

# Randomized controlled trial of levetiracetam versus fosphenytoin for convulsive status epilepticus in children

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## Abstract

**Introduction:** Convulsive status epilepticus (CSE) is a common neurological emergency in childhood carrying a risk of significant morbidity and mortality. The current recommended first choice second line treatment in children is phenytoin / fosphenytoin although there is lack of evidence for its use and it is associated with significant side effects. Emerging evidence suggest that intravenous (IV) levetiracetam may be more effective with fewer side effects. The objective of this study was to compare the efficacy and safety of IV levetiracetam as a second line treatment for CSE with IV fosphenytoin in Indian children. **Methods:** Design: Prospective randomized controlled trial. Study setting: Paediatric emergency department of a Medical College in Tamilnadu, India from January 2017 to June 2017. Study population: 50 children aged 3 months to 12 years admitted for CSE and in whom seizure has failed to terminate with 2 doses of benzodiazepine. Intervention: 20mg Phenytoin equivalent (PE)/kg of fosphenytoin or 30mg/kg of levetiracetam administered intravenously over 7 minutes. Primary outcome: clinical cessation of seizures five minutes following the completion of the infusion of the study medication. Secondary outcome: seizure recurrence within 24 hours, drug related adverse events and length of PICU and hospital stay. **Results:** Fosphenytoin terminated seizures earlier than levetiracetam ( $p=0.029$ ). There was no significant difference between the two drugs in other parameters including seizure control rate ( $p=0.667$ ), seizure recurrence ( $p=0.44$ ), seizure free duration ( $p=0.8$ ), PICU stay ( $p=0.105$ ) and hospital stay ( $p=0.311$ ). **Conclusion:** Levetiracetam may be an effective alternative to fosphenytoin in the management of convulsive status epilepticus in children.

**Key words:** Fosphenytoin, Levetiracetam, Randomized Trial, Status epilepticus.

## Introduction

Convulsive status epilepticus (CSE) is the most common life threatening paediatric neurological emergency [1]. It has an annual incidence of 17–23 cases/100000 children per year [2]. Immediate treatment of status epilepticus is essential to prevent neurological sequelae which occurs in up to 39% of children and mortality which is reported at 3-5% [3].

Status epilepticus is most widely defined as a seizure lasting more than 30 minutes or recurrent seizures more than 30 minutes during which the patient does not regain consciousness [4,5]. An operational definition of SE suggested for adults and children older than 5 years by Lowenstein DH et al., refers to more than 5 minutes of continuous seizures or two or more discrete seizures

between which there is incomplete recovery of consciousness [6]. Benzodiazepines are the preferred class of medication for the initial treatment of status epilepticus [7]. Historically lorazepam has been the preferred benzodiazepines for emergent medical therapy of status epilepticus. Recent data support the use of diazepam and midazolam in addition to lorazepam for seizures in paediatric status epilepticus.

Because of the unfavourable side effects phenytoin has been relegated to second line treatment following inadequate response or contraindication to benzodiazepines. Fosphenytoin (FPHT), prodrug of phenytoin is preferred in children in view of its lower potential for local tissue and cardiac toxicity [8].

Growing body of evidence suggest Levetiracetam (LEV) a broad spectrum nonenzyme inducing

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antiepileptic drug to be safe and effective drug in the treatment of status epilepticus with mild adverse effects [9]. The purpose of this study was to determine whether

intravenous fosphenytoin or intravenous levetiracetam is a better second line anticonvulsant based on efficacy and safety for the treatment of CSE in children.

## Methods

**Place of study:** Raja Mirasudar Hospital attached to Thanjavur Medical College, Thanjavur, South India.

**Period of study:** January 2017 to June 2017

**Study Design:** Prospective study

**Sampling method:** Simple random sampling

**Sample size:** Sample size for our study was calculated using open epi.com, keeping the type error ( $\alpha$ ) as 0.05, power ( $\beta$ ) as 0.8, ratio of sample as 1 and mean difference ( $\sigma$ ) as 0.5, the sample size required for each group is 25. Hence for two groups the sample required was 50.

**Inclusion criteria:** 68 children aged between 3 months and 12 years who presented to paediatric emergency department with convulsive status epilepticus and who were still seizing after two doses of benzodiazepines (diazepam/ lorazepam/ midazolam) administered by one of the following route (rectal/ buccal/ intranasal/ intravenous/intramuscular) at the recommended dose were included in the study.

CSE is defined as a child who was unresponsive with continuing abnormality of movement (increased tone or jerking) of greater than five minutes duration, or two or more recurrent convulsions without recovery of consciousness between convulsions [6].

This definition encompasses the International League against Epilepsy (ILAE) seizures types of generalized tonic clonic convulsions, secondarily generalized tonic clonic convulsions and complex partial status epilepticus but not absence, myoclonic, tonic and simple partial status epilepticus.

**Exclusion criteria:** Children on regular oral phenytoin and levetiracetam use, CSE due to an obvious major head injury, known contraindication or allergy to levetiracetam or fosphenytoin, administration of second line anticonvulsant (phenytoin, fosphenytoin, phenobarbitone, sodium valproate) in the previous 24 hours, previous randomization and who were discharged against medical advice were excluded from the study.

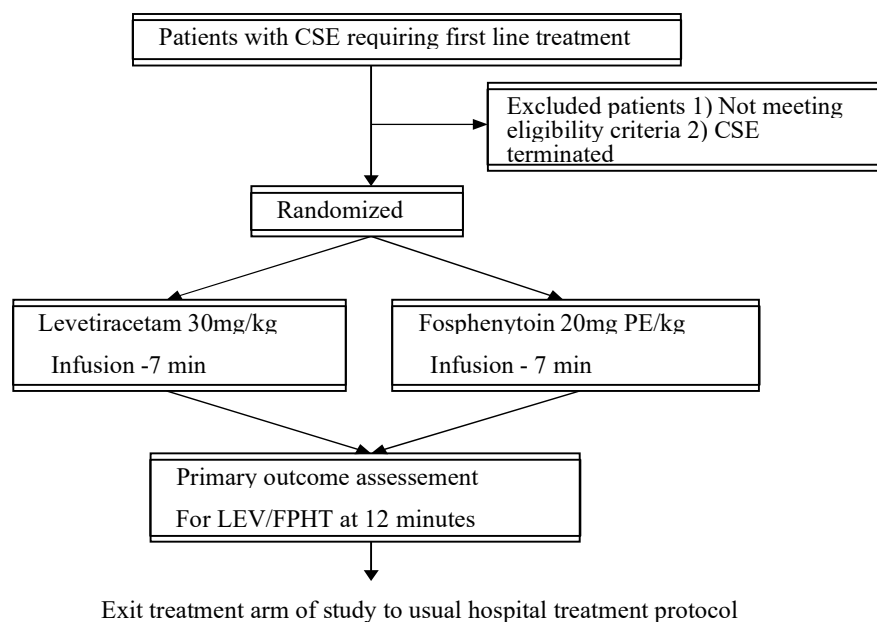
**Study procedure:** All recruited children were randomized to receive either 30mg/kg of LEV infusion over 7 minutes diluted 1:1 with 0.9% sodium chloride to a minimum volume of 10ml or 20mg/kg PE of FPHT diluted 1 in 4 with 0.9% sodium chloride to a minimum volume of 20ml.

The primary outcome was assessed five minutes following the infusion of study medication for successful clinical cessation of seizures. Secondary outcome includes a) recurrence of seizure within 24 hours, b) drug related adverse events like death, airway complication and cardiovascular instability (cardiac arrest, arrhythmias, hypotension requiring intervention), c) length of PICU and hospital stay.

The participant were examined for the following: 1) increased tone, 2) jerking movements including nystagmatoid eye movement 3) Level of consciousness according to Alert, Voice, Pain, Unresponsive (AVPU) Scale. Continued seizure activity was defined as the presence of increased tone or jerking movements.

If seizure activity ceases, then the time is recorded. If the seizure activity was present after 5 minutes following infusion of medication, then alternate medications as per hospital treatment protocol was administered.

**Statistical analysis:** Differences were assessed using Mann-Whitney U test, Fischer's exact test and unpaired 't' test. Results were expressed as mean  $\pm$  standard deviation values. P value of  $<0.05$  was considered to be significant. The study was approved by the Institutional Ethical Committee. Written informed consent was obtained from the parents.



**Fig 1: Study protocol**

## Results

A total of 68 children presented with convulsive status epilepticus during the study period. Of them 12 children who were administered second line anticonvulsants prior to hospitalization, three on regular oral phenytoin, one with obvious head injury and two discharged against medical advise were excluded from the study. In our study, 50 children were randomized to receive either iv fosphenytoin or iv levetiracetam. There were no significant differences between the groups with regard to age, sex, weight, type, duration of seizure and developmental status of the children. Socio-demographic characteristics of the enlisted children are provided in table I.

**Table-I: Socio-demographic and seizure characteristics: ( N= 50).**

VARIABLE	FPHT (n=25)	LEV(n=25)	“P” Value
Age	3.34 + 3.36	2.28 + 2.19	0.657
<b>Gender</b>			
Male	16(64%)	18(72%)	0.762
Female	9(36%)	7(28%)	
Weight	11.86 + 8.9	10.42 + 5.9	0.95
Past history of seizures	9(36%)	7(28%)	0.762
<b>Type of seizure</b>			
Focal seizure	1(4%)	1(4%)	0.999
GTCS	24(96%)	24(96%)	
<b>Development status</b>			
Abnormal	8(32%)	7(28%)	0.999
Normal	17(68%)	18(72%)	
Duration of seizures	21.48 + 4.28	22.12 + 4.97	0.628

P value <0.05 was considered statistically significant

The etiology of seizures in the study group with decreasing order of frequency based on clinical findings were acute symptomatic (acute CNS infection, hypoglycemia, and intoxication), cryptogenic status epilepticus and febrile status epilepticus. The etiological profile of the study population is shown in table II.

**Table- II: Etiological profile in enrolled children (N=50):**

ETIOLOGY	FPHT (n=25)	LEV (n=25)
Cryptogenic	7(28%)	5(20%)
Acute CNS infection	4(16%)	6(24%)
Febrile seizures	4(16%)	4(16%)
HIE sequelae	3(12%)	4(16%)
Seizure disorder (non-compliance)	3(12%)	1(4%)
Syndromic association	1(4%)	1(4%)
Hypoglycemia	1(4%)	1(4%)
Thulasi oil ingestion	1(4%)	-
Seizure disorder(break through seizures)	-	1(4%)
Sepsis	1(4%)	-
Camphor ingestion	-	1(4%)
Post meningo-encephalitic sequelae	-	1(4%)

The study outcomes are shown in table III. Fosphenytoin terminated seizures in 84% of the children whereas levetiracetam efficacy in terminating seizure was 92%. Fosphenytoin ( $2.5 \pm 1.4$  minutes) terminated seizure earlier than levetiracetam ( $3.3 \pm 1.16$  minutes)  $P= 0.029$ , which was statistically significant. Recurrence of seizures, seizure free duration and hospital stay were comparable between both the groups.

**Table-III: Primary and secondary outcome variable of the study groups:**

Variable	FPHT Group	LEV Group	P Value	Statistical Test
Seizure termination rate	84%	92%	0.6671	Fischer's exact test
Time taken to_terminate seizures (minutes)	$2.5 + 1.4$	$3.3 + 1.16$	0.029	Unpaired "t" test
Recurrence of seizures	9.5%	17.5%	0.44	Fischer's exact test
Seizure free interval in case of seizure recurrence	$1.6 \pm 1.1$	$3.8 \pm 6.3$	0.8	Mann Whitney U test
PICU stay (hours)	$42.3 \pm 65.1$	$44 \pm 26.7$	0.105	Mann Whitney U test
Hospital stay(days)	$5.8 \pm 4.9$	$6.3 \pm 3.7$	0.311	Mann Whitney U test

P value <0.05 was considered statistically significant

Adverse drug effect was observed in two cases in both the groups. Respiratory depression requiring nasal oxygen and ataxia were the adverse effects noted following fosphenytoin administration..In the levetiracetam group behavioural change in the form of irritable cry and thrombocytopenia were the adverse events noted.

## Discussion

In this study, efficacy of levetiracetam and fosphenytoin as second line therapy was compared for use after benzodiazepine treatment in children who presented with convulsive status epilepticus.

The exact mechanism by which levetiracetam exerts its antiepileptic effect is unknown. The drug binds to the synaptic vesicle glycoprotein SV2A and reduces neurotransmitter release by inhibition of presynaptic calcium channels [10,11]. By this neuromodulatory effect, it is believed to impede impulse conduction across synapses [12].

Fosphenytoin is a water soluble prodrug of phenytoin. Its anticonvulsant effects are attributable to phenytoin which acts on sodium channel on the neuronal cell membrane, limiting the spread of seizure activity and reducing the seizure propagation.

In our study, termination of seizure following fosphenytoin administration was 84% when compared to 92% for levetiracetam. In a meta analysis of published studies on relative effectiveness of antiepileptic drugs in treatment of benzodiazepine resistant convulsive status epilepticus by Yasiry Z & Shorvon SD the efficacy of

levetiracetam was 68.5% whereas the mean efficacy of phenytoin was 50.2% [13]. In our study, fosphenytoin ceased the seizure earlier than levetiracetam. The mean time to halt the seizures was  $2.5 \pm 1.4$  minutes in fosphenytoin group whereas in levetiracetam group it was  $3.3 \pm 1.16$  minutes.

The time to seizure cessation in Jaclyn O' Connor et al., study in adults comparing levetiracetam with phenytoin in status epilepticus was similar in both groups [14]. Recurrence of seizure occurred in 9.5% (2/21) in the FPHT group and 17.5% (4/23) in the LEV group which was similar to the study comparing levetiracetam versus phenytoin conducted in adults by Chakravarthy et al [15].

In our study, there was no significant variation in seizure free duration following study medication between both groups. None of the previous studies compared this parameter. There was no variation between the two groups in hospital stay (5.8 days vs 6.3 days:  $p=0.311$ ) which was similar to Jaclyn O Connor et al., study [14].

In a systematic review by Egunsola O et al on the safety of levetiracetam in paediatric patients with epilepsy, it was found that behavioral problems and somnolence to be the most prevalent adverse event [16]. In our study one child who received levetiracetam had behavioral changes in the form of irritable cry. Levetiracetam induced thrombocytopenia is a rare but a reversible complication. The mechanism of this adverse effect remains unknown. In our study, one child had thrombocytopenia which could not be attributed to levetiracetam in view of concomitant sepsis.

Fosphenytoin is a biological inert phosphate ester prodrug of phenytoin. It is water soluble at physiological pH and rapidly transformed by endogenous esterases to phenytoin (conversion half life of 8-15mins) following parenteral injection. Advantage of fosphenytoin over phenytoin includes better tolerability, faster infusion rate and ability for intramuscular administration.

Phenytoin which contains propylene glycol causes hypotension which is less common with fosphenytoin [17]. In our study no case of hypotension was documented. Central nervous system side effects like ataxia, giddiness, tinnitus are identical with fosphenytoin and phenytoin [18]. One case of ataxia was noted in our study. The limitation of this study was the relatively small sample size. There may have been a bias in the subject inclusion or the analysis of seizure

control as the study was done in a single institution. The therapeutic end point of any antiepileptic drug would be cessation of all electrical seizures but in our study, primary outcome did not include electro encephalography (EEG) for confirmation of seizure termination. The dose of levetiracetam in our study was 30mg/kg whereas reported levetiracetam dose range from 20-60mg/kg in CSE.

## Conclusion

Levetiracetam may be an effective alternative to fosphenytoin as a second line drug in the management of convulsive status epilepticus in children. However we need further clinical studies with large sample size with higher doses of levetiracetam to further define the efficacy of levetiracetam in CSE in paediatric population.

## What the study adds?

Levetiracetam is an effective alternative to fosphenytoin as a second line drug in the management of benzodiazepine resistant CSE in children.

**Contributors:** SP: finalized the protocol, supervised the study, reviewed the manuscript and will serve as the guarantor of the study. SCS: manuscript writing and supervision of study. KM: patient recruitment and data collection.

**Abbreviations:** CSE: Convulsive status epilepticus, LEV: Levetiracetam, FPHT: Fosphenytoin, PE: Phenytoin equivalent

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