COMPARISON OF LEVETIRACETAM AS A SECOND LINE DRUG IN PLACE OF FOSPHENYTOIN IN STATUS EPILEPTICUS AMONG CHILDREN

Dissertation submitted in partial fulfillment of

M.D. DEGREE EXAMINATION

M.D. PEDIATRICS, BRANCH-VII CHENGALPATTU MEDICAL COLLEGE AND HOSPITAL

CHENGALPATTU

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY CHENNAI, TAMILNADU

MAY 2018

DECLARATION

I **Dr. ANUPAMA S** have proposed study titled **"COMPARISON OF LEVETIRACETAM AS A SECOND LINE DRUG IN PLACE OF FOSPHENYTOIN IN STATUS EPILEPTICUS AMONG CHILDREN"** in Department of Pediatrics at Chengalpattu Medical College and Hospital; I hereby ensure that I will abide by the rules of the institutional ethics committee.

A RANDOMIZED CONTROLLED TRIAL STUDY

A bonafide work done by me in the Department of Pediatrics, Chengalpattu Medical College, Chengalpattu, under the guidance of **Prof .Dr. J. SATHYA, M.D., D.C.H.,** Head of the Department, Department of Pediatrics, Chengalpattu Medical College, Chengalpattu.

(Dr. ANUPAMA S)

Signature of the candidate

CERTIFICATE

This is to certify that the dissertation titled **"COMPARISON OF LEVETIRACETAM AS A SECOND LINE DRUG IN PLACE OF FOSPHENYTOIN IN STATUS EPILEPTICUS AMONG CHILDREN"** is the bonafide work of **Dr. ANUPAMA S** in partial fulfillment of the requirements for **M.D. BRANCH-VII (PEDIATRICS)** examinations of **THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY** to be held in 2018.the period of study was from August 2016- September 2017

Signature of the H.O.D

Professor and Head
Department of Pediatrics
Chengalpattu Medical College
Chengalpattu.

Dean

Chengalpattu Medical College
Chengalpattu.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation titled **"COMPARISON OF LEVETIRACETAM AS A SECOND LINE DRUG IN PLACE OF FOSPHENYTOIN IN STATUS EPILEPTICUS AMONG CHILDREN"** submitted by **Dr. ANUPAMA S, M.D.** in partial fulfillment for the award of the degree of DOCTOR OF MEDICINE IN PEDIATRICS by The Tamilnadu Dr.M.G.R Medical University, Chennai is bonafide work done by her in the Department of Pediatrics, CHENGALPATTU MEDICAL COLLEGE, CHENGALPATTU, during the academic year 2016-2017 under my guidance.

PLACE: Chengalpattu

DATE:

Dr. J. SATHYA, M.D., D.C.H.,

Professor and Head

Department of Pediatrics

Chengalpattu Medical College,

Chengalpattu.

ACKNOWLEDGEMENT

I take this opportunity to express my respect and heartfelt gratitude to all my Teachers. First and foremost I would like to express my sincere gratitude ,heartfelt thanks and appreciation for my guide **Dr. J Sathya M.D.,D.C.H.,** for her unparalleled encouragement and everlasting patience from the start of my study, my thesis protocol preparation till the completion of my dissertation. I would like to express my sincere gratitude and heartfelt thanks to my co-guide **Dr. V. Poovazhagi, M.D., D.C.H., Ph.D.,** for her valuable suggestions, encouragement and co- operation provided to me throughout my study.

I would like to express my sincere gratitude to **Dr. Usha Sadhasivan M.D., Ph.D.,** The DEAN of this institution for allowing me to utilize the facilities in the institution.

I would like to express my sincere gratitude **to Dr.J.Hemachitra M.D.**, for giving constant support and suggestions for my study. I would like to express my sincere gratitude to **Dr. P. Senthil kumarM.D.,** for his valuable suggestions and guidance for my study. I also like to express my sincere gratitude to **Dr. G. Durai Arasan M.D.,** for the support provided by him.

I express my sincere gratitude and thanks to Dr.S.A.Ravikumar M.D., Dr.S.Suresh Kumar M.D., Dr.A.Jagadeeswari DCH., Dr. D.Suresh M.D., Dr.R.Diana Grace M.D., Dr.M.Sabarinath M.D., for their valuable support and guidance during the course of Study. I express my gratitude to all my colleagues and Staff nurses in our Department. I am extremely thankful to all the children and their parents who have participated in this study

INSTITUTIONAL ETHICAL COMMITTEE

CHENGALPATTU MEDICAL COLLEGE, CHENGALPATTU

Title of Work	:	**Comparison of Levitiracetam as a second line drug in place of fosphenytoin in status epilepticus among children**
Principal Investigator	:	Dr.S.Anupama,
Designation	:	Post graduate in Peadiatrics,
Co-Investigators	:	1.Dr.Sathya., MD., DCH., Professor of Peadiatrics,
Department	:	Peadiatrics

The request for an approval From the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 25.10.2016 at the Medical Education Unit, Government Chengalpattu Medical College, Chengalpattu at 12.00 PM.

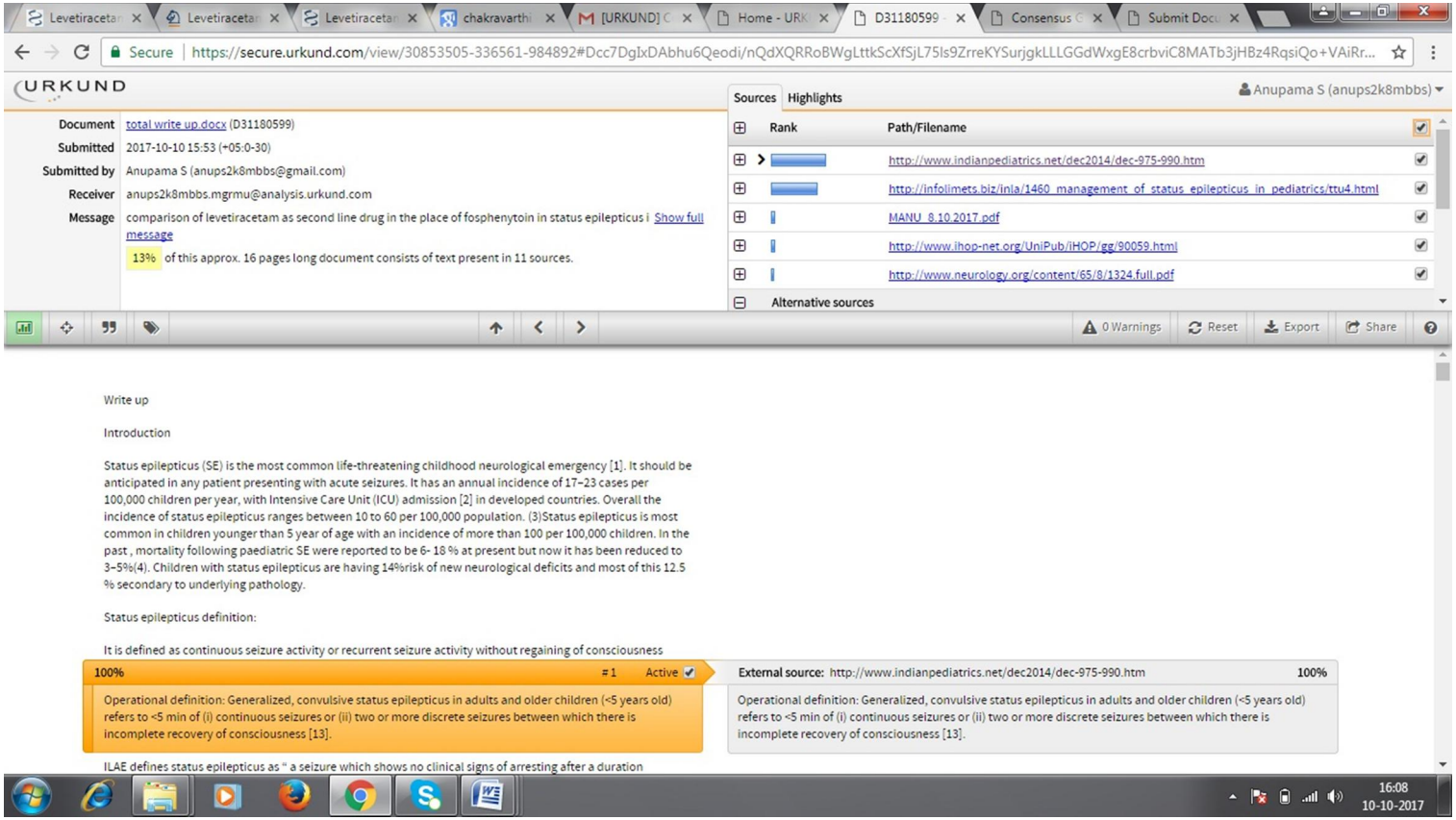
The Members of the committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal Investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of any changes in study procedure, site, investigator investigation or guide or any other changes.
2. You should not deviate From the area of work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
4. You should abide to the rules and regulations of the institution(s).
5. You should complete the work within the specific period and if any extension is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of work.

MEMBER SECRETARY,
IEC, CHENGALPATTU MEDICAL COLLEGE
CHENGALPATTU.

DEAN
CHENGALPATTU MEDICAL COLLEGE
CHENGALPATTU


Secure https://secure.urkund.com/view/30853505-336561-984892#Dcc7DgIxDAbhu6Qeodi/nQdXQRRoBWgLttkScXfSjL75Is9ZrreKYSurjgkLLLGGdWxgE8crbviC8MATb3jHBz4RqsiQo+VAiRr...
URKUND
Anupama S (anups2k8mbbs)
Document total write up.docx (D31180599)
Submitted 2017-10-10 15:53 (+05:0-30)
Submitted by Anupama S (anups2k8mbbs@gmail.com)
Receiver anups2k8mbbs.mgrmu@analysis.urkund.com
Message comparison of levetiracetam as second line drug in the place of fosphenytoin in status epilepticus i Show full message
13% of this approx. 16 pages long document consists of text present in 11 sources.
Sources Highlights
Rank
Path/Filename
http://www.indianpediatrics.net/dec2014/dec-975-990.htm
http://infolimets.biz/inla/1460_management_of_status_epilepticus_in_pediatrics/ttu4.html
MANU_8.10.2017.pdf
http://www.ihop-net.org/UniPub/iHOP/gg/90059.html
http://www.neurology.org/content/65/8/1324.full.pdf
Alternative sources
0 Warnings
Reset
Export
Share
Write up
Introduction
Status epilepticus (SE) is the most common life-threatening childhood neurological emergency [1]. It should be anticipated in any patient presenting with acute seizures. It has an annual incidence of 17–23 cases per 100,000 children per year, with Intensive Care Unit (ICU) admission [2] in developed countries. Overall the incidence of status epilepticus ranges between 10 to 60 per 100,000 population. (3)Status epilepticus is most common in children younger than 5 year of age with an incidence of more than 100 per 100,000 children. In the past , mortality following paediatric SE were reported to be 6- 18 % at present but now it has been reduced to 3–5%(4). Children with status epilepticus are having 14%risk of new neurological deficits and most of this 12.5 % secondary to underlying pathology.
Status epilepticus definition:
It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness
100% #1 Active
Operational definition: Generalized, convulsive status epilepticus in adults and older children (<5 years old) refers to <5 min of (i) continuous seizures or (ii) two or more discrete seizures between which there is incomplete recovery of consciousness [13].
External source: http://www.indianpediatrics.net/dec2014/dec-975-990.htm 100%
Operational definition: Generalized, convulsive status epilepticus in adults and older children (<5 years old) refers to <5 min of (i) continuous seizures or (ii) two or more discrete seizures between which there is incomplete recovery of consciousness [13].
ILAE defines status epilepticus as " a seizure which shows no clinical signs of arresting after a duration
16:08
10-10-2017

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

PICU	-	PEDIATRIC INTENSIVE CARE UNIT
SE	-	STATUS EPILEPTICUS
FIRES	-	FEVER INDUCED REFRACTORY EPILEPTICUS ENCEPHALOPATHY
EEG	-	ELECTROENCEPHALOGRAM
SSPE	-	SUBACUTE SCLEROSING PAN ENCEPHALITITS
PML	-	PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY
MELAS	-	MITOCHONDRIAL ENCEPHALOPATHY LACTIC ACIDOSIS SEPSIS
MERRF	-	MYOCLONIC ENCEPHALOPATHY RAGGED RED FIBRES
AED	-	ANTI EPILEPSY DRUGS
GCS	-	GLASGOW COMA SCALE

INTRODUCTION

Status epilepticus (SE) is the most common life-threatening childhood neurological emergency [1]. It should be anticipated in any patient presenting with acute seizures. It has an annual incidence of 17–23 cases per 100,000 children per year, with a need for Intensive Care Unit (ICU) admission [2] in developed countries. Overall the incidence of status epilepticus ranges from 10 to 60 per 100,000 population. [3] Status epilepticus is most common in children younger than 5 years of age with an incidence of more than 100 per 100,000 children. In the past , mortality following pediatric SE were reported to be 6- 18 % , but now it has been reduced to 3–5% [4],[6]. Children with status epilepticus have14% risk of neurological deficits and 12.5 % is secondary to underlying pathology. [5]

Status epilepticus

It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness, lasting for more than 5 minutes as part of an operational definition put forth within the past few years. Operational definition: Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to >5 min of (i) continuous seizures or (ii) two or more discrete seizures between which there is incomplete recovery of consciousness [7].

ILAE defines status epilepticus as " a seizure which shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without resumption of baseline central nervous system function interictally[8] In the past Status epilepticus (SE) was defined as seizure lasting more than 30 minutes or recurrent seizures for more than 30 minutes during which the patient does not regain consciousness.

Refractory SE: Seizures persist despite the administration of two appropriate anticonvulsants at acceptable doses, with a minimum duration of status of 60 minutes (by history or observation).

New onset refractory status epilepticus It is identified as a distinct entity that can be caused by almost any of the causes of status epilepticus in a patient without prior epilepsy. It is also of unknown etiology presumed to be encephalitic or post encephalitic, can last for several weeks or longer and often not always has a poorer prognosis.

Super-refractory SE [9] SE that continues 24 hours or more after the onset of anesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anesthesia.

FIRES: Fever induced refractory epileptic encephalopathy in school age children is a syndrome of refractory status epilepticus associated with acute febrile infections, appears to be parainfectious in nature and to be highly drug resistant but responsive to the ketogenic diet.

ILAE classification [10]:

Classification of Status Epilepticus

For classification of SE following four axes are proposed:

1. Semiology
2. Etiology
3. EEG correlates
4. Age

Axis 1: Semiology

The semiology axis is the clinical presentation of Status epilepticus and forms the basis of this classification. The two major criteria are:

- The presence or absence of prominent motor symptoms
- The qualitative or quantitative degree of impaired consciousness.

CLASSIFICATION OF STATUS EPILEPTICUS

A. With prominent motor symptoms

A.1. Convulsive Status Epilepticus

A.1a. Generalised convulsive

A.1b. Focal onset evolving into B/L convulsive SE

A.1c. Unknown whether focal or generalised

A.2. Myoclonic Status Epilepticus

A.2a. With Coma

A. 2b. Without Coma

A.3. Focal motor

A.3a. Repeated focal motor seizures (Jacksonian)

A.3b. Epilepsia Partialis continua

A.3c. Adversive status

A. 3d. Oculoclonic status

A. 3e. Ictal paresis

A. 4. Tonic Status

A. 5. Hyperkinetic Status

B. Without prominent motor symptoms

B1. Nonconvulsive status epilepticus with Coma

B2. Nonconvulsive status epilepticus without Coma

B. 2a. Generalised

B. 2b. Focal

B. 2c. Unknown whether local or generalised

Axis 2: Etiology

1. Known or symptomatic Status Epilepticus caused by a known disorder that can be of any cause due to structural, infectious, metabolic, inflammatory, toxic or genetic.

2. Idiopathic or Genetic-cause of Status Epilepticus not the same as for the disease but it is triggered by metabolic, toxic or intrinsic factors in these syndromes.

Currently intermediate conditions (or boundary syndromes)

i) Epileptic encephalopathies

ii) Coma with non evolving epileptiform EEG pattern

iii) Behavioural disturbance

iv) Acute confusional states with Epileptiform EEG pattern

Etiology of Status Epilepticus

i) Known (symptomatic)

Acute

Remote

Progressive

Status Epilepticus in defined electroclinical syndromes

ii) Unknown

The term unknown or cryptogenic is presumed to be of unknown cause

Axis 3: Electroencephalographic correlates

There are no evidence based Electroencephalographic criteria for status epilepticus. Terminologies to describe EEG pattern in status epilepticus are:

1. Location: Generalised, Lateralised, Bilateral, Independent, Multifocal
2. Name of the Pattern: Rhythmic Delta activity or spike-and-wave/sharp-and-wave subtypes, Periodic discharges
3. Morphology: Sharpness, Number of faces, Absolute and Relative amplitude, Polarity
4. Time related features: Prevalence, frequency, duration, daily pattern, onset, dynamics
5. Modulation: Stimulus induced vs. Spontaneous
6. Effect of intervention on EEG

Axis 4: Age

1. Neonatal (0 to 30 days)
2. Infancy (1 month to 2 years)
3. Childhood (>2 to 12 years)
4. Adolescence and Adulthood (>12 to 59 years)
5. Elderly

SE IN SELECTED ELECTROCLINICAL SYNDROMES ACCORDING TO AGE

1. SE occurring in neonatal and infantile-onset epilepsy syndromes
2. SE occurring mainly in childhood and adolescence
3. SE occurring mainly in adolescence and adulthood
4. SE occurring mainly in the elderly

List of Etiologies That May Cause Status Epilepticus [11]

1. Cerebrovascular diseases

   Ischemic stroke

   Intracranial bleeding

   Subdural hematoma

   Vascular dementia

   Sinus venous thrombosis and Cortical venous thrombosis

2. CNS infections

   Acute and chronic bacterial meningitis

   Cerebral malaria

   Tuberculosis

   Neurocysticercosis

   Acute viral encephalitis

   Progressive Multifocal Leukoencephalopathy (PML)

   Subacute Sclerosing Panencephalitis (SSPE)

3. Neurodegenerative diseases

   Alzheimer's disease

   Frontotemporal dementia

4. Intracranial tumors

   Meningioma

   Ependymoma

   Glial Tumors

   Primitive neuroectodermal tumor (PNET)

   Lymphoma

5. Cortical dysplasias

   Focal cortical dysplasia (FCD) II, Tuberous Sclerosis complex (TSC) hemimegalencephaly

   Ganglioma, gangliocytoma, dysembryoplasticneuroepithelial tumor (DNET)

   Familial and sporadic schizencephaly

   Infratentorial malformations (dentate dysplasia, mamillary dysplasia etc.)

6. Head trauma

7. Alcohol related

   Intoxication

   Wernicke encephalopathy

   Alcohol withdrawal

8. Intoxication

   Neurotoxins

   Heavy metals

9. Cerebral hypoxia or anoxia

10. Withdrawal of or low levels of antiepileptic drugs

11. Metabolic disturbances

   Renal failure

   Acidosis

   Glucose imbalance

   Electrolyte imbalances

12. Autoimmune disorders causing SE

   Multiple sclerosis

   Cerebral lupus (systemic lupus erythematosus)

   Seronegative autoimmune encephalitis

   CREST syndrome

   Henoch Schonlein purpura

   Goodpasture syndrome

13. Mitochondrial diseases causing SE

Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

Myoclonic encephalopathy with ragged red fibres (MERRF)

Leigh syndrome

14. Metabolic disorders

Wilson disease

Maple syrup urine disease

Porphyria

Lafora disease

Adrenoleukodystrophy

Menkes disease

15. Chromosomal aberrations and Genetic anomalies

Down syndrome (trisomy 21)

Fragile X syndrome

Angelman syndrome

Ring chromosome 20

Ring chromosome 17

16. Neurocutaneous syndromes

    Sturge-Weber syndrome

17. Others

    Cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy (CADASIL)

    Juvenile Huntington's disease (Westphal variant)

    Wolfram syndrome

    Cockayne syndrome

    Familial hemiplegic migraine

    Infantile onset spinocerebellar ataxia (SCA)

Pathophysiology of status epilepticus

Mechanism leading to sustained seizure activity in status epilepticus are due to persistence of increased excitability because of failure of desensitization of AMPA glutamate receptors and reduction of GABA-mediated inhibition as a result of intracellular internalization of GABA-A receptors[12].

FIGURE 1: PATHOPHYSIOLOGY OF STATUS EPILEPTICUS

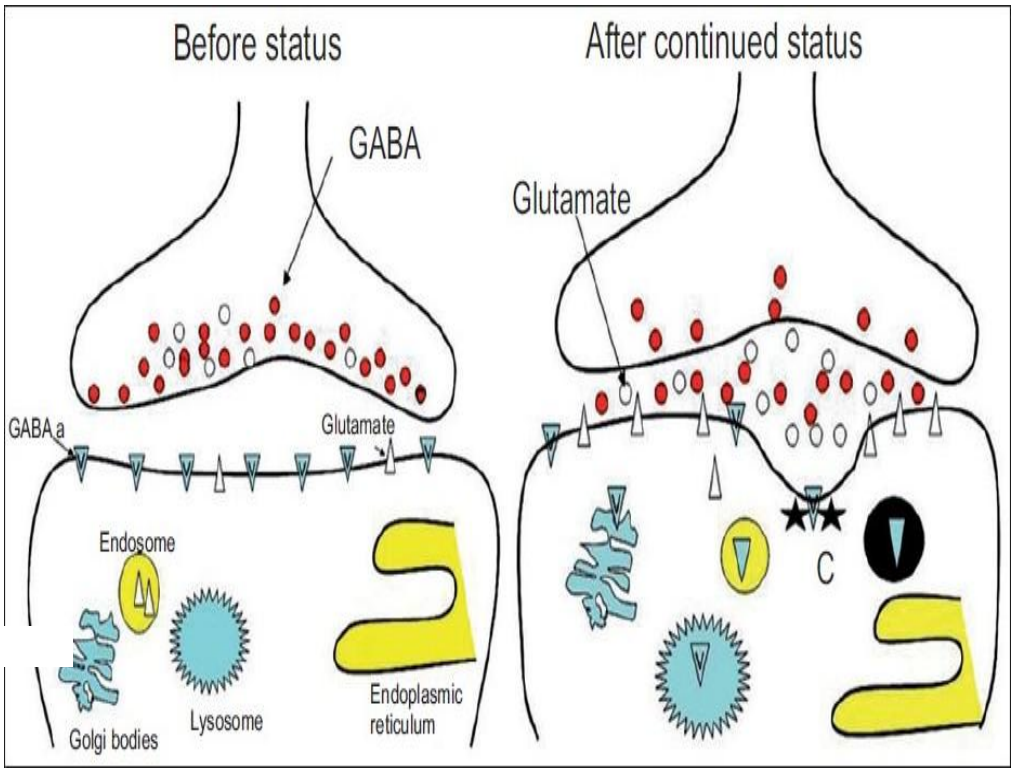


Figure 1: Journal of post graduate medicine : PP Nair, J Kalita, UK Misra Department of Neurology, Sanjay Gandhi PGIMS, Lucknow, Uttar Pradesh, India.

Stages of status epilepticus

Clinically there are two stages of status epilepticus

The first stage is characterized by generalized convulsive tonic–clonic seizures that are associated with an increase in autonomic activity, resulting in hypertension, hyperglycemia, sweating, salivation, and hyperpyrexia. During

this phase, cerebral blood flow is increased due to increased cerebral metabolic demands. After 30 min of seizure activity, children enter into the second phase, characterized by the failure of cerebral autoregulation which results in decrease in cerebral blood flow, increase in intracranial pressure, and systemic hypotension. During this phase, electromechanical dissociation occurs , although electrical cerebral seizure activity continues, the clinical manifestations may be restricted to minor twitching alone[13].

An EEG (electroencephalogram) can detect up to five separate stages of status epilepticus –

1) individual seizures
2) merging of the seizures
3) continuous seizure
4) nearly continuous seizure with some quiet periods
5) mostly quiet with intermittent indications of activity.

Management of Status epilepticus[14]

Status epilepticus is a medical as well as neurologic emergency. Support of airway, breathing, and circulatory functions should be focused first while identifying medical complications and seizure precipitants. Medical management should proceed with subsequent testing once stabilization of airway, breathing, and circulation occurs. This is followed by intubation and mechanical ventilation to support pulmonary function and vasopressors and fluid resuscitation to support circulation. As hyperthermia and

hyperglycemia are associated with unfavorable outcomes in some types of neurologic injury which may cause status epilepticus, close attention to these parameters is recommended.

STAGE I (0-10 MINUTES)

Assess the cardiorespiratory function

Secure airway and resuscitate

Administer oxygen

STAGE II (0-60 MINUTES)

Institute regular monitoring

Emergency AED therapy

Setup intravenous lines

Emergency investigations

STAGE III (0-60/90 MINUTES)

Establish etiology

Identify and treat medical complications

Vasopressor therapy when appropriate

STAGE IV (30-90 MINUTES)

Transfer to intensive care

Establish intensive care and EEG monitoring

Initiate intracranial pressure monitoring where appropriate

Initiate long-term, maintenance, antiepileptic therapy

C. Supportive Care and Stabilization[15]

Convulsive seizures are the most obvious manifestation, apart from attempts to rapidly control seizures, important goals of therapy are neuro-protection and prevention and treatment of systemic complications associated with intravenous AEDs, anesthetic drugs and prolonged unconsciousness . The supportive care should be tailored to the health care setting, the clinical presentations of SE, for encephalopathy and degree of impairment of vital functions.

Airway, Breathing and Circulation

Assessment of vital functions is essential at all stages of managing any child with SE. Before any pharmacological therapy adequate care of airway, breathing and circulation takes precedence.

Airway: It is essential to maintain a patent airway during all stages of management of SE.

- In all children with brief seizures and altered sensorium, clearing the oral secretions keeping them in recovery position is advised to prevent aspiration. Immobilisation of cervical spine is essential if trauma is suspected. In more severe cases , an airway is used to prevent the tongue fall back.
- Endotracheal intubation in children whose airway is not maintainable with above measures.
- The airway compromise can occur at any stage of status epilepticus ; either as complication of prolonged or ongoing seizure, or due to respiratory depressant effect of medications.[16]

Breathing: Hypoxemia may result from respiratory depression/apnea, aspiration, airway obstruction, and neurogenic pulmonary edema .

- All children with SE should have their breathing and SpO2 monitored continuously.
- Children with ongoing seizures should be given supplemental oxygen to ameliorate cerebral hypoxia, because the degree of hypoxia is often underestimated.
- Depending on the duration of SE and degree of altered sensorium, maintain oxygen saturation by: supplemental oxygen, AMBU bag, non-invasive continuous positive airway

pressure (CPAP), and invasive ventilation by endotracheal intubation. Mechanical ventilation also become necessary when children are started on continuous infusions of anesthetic agents.

Circulations: Monitoring of pulse, blood pressure and perfusion should be done continuously in all SE patients.

- Ensure good venous access (preferably have at least two venous lines); draw necessary blood samples, and start fluids and anti-epileptic drugs as necessary.
- Maintain blood pressure in the normal range with necessary measures including: intravenous fluids, fluid boluses, and inotropes.
- The choice of IV fluids depends on the metabolic and glycemic status. In case of hyperglycemia (especially initial phase of catecholamine excess) it is preferable to give dextrose normal saline (DNS) or normal saline. However, in general, hypotonic fluid should be avoided for initial resuscitation.

Precipitating Factors and Complications[17]

The treating team should anticipate one or more of the above mentioned problems depending on the duration of SE, age, underlying etiology and the associated systemic co-morbidities. Initially there will be compensatory phase followed by a later stage of decompensation. During the

initial phase, prolonged seizures result in increased cerebral blood flow and metabolism, excessive catecholaminergic activity and cardiovascular changes. These in turn result in hyperglycemia, hyperpyrexia, tachycardia, sweating, hypertension, incontinence, cardiac arrhythmias, and lactic acidosis. If the SE is prolonged, the cerebral autoregulation progressively fails and cerebral perfusion becomes dependent on systemic blood pressure resulting in hypoxia, cerebral ischemia, hypoglycemia, and lactic acidosis [(18)] . Both hypernatremia (serum sodium >145 meq/L) and hyponatremia (<135 meq/L) are deleterious for the brain. Major risks associated with hypernatremia are intracranial hemorrhage (subdural, subarachnoid and intraparenchymal) and osmotic demyelination (pontine or extra-pontine) with rapid correction.

Risk of infections is greatly increased in those with SE, especially when the duration is prolonged. Common infections include Ventilator-associated pneumonia, urinary tract infection, pseudomembranous colitis, oral candidiasis, and septicemia . Commonest organisms are P. aeruginosa, A. spp, K. pneumoniae, and Enterobacteriaceae . Hyperpyrexia, rhabdomyolysis and raised intracranial pressure are the other common accompaniments. Rarely, SE is associated with ictal bradycardia, stress cardiomyopathy, neurogenic pulmonary edema, renal failure, or bone fractures. Hypotension is common due to prolonged seizures, IV benzo-diazepines, or anesthetic agent infusions, and stress cardiomyopathy (Takotsubo cardiomyopathy) .

Early identification and aggressive treatment of rhabdomyolysis prevents complications like renal failure and compartment syndrome. The initial fluids for resuscitation may include normal saline or 5% dextrose in water (approximately 2-3 times the daily maintenance). Sodium bicarbonate may be added to IV fluids, especially if there is associated metabolic acidosis and/or hyperkalemia

Anti- convulsants in children:

Benzodiazepines are used as the first line drug and it is the most effective drug in the treatment of acute seizures and status epilepticus. The benzodiazepines most commonly used to treat status epilepticus are diazepam ,lorazepam , and midazolam. All three compounds work by enhancing the inhibition of γ-aminobutyric acid (GABA) by binding to the benzodiazepine-GABA and barbiturate-receptor complex. Experience with benzodiazepines in the treatment of status epilepticus (SE) is large. This class of drugs has been used as the most potent drug in SE management[19].

Phenytoin

It is the second most effective drugs in the treatment of status epilepticus. The main advantage of phenytoin is the lack of sedation effect[20]. However, a number of serious adverse effects can occur with phenytoin and they are likely to be associated with more rapid rate of administration and the propylene glycol vehicle used as its diluent. Arrhythmias and hypotension are

among the commonest adverse effect. Other side effects includes local irritation, phlebitis, and dizziness.

FOSPHENYTOIN

Food and Drug administration approved fosphenytoin for the treatment of status epilepticus in 1996. Fosphenytoin is a water-soluble pro-drug of phenytoin that completely converts to phenytoin following parenteral administration. Thus, the adverse events that are related to propylene glycol are avoided. Like phenytoin, fosphenytoin is useful in treating acute seizures. Fosphenytoin is converted to phenytoin within 8 to 15 minutes. It is metabolized by the liver and has a half-life of 14 hours. The initial dose of fosphenytoin is 15 to 20 mg PE per kg, so it can be infused at a rate as high as 150 mg PE per minute, a rate of infusion that is three times faster than that of intravenous phenytoin. Intramuscular doses can also be given with fosphenytoin[21] .

Adverse effects that are unique to fosphenytoin include perineal paresthesias and pruritus; however, they are related to higher rates of administration. Unlike phenytoin, fosphenytoin does not cause local irritation however intravenous therapy has been associated with hypotension, so continuous cardiac and blood pressure monitoring are recommended along with this drug administration . Although fosphenytoin needs less cardiac monitoring , it is costlier, risk over the benefit should be considered.

Levetiracetam

The drug which was first introduced in 1999 is now widely used due to its pharmacologiclal properties like minimal protein binding and drug interactions[22]. Also it has a favorable side effect profile unlike other anticonvulsant drugs. Unlike other anticonvulsant drugs, it is not extensively metabolized in the liver by the cytochrome P450 enzyme system and its primary excretion is through kidney (hence safer to use in liver disease). It has linear pharmacokinetics and so drug level monitoring is not required. Its mechanism of action is by binding with synaptic vesicle protein SV2A. Though Levetiracetam is known to be safe and efficacious in the management of seizures[33], its use in Status Epilpeticus is based largely on experience from case reports and small case series. There is lack of prospective studies or randomized trials supporting Levetiracetam as second line drug for Status Epilepticus. Hence, a randomized open label study to determine the role of Levetiracetam as an alternative to Fosphenytoin in Status Epilepticus was planned.

FIGURE 2: ALGORITHM FOR MANAGEMENT OF STATUS EPILEPTICUS[10]

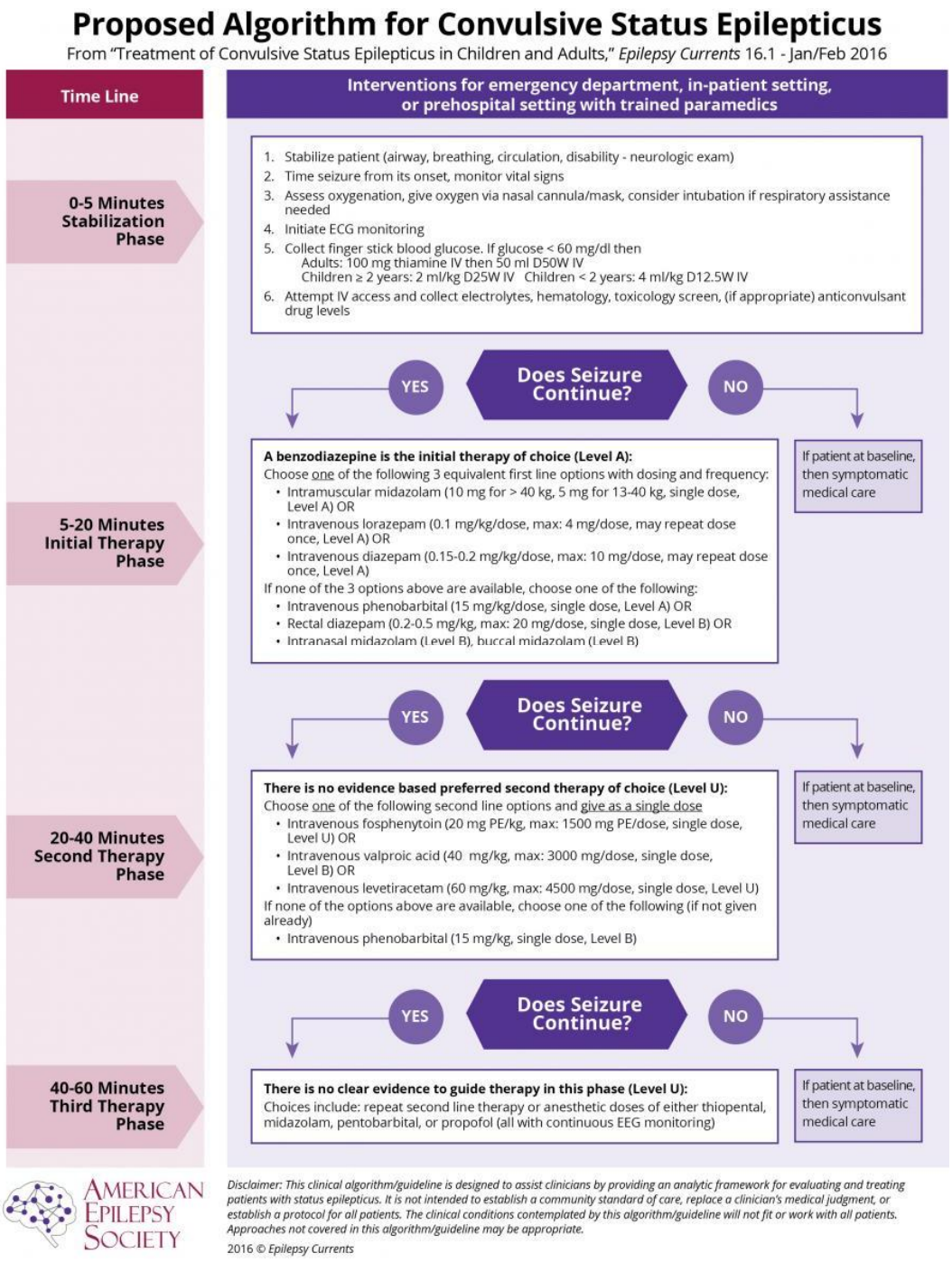


Figure -2: Epilepsy Currents 16.1 – Jan/Feb 2016 " Treament of convulsive status epilepticus in children and adults"

STATUS EPILEPTICUS UNIT PROTOCOL[23]

Children admitted with Status Epilepticus (ABC stabilised) were loaded with IV Midazolam 0.1 mg/kg over one minute followed by second dose of IV Midazolam 0.1 mg/kg over 1 minute if seizure persists. If seizure continues after 2 doses of Benzodiazepines, the second line anticonvulsant Inj. Fosphenytoin 20 mg PE/kg was loaded followed by another dose of 10 mg PE/kg if the child is still seizing. Further seizures are managed with Inj. Levetiracetam/ Phenbarbitone/Midazolam infusion/Sodium Valproate (Plan intubation/anaesthetic agent)

AIMS AND OBJECTIVES

Comparison of levetiracetam as second line drug in place of fosphenytoin in status epilepticus in children.

Primary outcome: Clinical cessation of seizures at the end of infusion

Secondary outcome: Time to control seizures , recurrence of seizures within 24 hours of control, any adverse events following the drug administration

Outcome – death and discharge from hospital.

Justification

Traditionally, benzodiazepines have been the first line treatment of Status Epilepticus in children followed by Phenytoin/Fosphenytoin, phenobarbitone and anesthetic agents. However, phenytoin has the side effects of cardiac toxicity which has led to the development of Fosphenytoin with lesser cardiac toxicity however it also requires cardiac monitoring. Many newer anticonvulsants like Levetiracetam have been introduced recently, with lesser side effects. However large clinical trials about the efficacy of such drugs is lacking. With extensive search of literature, it was found that there is no clinical trial comparing the efficacy of Levetiracetam and Fosphenytoin in children hence a study was planned to determine the usefulness of levetiracetam in comparison to fosphenytoin in children with status epilepticus..

REVIEW OF LITERATURE

With the existing literature search

There are only few randomized clinical trials comparing the medications for status epilepticus in children. Acute cessation of seizures is necessary to reduce the morbidity and mortality following status epilepticus .The benzodiazepines are used as the first line drug and it is the most effective drug in the treatment of acute seizures and status epilepticus[24]. Experience with benzodiazepines in the treatment of status epilepticus (SE) is large [25],[26]. This class of drugs has been described as the most potent use in status epilepticus management[27-29].Benzodiazepine resistant seizures are treated with Phenytoin/Fosphenytoin whose efficacy and safety are established in Status Epilepticus in children. However, few studies are available to support the efficacy of Levetiracetam in Status Epilepticus in children. Only few clinical trials are available in comparing Fosphenytoin and Levetiracetam in adults with none available in children.

A retrospective study was conducted by Kensuke Nakamura [30]et al in adult patients in the emergency and critical care centre in Hitachi General Hospital on the efficacy of levetiracetam vs fosphenytoin for the recurrence of seizures after status epilepticus. In this study 42 were included in fosphenytoin group and 21 were included in levetiracetam group in the ratio of 2:1. Parameters analyzed were previous medication history of any antiepileptic drugs , administered diazepam dose , type of status epilepticus

(GTCS, repeated focal seizures, non convulsive seizures), estimated duration of status epilepticus (mins) , basic disease causing status epilepticus,, control of seizures (number of recurrence of seizures following AED administration). Primary outcome were presence or absence of recurrence of convulsions after the administration of fosphenytoin or levetiracetam that is control of epilepsy . Secondary outcome was switching over of IV injections to oral administration, adverse effects. Differences were analyzed using student's test and one way analyses of variants. Absence of recurrence of seizures was achieved in 34 out of 42 patients (84%) in the fosphenytoin group and 18 out of 21 (85.1%) in the levetiracteam group (p value=0.69) which was not statistically significant. The estimated duration of status epilepticus in the fosphenytoin and the levetiracetam group were 63.2 ± 6.6 and 82.3 ± 9.5 minutes respectively (p=0.10) which was not statistically significant. Serious adverse drug reactions following drug administration was compared which also did not show any statistical significance (p=0.21)

A study was conducted by Puneet Agarwal et al[31]in the Neurology Unit, KPS PG Institute of Medicine, Kanpur in which 100 patients comparing IV valproate in one group with IV phenytoin in the other group .50 patients were included in the IV Valporate group and 50 patients in the IV phenytoin group. Primary outcome was the complete control of all motor or EEG activity within 20 mins of starting the drug infusion with the seizure activity not returning within the next 12 hours; while the secondary outcomes

included adverse events to treatment, in-hospital complications and neurological outcome during discharge. All patients were monitored for vitals, ECG, seizure activity and GCS where ever required every 5 minutes for 2 hrs and every 15 minutes for 12 hrs and laboratory parameters were analysed. Cerebrospinal fluid examination, Computed tomography and Magnetic Resonance Imaging were done to determine the etiology of status epilepticus. Results were analysed using student's t test. IV Valproate was successful in 88% and IV phenytoin in 84% (P> 0.05). There was no significant difference among the recurrence during the 12-hour study period or outcome in 7 days.

A study conducted by Vincent Alvarez et al[32] in the department of Clinical Neurosciences , Lausanne University Hospital (CHUV) compared phenytoin, valproate and levetiracetam as the second line drug in status epilepticus treatment. In their study they analysed data from a prospective registry including all patients treated over 4 years for status epilepticus in their hospital in which 187 episodes of status epilepticus were identified and analysed.. Patients in whom one of the three drugs which were given after benzodiazepine failure [34] were analysed. Post-anoxic Status epilepticus were excluded. Demographics, clinical Status epilepticus features , failure of second line treatment to control status epilepticus , new handicap and mortality at hospital discharge were assessed. Comparison among the three treatment groups were performed using two-tailed Fisher's exact,chi-square or

analysis of variance tests . they have also found population attributable fraction (PAF) of failure of the second line treatment and used Miettinen formula for worst acting agent. In their study ,each drug were used in about one third of the status epilepticus episodes.. Valproate failed to control status epilepticus in 25.4% , phenytoin in 41.4 % and levetiracetam in 48.3 %. Levetiracetam failed more often than valproate (odds ratio 2.69; 95% confidence interval (CI) 1.19-6.08); about 16.8%(CI:6.0-31.4%) of the treatment failures were attributed to levetiracetam. The drug failed more often than valproate while phenytoin was not statistically significant from the two.

A randomised open label pilot study was conducted by Misra UK et al[36]which compared Levetiracetam and Lorazepam in the management of Convulsive status Epilepticus Consecutive patients with convulsive or subtle convulsive SE were randomized and was loaded with LEV 20 mg/kg IV over 15 min or LOR 0.1 mg/kg over 2-4 min. In this study if the first drug failed to control SE within 10 min of administration of one study drug it was subsequently treated by the other study drug[37]. The primary endpoint was clinical seizure cessation and secondary endpoints were 24 h freedom from seizure, mortality, and adverse events. Results were based on 79 patients in which SE was controlled by LEV in 76.3% (29/38) and by LOR in 75.6% (31/41) of patients. In those resistant to the above regimen, LEV controlled SE in 70.0% (7/10) and LOR in 88.9% (8/9) patients. The 24-h freedom from seizure was also comparable: by LEV in 79.3% (23/29) and LOR in 67.7%

(21/31). Significantly higher need for artificial ventilation were associated with lorazepam administration. and insignificantly higher frequency of hypotension. . Both LEV and LOR were equally effective in cessation of seizures. For the treatment of SE, LEV is an alternative to LOR and may be preferred in patients with respiratory compromise and hypotension.

Khongkhatithum et al conducted a study in Thai children and adolescents with status epilepticus and acute repetitive seizures about the use of Intravenous Levetiracteam.in Ramathibadi Hospital , Bangkok , Thailand . It is a retrospective study in which medical records of 19 male and 31 female patient under 18 years of age who had received intravenous levetiracetam treatment either for acute repetitive seizures or for convulsive status epilepticus.[38] Descriptive analyses were applied, student's t – test and chi-square analysis for continuous and discrete variables. . Mean age were 76.6 months 52 episodes of 34 acute repetitive seizures (63.4%) and 18 convulsive status epilepticus (34.6%). Cessation of seizures were obtained in 59.6% of 52 episodes. Among the 52 episodes there was no significant difference between the etiology(p= 0.54) and in subgroup analysis there was no significant statistical difference of the response rate (p= 1.297) levetiracetam can be used in status epilepticus in children safely and it is effective for treatment of convulsive SE and acute repetitive seizures in children.

A study done by Sudheer Chakravarthi[40] et al in the Postgraduate Institue of Medical Education and Research , Chandigarh comparing relative

efficacy of second line agents – levetiracetam and phenytoin in status epilepticus in adult patient. In this study, consecutive patients of status epilepticus (n=44) were randomized using a simple random sampling method in which patients were assigned to either levetiracetam or phenytoin group (the patients were divided into two groups. Group A received PHT (n = 22) and group B received LEV (n = 22). depending upon the order of recruitment .odd numbered patients received phenytoin (n=22 , group A) and those with even numbered patients were administered levetiracetam (n=22; Group B) were either administered IV PHT (20mg/kg) or IV LEV (20mg/kg)[35]. Successful clinical termination of seizure activity within 30min after the beginning of the drug infusion was considered as primary end point. Secondary end points included recurrence of seizures within 24 hours, drug related adverse effects, neurological outcome at discharge, need for ventilatory assistance, and mortality during hospitalization. Descriptive statistics were used between two groups. Comparisons between the groups were done using Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables. . Mean age of patients was 31.82 ± SD 12.68 years in group A and 39.00 ± SD 18.40 years in group B. Mean duration of hospital stay was 1.57 ± SD 1.36 days in group A and 1.82 ± SD 1.29 days in group B. Mean duration of SE was 72.05 ± SD 48.57 min in group A and 55.91 ± 73.75 min in group B. Duration of SE was 35.7 ± 31.7 min (median: 30) in the patient who responded to treatment while among the non-responders it was 120 ± 108 min (median: 60). Among the patients who

responded well to treatment in group B, duration of SE was 37.9 ± 26.5 min (median: 30) while among the non-responders it was 114.4 ± 107.9 min (median: 60). Past history of epilepsy was reported in 66.6% of group A and in 77.3% of group B. In group A, 21 patients had GCSE and one had FCSE while in group B 20 had GCSE and two had FCSE. These parameters were comparable between the two groups. Past history of SE was noted in only two (4.5%) patients.PHT achieved control of SE in 15 (68.2%) patients compared to LEV in 13 (59.1%; p=0.53). Both the groups showed comparable results with respect to recurrence of seizures within 24 hours (p=0.34), outcome at discharge was assessed by functional independence measure (p=0.68), need of ventilator assistance (p=0.47) and death (p=1). They concluded that LEV may be an attractive and effective treatment , alternative to PHT in management of SE.[39]

A retrospective study was done by Yun- Jeong Lee[41] in Asan Medical Centre , in korea comparing intravenous levetiracetam versus phenobarbital in children with for benzodiazepine refractory status epilepticus or acute repetitive seizures.Medical records of children aged between 1month to 15 years who were treated with intravenous phenobarbitone and levetiracetam. i.v. PHB and i.v. LEV were randomly given to the patients with ARS or SE. The loading dose of i.v. PHB was 10–20 mg/kg and that of i.v. LEV was 20–30 mg/kg. The loading dose of i.v. LEV was administered over 15 minutes and was followed by a maintenance dose of 10–15 mg/kg every 12 hours .In

this study patients who were excluded were who required immediate neurosurgery, or if they were alleged patients with refractory epilepsy who were treated with more than two antiepileptic drugs.[42]

Ogutu et al[43] conducted a study in the Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus in which they surveyed the three different modes of administration of phenytoin and fosphenytoin(intravenous administration o phenytoin and fosphenytoin and intramuscular fosphenytoin) . Statistical method used were Pearson's χ^2 test (two-tailed) to compare categorical variables, the Student's *t* test to compare the means of normally distributed data, and the Mann-Whitney test to compare non-parametric data. Of 388 episodes of CSE, 155 (40%) were confirmed CSE and 274 (71%) were caused by an infection. The incidence of confirmed CSE was 35 (95% CI 27–46) per 100 000 children per year overall, and was 52 (21–107) and 85 (62–114) per 100 000 per year in children aged 1–11 months and 12–59 months, respectively. Mortality of children with confirmed CSE while in hospital was associated with bacterial meningitis (adjusted relative risk [RR]=2·6; 95% CI 1·4–4·9) and focal onset seizures (adjusted RR=2·4; 1·1–5·4), whereas neurological sequelae were associated with hypoglycaemia (adjusted RR=3·5; 1·8–7·1) and age less than 12 months (adjusted RR=2·5; 1·2–5·1). 9 (15%) children died in hospital, 28 (47%) of these within 24 h of admission and 44 (75%) within 48 h; 81 (21%) died during the following 3 years. 46 (12%)

children had neurological sequelae at discharge. Motor deficits were the most common disorder, affecting 40 (87%) children who had sequelae. Death before discharge was more common in children with confirmed CSE than in those with probable CSE difference between groups 13%, 95% CI 6–21; p=0·0003). The proportion of children who had neurological sequelae at discharge was also higher in the group with confirmed CSE than in the group with probable CSE difference between groups (10%, 3–17; p=0·0020).The mean steady state free phenytoin concentrations attained in the plasma after IV Fosphenytoin, IV Phenytoin and IM Fosphenytoin were not significantly different. However, the mean time to reach the peak plasma phenytoin concentrations were 0.08 hrs for IV Fosphenytoin, 0.37 hrs for IV Phenytoin and 0.38 hrs for IM Fosphenytoin which concluded phenytoin and fosphenytoin administration at the currently recommended doses achieved plasma unbound phenytoin concentrations within the therapeutic range with minimal cardiovascular effects. Thus administration of fosphenytoin i.v. or i.m. offers a practical and convenient alternative to i.v. phenytoin.

A prospective Study (Emergency treatment with levetiracetam or phenytoin in status epilepticus in children) EcLIPSE trial[44] is being done by Mark D Lyttle in the Emergency department in UK. This is a parallel group phase IV multicentered randomized control trail (open level trial) comparing IV levetiracetam with phenytoin. In this study 140 participants were recruited in each group. Children aged between 6 months to 18 years presenting with

GTCS were included. Primary outcome was cessation of all visible signs of seizure activity and secondary outcome were need for further antiseizure medication, or rapid sequence induction for ongoing Convulsive status epilepticus, admission to critical care areas and serious adverse reactions. Patients were recruited without prior consent, with deferred consent sought at an appropriate time for the family. The primary analysis will be by intention-to-treat. The primary outcome were time to event outcome and a sample size of 140 participants in each group with power of 80% to detect an increase in CSE cessation rates from 60% to 75%. total sample size of 308 randomised and treated participants allowed for 10% loss to follow-up Data collection was done in three time periods; first in the emergency department, second was 24 hrs after allocated treatment (which includes concomitant anticonvulsants) and finally follow up done 14 days after the administration of treatment in the hospital. Statistical analysis are being done using log-rank test and Kaplan Meier curves. Dichotomotous outcome were being analysed using Chi square. This study is yet to get completed by 2018 this is a large multicentric trial being conducted in pediatrics in status epilepticus. Recruitment of the participants are being done and 160 patients were been enrolled 29 sites were currently open for trial, recruitment is scheduled to finish in March 2018 and analysis to be completed by December 2018.

MATERIALS AND METHODS

STUDY DESIGN

Open label randomised parallel group trial

STUDY SETTING

This was done at the Pediatric intensive care unit of a semi-urban pediatric tertiary care institute, Chengalpattu Medical College and Hospital

DURATION

August 2016 to September 2017

INCLUSION AND EXCLUSION CRITERIA

Children aged between 1 month and 12 years were included in this study according to inclusion and exclusion criteria.

INCLUSION CRITERIA

Children from 1 month to 12 year of age who presented with status epilepticus refractory to 2 doses of benzodiazepine .

EXCLUSION CRITERIA

1. Children who received drugs other than 2 doses of benzodiazepines
2. Children who received pre-hospital treatment
3. Children who presented with shock .

SAMPLING TECHNIQUE

Randomization were done by computer generated random number table for 100 numbers with 50 odd and 50 even numbers. Children admitted with status epilepticus were assigned odd and even number according to the order of numbers in the table and odd number children were given inj.fosphenytoin and even number inj.levetiracetam

SAMPLE SIZE

Sample size of 100 with 50 in levetiracetem group and 50 in fosphenytoin group was calculated with the power of 80% and beta error of 5 %

Maneuver 180 children were admitted with status epilepticus of which 100 were recruited according to inclusion and exclusion criteria. Randomisation were done by computer generated random number table for with 50 odd and 50 even numbers. children admitted with status epilepticus were assigned odd and even number according to the order of numbers in the table and odd number children were loaded with inj.fosphenytoin 20 mg PE/ kg over 20 minutes at the rate of 3 mg/kg/min and even number children were loaded with levetiracetam 20 mg/kg at the rate of 5 mg/kg/min. Children whose seizures not controlled at the end of the infusion were managed further according to status epilepticus unit protocol.

Study parameters were age, sex ,weight ,history ,febrile or afebrile

episode , onset of seizures , family history of seizures , history of asphyxia, NICU admission, neurological development , previous oral intake of any anti- convulsant , comorbid conditions, clinical features of type of seizures , heart rate, blood pressure , capillary blood glucose, signs of raised intra cranial pressure (hypertension, bradycardia, abnormal breathing), lab parameters of sodium , potassium , total count, haemoglobin , neuro-imaging , lumbar puncture and EEG, outcome measures were clinical cessation of seizures at the end of the infusion, time to control seizures, recurrence of seizures within 24 hours, mean time for recurrence of seizures, number for further anti- convulsant required , time required to regain GCS 15/15, children requiring mechanical ventilation , adverse event following the drug administration-shock , arrythmia, phlebitis , total hours of PICU stay, outcome death or discharge . comparison was done between the two groups with respect to the study parameters to look for any statistically significant difference using student's t-test for continuous variable and chi-square for discrete variable. SPSS version 21 were used for statistical tests. Children were recruited for the study after informed written consent from the parents or caregivers. Study was undertaken after Institutional Ethical Committee approval and with CTRI registration .Children were followed up till discharge or death in case of mortality.

OBSERVATION AND RESULTS

FIGURE : 3 SCHEMATIC REPRESENTATION OF RESULTS

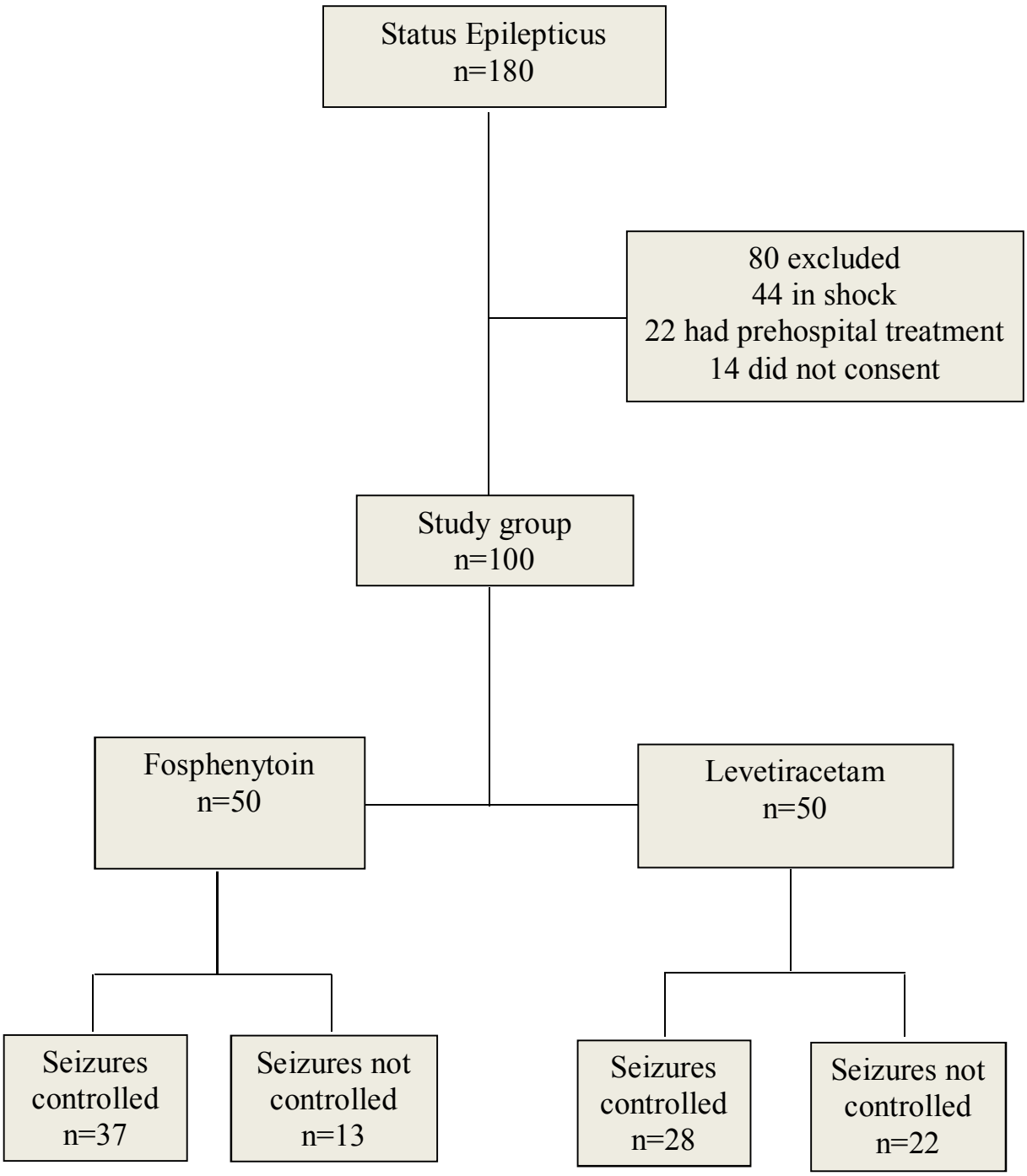


FIGURE: 4 OVERVIEW OF RESULTS IN FOSPHENYTOIN GROUP

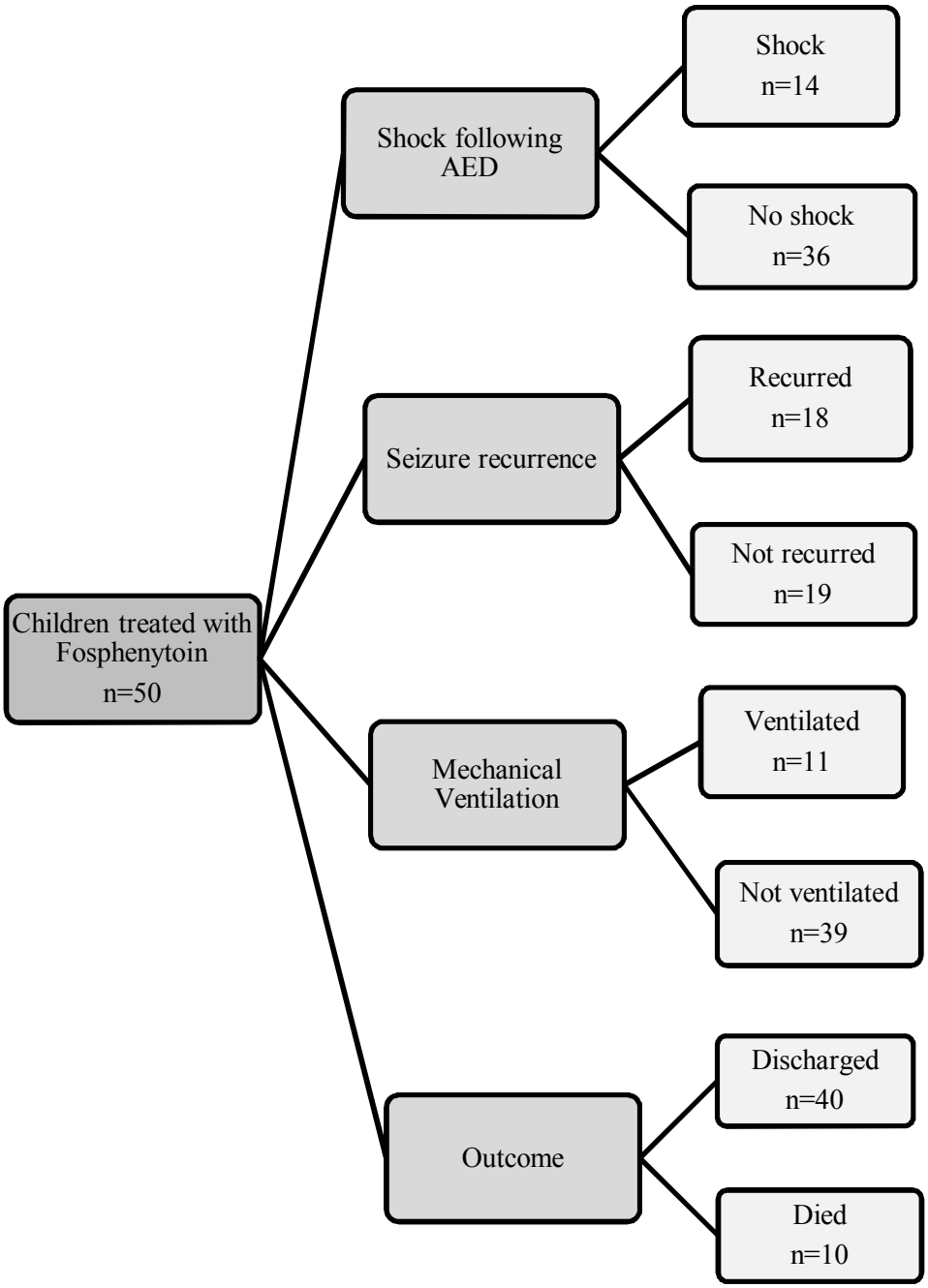
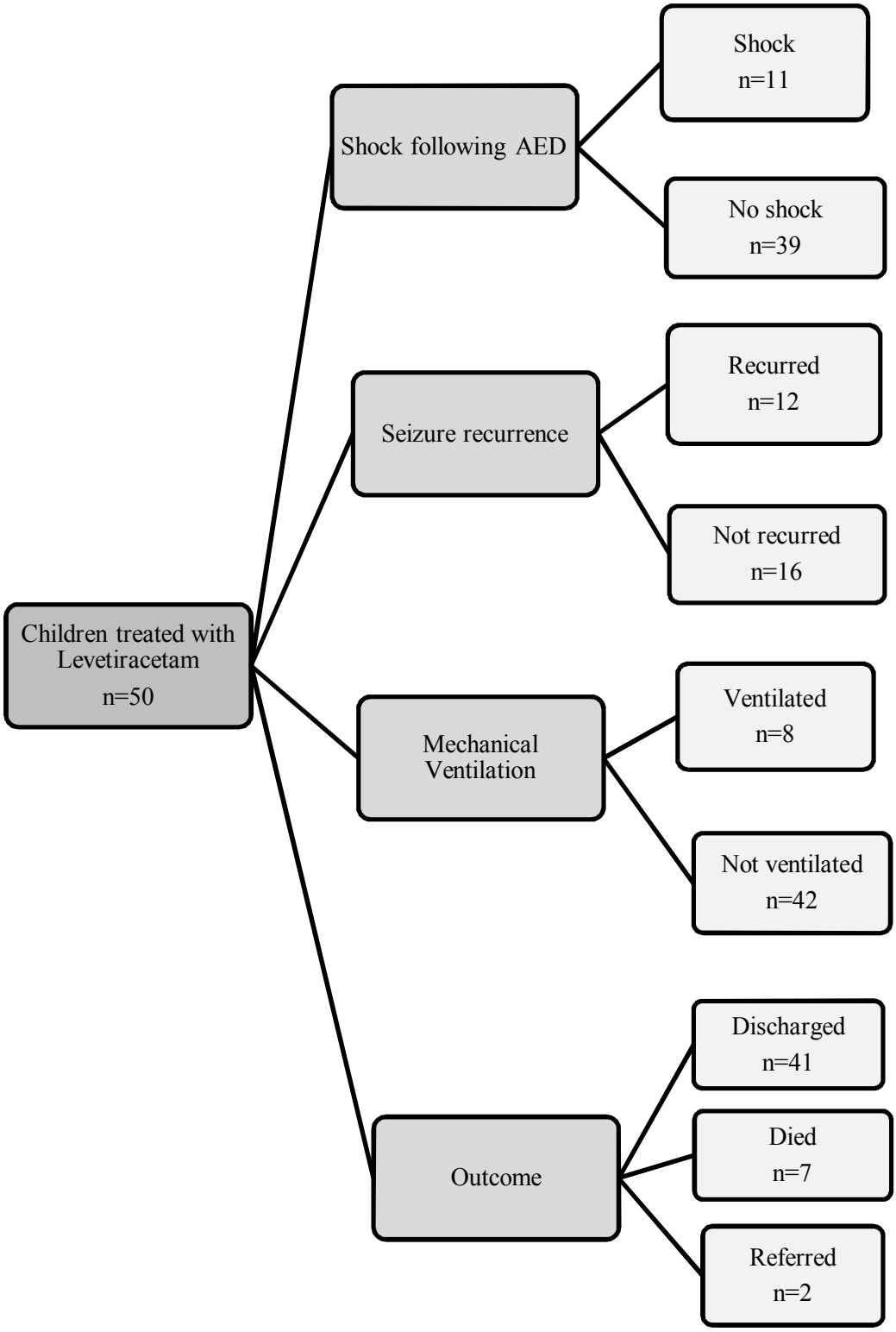


FIGURE : 5 OVERVIEW OF RESULTS IN LEVETIRACETEM GROUP



TABLES

Table 1: Gender distribution

Gender	Fosphenytoin N(%)	Levetiracetam N(%)	Total	p value
Male	33 (66)	26 (54)	**59**	0.309
Female	17 (34)	24 (46)	**41**	
Total	**50**	**50**	**100**	

FIGURE 6: GENDER DISTRIBUTION

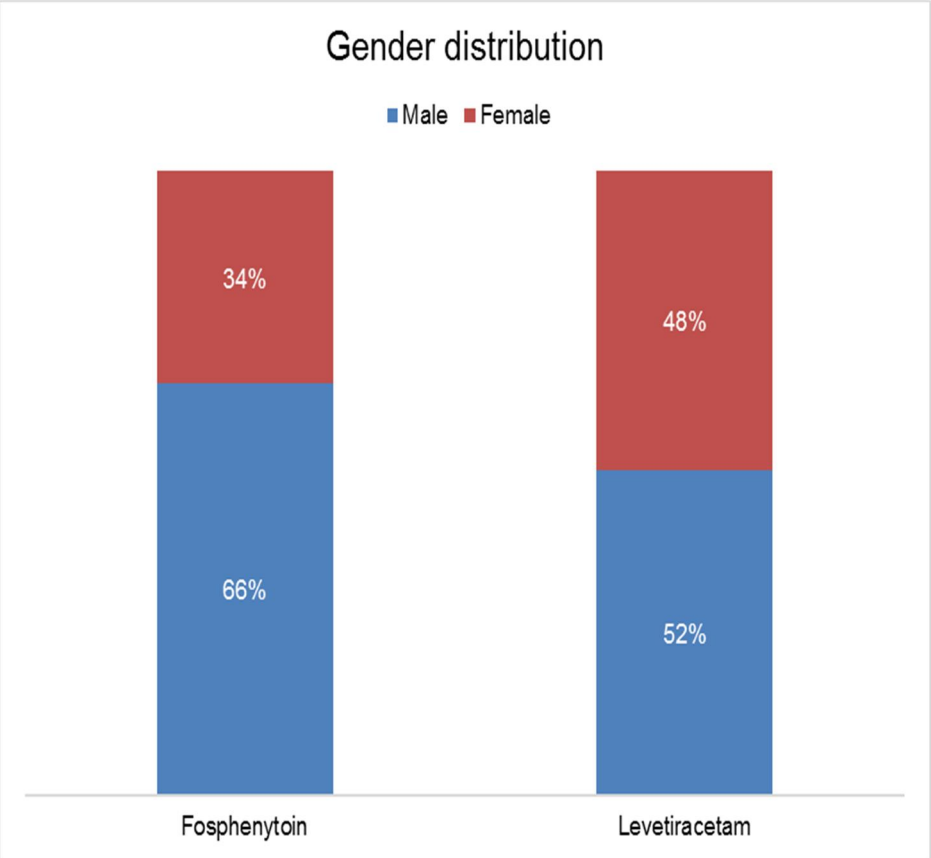


Table 1 and fig 6 shows male in fosphenytoin group were 33(66) and female were 17(34) and male in levetiracetam group were 26(54) and female were 24(46) p value by chi-square is 0.309

Table 2: Age distribution

Drug group	Median with 25th percentile to 75th percentile(months)	p value
Fosphenytoin(n = 50)	30(13.50 to 102.00)	0.730
Levetiracetam(n = 50)	26(13.5 to 84)	

FIGURE 7: AGE DISTRIBUTION

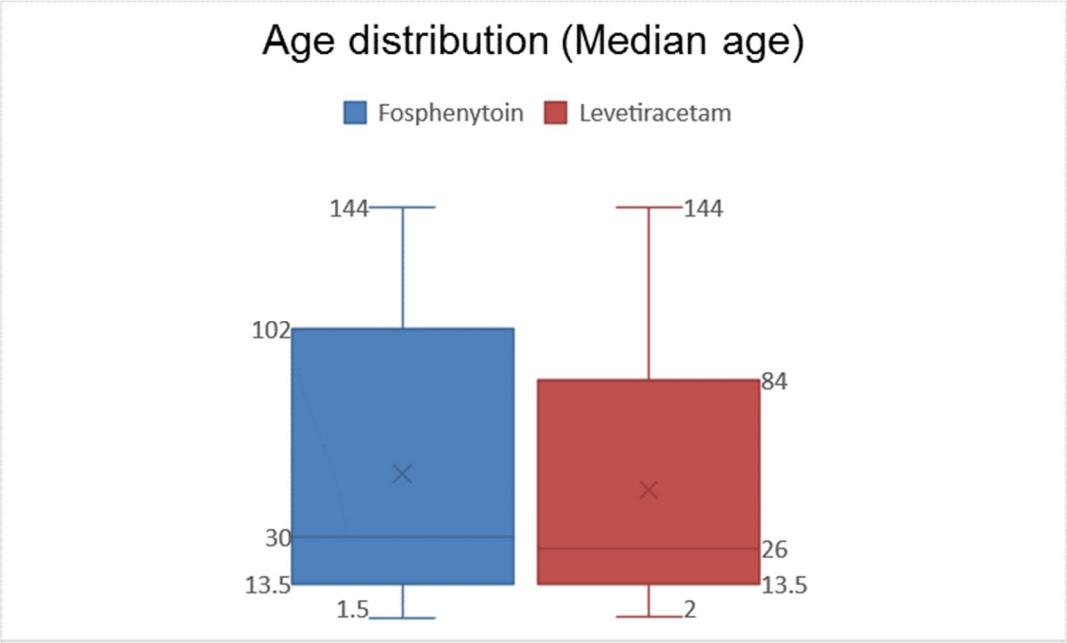


Table 2 and Fig 7 shows - Median age in Fosphenytoin group were 30 months with 25th to 75th interquartile percentile of 13months and 104 months respectively

Median Age in Levetiracetam were 26 months with 25th to 75th interquartile percentile of 13.5 months and 84 months respectively

Median p = 0.730 by Mann Whitney U test

Table 3 :Weight distribution

Drug group	Median with 25th percentile to 75th percentile(months)	p value
Fosphenytoin(n = 50)	12(8.87to 22.00)	0.844
Levetiracetam(n = 50)	12(8.9to19.25)	

FIGURE 8: WEIGHT DISTRIBUTION

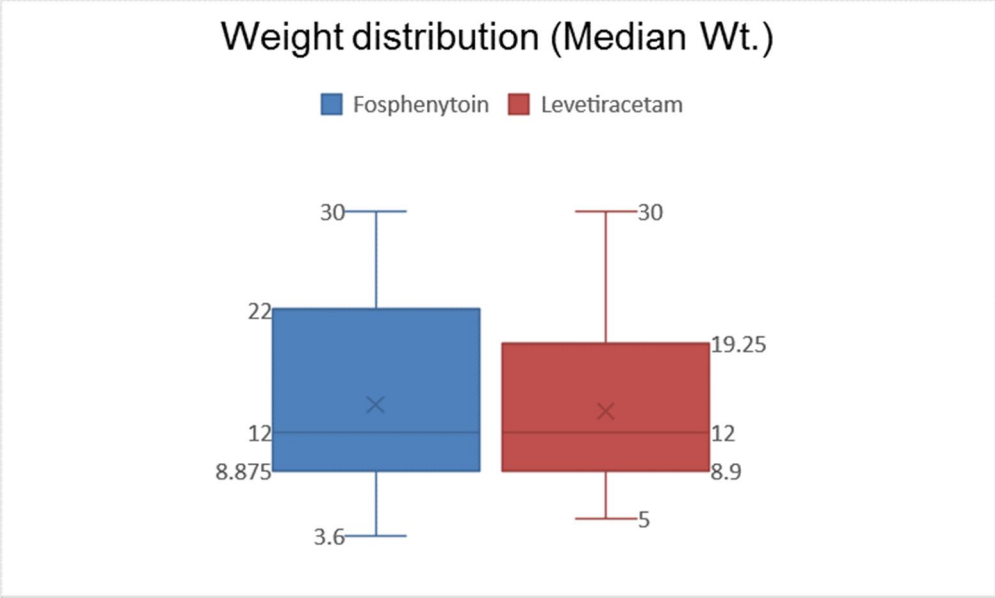


Table 3 and Fig 8 shows Median weight among children in fosphenytoin were 12kg with25th to 75th inter quartile range of 8.8kg to 22 kg respectively

Median weight in levetiracetam group were 12kg with 25th to 75th inter quartile range of 8.9kg to 19.2 kg respectively. p=0.844 by Mann whitney U test

Table 4:History

S.no	Study Parameter	Fosphenytoin N(%)	Levetiracitam N(%)	p value
1.	Fever	26 (52%)	24(48%)	0.689
2.	Type of seizures GTCS	42(84%)	48(96%)	0.133
3	Family h/o Seizure disorder	12 (24%)	8 (16%)	0.269
4.	Development Normal	35 (70%)	33 (66%)	0.668
5.	New Onset of seizures	29 (58%)	31 (62%)	0.711
6.	Birth asphyxia	14 (28%)	12 (24%)	0.648
7.	NICU admission	17 (34%)	16 (32%)	0.832

Table 4 : Among fosphenytoin group 26(52%) were febrile and in levetiracetam group 24(48%) were febrile p value 0.689 , 42(84%) in fosphenytoin group and 48(96%) in levetiracetam group , p value 0.133 presented with GTCS , 12(24%) in fosphenytoin group and 8(16%) in levetiracetam group , p value 0.269 had family history of seizure disorder, 35

(70%) in fosphenytoin group and 33 (66%) in levetiracetam group with p value =0.668 had normal neurological development, 29 (58%) in fosphenytoin group and 31 (62%) in levetiracetam group with p value 0.711 presented with new onset seizures,14 (28%) in fosphenytoin group and 12 (24%) in levetiracetam group p value 0.648 had history of birth asphyxia and 17 (34%) in fosphenytoin group and 16 (32%) in levetiracetam group with p value 0.832 had NICU admission in newborn period.

FIGURE 9: HISTORY

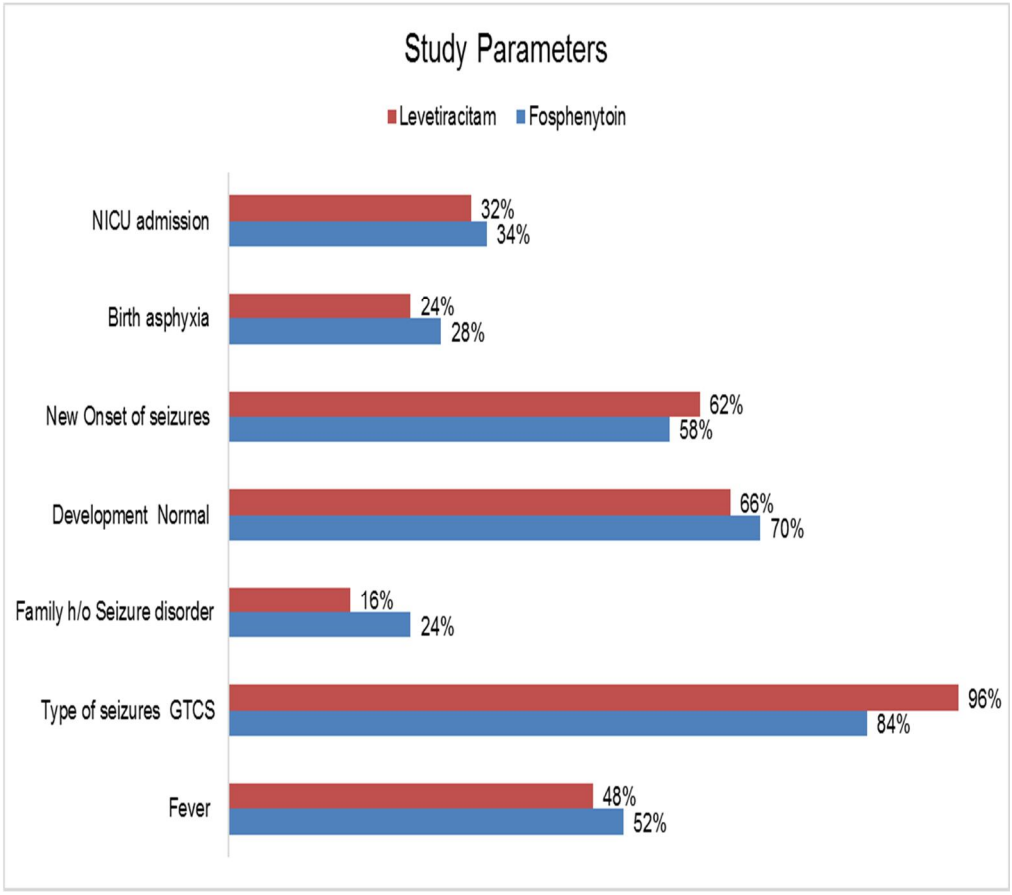


Table 5: Associated illness

Comorbid	Fosphenytoin N(%)	Levetiracetam N(%)	Total
Hypoglycaemia	2 (4)	7 (14)	**9**
ADD	8 (16)	10 (20)	**18**
Skin lesion	1 (2)	3 (6)	**4**
Renal	1 (2)	0	**1**
Liver	1 (2)	0	**1**
Toxin	2 (4)	3 (6)	**5**
Pneumonia	6 (12)	2 (4)	**8**
Vomiting	7(14)	9 (18)	**16**
No	22 (44)	16 (32)	**38**
Total	**50**	**50**	**100**

p value by chi-square 0.471

Among fosphenytoin group 2 (4%) children had hypoglycaemia, 8(16%) had acute diarrhoeal disease, 1 (2%) skin infection (left leg cellulitis), renal disease 1 (2%), liver disease 1 (2%) , toxin – camphor 2 (4%), pneumonia 6 (12%), vomiting 7 (14%) , not associated with any co-morbid illness 20 (40%)

Among levetiracetam group 7 (14%) children had hypoglycaemia , 10

(20%) presented with ADD , 3 (6%) had skin disorder , 3 (6%) had camphor ingestion ,2 (4%) had pneumonia, 9 (18%) presented with vomiting , 18 (36%) had no comorbid illness.

FIGURE 10: ASSOCIATED ILLNESS IN FOSPHENYTOIN GROUP

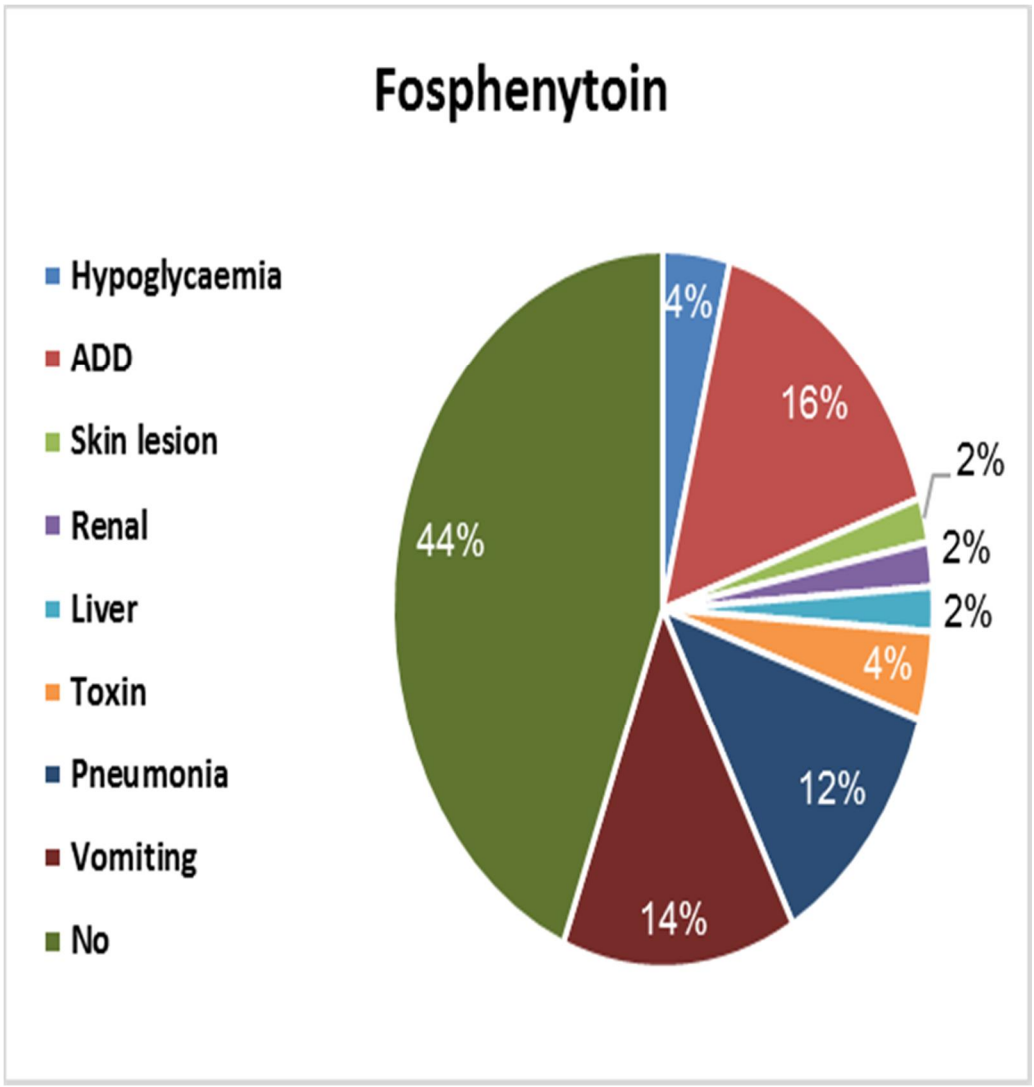


FIGURE 11: ASSOCIATED ILLNESS IN LEVETIRACETAM GROUP

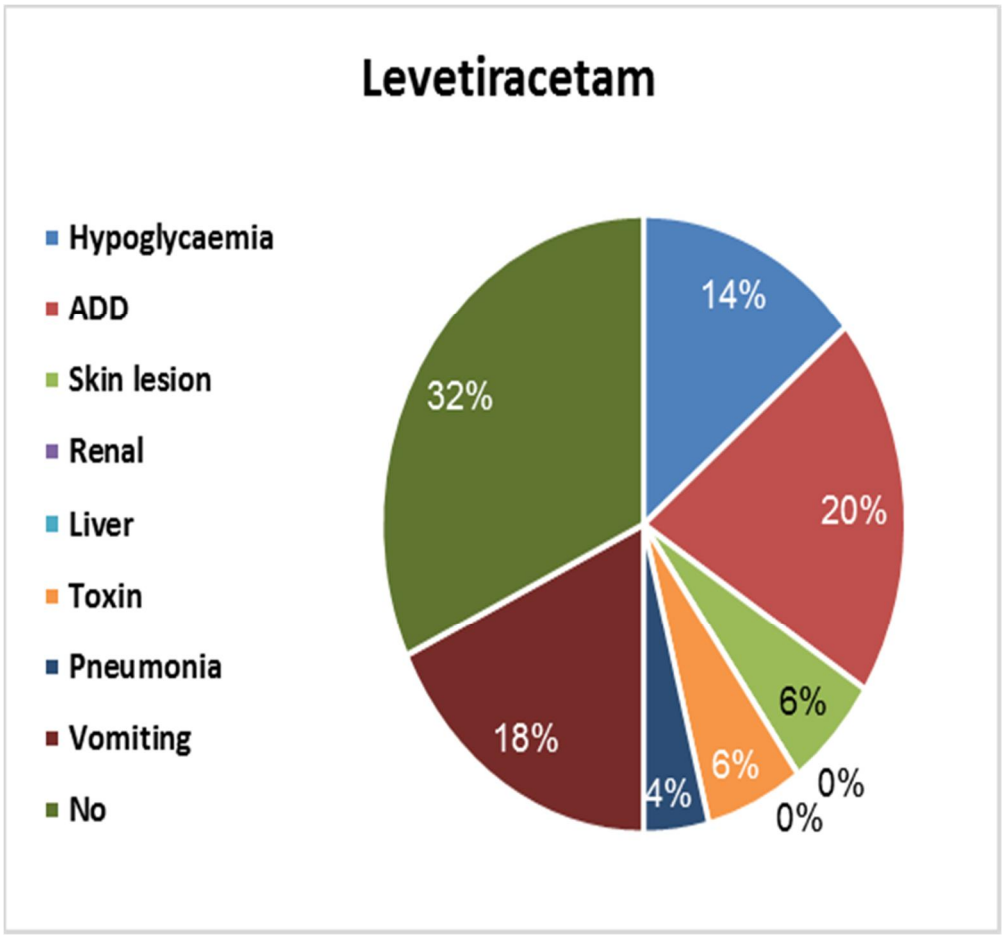


Table 6:Vital signs:

S.no	Study Parameter	Fosphenytoin(n=50)	Levetiracetam(n=50)	p value
1.	Heart rate	122.08±29.64	119.02±30.03	0.609
2.	SBP	104.64±13.04	105.84±13.69	0.655
3.	DBP	61.80±13.04	66.20±12.10	0.084

Table 6- Mean heart rate in fosphenytoin group were 122.08±29.64 and in levetiracetam group were 119.02±30.03 with p value 0.609, mean SBP in fosphenytoin group were 104.64±13.04 and in levetiracetam group were 105.84±13.69, p value 0.655, mean DBP in fosphenytoin group were 61.80±13.04 and in levetiracetam group were 66.20±12.10 p value = 0.084

Table 7: With raised Intra cranial pressure

ICP	Fosphenytoin N(%)	Levetiracetam N(%)	Total	p value
ICP	4 (8)	7 (14)	**11**	0.338
No ICP	46 (92)	43 (86)	**89**	
Total	**50**	**50**	**100**	

Among fosphenytoin group 4(8%) and in levetiracetam group 7(14%) presented with raised ICP with p value 0.338

FIGURE 12: RAISED ICP

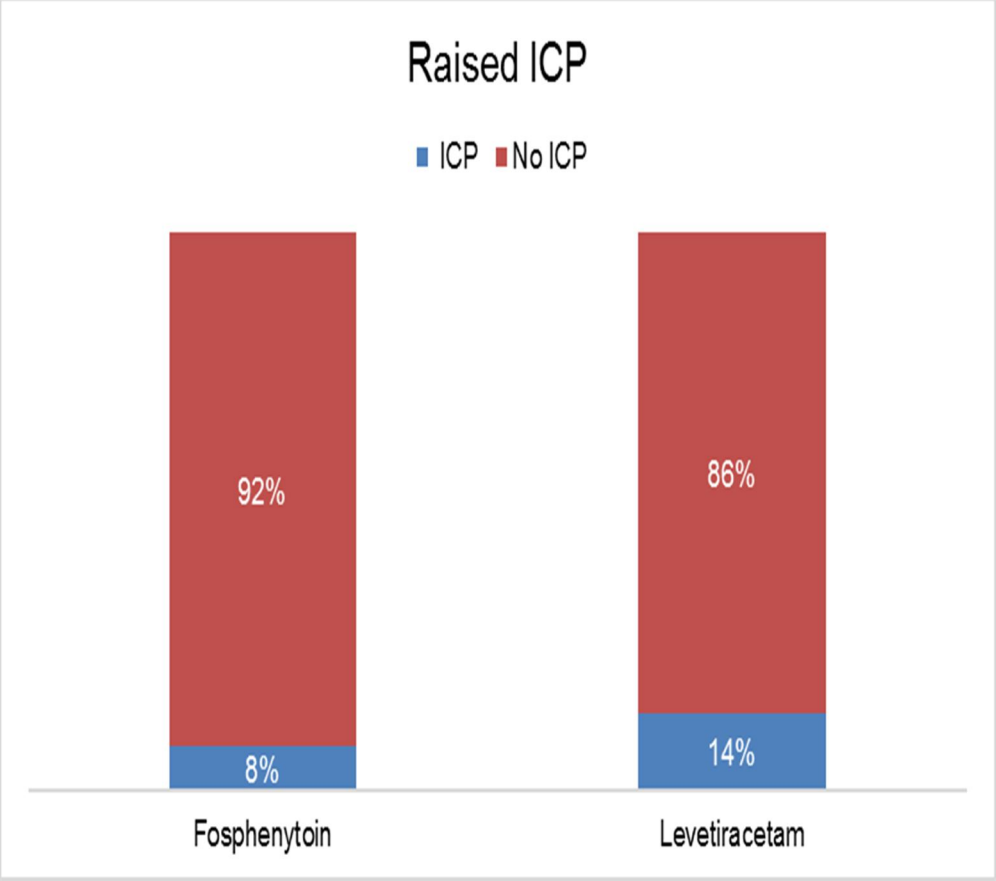


Table 8: Lab parameters

S.no.	Parameter	Fosphenytoin(n=50)	Levetiracetam(n=50)	p value
1.	Sodium	136.32±6.550	132.52±20.55	0.216
2.	Potassium	4.34± 0.885	4.42±1.01	0.669
3.	CBG	148.64 ± 58.9	136.98 ± 46.53	0.275
4.	Total count	11624.40 ±3143.67	12175.96 ± 4042.23	0.448
5.	Hb	9.76 ±1.42	9.54 ± 1.129	0.421

Table 8 shows mean sodium value in fosphenytoin group was 136.32±6.550 whereas in levetiracetam group it was 132.52± 20.55 with p value 0.216, mean potassium value in fosphenytoin group was 4.34± 0.885, in levetiracetam group it was 4.42±1.01 , p value 0.669, mean CBG in fosphenytoin group was 148.64 ± 58.9 and in levetiracetam group it was 136.98 ± 46.53, with p value 0.275, mean total count in fosphenytoin group was 11624.40 ± 3143.67 and in levetiracetam group it was 12175.96 ± 4042.23, p value 0.448 and mean haemoglobin in fosphenytoin group was 9.76 ± 1.42 and in levetiracetam group it was 9.54 ± 1.129 , p value 0.421

Table 9: Seizure control

Seizure	Fosphenytoin N(%)	Levetiracetam N(%)	Total	p value
Control	37((74.0)	28(56.0)	65	0.059
Not Controlled	13(26.0)	22 (44.0)	35	
Total	**50**	**50**	**100**	

37(74%) out of 50 children in fosphenytoin group had control of seizures and 28(56%) out of 50 children in levetiracetam group had control of seizures , 13(26%) in fosphenytoin group and 22(44%) in levetiracetam group did not have seizure control , p value =0.059 .

FIGURE 13: SEIZURE CONTROL

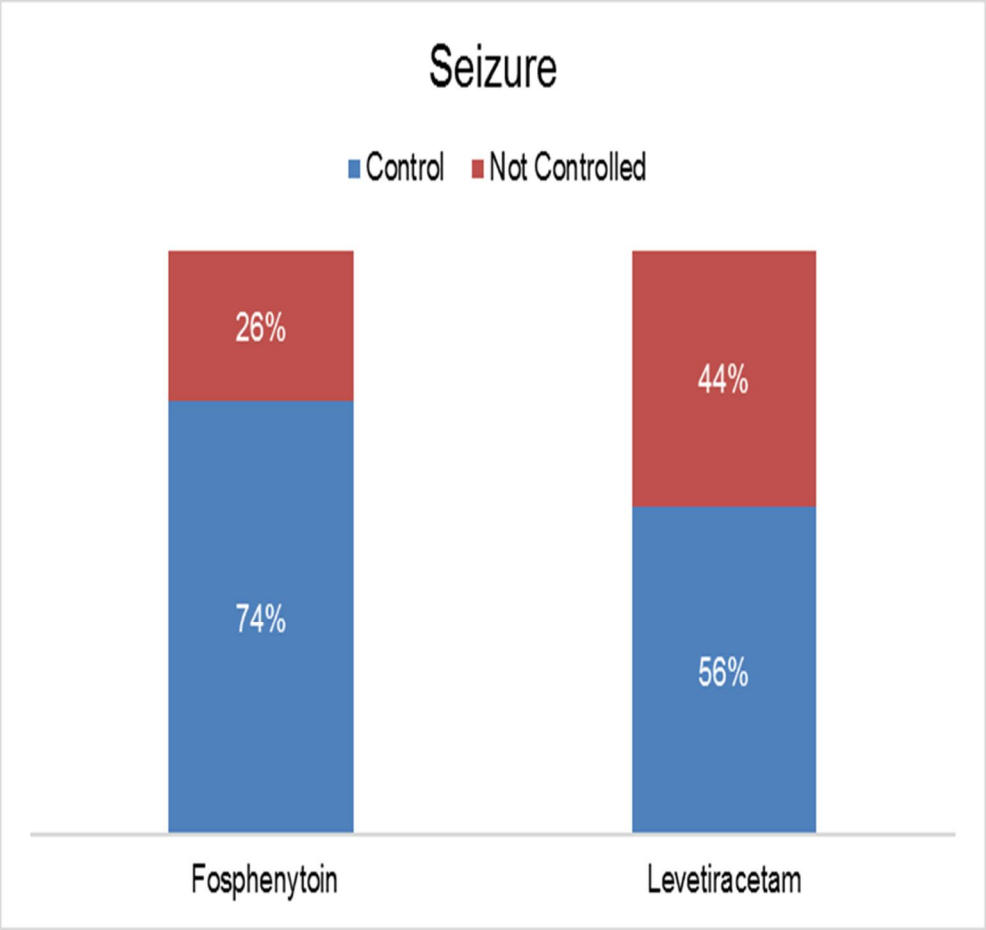


Table 10:Mean Time for Seizure control (n=65)

Drug group	N	Mean±Std. Deviation	p value
Fosphenytoin	37	11.16± 3.58	0.059
Levetiracetam	28	12.78± 3.07	

Note: p value based on independent sample t test

Mean time of seizure control in fosphenytoin group were 11.16+ 3.58

and in levetiracetam group were 12.78+ 3.07 with p value 0.059

Table 11: Shock following AED administration

Shock	Fosphenytoin Group N(%)	Levetiracetam Group N(%)	Total	p value
Shock	14 (28)	11 (22)	**25**	**0.488**
No shock	36 (72)	39(78)	**75**	
Total	**50**	**50**	**100**	

Table 11shows Among fosphenytoin group 14(28%) and 11(22%) in levetiracetam group developed shock and 36(72%) and 39(78%) in each group did not develop shock following infusion of the drug respectively , p value 0.488 by chi- square .

FIGURE 14: SHOCK FOLLOWING AED ADMINISTRATION

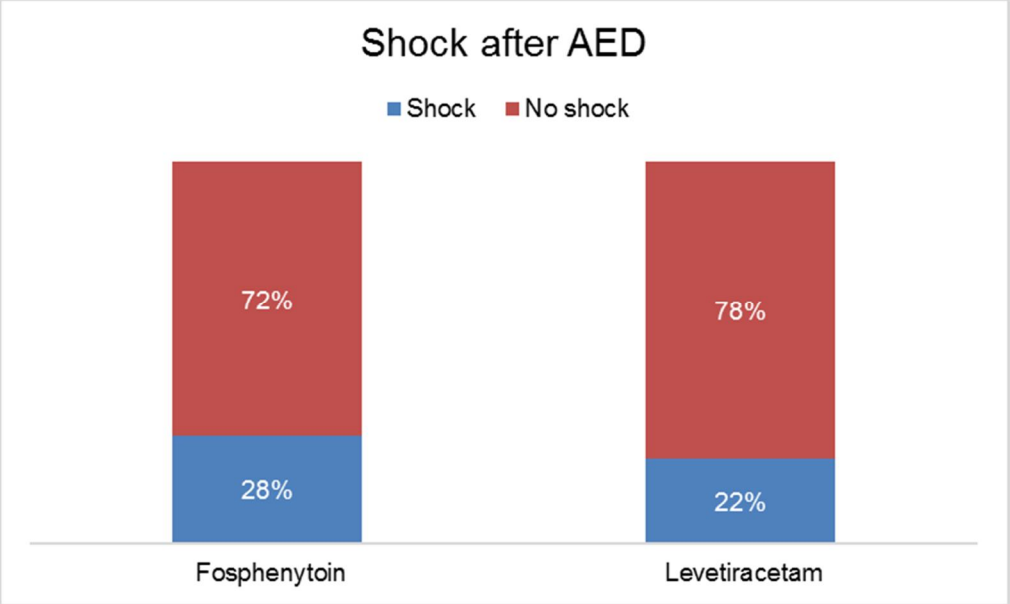


Table 12: Recurrence of seizures< 24 hours

Parameter	Fosphenytoin N(%)	Levetiracetam N(%)	Total	p value
Recurred	18(48.6)	12(42.9)	**30**	0.643
Not recurred	19(51.4)	16(57.1)	**35**	
Total	**37**	**28**	**65**	

Table 12: Among fosphenytoin group 18(48.6%) and 12(42.9%) in levetiracetam group had seizure recurrence within 24 hours and 19(51.4%) and 16(57.1%) had no further seizures in each group respectively , p value 0.643

FIGURE 15: RECURRENCE OF SEIZURES < 24 HOURS

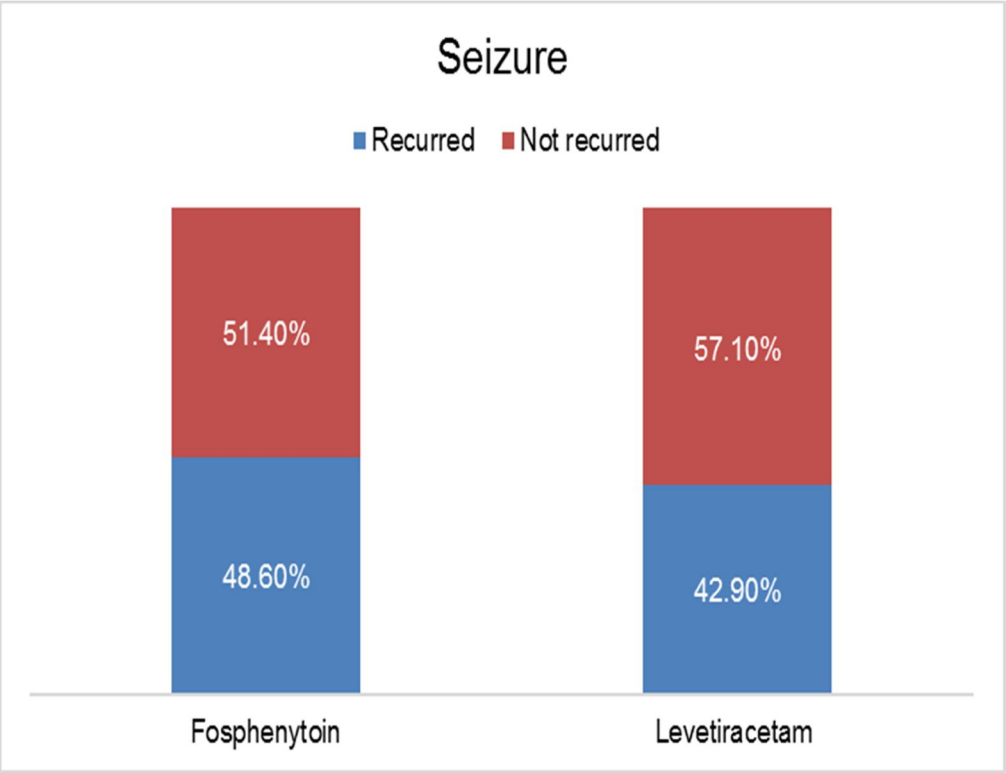


Table 13: Median time for recurrence of seizures

Drug group	Median with 25th percentile to 75th percentile (minutes)	p value
Fosphenytoin (n=18)	60 (30 to 150)	0.966
Levetiracetam (n=12)	65 (22.5 to 320)	

p=0.966 p value based on Mann Whitney U test

Table 13: Median time for seizure recurrence in fosphenytoin group were 60 minutes (30mins to 150mins) and for levetiracetam group were 65 minutes (22.5mins to 320mins) with p value 0.966

FIGURE 16: MEDIAN TIME FOR RECURRENCE OF SEIZURES

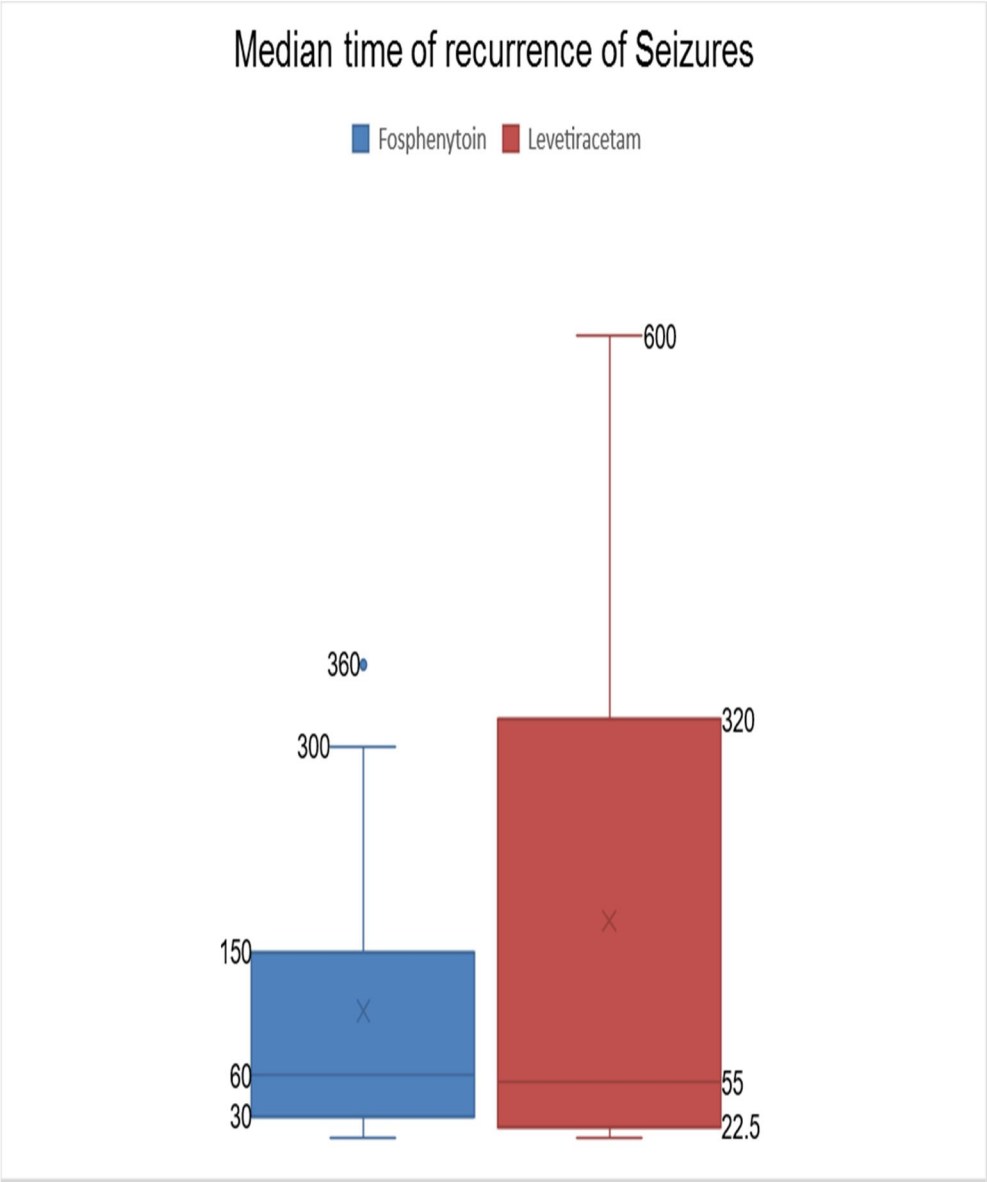


Table 14: Requirement of mechanical ventilation

Parameter	Fosphenytoin (n=50)(n%)	Levetiracetam (n=50) ((n%)	Total	p value
Ventilated	11 (22)	8 (16)	**19**	0.444
Not Ventilated	39 (78)	42 (84)	**81**	
Total	**50**	**50**	**100**	

Table 14: Among fosphenytoin group 11(22%) children among 50 children were mechanically ventilated and 39(78%) did not require mechanical ventilation whereas in levetiracetam group 8(16%) needed ventilator support and 42(84%) did not require ventilator support , p value 0.444

FIGURE 17: REQUIREMENT OF MECHANICALVENTILATION

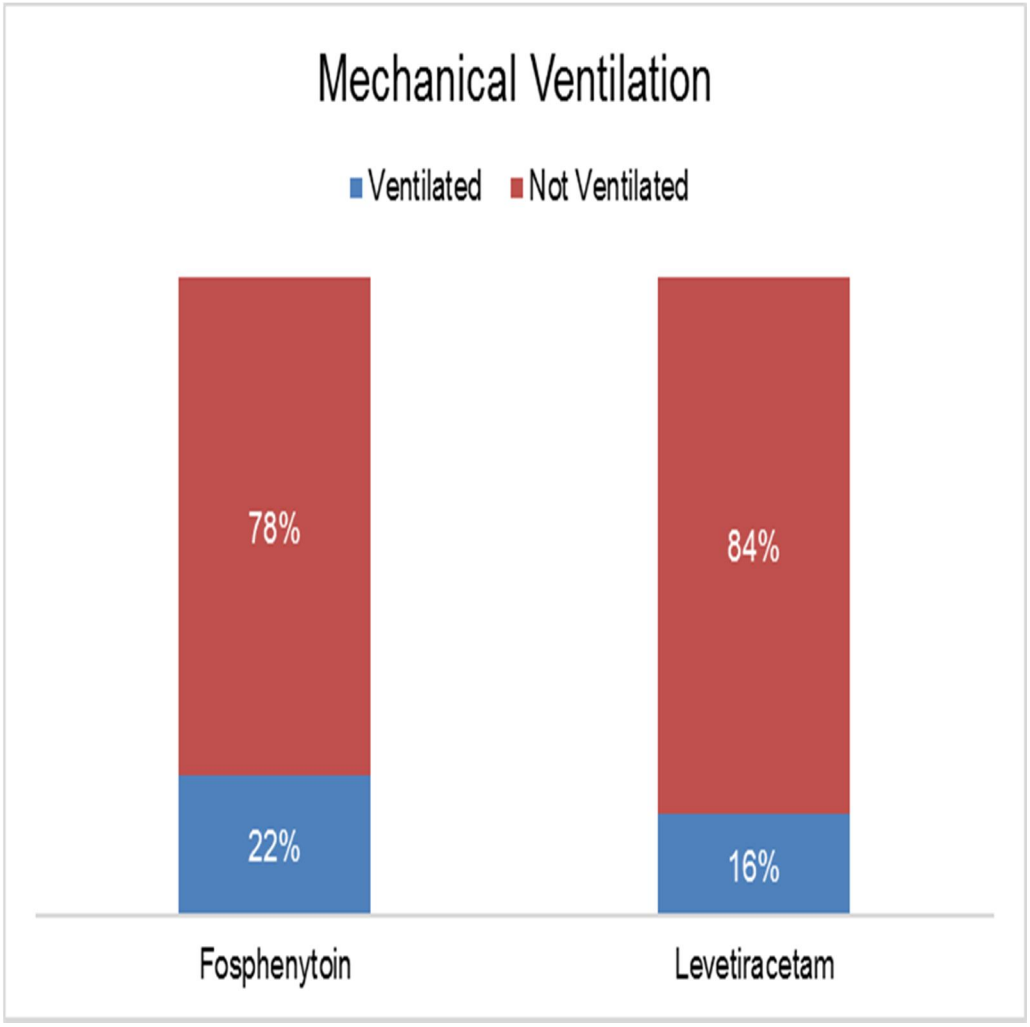


Table 15:Requirement of further AED

AED	Fosphenytoin (n=50) (n%)	Levetiracetam (n=50)(n%)	Total	p value
Did not require	23(46)	23 (46)	**46**	
1 AED	15 (30)	9(18)	**24**	
2 AED	7 (14)	13 (26)	**20**	0.348
3 AED	5 (10)	5 (10)	**10**	
TOTAL	**50**	**50**	**100**	

Table 15: Among fosphenytoin group 23(46%) did not require any further AED , 15(30%) required 1 AED, 7(14%) required 2 AED and 5(10%) required 3 AED , among levetiracetam group 23(46%) did not require any AED , 9(18%) required 1 AED, 13(26%) required 2 AED, 5(10%) required 3 AED further.

FIGURE 18: REQUIREMENT OF FURTHER AED

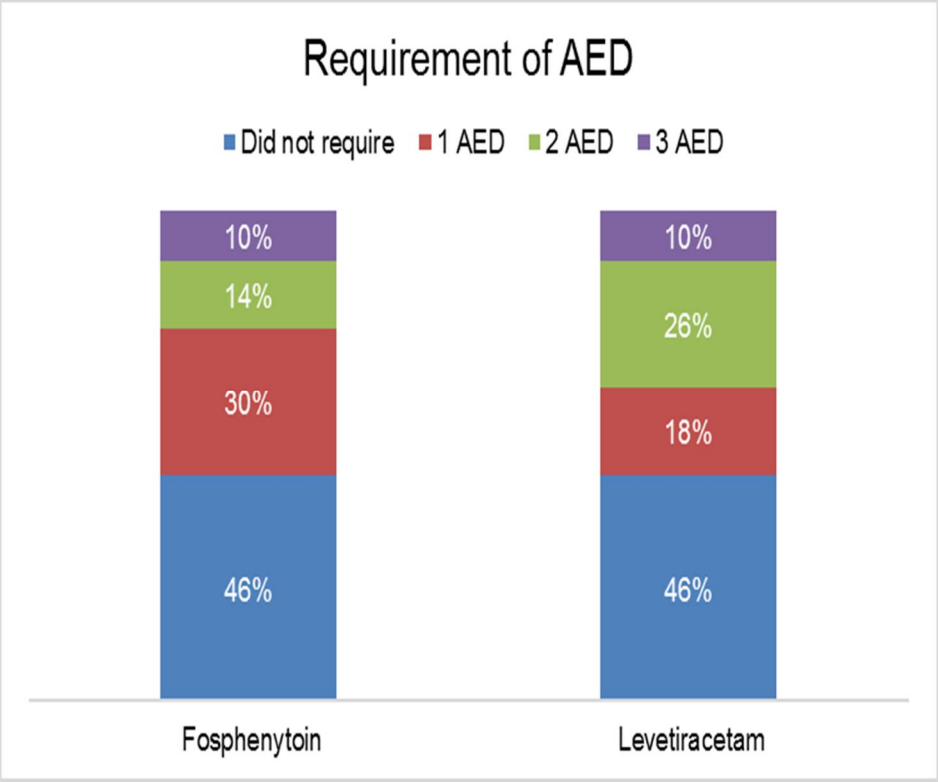


Table 16: Time to Regain GCS 15/15

Drug group	Median with 25th percentile to 75th percentile(hours)	p value
Fosphenytoin(n= 41)	12(6 to 24)	0.164
Levetiracetam(n =44)	18(6 to 48)	

p value by Mann Whitney U test

Median time to regain GCS 15/15 in fosphenytoin group were 12 hours (6 to 24) and in levetiracetam group were 18 hours (6 to 48), p value = 0.164

FIGURE 19: TIME TO REGAIN GCS 15/15

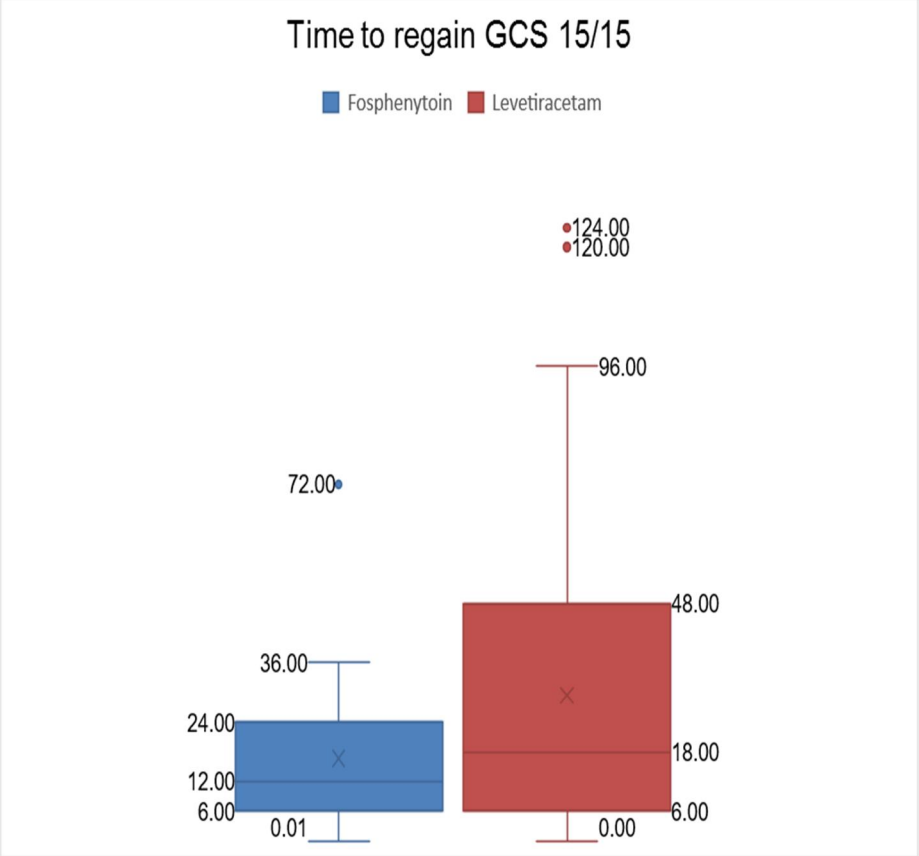


Table 17: Duration of PICU stay

Drug group	Median with 25th percentile to 75th percentile (hours)	p value
Fosphenytoin (n = 50)	89(55.50 to 150.50)	0.907
Levetiracetam (n = 50)	83(52 to 180)	

p=value by Mann Whitney U method

Table 17: total hours of stay in PICU among fosphenytoin group were 89 hours(55.50 to 150.50) and in levetiracetam group were 83 hours (52 to 180), p value 0.907

FIGURE 20: DURATION OF PICU STAY

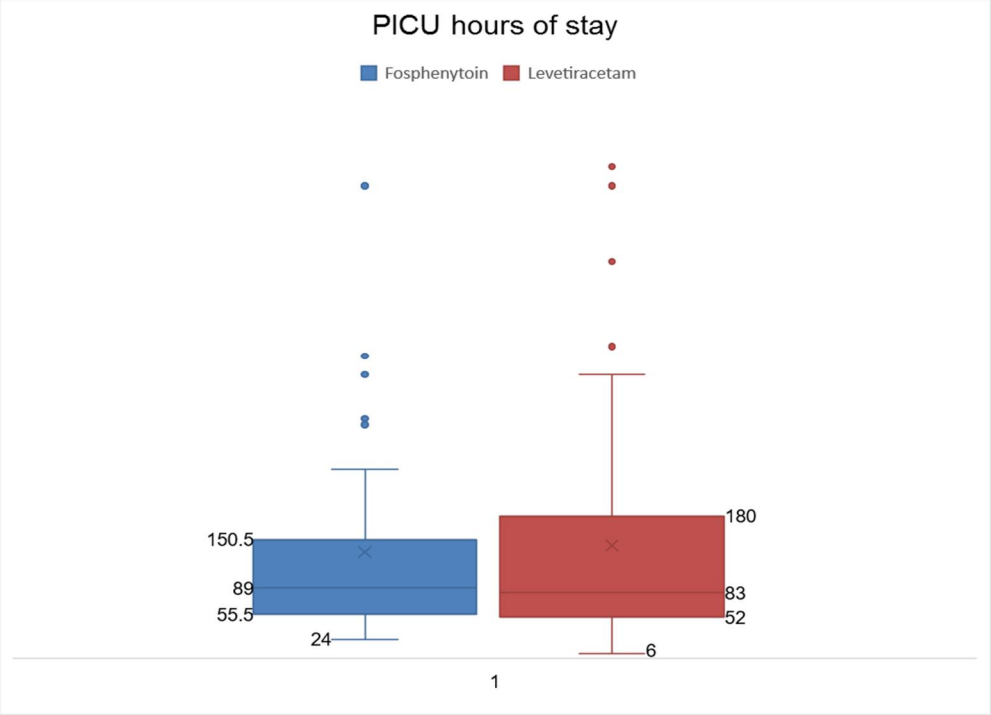


Table 18: Outcome

Outcome	Fosphenytoin (n=50)(n%)	Levetiracetam (n=50)(n%)	Total	p value
Discharged	40 (80)	41 (82)	**81**	0.281
Died	10 (20)	7 (14)	**17**	
Referred	0	2 (4)	**2**	
Total	**50**	**50**	**100**	

Table 18 : 40 (80%) among fosphenytoin group were discharged and 41 (82%) in levetiracetam group were died , 10(20%) in fosphenytoin group and 7 (14%) in levetiracetam group died , p value 0.281, 2(4%) in levetiracetam group were referred

FIGURE 21: OUTCOME IN FOSPHENYTOIN GROUP

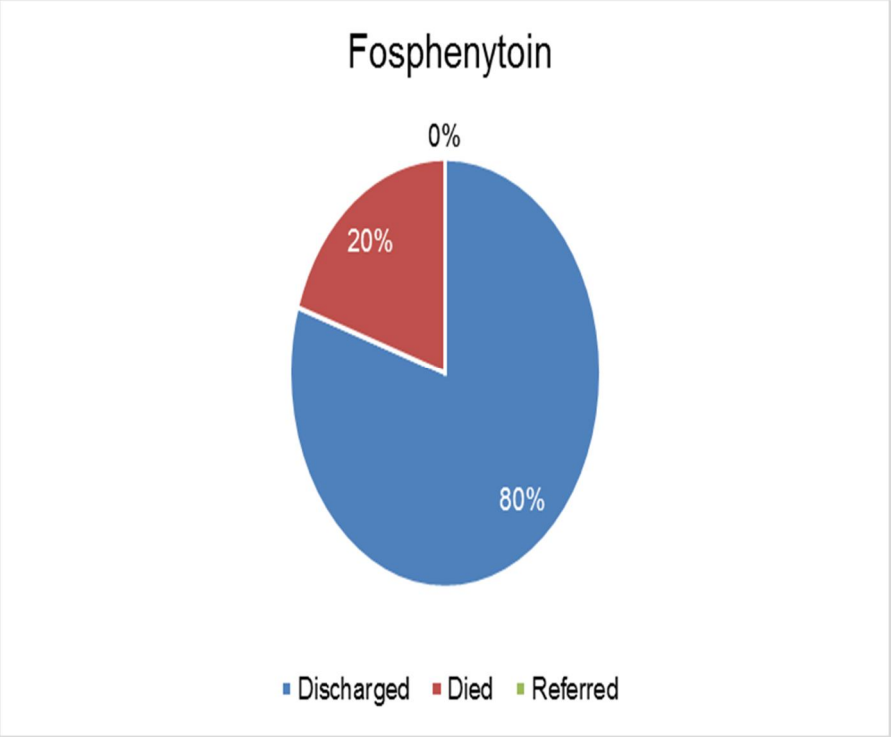


FIGURE 22: OUTCOME IN LEVETIRACETAM GROUP

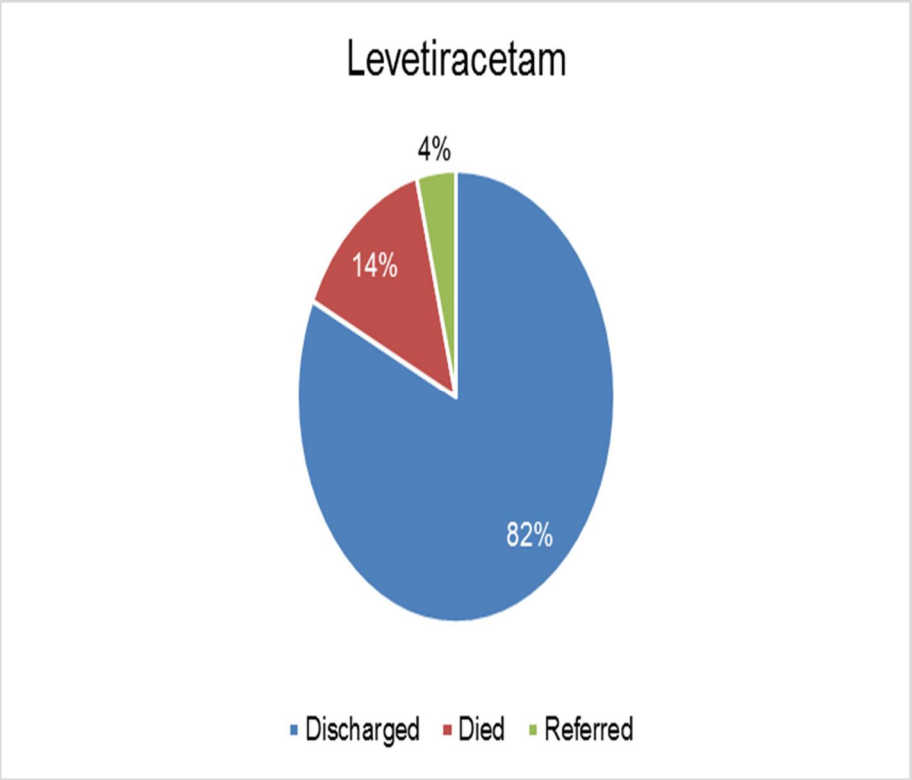


TABLE 19: CAUSE OF DEATH

CAUSE OF DEATH	FOSPHENYTOIN GROUP (N= 10)	LEVETIRACETAM GROUP (N=7)
Acute Meningoencephalitis	4	1
Seizure disorder	2	2
TB Meningitis	1	2
Intracranial tumor	2	-
Intracranial bleed	1	-
Metabolic seizures	-	1
Neurodegenerative disorder	-	1

p value 0.303 , statistically not significant

Table 19: 10 children died in Fosphenytoin group of which 4 children died of acute meningoencephalitis , 2 were Intra Cranial tumour , 1 was due to TB meningitis , 1 due to IC bleed, 2 were due to seizure disorder (drug withdrawal seizures) 7 children in levetiracetam group died of which 2 were TB meningitis , 1 was acute CNS infection , 1 was symptomatic seizures /metabolic (refractory hypocalcemic seizures) , 2 were seizure disorder (breakthrough seizure), and 1 Mitochondrial disorder with refractory seizure.

DISCUSSION

100 children were recruited for the study based on inclusion and exclusion criteria of which 50 children were included in fosphenytoin group and 50 children were included in levetiracetam group. Gender , age , weight , etiology , outcome and complication were compared between two groups. Gender distribution revealed male female ratio of 1.45:1 (59 males versus 41 females) . Overall median age of children in this study were 29 months, with median age of 30 months in fosphenytoin group and 26 months in levetiracetam group. Median weight distribution in both the groups were 12kg(9 to 20 kg)

When the etiology of status epilepticus were analysed, overall most common were drug withdrawal seizures(27), with 14 in fosphenytoin group and 13 in levetiracetam group, second common etiology were acutemeningoencephalitis (17), with 10 in fosphenytoin group and 7 in levetiracetam group, which is similar to a study done by SariceBassin et al[45],[46] on clinical review of status epilepticus in which most common etiology were drug withdrawal seizures (25%) . When the type of seizures,in the study group were analysed it was predominantly found to be GTCS(84% in fosphenytoin group and 96% in levetiracetam group). When the onset of seizures were compared, 60 children had new onset seizures (39 in fosphenytoin group and 21 in levetiracetam group) and 40 had past history of seizures (21in fosphenytoin group and 19 in levetiracetam group) .In this

study most common associated illness were acute diarrhoeal disease 18 (8 in fosphenytoin group and 10 in levetiracetam group) ,followed by vomiting 16(7 in fosphenytoin and 9 in levetiracetam group and pneumonia 8 (6 in fosphenytoin group and 2 in levetiracetam group) whereas in a study done by Puneet Agarwal et al[31] in comparing intravenous valproate and phenytoin in status epilepticus in 100 patient most common associated illness were septicemia (14) and viral fever(8).

Outcome of this study were analysed based on clinical cessation of seizures, mean time for control seizures, shock following AED, recurrence of seizures within 24 hours, mean time for recurrence of seizures, number of further AED further required need for mechanical ventilation and mortality were compared between two groups. children whose seizures controlled at the end of administration of the drug were 65(37 (74%) in fosphenytoin group and 28(56%) in levetiracetam group) with p value 0.059 which was not statistically significant .In a study done by Kensuke nakamura et al[30]comparing levetiracetam and fosphenytoin in status epilepticus in adults 81% in fosphenytoin group and 85.1% in levetiracetam group had control of seizures with p value 0.69 which was statistically not significant and this finding is similar to our study.

Mean time for clinical cessation of seizures were noted and were compared between two groups. Overall mean time for cessation of seizures were 11.86 minutes (fosphenytoin mean time=11.16 ±3.58 minutes and

levetiracetam mean time=12.78±3.07 minutes) . when adverse events were analysed 25% of the children developed shock(fosphenytoin 14(28%) and levetiracetam 11(22%)) with p value 0.488 which was statistically not significant. Among 14 children in fosphenytoin group , 57% required fluid boluses alone and 43% required inotrope and in levetiracetam group 63% required fluid boluses alone 37% required inotrope . seizure recurrence within 24 hours were found in 30 children (18 in fosphenytoin group and 12 in levetiracetam group) with p value 0.643.

Similar to a study done by PuneetAgarwal et al[31] comparing IV valproate and phenytoin in adult patients with status epilepticus showed 6 in valproate group and 8 in phenytoin group had seizure recurrence within 12 hours with p value >0.05 which was also not statistically significant .

Median time for seizure recurrence were 133minutes (fosphenytoin 60 minutes (30mins to 150 mins) and levetiracetam 65 minutes (22.5mins to 320 mins) .In this study 46 children did not require any further AED for seizure control (23 in fosphenytoin and 23 in levetiracetam group) children who required more than two AED (refractory status epilepticus) were 30(12 in fosphenytoin group and 18 in levetiracetam group) . Among those with refractory status epilepticus 6 children in fosphenytoin group had acute meningoencephalitis and 2 children in levetiracetam group were Japanese encephalitis. Children requiring mechanical ventilation were 19 (11(22%) in fosphenytoin group of which one child survived and 10 died) and in

levetiracetam 8(16%) one child survived and 7 died. In a study done by Sudheerchakravarthi[40] et al comparing phenytoin and levetiracetam in adults in status epilepticus 6 out of 22 adults in phenytoin group and 4 out of 22 in levetiracetam group needed mechanical ventilation with p value 0.47 which was not statistically significant. Median time to regain GCS of 15/15were 23.5 hours (in fosphenytoin group were 12 hours (range 6 to 24 hours) and in levetiracetam were 18 hours(6 to 48 hours). Median hours of PICU stay 87 hours (in fosphenytoin89 hours (55.5 to 150.50 hours and in levetiracetam 83 hours (52 to 180hours). Of 100 children in this study group 81 children discharged (fosphenytoin group 40(80%) and 41(82%) in levetiracetam group) and 17 children died (10(20%) in fosphenytoin group and 7(14%) in levetiracetam) . In this study 30 % of the mortality was due to acute meningoencephalitis[47-50] .

SUMMARY

Status epilepticus (SE) is the most common life-threatening childhood neurological emergency. Incidence of status epilepticus is higher in developing countries probably due to CNS infection and more common in children younger than 5 year of age with an incidence of more than 100 per 100,000 children. With the existing literature Benzodiazepines were the first line anticonvulsant in status epilepticus and second line treatment in status epilepticus were phenytoin / fosphenytoin. Phenytoin has the disadvantage of hypotension , arrhythmia, phlebitis, fosphenytoin with less adverse events , newer anticonvulsant levetiracetam which needs less continuous monitoring can be preferred over the other drugs. However limited data were available regarding efficacy and safety of levetiracetam in children . Very few studies were only available comparing levetiracetam and fosphenytoin and with literature search no study were available comparing levetiracetam and fosphenytoin in children, this study was conducted among children with status epilepticus who were refractory to two doses of benzodiazepines. 100 children were included in the study group according to inclusion and exclusion criteria with 50 in fosphenytoin group and 50 in levetiracetam group. Two groups were compared with respect to clinical cessation of seizures, time to control seizures, shock following AED, recurrence of seizures within 24 hours, mean time for recurrence of seizures , need for mechanical ventilation, time to regain GCS 15/15, total hours of PICU stay and complications were analysed and was found statistically not significant.

Thus levetiracetam was found to be as effective as fosphenytoin , with better tolerability as compared to fosphenytoin. Intravenous levetiracetam can be used as second line drug in status epilepticus among children after benzodiazepine failure.

CONCLUSION

In this study comparing levetiracetam and fosphenytoin in status epilepticus in children it was found that levetiracetam is equally effective as fosphenytoin with respect of cessation of seizures, time to control seizures, shock following AED, recurrence of seizures within 24 hours, mean time for recurrence of seizures , need for mechanical ventilation, time to regain GCS 15/15, total hours of PICU stay and complications. With the ease of administration and and lesser need for continuous monitoring during infusion, levetiracetam can very well be used as an alternative 2nd line drug in status epilepticus in children**.**

LIMITATIONS

1. This a open label study, however it would have been more preferable to do a double blinded study
2. EEG confirmation of cessation of seizures could have been more scientific .
3. Convulsion Recurrence was determined by the presence/ absence of convulsive/non-convulsive seizures however subclinical seizures could have been documented if 24 hours continuous EEG were done.

RECOMMENDATION

Levetiracetam can be used as a second line drug in the place of fosphenytoin in status epilepticus among children.

BIBLIOGRAPHY

1. Novorol CL, Chin RFM, Scott RC. Outcome of convulsive status epilepticus: a review. Arch Dis Child. 2007;92:948–951. doi: 10.1136/adc.2006.107516.

2. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368(9531):222–229. doi: 10.1016/S0140-6736(06)69043-0

3. Expert Committee on Pediatric Epilepsy, Indian Academy of Pediatrics. Guidelines for diagnosis and management of childhood epilepsy. Indian Pediatr. 2009;46:681-98.

4. Epilepsy Foundation of America's Working Group on Status Epilepticus. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. J Am Med Assoc. 1993; 270:854-59.

5. Sadarangani M, Seaton C, Scott JA, Ogutu B, Edwards T, Prins A, Gatakaa H, Idro R, Berkley JA, Peshu N, Neville BG. Incidence and outcome of convulsive status epilepticus in Kenyan children: a cohort study. The Lancet Neurology. 2008 Feb 29;7(2):145-50.

6. Gilbert DL, Gartside PS, Glauser TA. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in

children: a meta-analysis. Journal of child neurology. 1999 Sep;14(9):602-9.

7. Epilepsy Foundation of America's Working Group on Status Epilepticus. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. J Am Med Assoc. 1993; 270:854-59.

8. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia. 1993;34:592-96.

9. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999; 40:120-2.

10. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015 Oct 1;56(10):1515-23.

11. Aicardi J, Chevrie J. Convulsive status epilepticus in infants and children. Epilepsia. 1970 Jun 1;11(2):187-97.

12. Lowenstein DH, Alldredge BK. Status epilepticus. New England Journal of Medicine. 1998 Apr 2;338(14):970-6.

13. Treiman DM. Electroclinical features of status epilepticus. Journal of Clinical Neurophysiology. 1995 Jul 1;12(4):343-hyhen.

14. Capovilla G, Beccaria F, Beghi E, Minicucci F, Sartori S, Vecchi M.

Treatment of convulsive status epilepticus in childhood: Recommendations of the Italian League Against Epilepsy. Epilepsia. 2013;54:23-34.

15. Tripathi M, Vibha D, Choudhary N, Prasad K, Srivastava MV, Bhatia R, *et al*. Management of refractory status epilepticus at a tertiary care centre in a developing country. Seizure. 2010;19:109-11.

16. Mishra D, Sharma S, Sankhyan N, Konanki R, Kamate M, Kanhare S, et al. Consensus guidelines on management of childhood convulsive status epilepticus. Indian Pediatr. 2014; 51: 975-990.

17. Maegaki Y, Kurozawa Y, Hanaki K, Ohno K. Risk factors for fatality and neurological sequelae after status epilepticus in children. Neuropediatrics. 2005 Jun;36(03):186-92.

18. Fountain NB. Status epilepticus: risk factors and complications. Epilepsia. 2000;41:S23-30.

19. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. New England Journal of Medicine. 2001 Aug 30;345(9):631-7.

20. Wilder BJ, Ramsay RE, Willmore LJ, Feussner GF, Perchalski RJ, Shumate JB. Efficacy of intravenous phenytoin in the treatment of status epilepticus: kinetics of central nervous system penetration. Annals of neurology. 1977 Jun 1;1(6):511-8.

21. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE. A comparison of four treatments for generalized convulsive status epilepticus. New England Journal of Medicine. 1998 Sep 17;339(12):792-8.

22. Knake S, Gruener J, Hattemer K, Klein KM, Bauer S, Oertel WH, Hamer HM, Rosenow F. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. Journal of Neurology, Neurosurgery & Psychiatry. 2008 May 1;79(5):588-9.

23. Santhanam I, editor. Pediatric Emergency Medicine Course (PEMC). JAYPEE BROTHERS PUBLISHERS; 2013.

24. Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, *et al*. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345:631-7.

25. Ahmad S, Ellis JC, Kamwendo H, Molyneux E. Efficacy and safety ofintranasallorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomized trial. Lancet. 2006;367:1591-7.

26. Dreifuss FE, Rosman NP, Cloyd JC, Pellock JM, Kuzniecky RI, Lo WD, *et al*. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med. 1998;338:1869-75.

27. Cereghino JJ, Mitchell WG, Murphy J, Kriel RL, Rosenfeld WE, Trevathan E. Treating repetitive seizures with a rectal diazepam formulation: a randomized study. The North American Diastat Study Group. Neurology. 1998;51:1274-82.

28. Pellock JM. Safety of Diastat, a rectal gel formulation of diazepam for acute seizure treatment. Drug Saf. 2004; 27:383-92.

29. Holsti M, Sill BL, Firth SD, Filloux FM, Joyce SM, Furnival RA. Prehospital intranasal midazolam for the treatment of pediatric seizures. PediatrEmerg Care. 2007;23:148-53.

30. Nakamura K, Inokuchi R, Daidoji H, Naraba H, Sonoo T, Hashimoto H, Tokunaga K, Hiruma T, Doi K, Morimura N. Efficacy of levetiracetam versus fosphenytoin for the recurrence of seizures after status epilepticus. Medicine. 2017 Jun;96(25).

31. Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure. 2007 Sep 30;16(6):527-32. Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: Comparison of phenytoin, valproate, and levetiracetam. Epilepsia. 2011 Jul 1;52(7):1292-6.

33. Berning S, Boesebeck F, Van Baalen A, Kellinghaus C. (2009) Intravenous levetiracetam as treatment for status epilepticus. *J Neurol* **256**:1634–1642.

34. Novy J, Logroscino G, Rossetti AO. (2010) Refractory status

epilepticus: a prospective observational tudy. *Epilepsia* 51:251– 256.

35. Pilz C, Dreyer R. (1969) Results of parenteral diphenylhydantoin therapy of status epilepticus from the years 1959–1965. *Arch PsychiatrNervenkr* 212:254–270.

36. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. Journal of neurology. 2012 Apr 1;259(4):645-8.

37. DeSmedt T, Raedt R, Vonck K, Boon P (2007) Levetiracetam: part II, the clinical profile of a novel anticonvulsant drug. CNS Drug Rev 13(1):57–78

38. Ng YT, Hastriter EV, Cardenas JF, Khoury EM, Chapman KE (2010) Intravenous levetiracetam in children with seizures: a prospective safety study. J Child Neurol 25:551–555

39. O'Brien TJ, Cascino GD, So EL, Hanna DR (1998) Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. Neurology 51:1034–1039

40. Chakravarthi S, Goyal MK, Modi M, Bhalla A, Singh P. Levetiracetam versus phenytoin in management of status epilepticus. Journal of Clinical Neuroscience. 2015 Jun 30;22(6):959-63.

41. Khongkhatithum C, Thampratankul L, Wiwattanadittakul N, Visudtibhan A. Intravenous levetiracetam in Thai children and adolescents with status epilepticus and acute repetitive seizures.

european journal of paediatric neurology. 2015 Jul 31;19(4):429-34.

42. Lee SY, Jung KY, Lee IK, Yi SD, Cho YW, Kim DW, Hwang SS, Kim S. Prevalence of treated epilepsy in Korea based on national health insurance data. Journal of Korean medical science. 2012 Mar 1;27(3):285-90.

43. Ogutu BR, Newton CR, Muchohi SN, Otieno GO, Edwards G, Watkins WM, Kokwaro GO. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. British journal of clinical pharmacology. 2003 Jul 1;56(1):112-44. Lyttle MD, Gamble C, Messahel S, Hickey H, Iyer A, Woolfall K, Humphreys A, Bacon NE, Roper L, Babl FE, Dalziel SR. Emergency treatment with levetiracetam or phenytoin in status epilepticus in children—the EcLiPSE study: study protocol for a randomised controlled trial. Trials. 2017 Jun 19;18(1):283.

45. Bassin S, Smith TL, Bleck TP. Clinical review: status epilepticus. Critical Care. 2002 Mar 15;6(2):137.

46. Krumholz A: Epidemiology and evidence for morbidity of non-convulsive status epilepticus. *J ClinNeurophysiol* 1999, **16:** 314-322. 10.1097/00004691-199907000-00003

47. Boggs JG, Painter JA, DeLorenzo RJ: Analysis of electrocardiographic changes in status epilepticus**.***Epilepsy Res* 1993, 14: 87-94. 10.1016/0920-1211(93)90077-K

48. Boggs JG, Marmarou A, Agnew JP, Morton LD, Towne AR,

Waterhouse EJ, Pellock JM, DeLorenzo RJ**:** Hemodynamic monitoring prior to and at the time of death in status epilepticus. *Epilepsy Res* 1998, 31: 399-409. 10.1016/S0920-1211(98)00031-X

49. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994;35: 27–34. [PubMed]

50. Aicardi J, Chevrie J. Convulsive status epilepticus in infants and children. Epilepsia. 1970 Jun 1;11(2):187-97.

ANNEXURES

1.PROFORMA

CHENGALPATTU GOVERNMENT MEDICAL COLLEGE AND HOSPITAL

DEPARTMENT OF PEDIATRICS

IP NO:

Name :

Age :

Sex :

Weight :

HISTORY :

Presenting illness	Yes	No	Duration
Fever			
Onset			
Developmental history			
Family history of seizures			
Comorbid conditions			
History of birth asphyxia			

NICU admission			
History of oral AED			

ON EXAMINATION

Paramaters	Yes	No
GCS		
Heart rate		
Systolic BP		
Diastolic BP		
Pulse pressure		
ICP		
Other system involvement		

Study Parameters	LEVETIRACETAM	FOSPHENYTOIN
Time to control seizures (mins)		
Stopped (yes or no)		
Recurred (yes or no)		
Time for recurrence (mins)		
No.of episodes		

Shock following AED (yes or no)		
Time taken to regain GCS 15/15		
Mechanical Ventilation		

Investigations	Elevated	Decreased	Normal
Total count			
Hb			
Platelet			

MRI BRAIN	
CT BRAIN	
LP FINDINGS	
EEG	

- HOSPITALSTAY:
- INOTROPE SUPPORT:
- FINALOUTCOME:

FINAL DIAGNOSIS

2.CONSENT FORM

COMPARISON OF LEVITIRACETAM AS A SECOND LINE DRUG IN PLACE OF FOSPHENYTOIN IN STATUS EPILEPTICUS AMONG CHILDREN

STUDY CENTER: CHENGALPATTU MEDICAL COLLEGE &

HOSPITAL, CHENGALPATTU

PATIENTNAME: PATIENT AGE:

IDENTIFICATIONNUMBER: FATHER'SNAME:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I understand that my child participation in the study is voluntary and that I am free to withdraw my child at anytime without giving any reasons, without my legal rights being affected.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if withdraw from the study, I understand that my child identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I agree my child to take part in the above study and to comply with the instructions given during the study and faithfully cooperative with the study team and to immediately inform the study staff if my child suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms.

I hereby give consent for my child to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic test on my child .

Signature/Thumb impression: Place:

Parent name and address: Date:

Signature of the investigator: Place:

Study investigator's name: Date:

Since the child was on altered level of consciousness assent was also obtained from the parent.

3. Master Chart

S.no	Gender	Weight	Age	Fever	Type	Neuro D	Onset	Family h	Comorbi	Birth As	Nicu adr	Dev	On oral	HR	BP	SBP	DBP	ICP	Refer	AED	Time to	Stop
1	2	6.5	6	2	4	1	1	3	11	2	1	1	NO	64	160/100	160	100	1	1	1	8	1
2	1	25	144	2	1	1	1	3	2	2	2	1	NO	128	100/60	100	60	2	2	2	15	1
3	1	23	120	2	1	1	2	3	11	2	2	1	SVP	98	102/50	102	50	2	2	1	14	1
4	1	30	144	2	1	1	1	3	2	2	2	1	NO	128	110/60	110	60	2	4	2	15	1
5	1	20	108	2	6	1	1	3	10	2	2	1	NO	89	90/60	100	60	2	4	2	0	2
6	2	7	8	1	1	1	1	3	11	2	2	1	NO	136	80/60	90	60	2	2	1	15	1
7	2	9	18	2	1	1	1	3	6	2	2	1	NO	102	100/50	100	50	2	4	2	10	1
8	1	12	24	1	6	1	1	3	2	2	2	1	NO	99	90/60	90	60	2	1	1	6	1
9	2	8	12	2	1	1	4	2	2	2	2	1	NO	87	80/60	80	60	2	3	2	16	1
10	1	8.5	14	1	1	2	2	3	11	1	1	2	PBT	85	90/50	90	50	2	3	1	0	2
11	1	22	84	1	1	2	3	3	11	2	2	2	SVP AND	132	100/70	100	70	2	4	1	18	1
12	1	20	72	2	1	1	2	3	10	2	2	1	SVP	98	110/80	110	80	2	4	2	0	2
13	2	22	96	2	1	1	3	3	2	2	2	1	SVP AND	86	108/80	108	80	2	4	2	12	1
14	1	8	12	1	1	1	4	2	11	2	2	1	NO	112	90/60	100	60	2	4	1	7	1
15	1	8	14	1	1	1	1	3	10	2	2	1	NO	140	102/70	110	70	2	4	2	8	1
16	1	20	84	1	1	1	1	3	10	2	2	1	NO	76	120/70	120	70	2	1	1	0	2
17	1	12	24	1	1	1	1	3	11	2	2	1	NO	142	100/80	100	80	2	4	2	18	1
18	1	24	108	1	1	1	1	3	10	2	2	1	NO	102	100/70	100	70	2	2	2	15	1
19	1	25	120	2	1	1	1	3	10	2	2	1	NO	98	900/70	100	70	2	4	2	0	2
20	1	25	144	1	1	1	1	3	11	2	2	1	NO	100	110/40	110	40	2	4	1	18	1
21	2	7	7	1	1	1	1	3	11	2	2	1	NO	132	80/50	90	50	2	4	2	12	1
22	1	13	36	1	1	1	1	3	11	2	2	1	NO	140	90/70	110	70	1	2	1	0	2
23	2	9	10	2	1	2	2	3	11	2	1	1	clobazam	138	100/60	100	60	2	4	2	0	2
24	2	6.5	6	1	1	1	1	3	11	2	2	1	NO	186	90/70	90	70	2	4	2	10	1
25	1	22	120	1	1	1	1	3	10	2	2	2	NO	100	100/60	100	60	2	2	1	0	2
26	2	23	132	2	1	2	2	3	11	1	1	1	SVP	110	110/50	110	50	2	4	2	0	2
27	2	10	24	1	1	2	1	3	3	2	2	2	NO	142	106/50	106	50	2	2	2	0	2
28	2	18	96	2	1	2	2	3	9	1	1	2	PBT	128	90/50	100	50	2	4	1	12	1
29	1	10	24	2	1	2	1	3	11	2	2	2	NO	142	110/60	110	60	2	4	2	0	2
30	2	13	36	2	1	2	4	3	11	1	1	2	NO	154	102/70	102	70	2	3	1	0	2
31	2	9	18	2	1	2	1	3	11	2	1	2	NO	160	90/60	100	60	2	3	2	10	1
32	2	6.5	7	1	1	2	1	3	2	2	2	2	NO	156	90/60	120	60	2	4	1	10	1
33	2	12	32	1	1	1	1	3	11	2	2	2	NO	94	110/50	110	50	2	4	2	15	1

S.no	Gender	Weight	Age	Fever	Type	Neuro De	Onset	Family h	Comorbi	Birth As	Nicu adr	Dev	On oral a	HR	BP	SBP	DBP	ICP	Refer	AED	Time to	Stop
34	2	25	120	2	1	1	2	3	11	2	2	1	SVP AND	122	100/60	100	60	2	4	1	6	1
35	2	20	84	1	1	1	2	1	11	2	2	1	clobazam	142	110/50	110	50	2	1	2	10	1
36	2	7	8	1	1	2	2	1	11	2	2	1	SVP	130	90/60	90	60	2	2	2	8	1
37	1	6	6	1	1	1	1	3	9	2	2	1	NO	80	110/60	110	60	2	4	1	10	1
38	1	19	96	1	1	1	1	3	11	2	2	1	NO	94	100/60	100	60	2	4	2	12	1
39	1	10.5	30	2	1	2	2	3	10	1	1	2	PBT	106	102/50	102	50	2	4	1	10	1
40	2	7.5	11	2	2	2	2	3	10	1	1	1	clobazam	110	90/20	120	20	2	4	1	8	1
41	1	30	144	2	1	1	2	1	11	2	2	1	SVP	115	100/50	100	50	2	4	1	14	1
42	1	25	120	2	1	1	1	1	11	1	1	1	NO	105	110/40	110	40	2	4	1	10	1
43	1	12	28	1	1	1	1	3	2	2	2	2	NO	156	106/70	106	70	2	4	2	0	2
44	2	18	84	1	6	1	1	3	11	2	2	1	NO	62	120/70	120	70	1	2	2	8	1
45	1	24	120	1	1	1	1	3	10	2	2	1	NO	56	106/60	106	60	1	1	1	0	2
46	1	8	8	1	1	1	1	3	9	1	1	1	NO	128	110/70	110	70	1	1	2	15	1
47	1	10	18	1	1	1	1	1	10	2	2	1	NO	156	90/60	130	60	2	1	1	12	1
48	1	9	10	1	1	1	1	1	2	2	2	1	NO	170	80/50	90	50	2	2	1	10	1
49	1	7	8	1	1	1	4	2	2	2	2	1	PBT	165	110/60	110	60	2	1	2	0	2
50	2	14	30	1	1	1	1	3	2	2	1	1	NO	108	100/80	100	80	2	2	2	12	1
51	1	10	20	2	1	2	2	1	11	1	1	4	PBT	158	110/50	110	50	2	2	1	8	1
52	2	8	10	1	1	2	2	2	1	1	1	1	NO	145	108/80	108	80	2	1	2	0	2
53	2	24	144	1	1	2	2	1	10	1	1	2	SVP AND	108	116/70	116	70	2	2	2	0	2
54	1	13	36	2	1	2	2	1	2	1	1	4	SVP AND	116	120/70	120	70	2	2	2	13	1
55	2	12	30	1	2	2	3	1	1	1	2	1	NO	144	90/60	90	60	2	4	1	10	1
56	2	14	36	2	1	2	2	3	9	1	1	4	SVP	60	120/80	120	80	2	1	1	0	2
57	1	11	20	1	1	1	1	3	9	2	2	1	NO	64	90/60	90	60	1	2	2	10	1
58	1	26	132	2	2	1	1	3	11	2	2	1	NO	142	100/50	100	50	2	2	1	15	1
59	1	23	120	2	6	1	1	3	11	2	1	1	NO	102	110/70	110	70	2	1	1	12	1
60	1	5	2	2	1	1	1	1	1	2	2	1	NO	168	90/60	90	60	2	1	2	0	2
61	2	25	132	2	1	1	1	1	11	2	2	1	NO	100	100/70	100	70	2	2	1	7	1
62	2	14	36	2	1	2	1	3	10	2	2	2	NO	156	120/70	120	70	2	2	2	14	1
63	1	12.5	30	1	1	1	1	3	9	2	2	1	NO	158	90/60	110	60	2	2	1	0	2
64	2	8	12	1	1	1	1	3	11	1	1	1	NO	146	102/60	102	60	2	2	1	18	1
65	1	23	120	2	1	2	2	3	11	1	1	4	SVP AND	134	110/90	110	90	2	2	1	0	2
66	1	7	10	1	1	1	1	3	2	2	2	1	NO	144	100/60	100	60	2	2	2	0	2
67	1	13	6	1	1	1	1	2	3	2	2	1	NO	118	106/70	106	70	2	2	2	15	1

S.no	Gender	Weight	Age	Fever	Type	Neuro De	Onset	Family h	Comorbi	Birth As	Nicu adr	Dev	On oral a	HR	BP	SBP	DBP	ICP	Refer	AED	Time to	Stop
68	1	12	30	1	1	1	1	2	9	2	2	1	NO	126	90/70	90	70	2	1	1	0	2
69	2	8.6	14	2	1	2	2	1	1	1	1	4	clobazam	65	150/90	150	90	1	4	2	0	2
70	2	4.5	2	2	1	1	1	3	5	2	2	1	NO	58	80/60	100	60	1	1	1	8	1
71	1	25	120	2	6	1	1	1	11	2	1	1	NO	145	110/70	110	70	2	1	1	10	1
72	1	13	36	2	1	1	1	3	3	2	1	2	NO	97	100/80	100	80	1	1	2	12	1
73	1	14	36	2	1	1	1	3	6	1	1	1	NO	86	100/70	100	70	2	4	2	16	1
74	2	20	84	1	1	2	2	1	1	1	1	2	SVP	112	98/60	98	60	2	2	2	0	2
75	1	5.6	2	2	1	1	1	3	6	2	2	1	NO	168	90/70	90	70	2	2	1	15	1
76	1	14	42	2	1	1	1	3	6	2	2	1	NO	118	100/50	100	50	2	3	2	18	1
77	2	12	24	1	1	1	1	2	2	2	2	1	NO	155	110/90	110	90	2	2	1	7	1
78	1	10	18	1	1	1	4	2	2	2	2	1	clobazam	130	90/70	90	70	2	2	1	10	1
79	2	10	20	1	1	1	1	2	4	1	2	2	clobazam	142	100/60	100	60	2	1	2	0	2
80	1	17	96	2	1	2	3	1	10	1	1	1	SVP AND	116	90/60	90	60	2	4	1	0	2
81	2	12	24	1	1	1	4	2	1	2	2	1	clobazam	135	100/50	100	50	2	2	2	0	2
82	1	10	18	2	1	1	1	3	1	2	2	1	NO	118	90/60	90	60	2	4	1	15	1
83	1	12	24	2	1	1	1	3	11	2	2	1	NO	156	90/70	120	70	2	2	1	17	1
84	2	10.5	18	1	1	1	4	2	2	2	2	1	PBT	148	100/60	100	60	2	2	1	12	1
85	1	12	24	2	1	2	3	1	11	1	1	4	PBT	123	90/70	110	70	2	2	1	15	1
86	1	19	84	2	1	2	2	4	11	1	1	4	SVP AND	62	140/100	140	100	2	2	2	0	2
87	1	7	10	1	1	1	1	2	2	2	1	1	NO	142	108/60	108	60	2	1	2	16	1
88	2	10	18	2	1	1	3	4	1	2	2	1	NO	128	110/70	110	70	2	2	2	0	2
89	1	20	96	2	1	1	1	3	11	2	2	1	NO	102	120/80	120	80	1	1	2	10	2
90	2	14	30	2	1	2	3	1	11	1	1	4	PBT	134	90/60	90	60	2	2	2	0	2
91	1	19	84	1	1	1	4	2	2	2	2	1	SVP	120	110/70	110	70	2	2	1	8	1
92	2	7.9	11	1	1	1	1	3	9	2	2	1	NO	154	100/60	100	60	2	2	1	6	1
93	1	15	42	2	1	2	2	3	10	1	1	4	phenytoin	118	106/70	106	70	2	3	2	15	1
94	2	12	24	2	1	2	2	4	10	2	2	4	NO	60	150/100	150	100	1	2	2	0	2
95	1	10	20	2	1	1	1	3	11	2	2	1	NO	142	90/60	90	60	2	1	2	8	1
96	2	12	30	1	1	1	4	2	2	2	1	1	PBT	138	108/60	108	60	2	2	1	10	1
97	1	14	36	2	1	2	2	1	11	1	1	4	PBT	134	90/70	90	70	2	2	1	0	2
98	2	3.6	1.5	1	1	1	1	2	3	2	2	1	NO	145	110/60	120	60	2	2	1	12	1
99	1	10	18	2	1	1	1	3	6	2	2	1	NO	118	90/50	90	50	2	2	1	0	2
100	1	12	24	2	2	2	1	1	1	2	2	2	clobazam	108	100/60	100	60	2	1	1	10	1

REC	Time for	No of Ep	Shock	Time GC	CBG	Na	K	WBC	Hb	PLT	CT	MRI	LP	EEG	AED Fu	DEX	Shock bo	MV	PICU ST	Diagnosis	Outcome
2		0	1		38	150	3.4	10,500	9	2.2	hypodense in ventr	3	2	3	0	2	Bolus 1 +	1	96	10	2
2		0	2		40	138	3.6	9800	11.5	3.2	tetra ventri hydroce	3	1	3	0	2	Bolus 2	1	600	11	2
1	120	2	2	1080	45	136	4.1	6900	10.7	2.5	normal	not done	1	2	0	2	Not requir	2	360	1	1
2		0	2	60	45	138	5.5	6300	8.8	3.2	dialated ventricles,	3	3	2	0	2	Not requir	2	624	10	3
2		3	2	720	46	140	3.1	10500	9.9	2	hypodense in midli	3	3	3	1	2	Not requir	2	42	10	3
1	30	2	1	1440	52	130	5.2	13480	8.9	1.9	normal	not done	1	1	0	2	Not requir	2	144	3	1
1	70	1	2	240	54	142	3.2	12670	11.8	2.3	normal	not done	3	1	0	2	Not requir	2	48	7	1
1	60	3	1	2160	56	128	5.2	10245	9.2	2.8	normal	not done	2	2	1	2	Not requir	2	384	1	1
2		0	2	240	58	132	4.2	11500	8.8	4.4	normal	not done	1	1	0	2	Not requir	2	88	3	1
2		4	2	1440	58	144	3.3	9870	9.2	3	normal	not done	3	2	2	2	Not requir	2	150	2	1
1	30	1	2	1440	90	138	4.3	15800	11.2	3.6	normal	not done	3	3	1	2	Not requir	2	72	1	1
2		3	2	1080	92	140	5.3	19876	10.9	4.2	normal	not done	3	3	1	2	Not requir	2	58	2	1
1	20	1	2	360	98	136	5.4	12050	8.7	2.6	normal	not done	3	3	1	2	Not requir	2	52	2	1
1	60	2	2	2160	108	134	4.4	13905	9	3.6	normal	not done	2	3	2	2	Not requir	2	90	1	1
1	40	5	2	4320	108	139	5.4	11786	11.5	1.9	normal	not done	1	1	0	2	Not requir	2	78	1	1
2		10	2		108	145	3.5	16800	8.7	2.7	ring lesion	lioma, dem	1	3	3	2	Not requir	1	152	10	2
1	30	1	2	1440	108	132	5.5	19050	9.6	4.2	normal	not done	2	3	2	2	Not requir	2	84	1	1
1	85	5	2	2880	110	137	4.5	10650	10.4	3	normal	not done	3	3	2	2	Not requir	2	74	2	1
2		11	2	4080	110	144	3.6	9560	10.2	1.8	normal	not done	3	3	0	2	Bolus 2	2	104	4	1
1	60	4	1	960	111	138	4.6	8900	9.2	2.9	not done	not done	1	3	0	2	Not requir	2	110	2	1
1	30	10	2	720	112	136	5.6	10800	8.6	3.6	normal	not done	1	2	0	2	Not requir	2	288	3	1
2		8	2	480	112	140	3.7	12050	9.5	2.5	diffuse cerebral ed	3	1	1	0	2	Not requir	1	304	4	1
2		2	2	2880	112	138	4.7	18900	8.3	3	dilated ven	ie sequela	3	1	0	2	Not requir	2	356	2	1
2		0	2	30	113	126	5.7	12,900	9.2	2.4	normal	not done	1	1	0	2	Not requir	2	18	3	1
2		3	2	1440	114	135	3.8	13400	11.7	4.2	cerebral edema	3	1	3	1	2	Not requir	2	120	1	1
2		10	2	2880	114	138	4.4	15490	10.9	3.2	normal	not done	1	1	0	2	Not requir	2	48	3	1
2		10	2	7200	114	144	5	5480	8.4	90,000	cerebral edema	3	1	3	3	2	Bolus 1	1	504	1	2
1	30	1	2		115	143	5.8	10980	11.2	2.7	ventricular dilatatio	phy, exvac	3	3	1	1	Bolous 3	1	600	2	2
2		3	2	60	116	138	3.2	7650	9	4.8	diffuse cerebral ed	3	3	1	0	2	Not requir	2	240	2	1
2		4	2	120	118	140	3.8	11200	7.2	5.5	hronic infarct in th	3	1	1	0	2	Not requir	2	72	2	1
1	20	10	2	10	119	132	4.7	8760	8.3	6	bilateral parietal in	3	3	1	0	2	Not requir	2	280	2	1
1	240	4	2	120	120	141	5.2	17500	10.1	2	hydrocephalus	lus-infarct	1	3	0	2	Not requir	1	360	11	2
1	600	3	2	4320	120	139	3.1	19875	11.3	2.4	normal	not done	2	3	2	2	Not requir	2	96	16	1
2		0	2	30	121	143	4.5	10342	10.7	3.1	normal	not done	3	2	3	2	Not requir	2	24	2	1

REC	Time for	No of Ep	Shock	Time GC	CBG	Na	K	WBC	Hb	PLT	CT	MRI	LP	EEG	AED Fu	DEX	Shock bo	MV	PICU ST	Diagnosis	Outcome
1	15	0	2	30	122	135	3.4	11000	11.6	6.5	normal	not done	3	1	1	2	Not requir	2	48	4	1
2		0	1		123	132	3.3	8750	10.5	2.5	normal	not done	3	3	2	1	Bolous 3	2	120	4	1
2		0	2	120	125	141	3.8	9850	9.2	3.3	mild hydrocephalu	3	3	3	1	2	Not requir	2	120	3	1
2		0	2	180	126	144	4.7	18500	11.2	2.5	normal	not done	3	3	0	1	Not requir	2	24	4	1
2		0	2	360	126	126	5.4	12560	11.8	4	normal	not done	3	3	0	2	Not requir	2	36	2	1
1	120	2	2	30	127	135	3.3	8568	10.4	3.6	premature closure	3	3	2	1	2	Not requir	2	48	2	1
2		2	2	60	128	128	4.2	10200	10.3	2.5	normal	not done	3	2	1	2	Not requir	2	48	2	1
2		0	2	360	128	126	5.5	15400	11.2	2	normal	not done	3	2	1	2	Not requir	2	24	2	1
2		4	2	480	130	130	3.6	12675	8.2	1.8	normal	not done	1	1	2	2	Not requir	2	48	4	1
2		0	2	4320	130	132	3.8	9856	10.4	2.2	normal	not done	E positiv	3	2	2	Not requir	2	120	16	1
2		5	1		132	137	4.2	10980	8.5	3.6	normal	not done	3	3	2	2	Bolus 1 +	1	96	1	2
1	200	3	1	2880	132	141	5.8	15600	9.6	2.4	normal	not done	1	3	2	2	Not requir	2	24	4	1
1	360	6	1	1440	132	145	5.3	8900	11.4	1.9	normal	not done	1	2	1	2	Bolus 2 +	2	96	1	1
2		0	2	360	132	138	4.4	12560	9.5	3.2	normal	not done	3	1	0	2	Not requir	2	48	4	1
2		4	2	1080	132	136	3.6	18900	9.9	2.6	normal	not done	1	1	1	2	Not requir	2	72	4	1
2		0	2	600	132	140	4.2	16700	8.7	2.1	normal	not done	1	3	0	2	Not requir	2	6	4	1
2		0	2	600	134	131	3.4	20500	9.5	4.2	not done	not done	3	2	0	2	Not requir	2	24	2	1
2		6	1	2880	135	128	4.8	9870	8.2	3.6	cerebral atrophy	not done	3	2	2	2	Not requir	2	96	2	1
2		5	1	7440	142	135	5.6	6540	9	4.3	tram track app	phy, exvac	E positiv	2	2	2	Not requir	2	192	16	1
2		0	2	360	142	132	3.3	10980	8.6	2.4	cerebral atrophy	not done	3	2	0	2	Not requir	2	48	2	1
2		0	2	600	142	138	3.7	9870	9.1	1.8	cerebral atrophy	ronic calcif	3	2	0	2	Not requir	2	48	2	1
2		4	1		142	134	5.2	16890	7.2	1.6	cerebral atrophy	not done	2	3	3	2	Bolous 3 +	1	240	1	2
1	600	3	1		142	144	5.4	16500	9.8	4.2	tetra ventri hydroce	not done	2	3	3	2	Bolus 1	1	360	11	2
2		0	2	1440	143	141	3.4	6780	10.5	2.3	not done	ng enhanci	3	3	0	2	Not requir	2	120	12	1
2		0	2	4320	145	132	4.8	12090	8.6	1.7	not done	normal	1	1	2	1	Not requir	2	360	1	1
2		5	1		145	132	3.7	18700	7.6	2.9	normal	not done	1	2	3	1	Bolus 2	1	192	6	2
2		0	2	720	146	150	4.8	12560	10.8	3.5	not done	normal	1	1	0	2	Not requir	2	72	2	1
2		0	2	1440	154	134	5.6	13200	9.4	4	cerebral atrophy	not done	1	2	2	2	Not requir	2	120	2	1
2		5	1		154	142	5.4	6700	8.2	2.4	cerebral edema	not done	3	3	3	2	Bolus 2 +	1	240	1	2
2		0	1	360	154	141	4.2	14500	11.8	3.2	normal	not done	1	1	0	2	Not requir	2	48	4	1
2		6	2	2160	154	132	3.6	7800	10.9	4.3	cerebral atrophy	not done	3	2	2	2	Not requir	2	120	2	1
2		0	2	1200	154	144	3.5	18790	8.5	2.8	normal	not done	1	3	0	2	Not requir	2	88	4	1
2		0	2	720	154	128	4.8	6750	8.2	2.6	normal	not done	1	1	0	2	Not requir	2	82	4	1
2		5	1		154	136	5.6	15670	9	3.1	cerebral edema	not done	3	3	3	2	Bolus 1 +	1	384	1	2

REC	Time for	No of Ep	Shock	Time GC	CBG	Na	K	WBC	Hb	PLT	CT	MRI	LP	EEG	AED Fu	DEX	Shock bo	MV	PICU ST	Diagnosis	Outcome
2		10	1		156	132	3.6	8760	9.8	3.2	cerebral atrophy	not done	3	3	3	1	Bolus 2	1	396	2	2
1	240	2	1		156	128	4.2	9500	7.2	1.8	intracranial hemorr	not done	3	3	1	1	Bolus 1 +	1	156	13	2
2		0	2	1440	158	138	5.1	8650	8.9	2.2	normal	not done	3	1	1	2	Not requir	2	86	1	1
1	360	1	2	600	162	130	4.4	12090	11.5	3.5	normal	not done	1	1	0	2	Not requir	2	66	4	1
2		0	2	360	165	128	5.3	9800	8.8	4.1	normal	not done	3	3	0	2	Not requir	2	62	7	1
2		4	1	5760	165	140	5.5	16780	7.6	3.3	cerebral atrophy	notdone	3	2	2	1	Not requir	2	78	2	1
2		0	2	360	167	138	5.2	10050	10.4	2.6	cyst in brain	notdone	3	1	0	2	Not requir	2	56	6	1
2		0	2	720	168	140	3.7	11890	9.8	4.6	normal	not done	3	1	0	2	Not requir	2	52	7	1
1	60	1	2	1080	168	132	4.9	17890	8.7	2.2	normal	not done	1	1	1	2	Not requir	2	58	4	1
1	30	2	1	1440	176	128	3.5	12890	11.8	2.8	normal	notdone	1	1	1	2	Bolus 1 +	2	114	4	1
2		6	1	2880	176	143	3.2	7800	8.6	3.4	normal	not done	2	1	1	2	Bolus 2	1	148	1	1
2		5	1		180	130	3.8	8760	10.5	3.7	cerebral atrophy	not done	3	3	2	2	Not requir	1	296	15	2
2		2	2	1440	182	140	5.7	12080	11.3	3.8	normal	not done	2	1	1	2	Not requir	2	110	4	1
1	15	0	2	720	185	130	3.5	11500	10.8	4.1	normal	not done	3	1	0	1	Not requir	2	44	4	1
2		0	2	600	187	131	3.9	10500	11.5	3.6	normal	not done	3	1	0	2	Not requir	2	36	7	1
1	30	1	1	1440	187	138	3.4	12890	9.5	2.7	normal	not done	1	1	0	2	Bolus 1 +	2	84	4	1
1	20	4	2	2160	190	128	5.7	8760	11.6	3.6	cerebral atrophy	not done	3	2	2	2	Not requir	2	88	15	1
2		6	1		190	130	4.8	7650	7.8	2.8	cerebral atrophy	not done	3	3	3	2	Bolus 1	1	312	2	2
2		0	2	1440	190	137	3.8	8900	8.5	3.7	normal	not done	1	3	0	2	Not requir	2	82	4	1
2		2	2	1440	200	42	3.2	13590	8	2.1	normal	not done	3	1	1	1	Not requir	2	48	6	1
2		2	2	2160	205	156	4.2	14500	10.7	3	normal	not done	3	1	1	2	Not requir	2	66	6	1
2		2	2	2160	209	132	4.7	12090	9.3	2.5	cerebral atrophy	3	3	2	2	2	Not requir	2	78	15	1
2		0	2	120	209	128	3.8	13800	7.2	4.2	normal	not done	1	1	0	2	Not requir	2	84	4	1
1	300	0	2	360	210	137	3.9	8500	9.4	3.8	normal	not done	1	1	0	2	Not requir	2	92	4	1
2		0	2	720	210	32	3.6	7600	8.3	2.8	cerebral atrophy	3	3	2	0	2	Not requir	2	96	2	1
2		10	1		242	126	4.2	8560	9.4	2.6	cerebral atrophy	not done	3	3	2	2	Bolus 2	1	176	9	2
2		0	2	720	245	142	3	9800	11.4	2.1	normal	not done	3	1	0	2	Not requir	2	70	7	1
2		0	2	120	254	134	3.8	11450	8.2	2.6	normal	not done	1	1	0	2	Not requir	2	64	4	1
2		2	2	1800	256	130	5.6	13500	11.2	2.9	hie changes	3	3	2	1	2	Not requir	2	62	2	1
1	120	0	2	720	286	151	5.2	7600	9.2	3	normal	not done	1	1	0	2	Not requir	2	54	1	1
2		2	2	2160	289	145	3.3	8650	10.9	2.8	normal	not done	3	1	1	2	Not requir	2	58	7	1
2		0	2	720	310	132	3.8	12080	8.2	2.1	normal	not done	1	1	0	2	Not requir	2	82	4	1