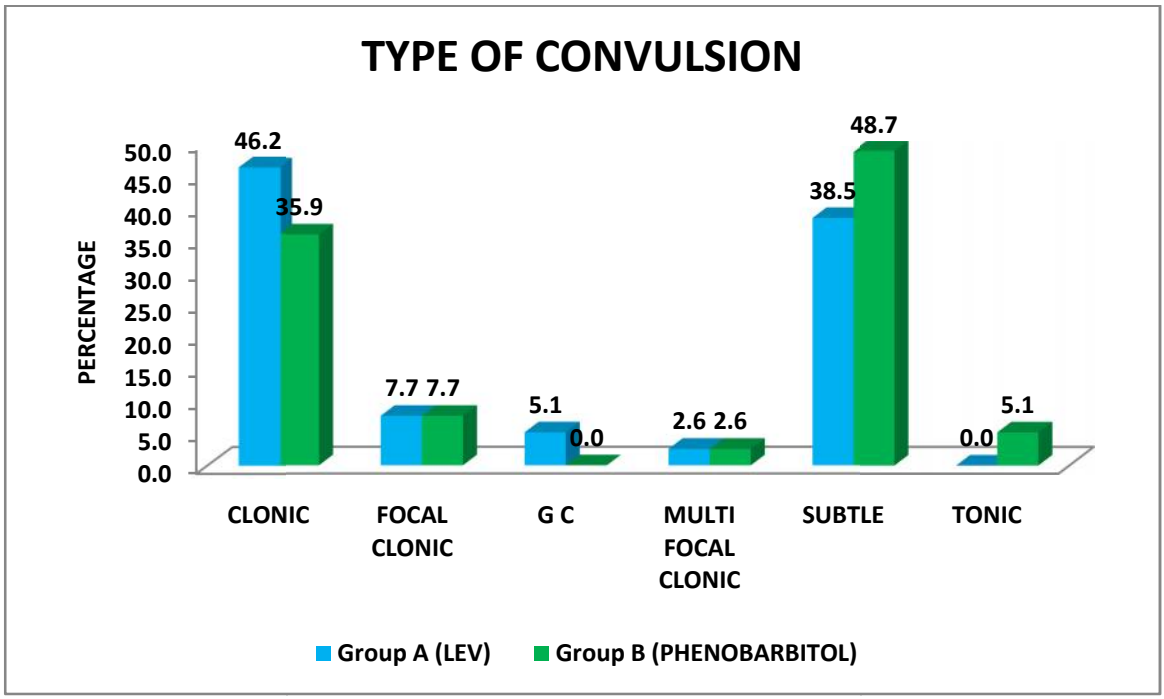


TABLE 11: COMPARISON OF MEAN RBS BETWEEN STUDY GROUPS

Parameters	Group A		Group B		p value
	Mean	SD	Mean	SD	
RBS	103.4	24.7	109.5	23.0	0.258

FIGURE 8: COMPARISON OF MEAN RBS BETWEEN STUDY GROUPS

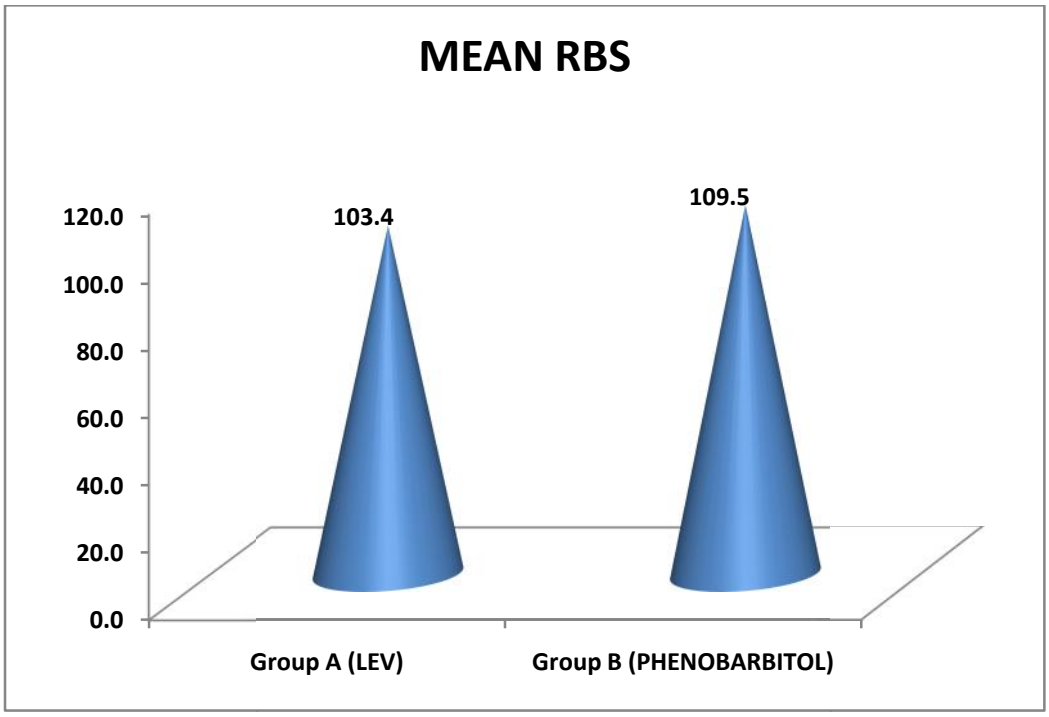


TABLE 12: COMPARISON OF MEAN SERUM CALCIUM BETWEEN STUDY GROUPS

Parameters	Group A		Group B		p value
	Mean	SD	Mean	SD	
SERUM CALCIUM	9.8	1.0	9.8	0.8	0.961

FIGURE 9: COMPARISON OF MEAN SERUM CALCIUM BETWEEN STUDY GROUPS

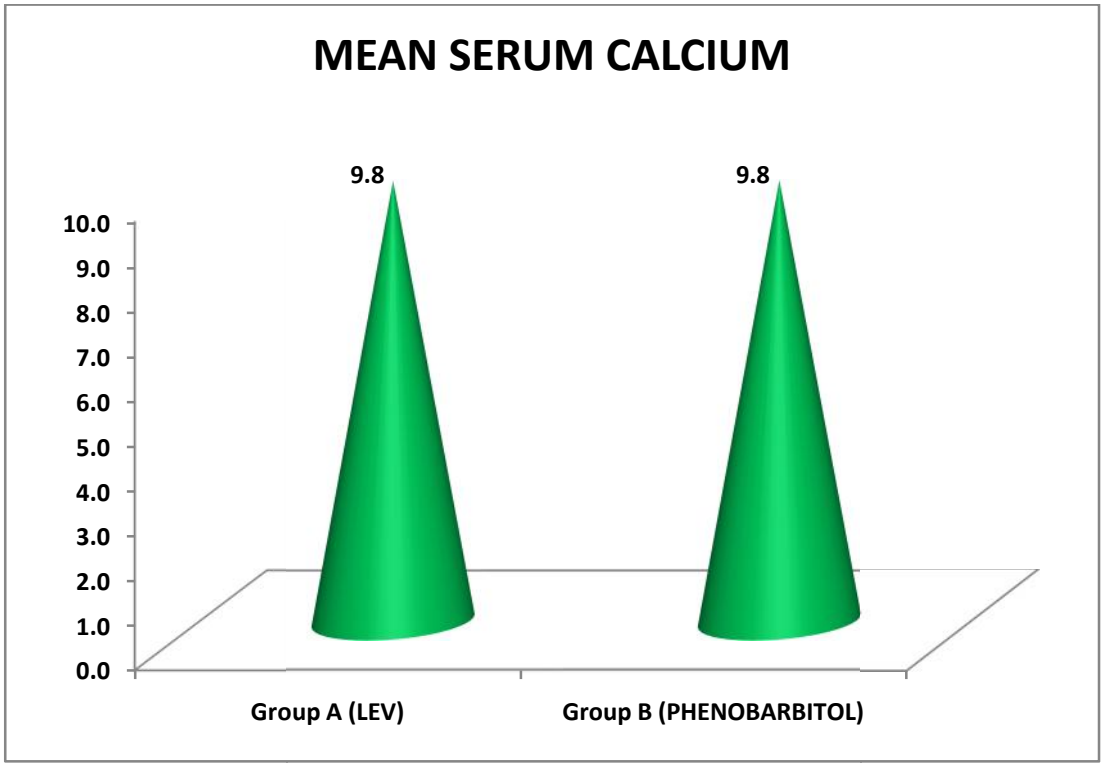
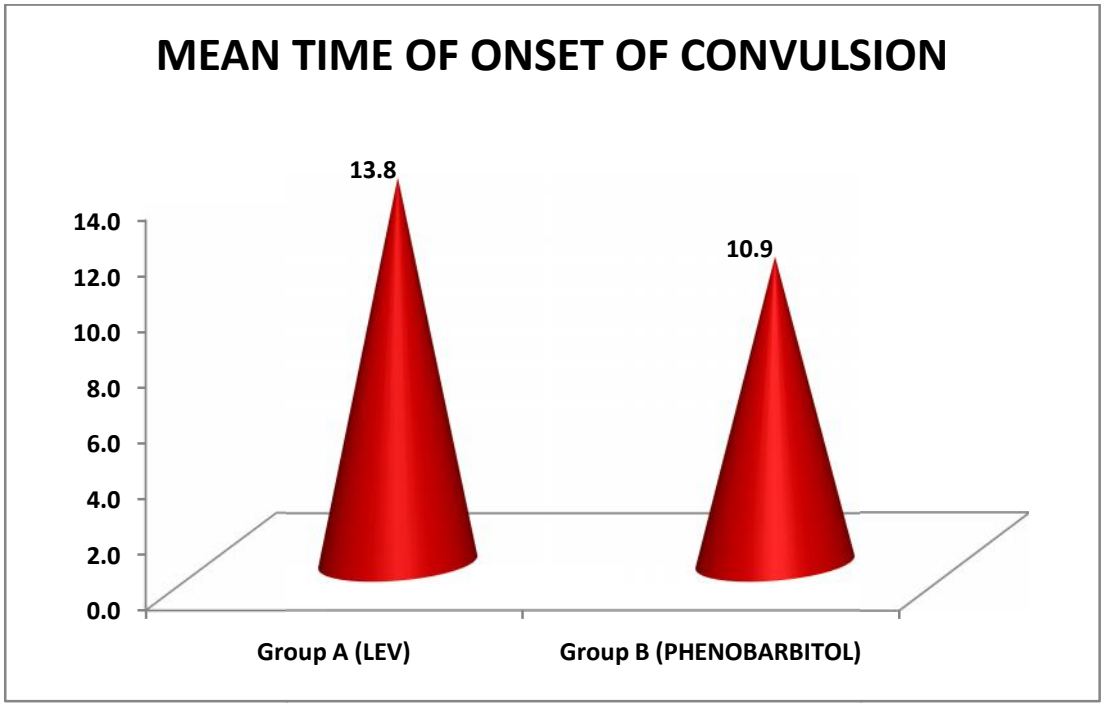


TABLE 13: COMPARISON OF MEAN TIME OF ONSET OF CONVULSION BETWEEN STUDY GROUPS

Parameters	Group A		Group B		p value
	Mean	SD	Mean	SD	
TIME OF CONVULSION	13.8	21.3	10.9	14.7	0.496

FIGURE 10: COMPARISON OF MEAN TIME OF CONVULSION BETWEEN STUDY GROUPS



Mean time taken to attain seizure control after the onset of NS in Group-A and Group-B is 10.2 hours and 16 hours respectively, which indicates there is an early seizure control in Group-A.

TABLE 14: COMPARISON OF MEAN TIME TAKEN TO ATTAIN SEIZURE CONTROL BETWEEN STUDY GROUPS

Parameters	Group A		Group B		p value
	Mean	SD	Mean	SD	
TIME TAKEN TO ATTAIN SEIZURE CONTROL	10.2	13.3	16.0	15.6	0.084

FIGURE 11: COMPARISON OF MEAN TIME TAKEN TO ATTAIN SEIZURE CONTROL BETWEEN STUDY GROUPS

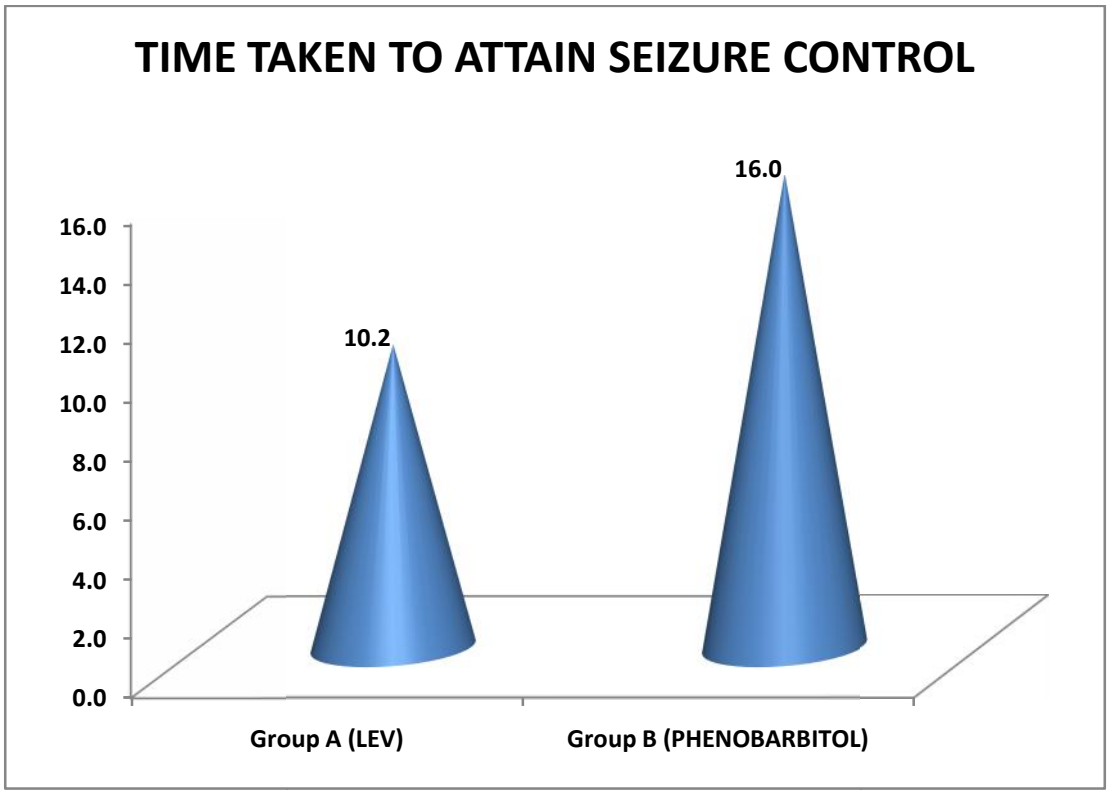


TABLE 15: RESPONSE TO LINE OF ANTIEPILEPTIC DRUGS IN GROUP A

Anti epileptic drug	Group A (LEV)	
	N	%
Levetiracetam(1st line)	16	41.0
Phenobarbital(2nd line)	14	35.9
Additional AED Fosphenytoin	7	17.9
Midazolam infusion	2	5.1

FIGURE 12: RESPONSE TO LINE OF ANTIEPILEPTIC DRUGS IN GROUP A

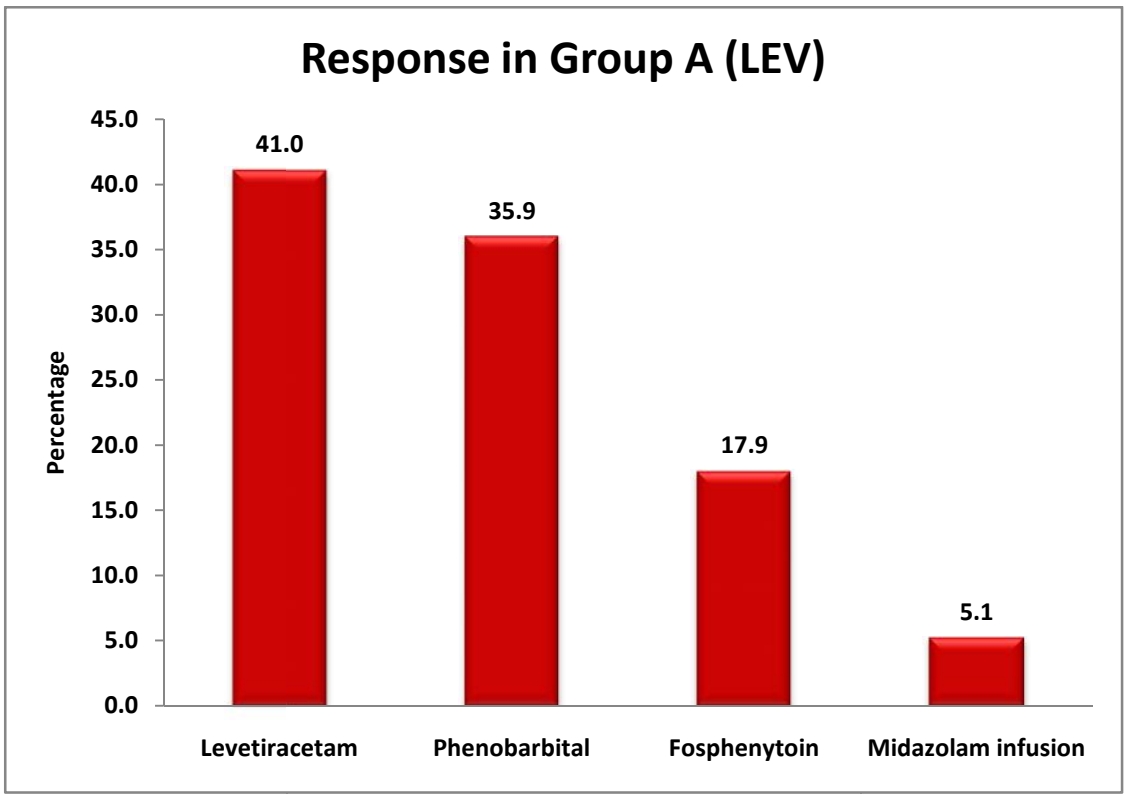


TABLE 16: RESPONSE TO LINE OF ANTIEPILEPTIC DRUGS IN GROUP B

Anti epileptic drug	Group B (PHENOBARBITOL)	
	N	%
Phenobarbital(1st line)	19	48.7
Levetiracetam(2nd line)	6	15.4
Additional AED Fosphenytoin	11	28.2
Midazolam infusion	3	7.7

FIGURE 13: RESPONSE TO LINE OF ANTIEPILEPTIC DRUGS IN GROUP B

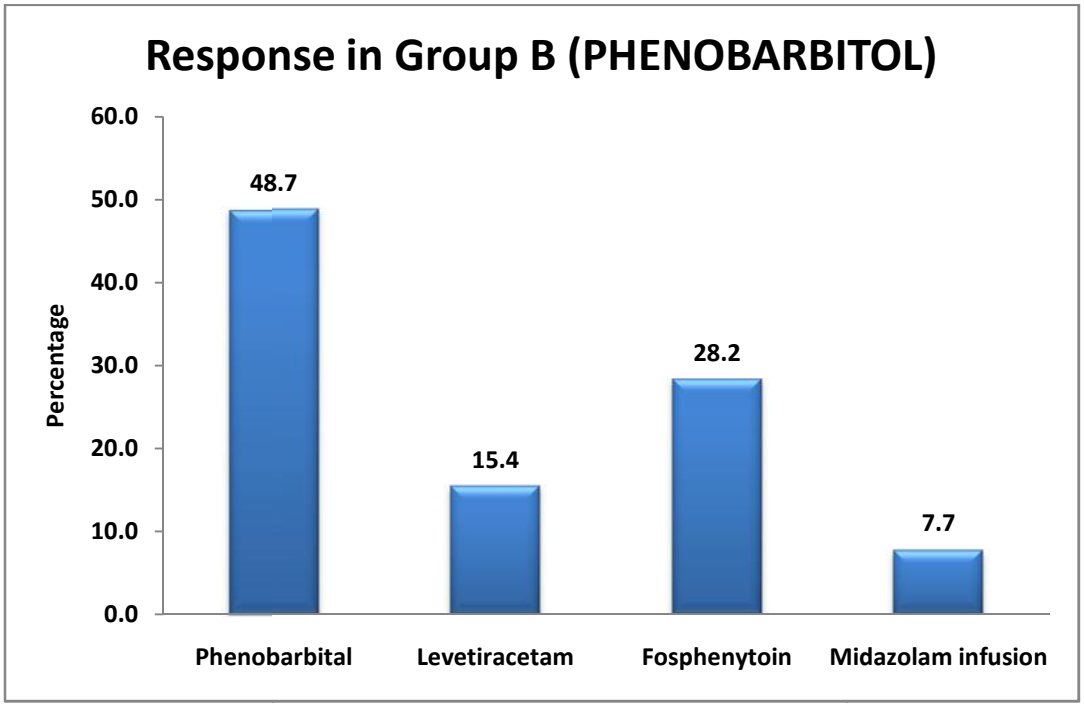
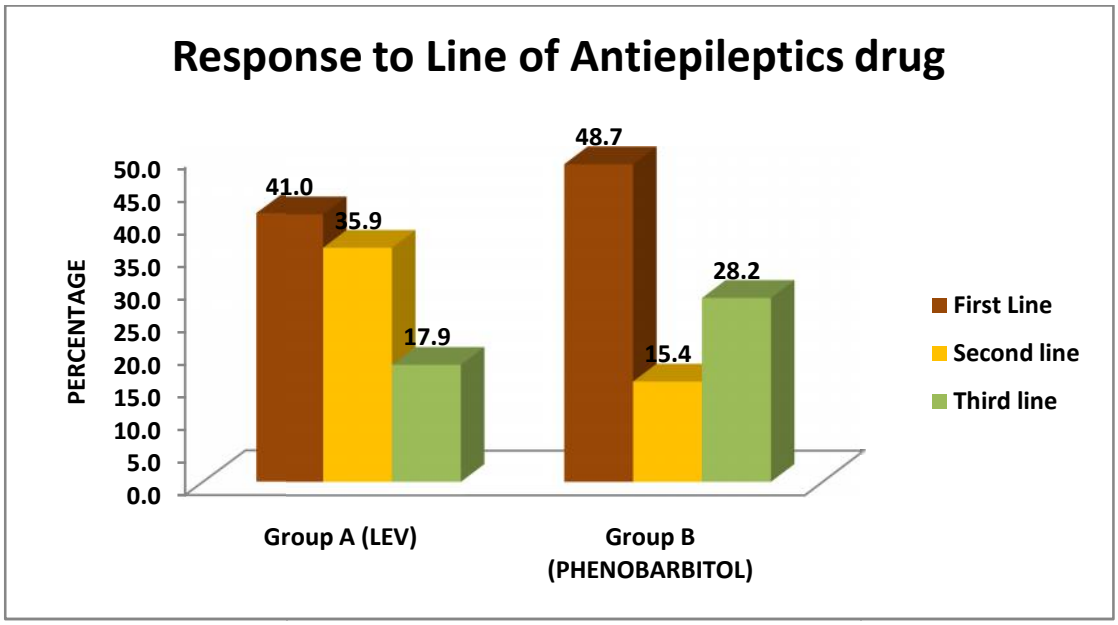


TABLE 17: RESPONSE TO LINE OF AEDs BETWEEN STUDY GROUPS

LINE of AED	Group A (LEV)		Group B (PHENOBARBITOL)		P value
	N	%	N	%	
First Line	16	41.0	19	48.7	0.495
Second line	14	35.9	6	15.4	0.038*
Additional AED (fosphenytoin)	7	17.9	11	28.2	0.282

note: * significant at 5% level of significance ($p<0.05$)

FIGURE 14: RESPONSE TO LINE OF ANTIEPILEPTIC DRUGS BETWEEN STUDY GROUPS



In Group-A following LEV therapy as first line, 23 patients(59%) required phenobarbitone as 2nd line therapy.

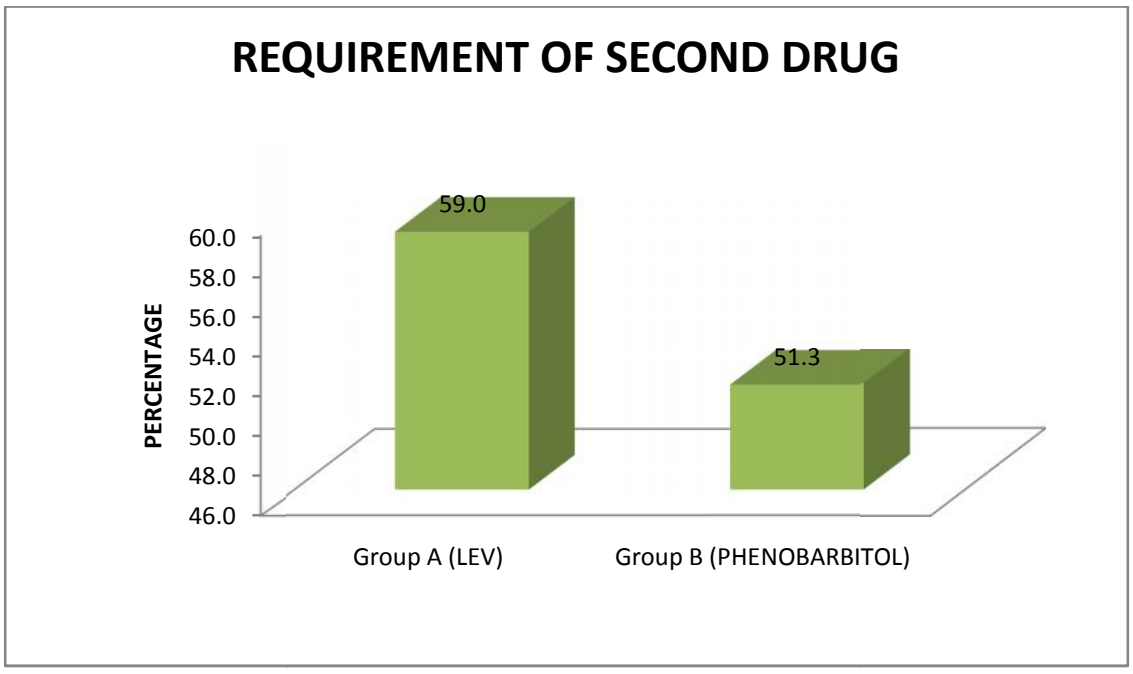
In Group-B following Phenobarbital therapy, 20 patients(51.3%) required LEV as 2nd line therapy.

In this comparison p value is 0.495 which is not significant.

TABLE 18: REQUIREMENT OF SECOND DRUG BETWEEN STUDY GROUPS

REQUIREMENT OF SECOND DRUG	Group A (LEV)		Group B (PHENOBARBITOL)		p value
	N	%	N	%	0.495
YES	23	59.0	20	51.3	

FIGURE 15: REQUIREMENT OF SECOND DRUG BETWEEN STUDY GROUPS



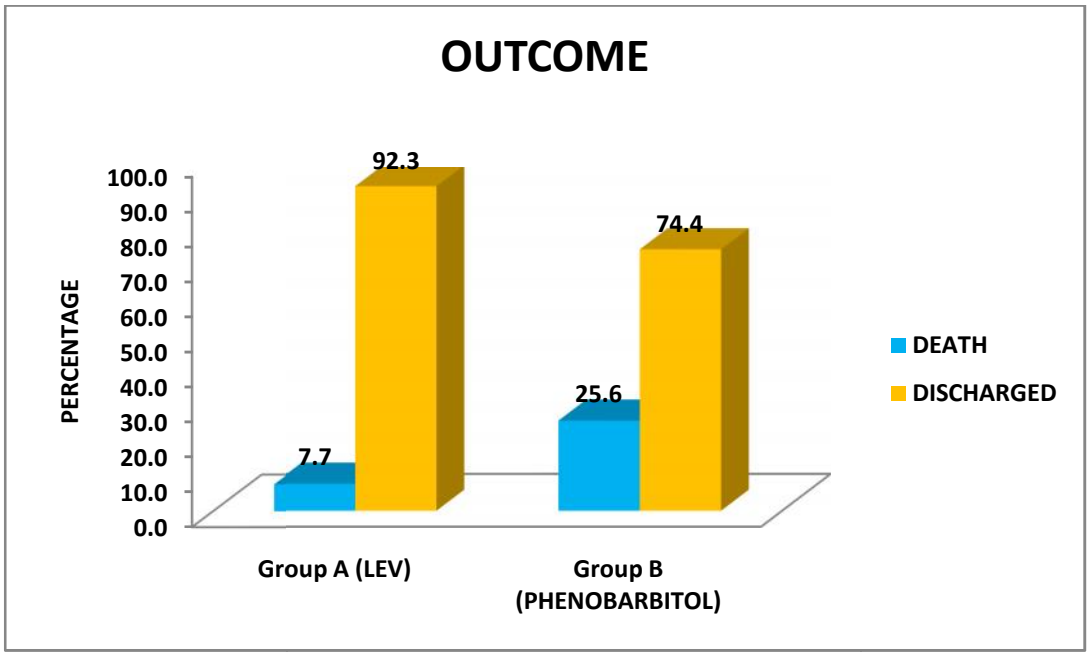
In Group-A 92.3% patients got discharged with mortality being 7.7%, whereas in Group-B only 74.4% patients got discharged with significant mortality of 25.6%, here P-value is 0.033, which is significant.

TABLE 19: DISTRIBUTION OF OUTCOME BETWEEN STUDY GROUPS

OUTCOME	Group A (LEV)		Group B (PHENOBARBITOL)		p value
	N	%	N	%	
DEATH	3	7.7	10	25.6	0.033*
DISCHARGED	36	92.3	29	74.4	
Total	39	100.0	39	100.0	

note: * significant at 5% level of significance (p<0.05)

FIGURE 16: DISTRIBUTION OF OUTCOME BETWEEN STUDY GROUPS



DISCUSSION

A total number of 78 newborns with Neonatal Seizures were enrolled in this study, with 39 newborns in each group. Sex distribution(P-value:0.624), birth weight(P-value: 0.329), GA , mean APGAR score at 1^{st} minute and 5^{th} 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 almost same in both the groups where P-value is not significant which indicates both the groups are comparable with same severity.

Results in single tabular form for the ease of comparison:

	Group A (LEV)	**Group B (PHENOBARBITOL)**	**P-value**
Sex distribution	M-28, F-11	M-26, F-13	0.624
Mean Birth weight(in kilograms)	2.7 kilograms(+/-0.4)	2.8 kilograms(+/-0.4)	0.329
Mean GA	39.3 weeks(+/-1.3)	39.3 weeks(+/-1.4)	-
Mean APGAR score at 1^{st} minute 5^{th} minute	 4(+/-1.5) 6.1(+/-1.5)	 4(+/- 1.6) 6.2(+/-1.5)	 0.987 0.827
Mean GRBS	103.4(+/-24.7)	109.5(+/-23)	0.258
Mean se.Ca^{++}	9.8(+/-1)	9.8(+/-0.8)	0.961
Mean time of onset of convulsion(in hours of life)	13.8 hours (+/-21.3)	10.9 hours (+/-14.7)	0.496
Most common type of convulsion	Clonic (46.2%)	Subtle (48.7%)	0.419

APGAR score at 5th minute is 6.1 in Group-A and 6.2 in Group-B, most common type of convulsion in Group-A is clonic type and in Group-B it is subtle seizures, which indicates severity of NS is comparably more in Group-A(LEV) than Group-B(Phenobarbital). Sixteen patients responded to LEV therapy alone(41%) ,and nineteen patients responded to Phenobarbital alone(48.7%). After failure of LEV therapy as 1st line AED in 23 patients(59%) , 14 patients (35.9%) responded to phenobarbital, and 7 patients(17.9%) responded to phenytoin, and remaining 2 patients(5.1%) required midazolam infusion. In Group-B 19 patients(48.7%) responded to Phenobarbital therapy, 6 patients(15.4%) required LEV as 2nd AED, and 11 patients required(28.2%) fosphenytoin as 3rd line AED, and 3 patients(7.7%) required midazolam infusion.

In both groups more than 50% of the patients required more than one AED, where P-value is 0.495 which is not significant, indicates that both LEV and Phenobarbital are of same efficacy . In Group-A mean time taken to attain seizure control is 10.2 hours after onset of seizures, whereas in Group-B it is 16 hours, which shows LEV has shown early seizure control than Phenobarbital with P-value 0.084, even though it is not significant. In Group-A 36 patients(92.3%) got discharged with seizure free and 3 patients(7.7%) died, and in Group-B only 29 patients(74.4%) got discharged with seizure free and 10 patients(25.6%) died.

In LEV group 3 patients died, all 3 were terms babies with severe BA secondary to thick meconium stained amniotic liquor with clonic type of seizures, all 3 were given mechanical ventilator support, in 2 patient NS controlled with LEV monotherapy, and in other NS controlled with fosphenytoin, after failure of LEV and Phenobarbital therapy. In these 3 patients NS got controlled, but cause for mortality in

2 was pulmonary hemorrhage and in other neonate severe pulmonary arterial hypertension was cause of death.

	Group A (LEV)	**Group B (PHENOBARBITOL)**	**P-value**
Response to 1st line AED	16(41%) (LEV)	19(48.7%) (Phenobarbital)	0.495
Response of 2nd AED	14(35.9%) (Phenobarbital)	6(15.4%) (LEV)	0.038*
Response of 3rd AED	7(17.9%) (fosphenytoin)	11(28.2%) (fosphenytoin)	0.282
Number of patients required MIDAZOLAM infusion	2(5.1%)	3(7.7%)	-
Mean Time taken to attain seizure control after onset of seizures	10.2 hours (+/-13.3)	16 hours (+/-15.6)	0.084
Number of patients discharged (seizure free)	36	29	0.033
Number of deaths	3	10	0.033

In Phenobarbital group 10 babies died, all were term babies, 8 were AGA and 2 were SGA babies, all 10 had BA, in 5 babies cause for BA was meconium stained amniotic liquor. Out of these 10, 5 had clonic type of seizures, 4 had subtle seizures, and 1 had tonic seizures, mechanical ventilator support was given in 8 patients, 1 patient had subgaleal hemorrhage, 1 patient had pericardial effusion. Out of these 10 patients, in 4 NS controlled with Phenobarbital alone, 1 responded to 2^{nd} line AED LEV, 2 patients responded to 3^{rd} line AED fosphenytoin, for 3 patients midazolam infusion was given.

Deaths in Phenobarbital group are 10 whereas in LEV group it is only 3, out of 39 in each group , even though LEV group were more asphyxiated and had more severe form of seizures(clonic in LEV group vs subtle seizures in Phenobarbital group). P-value of 0.033 in comparision of death in both groups is significant.

CONCLUSION

1. LEV as 1st line anti epileptic drug in neonatal seizures will lead to better seizure control, as only drug used and also when 2nd drug was added.
2. LEV use will lead to lower mortality and morbidity in neonates with seizures.
3. LEV use has early seizure control. Further larger studies can confirm our findings,

LIMITATIONS OF STUDY

1. Number of sample though statistically significant, may not reflect true efficacy of AED in neonatal seizures. Hence larger study is preferable.
2. Only clinical diagnosis of NS was done. No EEG/EEG video recording confirmation was done.
3. Long term follow up for developmental assessment which is more desirable was not done.

SUMMARY

A prospective randomized comparative study of Levetiracetam versus Phenobarbital as 1st line therapy for neonatal seizures was done at Shri B.M.Patil Medical College and Research Centre, Vijayapur. 78 babies satisfied the inclusion criteria and were enrolled in the study, with 39 babies in each group respectively, where Levetiracetam and Phenobarbital was used as 1st line AED in each group.

Both groups were comparable and has equal severity of NS as all parameters like 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 almost same in both the groups where P-value is not significant.

Though neonates in LEV group were more asphyxiated than Phenobarbital group, both LEV(41%) and Phenobarbital(48.7%) were found equally effective where P value 0.495 is not significant. LEV group has early seizure control than Phenobarbital group(10.2 hours vs 16 hours), but P value 0.084 is not significant. Mortality is significantly more in Phenobarbital group(25.6%) than LEV group(7.7%) , P value 0.033 is significant(Note again: LEV group were more severely asphyxiated than the Phenobarbital group).

In our study, LEV and Phenobarbital are equally effective, LEV use as 1st line AED has less mortality, better and early seizure control. Further larger studies are required to confirm our findings.

BIBLIOGRAPHY

1. Stafstrom CE. Neonatal seizures. Pediatr Rev 1995;16:248–255.
2. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 1999;341:485–489.
3. Manthey D, Asimiadou S, Stefovska V, Kaindl AM, Fassbender J, Ikonomidou C, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp Neurol 2005;193:497–503.
4. Bittigau P, Sifringer M, Genz K, Reith E, Pospischil D, Govindarajulu S, et al. Antiepileptic drugs and apoptosis in the developing brain. *Ann N Y Acad Sci.* 2003;993:103-114.
5. Hmaimess G, Kadhim H, Nassogne MC, et al. Levetiracetam in a neonate with malignant migrating partial seizures. Pediatr Neurol 2006;34:55–59.
6. Silverstein FS, Jensen FE. Neonatal seizures. Ann Neurol. 2007;62:112-120.
7. van Rooij LG, van den Broek MP, Rademaker CM, de Vries LS. Clinical management of seizures in newborns: diagnosis and treatment. Paediatr Drugs 2013;15:9–18.
8. Scher MS, Aso K, Beggarly ME. et al. Electrographic seizures in preterm and full term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. Pediatrics. 1993;91: 128-134.
9. Jensen FE. Neonatal seizure: an update on mechanisms and management. Clin Perinatol 2009;36:881–900.

10. Tekgul H, Gauvreau K, Soul J, Murphy L, Robertson R, Stewart J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 2006;117:1270–1280.
11. Volpe JJ, editor. Neurology of the newborn. 5th edn. Philadelphia: Saunders Elsevier, 2008; p.203-244.
12. Mizrahi EM, Kellaway P, eds. Diagnosis and management of neonatal seizures. Lippincott-Raven, 1998; p. 15-35.
13. National Neonatal Perinatal Database. Report for the year 2002-2003. http://www.newbornwhocc.org/pdf/nnpd_report_2002-03.
14. Hill A. Neonatal seizures. Pediatr Rev 2000;21:117–121.
15. Rennie JM. Neonatal seizures. Eur J Pediatr 1997;156: 83-87.
16. Laroia N. Controversies in diagnosis and management of neonatal seizures. Indian Pediatr 2000;37:367-372
17. Iype M, Prasad M, Nair PM, Geetha S, Kailas L. the newborn with seizures – A follow up study. Indian Pediatr 2008;45: 749-752.
18. Kumar A , Gupta A, Talukdar B. Clinic-etiological and EEG profile of neonatal seizures. Indian J Pediatr 2007;74:33-37.
19. Painter MJ, Minnigh B, Gaus L. et al. Neonatal Phenobarbital and phenytoin binding profiles. J Clin Pharmacol. 1994; 34: 312-317.
20. Mirkin BL. Perinatal pharmacology: placental transfer, fetal localization, and neonatal disposition of drugs. Anaesthesiology. 1975; 43: 156-170.
21. Assael BM. Pharmacokinetics and drug distribution during postnatal development. Pharmacol Ther. 1982; 18: 159-197.

22. Skinner AV. Neonatal pharmacology. Anesthesia and Intensive Care Medicine. 2011;12: 79-84.
23. Loughnan PM, Greenwald A, Purton WW. et al. Pharmacokinetic observations of phenytoin disposition in newborn and young infant. Arch Dis Child. 1977;52: 302-309.
24. Takashima S, Chan F, Becker LE, Armstrong DL. Morphology of the developing cortex of the human infant: a quantitative and qualitative Golgi study. J Neuropathol Exp Neurol. 1980;39: 487-501.
25. Abend NS, Gutierrez-Colina AM, Monk HM, Dlugos DJ, Clancy RR. Levetiracetam for treatment of neonatal seizures. J Child Neurol 2011;26:465–470.
26. Khan O, Chang E, Cipriani C, Wright C, Crisp E, Kirmani B. Use of intravenous levetiracetam for management of acute seizures in neonates. Pediatr Neurol 2011;44:265–269.
27. Ramantani G, Ikonomidou C, Walter B, Rating D, Dinger J. Levetiracetam: safety and efficacy in neonatal seizures. Eur J Paediatr Neurol 2011;15:1–7.
28. Maitre NL, Smolinsky C, Slaughter JC. et al. Adverse neurodevelopmental outcomes after exposure to Phenobarbital and Levetiracetam for the treatment of neonatal seizures. J Perinatol. 2013; 33: 841-846.
29. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 1999;341:485–489.
30. Hmaimess G, Kadhim H, Nassogne MC, et al. Levetiracetam in a neonate with malignant migrating partial seizures. Pediatr Neurol 2006;34:55–59.

31. Shoemaker MT, Rotenberg JS. Levetiracetam for the treatment of neonatal seizures. J Child Neurol 2007;22:95–98
32. Yau MLY, Fung ELW, Ng PC. Response of levetiracetam in neonatal seizures. World J Clin Pediatr 2015 August 8; 4: 45-49.
33. Raffaele F, Giovanna V, Laura Mauceri, Catia R, Piero p, Nazgol Motamed G, Nassim M, Riccardo L, Giovanni C. Levetiracetam in Neonatal Seizures as First-line Treatment: A Prospective Study. J Pediatr Neurosci. 2017 Jan-Mar; 12: 24–28.
34. Shama P, Abhishek S, Amit U, Neha S, Rashmi C. A randomized controlled trial on comparison of phenobarbitone and levetiracetam for the treatment of neonatal seizures: pilot study. Int J Res Med Sci. 2016 Jun;4:2073-2078.
35. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in Neonatal Seizures: A Review. J Pediatr Pharmacol Ther 2015 ; 20:76-89.
36. Kaminski RM, Matagne A, Leclercq K, Gillard M, Michel P, Kenda B et al. SV2A protein is a broad-spectrum anticonvulsant target: functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. Neuropharmacology.2008;54:715-720.
37. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet.2004;43:707–724.
38. Patsalos PN. Levetiracetam: pharmacology and therapeutics in the treatment of epilepsy and other neurological conditions. Rev Contemp Pharmacother. 2004;13:1–168.

39. Pellock JM, Glauser TA, Bebin EM, Fountain NB, Ritter FJ, Coupez RM, et al. Pharmacokinetic study of levetiracetam in children. Epilepsia. 2001;42:1574-1579.
40. Manthey D, Asimiadou S, Stefovska V, Kaindl AM, Fassbender J, Ikonomidou C, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp Neurol 2005;193:497–503.
41. Kilicdag H, Daglioglu K, Erdogan S, Guzel A, Sencar L, Polat S, et al. The effect of levetiracetam on neuronal apoptosis in neonatal rat model of hypoxic ischemic brain injury. Early Hum Dev.2013;89:355-360.
42. Pina-Garza JE, Nordli DR Jr, Rating D, Yang H, Schiemann-Delgado J, Duncan B. Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures. Epilepsia. 2009;50:1141-1149.

ANNEXURES

ETHICAL CLERANCE CERTIFICATE

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

No/58/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 *at* 03 pm *scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.*

Title "Randomized open lebel comparative study of levetiracetam versus phenobarbital as first line therapy for neonatal seizures"

Name of P.G. Student : Dr Goharsha Gaduputi
Dept of pediatrics

Name of Guide/Co-investigator : Dr R. H. Gobbur
professor

DR.TEJASWINI VALLABHA
CHAIRMAN

CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

CONSENT FORM

BLDEA's Shri B.M.PATIL Medical College, Hospital & Research Centre,

Bijapur-586103.

TITLE OF THE PROJECT	**:**	**"RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF LEVETIRACETAM VERSUS PHENOBARBITAL AS FIRST LINE THERAPY FOR NEONATAL SEIZURES".**
GUIDE	**:**	**Dr. R. H. GOBBUR, MD** **PROFESSOR,** **DEPARTMENT OF PEDIATRICS**
PG STUDENT	**:**	**DR. GOHARSHA GADUPUTI**

PURPOSE OF RESEARCH:

I have been informed that the present study will help in assessing efficacy of Levetiracetam versus Phenobarbital as first line of drug in neonatal seizures.

PROCEDURE:

I understand that after having obtained a detailed clinical history, thorough clinical examination and relevant investigations, a final work up of the procedure and its outcome is planned.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomforts during the examination or during my treatment. This is mainly the result of my condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in the study will have no direct benefit to me other than the potential benefit of the treatment.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time; Dr. Goharsha Gaduputi at the department of pediatrics is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Goharsha Gaduputi may terminate my participation in the study after he has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of injury to my baby resulting directly from baby's participation in this study, if such injury were reported promptly, the appropriate treatment would be available to the baby. But, no further compensation would be provided by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____ _____

Dr. Goharsha Gaduputi Date

(Investigator)

PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that Dr. Goharsha Gaduputi is doing a study on **RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF LEVETIRACETAM VERSUS PHENOBARBITAL AS FIRST LINE THERAPY FOR NEONATAL SEIZURES.** Dr. Goharsha Gaduputi has explained to us the purpose of research and the study procedure. We are willing to allow our baby to get treated with LEVETIRACETAM or PHENOBARBITAL for seizures.

We have been explained about the study, benefits and possible discomforts in detail in our native language and we understand the same. We are aware that baby will get best treatment ,and no compensation like financial benefits will be given if our baby's condition deteriorates and any untoward happens, and we will not sue anyone regarding this. Therefore we agree to give our full consent for baby's participate as a subject in this research project.

_____ _____

(Parents / Guardian) Date

_____ _____

(Witness to signature) Date

PROFORMA

SCHEME OF CASE TAKING:

Name: Group :

IP No: Case no:

Age: DOB:

Sex:

Birth weight: Head Circumference:

Mode of delivery: Length:

Apgar score: Liquor:

Onset of seizure & Dose of AED:

	Day of life(DOL) 1	**DOL 2**	**DOL 3**
Dose of LEV			
Dose of Phenobarbital			

Type of Seizure:

GRBS: Se.Calcium:

IEM Screening(if any):

Cessation of seizures (hours of life) :

AED used as first line:

AED used as second line(if) :

AED used as third line (if any) :

Antenatal factors:

1. Parity:
2. Age of mother:
3. On any medication:

4. Medical history: Hypertension/ PIH/Diabetes

Feeds starting time (in hours since birth):

Urine passed at (hours) :

Meconium passed at (hours) :

Family history of seizures & any other diseases:

Anomalie screening:

Assessment of gestational age:

SYSTEMIC EXAMINATION

- Cardiovascular System

- Respiratory System

- Gastro-intestinal system

- Central Nervous System

DIAGNOSIS:

OUTCOME: Discharge / Death

KEY TO MASTER CHART

M	-	Male
F	-	Female
G A	-	Gestational Age (in weeks)
RBS	-	Random Blood Sugar
Se.Ca	-	Serum Calcium
D O D	-	Date Of Delivery
BA	-	Birth Asphyxia
MSAF	-	Meconium Stained Amniotic Fluid
TMSAF	-	Thick Meconium Stained Amniotic Fluid
L	-	Levetiracetam
P	-	Phenobarbital
F	-	Fosphenytoin
M	-	Midazolam Infusion
HOL	-	Hours Of Life

MASTER CHARTS

GROUP-A

sl no	IP. No	NAME	SEX	G A in weeks	APGAR SCORE	APGAR SCORE	WEIGHT	TIME OF CONVULSION	TYPE OF CONVULSION	DRUGS USED	CONTROL OF SEIZURES IN HOURS	Time taken to attain seizure control	REQUIREMENT OF SECOND DRUG	OUTCOME
					1 MINUTE	5 MINUTES	IN KGS							
1	3868	B/O MALKAWWA	F	38	3	5	2.36	11 HOURS OF LIFE	G C	L P F	27 HOL	16 HOURS	YES	DISCHARGED
2	4217	B/O LAKSHMI	M	38	3	5	1.96	2 HOURS OF LIFE	G C	L P	8 HOL	6 HOURS	YES	DISCHARGED
3	6602	B/O BHABYASHREE	F	40	3	5	2.4	23 HOURS OF LIFE	SUBTLE	L P	41 HOL	18 HOURS	YES	DISCHARGED
4	7252	B/O JAYASHREE	F	36	3	5	2.51	2 HOURS OF LIFE	CLONIC	L P F	33 HOL	31 HOURS	YES	DISCHARGED
5	7383	B/O NAGAMMA	M	37	5	7	2.16	32 HOURS OF LIFE	FOCAL CLONIC	L	33 HOL	1 HOUR	NO	DISCHARGED
6	8162	B/O PAVITHRA	F	39	4	7	2.85	1 HOURS OF LIFE	SUBTLE	L	1.5 HOL	0.5 HOUR	NO	DISCHARGED
7	20718	B/O LAKSHMI	M	39	outborn	outborn	2.41	3 HOURS OF LIFE	SUBTLE	L P	10 HOL	7 HOURS	YES	DISCHARGED
8	20819	B/O VIJAYALAKSHMI	M	38	outborn	outborn	2.29	4 HOURS OF LIFE	CLONIC	L P F	20 HOL	16 HOURS	YES	DISCHARGED
9	21225	B/O SOMABAI	M	41	outborn	outborn	2.94	4 HOURS OF LIFE	SUBTLE	L	5 HOL	1 HOURS	NO	DISCHARGED
10	21332	B/O RESHMA	M	38	outborn	outborn	2.8	90 HOURS OF LIFE	CLONIC	L P	96 HOL	6 HOURS	YES	DISCHARGED
11	21596	B/O AKKAMAHADEVI	M	40	7	9	2.65	96 HOURS OF LIFE	SUBTLE	L	104 HOL	8 HOURS	NO	DISCHARGED
12	22650	B/O ASHWINI	F	39	3	5	2.84	8 HOURS OF LIFE	SUBTLE	L P	19 HOL	11 HOURS	YES	DISCHARGED
13	23458	B/O BHAGYASHRI	F	37	4	6	2.4	30 MINUTES OF LIFE	SUBTLE	L P F	4 HOL	3.5 HOURS	YES	DISCHARGED
14	24015	B/O FATIMA	M	39	3	5	2.7	1 HOURS OF LIFE	SUBTLE	L P F M	8 HOL	7 HOURS	YES	DISCHARGED
15	25655	B/O MUSKHAN	M	39	outborn	outborn	2.8	2 HOURS OF LIFE	CLONIC	L	8 HOL	6 HOURS	NO	DEATH
16	25863	B/O BIBIFATIMA	M	40	outborn	outborn	2.9	30 HOURS OF LIFE	CLONIC	L P	34 HOL	4 HOURS	YES	DISCHARGED
17	28630	B/O PUSHPA	M	40	3	4	3.3	2 HOURS OF LIFE	SUBTLE	L P	6 HOL	4 HOURS	YES	DISCHARGED
18	27564	B/O POOJA	M	40	3	6	3.6	2 HOURS OF LIFE	SUBTLE	L P	8 HOL	6 HOURS	YES	DISCHARGED
19	28178	B/O KAJAL	M	40	outborn	outborn	2.4	3 HOURS OF LIFE	CLONIC	L P F	17 HOL	14 HOURS	YES	DISCHARGED
20	28700	B/O MEENAKSHI	M	42	outborn	outborn	2.41	4.5 HOURS OF LIFE	CLONIC	L	5 HOL	0.5 HOUR	NO	DISCHARGED

sl no	IP. No	NAME	SEX	G A in weeks	APGAR SCORE	APGAR SCORE	WEIGHT	TIME OF CONVULSION	TYPE OF CONVULSION	DRUGS USED	CONTROL OF SEIZURES IN HOURS	Time taken to attain seizure control	REQUIREMENT OF SECOND DRUG	OUTCOME
					1 MINUTE	5 MINUTES	IN KGS							
21	28982	B/O SAVITRI	M	38	outborn	outborn	2.48	1 HOURS OF LIFE	SUBTLE	L P F	14 HOL	13 HOURS	YES	DISCHARGED
22	33714	B/O MASABEE	M	39	outborn	outborn	2	4 HOURS OF LIFE	FOCAL CLONIC	L P	52 HOL	48 HOURS	YES	DISCHARGED
23	35238	B/O SUVARNA	F	42	outborn	outborn	2.93	4 HOURS OF LIFE	CLONIC	L P F M	72 HOL	68 HOURS	YES	DEATH
24	35830	B/O KEERTHI	M	38	outborn	outborn	2.36	23 HOURS OF LIFE	MULTI FOCAL CLONIC	L	24 HOL	1 HOUR	NO	DISCHARGED
25	38422	B/O GANGAWWA	M	40	outborn	outborn	2.53	2 HOURS OF LIFE	CLONIC	L P F	22 HOL	20 HOURS	YES	DISCHARGED
26	721	B/O RAJASHREE	M	41	3	6	2.8	3 HOURS OF LIFE	CLONIC	L	4 HOL	1 HOUR	NO	DISCHARGED
27	959	B/O ANITHA	F	39	5	7	2.74	21 HOURS OF LIFE	SUBTLE	L P	26 HOL	5 HOURS	YES	DISCHARGED
28	1354	B/O SHREEDEVI	M	40	outborn	outborn	2.88	3 HOURS OF LIFE	CLONIC	L P	7 HOL	4 HOURS	YES	DISCHARGED
29	2837	B/O PARVATHI	M	40	outborn	outborn	2.91	2 HOURS OF LIFE	CLONIC	L P	6 HOL	4 HOURS	YES	DISCHARGED
30	7149	B/O MANJULA	M	40	7	9	2.78	20 HOURS OF LIFE	FOCAL CLONIC	L	26 HOL	6 HOURS	NO	DISCHARGED
31	7342	B/O SAVITHA	M	38	3	5	3.5	30 MINUTES OF LIFE	CLONIC	L	1 HOL	0.5 HOUR	NO	DISCHARGED
32	8442	B/O PREETHI	M	38	2	5	2.01	3.5 HOURS OF LIFE	SUBTLE	L	9 HOL	5.5 HOURS	NO	DISCHARGED
33	9602	B/O SAVITHA	M	38	7	9	2.8	4 HOURS OF LIFE	SUBTLE	L P	15 HOL	11 HOURS	YES	DISCHARGED
34	12117	B/O SUNANDA	F	41	5	7	3.37	22 HOURS OF LIFE	CLONIC	L	35 HOL	13 HOURS	NO	DISCHARGED
35	12692	B/O PARVATHI	F	40	5	7	2.56	5 HOURS OF LIFE	SUBTLE	L	6 HOL	1 HOUR	NO	DISCHARGED
36	15492	B/O LAKSHMI	M	40	4	5	2.58	10 HOURS OF LIFE	CLONIC	L	22 HOL	12 HOURS	NO	DISCHARGED
37	16819	B/O RENUKA	M	40	4	6	2.55	26 HOURS OF LIFE	CLONIC	L	27 HOL	1 HOUR	NO	DEATH
38	23108	B/O MEENAZ	F	40	outborn	outborn	3.32	1.5 HOURS OF LIFE	CLONIC	L	5.5 HOL	4 HOURS	NO	DISCHARGED
39	23937	B/O VIDYA	M	40	outborn	outborn	2.63	2 HOURS OF LIFE	CLONIC	L P	19 HOL	17 HOURS	YES	DISCHARGED

GROUP B																		
sl no	IP	NAME	SEX	G A in weeks	APGAR SCORE	APGAR SCORE	WEIGHT	D O D	RBS	Se.Ca	ETIOLOGY	TIME OF CONVULSION	TYPE OF CONVULSION	DRUGS USED	CONTROL OF SEIZURES IN HOURS	Time taken to attain seizure control	REQUIREMENT OF SECOND DRUG	OUTCOME
					1 MINUTE	5 MINUTES	IN KGS											
1	3633	B/O SHAILABAI	M	41	3	5	3.2	2/2/2016	83 mg/dl	8.8 mg/dl	TMSAF	2 HOURS OF LIFE	CLONIC	P L F M	21 HOL	19 HOURS	YES	DEATH
2	4334	B/O BHAGYASHREE	M	39	7	9	2.8	2/3/2016	119 mg/dl	10 mg/dl	BA	3 HOURS OF LIFE	FOCAL CLONIC	P	15 HOL	12 HOURS	NO	DISCHARGED
3	7222	B/O SUMA	M	41	5	8	3.03	3/2/2016	104 mg/dl	11 mg/dl	MSAF	3 HOURS OF LIFE	FOCAL CLONIC	P L F	50 HOL	47 HOURS	YES	DISCHARGED
4	7378	B/O SUSHEELA	M	38	7	9	2.14	3/3/2016	122 mg/dl	10 mg/dl	BA	10TH DAY OF LIFE	SUBTLE	P L	PLUS 3 HOURS	3 HOURS	YES	DEATH
5	8658	B/O SHABANA	M	39	3	5	2.94	3/15/2016	136 mg/dl	9.6 mg/dl	MSAF	1 HOURS OF LIFE	SUBTLE	P L F	29 HOL	28 HOURS	YES	DEATH
6	20368	B/O BISMILLAH	M	40	outborn	outborn	3.1	6/18/2016	152 mg/dl	10.5 mg/dl	MSAF	52 HOURS OF LIFE	SUBTLE	P	60 HOL	8 HOURS	NO	DISCHARGED
7	21198	B/O SHABANA	M	39	outborn	outborn	2.9	6/27/2016	85 mg/dl	10.7 mg/dl	TMSAF	3 HOURS OF LIFE	CLONIC	P L F	36 HOL	33 HOURS	YES	DEATH
8	21601	B/O PAVITHRA	M	38	outborn	outborn	2.88	6/30/2016	125 mg/dl	11 mg/dl	BA	4 HOURS OF LIFE	SUBTLE	P	13 HOL	9 HOURS	NO	DISCHARGED
9	21917	B/O BHUVANESHWARI	F	39	5	7	2.87	7/3/2016	98 mg/dl	9.2 mg/dl	TMSAF	20 HOURS OF LIFE	SUBTLE	P	26 HOL	6 HOURS	NO	DISCHARGED
10	22044	B/O SAVITRI	M	39	4	5	2.4	7/5/2016	108 mg/dl	10.2 mg/dl	BA	11 HOURS OF LIFE	SUBTLE	P	12 HOL	1 HOUR	NO	DEATH
11	24793	B/O LAKSHMI	F	40	outborn	outborn	2.5	7/5/2016	84 mg/dl	9.6 mg/dl	BA	24TH DAY OF LIFE	SUBTLE	P L F	PLUS 36 HOURS	36 HOURS	YES	DISCHARGED
12	22429	B/O SHREEDEVI	M	40	6	7	3.5	7/8/2016	86 mg/dl	9.6 mg/dl	BA	3 HOURS OF LIFE	CLONIC	P L F	12 HOL	9 HOURS	YES	DISCHARGED
13	23448	B/O DEVAMMA	F	39	3	7	3.2	7/16/2016	96 mg/dl	10 mg/dl	TMSAF	2 HOURS OF LIFE	SUBTLE	P L F	12 HOL	10 HOURS	YES	DISCHARGED
14	23844	B/O SHIRIN	M	39	5	8	2.54	7/20/2016	108 mg/dl	9.8 mg/dl	BA	26 HOURS OF LIFE	CLONIC	P	38 HOL	12 HOURS	NO	DISCHARGED
15	26711	B/O KAVERI	F	40	outborn	outborn	2.7	8/12/2016	102 mg/dl	8.3 mg/dl	MSAF	8 HOURS OF LIFE	CLONIC	P	20 HOL	12 HOURS	NO	DEATH
16	27623	B/O SAVITHA	F	41	outborn	outborn	2.9	8/20/2016	156 mg/dl	10 mg/dl	BA	4 HOURS OF LIFE	CLONIC	P L F M	72 HOL	68 HOURS	YES	DEATH
17	28249	B/O RENUKA	M	41	outborn	outborn	3.13	8/24/2016	106 mg/dl	9.2 mg/dl	BA	2 HOURS OF LIFE	SUBTLE	P L	16 HOL	14 HOURS	YES	DISCHARGED
18	28656	B/O NEELAMMA	M	40	outborn	outborn	2.98	8/28/2016	87 mg/dl	10 mg/dl	BA	3 HOURS OF LIFE	SUBTLE	P L F	13 HOL	10 HOURS	YES	DISCHARGED
19	28679	B/O SAVITHA	F	40	outborn	outborn	2.69	8/28/2016	109 mg/dl	9.5 mg/dl	BA	2 HOURS OF LIFE	CLONIC	P L	11 HOL	9 HOURS	YES	DISCHARGED
20	36196	B/O BAGAMMA	M	38	outborn	outborn	1.8	10/29/2016	98 mg/dl	8.3 mg/dl	BA	5TH DAY OF LIFE	SUBTLE	P	PLUS 1 HOUR	1 HOUR	NO	DISCHARGED
21	36028	B/O SHASHIKALA	M	42	outborn	outborn	2.75	10/29/2016	81 mg/dl	9.8 mg/dl	MSAF	5 HOURS OF LIFE	FOCAL CLONIC	P	20 HOL	15 HOURS	NO	DISCHARGED

sl no	IP	NAME	SEX	G A in weeks	APGAR SCORE	APGAR SCORE	WEIGHT	D O D	RBS	Se.Ca	ETIOLOGY	TIME OF CONVULSION	TYPE OF CONVULSION	DRUGS USED	CONTROL OF SEIZURES IN HOURS	Time taken to attain seizure control	REQUIREMENT OF SECOND DRUG	OUTCOME
					1 MINUTE	5 MINUTES	IN KGS											
22	37100	B/O MEENAKSHI	M	41	5	6	3.6	11/8/2016	88 mg/dl	10.8 mg/dl	BA	2 HOURS OF LIFE	SUBTLE	P	28 HOL	26 HOURS	NO	DISCHARGED
23	37396	B/O ROOPA	M	38	3	5	2.7	11/10/2016	105 mg/dl	9.9 mg/dl	BA	21 HOURS OF LIFE	SUBTLE	P	22 HOL	1 HOUR	NO	DEATH
24	37754	B/O REKHA	M	39	4	6	2.94	11/13/2016	109 mg/dl	9.7 mg/dl	MSAF	5 HOURS OF LIFE	CLONIC	P	6 HOL	1 HOUR	NO	DISCHARGED
25	84	B/O SHRIDEVI	F	40	2	6	3.5	1/1/2017	117 mg/dl	11.5 mg/dl	BA	16 HOURS OF LIFE	CLONIC	P L	28 HOL	12 HOURS	YES	DISCHARGED
26	1726	B/O SHABANA	M	38	outborn	outborn	2.16	1/14/2017	52 mg/dl	10.8 mg/dl	MSAF	72 HOURS OF LIFE	CLONIC	P L F	120 HOL	48 HOURS	YES	DISCHARGED
27	1713	B/O DEEPA	M	42	3	5	2.64	1/16/2017	154 mg/dl	10.8 mg/dl	BA	3 HOURS OF LIFE	SUBTLE	P	5 HOL	2 HOURS	NO	DISCHARGED
28	2877	B/O LAKSHMI	M	39	5	7	2.8	1/26/2017	156 mg/dl	10.1 mg/dl	BA	2 HOURS OF LIFE	SUBTLE	P L F	15 HOL	13 HOURS	YES	DISCHARGED
29	8215	B/O BHARATHI	M	38	2	5	2.7	3/14/2017	101 mg/dl	9.2 mg/dl	BA	3 HOURS OF LIFE	FOCAL CLONIC	P L F	8 HOL	5 HOURS	YES	DISCHARGED
30	8299	B/O JAKKAWWA	M	37	5	7	2.41	3/15/2017	106 mg/dl	10.1 mg/dl	BA	8 HOURS OF LIFE	SUBTLE	P L	48 HOL	40 HOURS	YES	DISCHARGED
31	8842	B/O SAVITHRI	F	37	3	5	2.33	3/19/2017	130 mg/dl	9.6 mg/dl	BA	5 HOURS OF LIFE	SUBTLE	P	13 HOL	8 HOURS	NO	DISCHARGED
32	9626	B/O RATNABAI	M	39	2	5	3.3	3/26/2017	101 mg/dl	9.5 mg/dl	TMSAF	20 MINUTES OF LIFE	SUBTLE	P	6 HOL	5.5 HOURS	NO	DISCHARGED
33	12125	B/O NEELAMMA	M	40	3	6	3.18	4/16/2017	135 mg/dl	11.1 mg/dl	MSAF	3 HOURS OF LIFE	TONIC	P	14 HOL	11 HOURS	NO	DEATH
34	12180	B/O DEEPA	F	38	7	9	2.56	4/17/2017	102 mg/dl	7.8 mg/dl	MSAF	28 HOURS OF LIFE	CLONIC	P	48 HOL	20 HOURS	NO	DISCHARGED
35	14916	B/O SHRUTHI	F	42	5	7	3	5/10/2017	99 mg/dl	9.9 mg/dl	MSAF	14 HOURS OF LIFE	SUBTLE	P L	36 HOL	22 HOURS	YES	DISCHARGED
36	14941	B/O SUDHA	F	38	3	5	2.04	5/10/2017	127 mg/dl	9.2 mg/dl	TMSAF	2 HOURS OF LIFE	TONIC	P	3 HOL	1 HOUR	NO	DISCHARGED
37	16916	B/O RENUKA	M	36	3	4	2.2	5/26/2017	123 mg/dl	8.4 mg/dl	BA	26 HOURS OF LIFE	CLONIC	P	27 HOL	1 HOUR	NO	DISCHARGED
38	17081	B/O MAMTAZ	F	39	outborn	outborn	2.39	5/28/2017	92 mg/dl	8.8 mg/dl	BA	2 HOURS OF LIFE	CLONIC	P L F M	NOT CONTOLLED		YES	DEATH
39	19383	B/O ANITHA	F	38	2	4	2.5	6/16/2017	129 mg/dl	10.2 mg/dl	BA	2 HOURS OF LIFE	CLONIC	P L F	32 HOL	30 HOURS	YES	DISCHARGED