Original Article

Intravenous levetiracetam versus intravenous phenytoin as second Line treatment in pediatric convulsive status epilepticus- open label randomized controlled trial

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Abstract

Background: Benzodiazepines (BZDs) are recommended as the initial therapy of choice in status epilepticus (SE). The age-old second-line treatment for BZD refractory convulsive SE is intravenous phenytoin (PHT) based predominantly on nonrandomized clinical trial data. We did this study to compare the efficacy and safety of intravenous levetiracetam (LEV) and PHT as second-line antiseizure medication (ASM) for children with SE. **Methodology:** A prospective, randomized controlled, open-label study was conducted in children 3 months to 15 years of age with SE in Pediatric Emergency. A total of 41 children were randomly allocated to either group 1 (Levetiracetam) or group 2 (Phenytoin) on the basis of computer-generated randomization. Children who were already on antiseizure medications, either LEV or PHT, or receiving these drugs outside for SE were excluded. Data analysis was done by SPSS V25. **Results:** The most common age group presenting with SE was 12 months to 5 years. Clinical cessation of seizure 5 minutes after the completion of drugs was 85% (17/20) in Levetiracetam group and 90.5% (19/21) in Phenytoin group. Recurrence of seizure within 24 hours was noted in 35% (7/20) in Levetiracetam group and 38.1% (8/21) in Phenytoin group. There was no statistically significant difference noted in both the groups in terms of seizure cessation, adverse events, and recurrence. **Conclusion:** The efficacy and safety of LEV were found to be comparable to those of PHT in controlling seizure as second-line ASM in SE.

Keywords: Antiseizure medication (ASM), levetiracetam (LEV), phenytoin (PHT), status epilepticus (SE)

Introduction

Status epilepticus (SE) is one of the most common critical neurological emergencies in pediatrics. The operational definition of SE is defined as seizure activity lasting for more than 5 minutes.[1] The definition is conceptual, with two operational dimensions: The first time point (t1) is the point at which the seizure should be regarded as an "abnormally prolonged seizure." The second time point (t2) is the time of ongoing seizure activity beyond which there is a risk of long-term consequences. The incidence of SE varies with age, showing a bimodal distribution, with the highest incidence in adults older than 50 years (28.4/100,000) and children younger than 10 years (14.3/100,000).[2] The longer the duration of the seizure, the greater the risk of morbidity.[3-5] In SE, 35%–45% of patients with convulsive SE do not respond to benzodiazepines and require second-line antiseizure medication (ASM) such as levetiracetam (LEV) and phenytoin (PHT). There are various randomized controlled trials (RCTs) in the literature to find the best second-line ASM, but still, there is no conclusive evidence.[3-6] We aimed to compare the efficacy of intravenous LEV and intravenous PHT as second-line treatment for children with SE using an open-labeled randomized controlled crossover trial.

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Methodology

This study was conducted in the All India Institute of Medical Sciences, Raipur, Chhattisgarh, after Institute Ethics Committee (IEC) approval 1335/IEC-AIIMSRPR/2020 from 13/11/2020 to 13/11/2022 and was also registered in the Clinical Trials Registry – India [CTRI/2020/12/029566]. Children aged 3 months to 15 years who presented to pediatric emergency with SE were included. Using the noninferiority formula from a Cleveland online calculator, the sample size was calculated using the alpha error as 0.05, 80% power, and the difference between the groups 20% and 15% attrition; the sample size was calculated to be 82 with 41 in each group with a noninferiority margin of 20%. This study failed to enroll adequate patients to achieve the calculated power, enrolling only half of the desired number due to a reduced number of admissions during COVID-19 pandemic that has led to the decrease in power of the study.

The primary outcome was clinical resolution of seizure after 5 minutes of completion of infusion of either of the drugs without additional anticonvulsant medication. The secondary outcome was requirement of further anticonvulsants to manage convulsive status epilepticus, recurrence of seizure within 24 hours, change in cardiorespiratory parameter, need for admission to PICU, and any medication-related serious adverse reactions.

Inclusion criteria included children aged 3 months to 15 years who presented with generalized tonic-clonic, generalized clonic, generalized tonic, generalized myoclonic, and focal seizure, who had received 2 doses of midazolam or lorazepam for convulsive seizures lasting more than 5 minutes and continued to have persistent or recurrent clinical seizure at least 5 minutes after the last dose of benzodiazepine. Exclusion criteria were absence of seizures or infantile spasms, correctable causes of SE such as hypoglycemia or electrolyte disturbances, patients who had received second-line anticonvulsants during the presenting episode of convulsive SE before, patients who had received ASM from outside the hospital for SE with no documentation available regarding which anticonvulsants were given, patients with arrhythmia, patients allergic to LEV and PHT, patients already on maintenance dose of PHT and LEV with good compliance, and parents/care providers not giving consent.

Deferred consent was obtained after initial management of convulsive SE from parents or guardians. The demographic details, seizure history (duration, type), past history of seizures, any history of allergy to LEV or PHT, history of chronic liver disease or chronic kidney disease, medication history, and history of trauma were recorded at the time of inclusion.

Children presenting with SE were administered intravenous midazolam at 0.2 mg/kg/dose over 2 minutes. If the seizure persisted, a second dose of midazolam was given within 5 minutes. Patients who fulfilled the inclusion criteria were randomized using computer-generated block randomization to receive either intravenous LEV at 40 mg/kg over 5 minutes or PHT at 20 mg/kg over 20 minutes.

Clinical cessation of seizures was assessed within 5 minutes after the completion of study drug infusion. If seizure still persisted after the first dose of LEV or PHT, then crossover was done. Group I received PHT, and Group II received LEV according to their need. The maintenance dose of LEV and PHT was started after 12 hours of loading. If seizures did not abort even after crossover, then the clinical decision on further management was given to treating clinicians and the outcome of the patient was followed up till the completion of trial that is till discharge or demise. Any recurrence of seizures within 24 hours, any drug-related adverse events, and need for admission to PICU were also noted. The final data were analyzed using intention to treat analysis [Figure 1].

Data were entered in MS Excel and analyzed in SPSS V25. Descriptive statistics were applied for demographic data. Shapiro–Wilk test was applied to find normality. Chi-square test and Fisher exact test were applied for comparison of proportions. Student T test for normal data and Mann–Whitney U test were applied for skewed data for comparison of means and medians. P-value < 0.05 was considered as statistically significant.

Results

A total of 49 patients were enrolled, out of which 41 were randomized and stratified between the groups, 20 were in LEV group, and 21 were in PHT group. The agewise distribution had 7 (17%) in 3 to ≤12 months, 13 (31%) in 12 months to ≤5 years, 12 (29%) in 6 to ≤10 years, and 9 (22%) in 11 to ≤15 years, which is detailed in Table 1. According to gender distribution of the total enrolled patients, 23 (56%) were males and 18 (44%) were females. Among the enrolled patients, 3 (7%) had severe acute malnutrition, 7 (17%) had moderate acute malnutrition, 11 (27%) were underweight, 1 (3%) was overweight, and 19 (46%) patients were in their normal nutritional status. Various types of seizure patterns in enrolled patients were generalized tonic-clonic in 35 (85%) and focal seizure in 6 (15%). Those with a duration of seizure on reaching PEM of ≤5 minutes were 5 (25%) in LEV and 5 (23.8%) in PHT, those with >5 to 30 minutes were 10 (50%) and 12 (57.1%), and those with >30 minutes were 5 (25%) and 4 (19%), respectively. The etiological profile of the enrolled patients is listed in Table 2. Past history of seizure was present in 6 (30%) and was not in 14 (70%) of patients. Family history of seizures was present, 1 (5%) in each group, and development delay was present, 3 (15%) in each group.

The clinical cessation of seizure after 5 minutes of completion of study drug was 17 (85%) in LEV and 19 (90.5%) in PHT group. The difference is not statistically significant (P-value 0.66). The median time taken to terminate seizure after initiation of study drug was 3 minutes (IQR 2) in LEV and 4 minutes (IQR 2) in PHT. This difference in time of termination of seizure was statistically significant (P-value 0.04). The recurrence of seizure

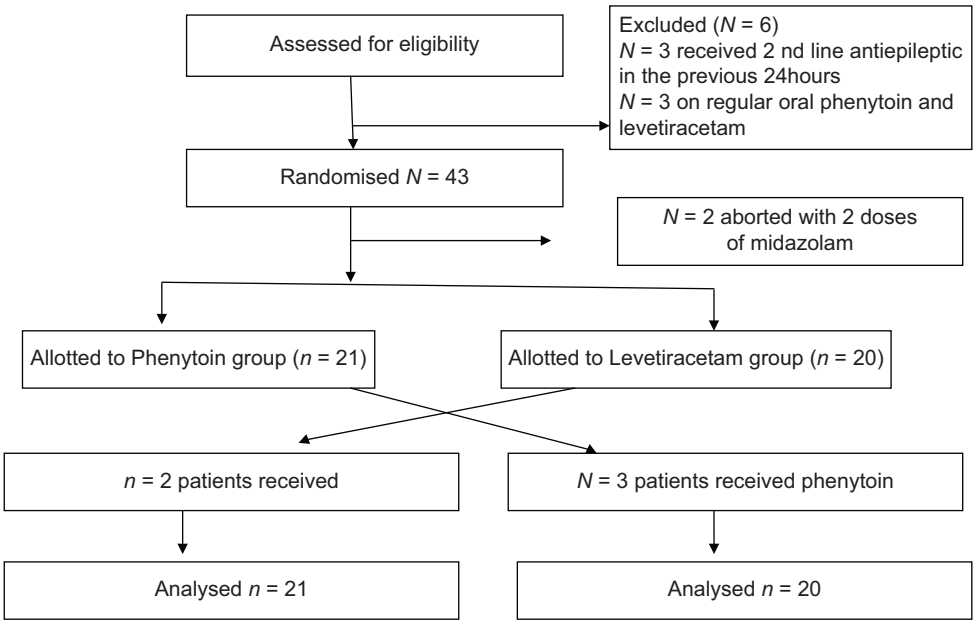

Figure 1: Flow of the study

Table 1: Baseline data

Demographic details	Enrolled patients (%)
Age	
3-≤12 months	7 (17%)
12 month-≤5 years	13 (32%)
6-≤10 years	12 (29%)
11-≤15 years	9 (22%)
Sex	
Male	23 (56%)
Female	18 (44%)
Nutritional status	
Severe acute malnutrition	3 (7%)
Moderate acute malnutrition	7 (17%)
Underweight	11 (27%)
Overweight	1 (3%)
Normal	19 (46%)
Seizure type	
Generalized tonic-clonic	35 (85%)
Focal seizure	6 (15%)
History of fever	
Yes	24 (59%)
No	17 (41%)
Etiological factor	
Breakthrough seizures	7 (17%)
Acute encephalitis syndrome	6 (14.6%)
Febrile seizures	4 (10%)
Trauma brain injury	3 (7.3%)
Malignancy	3 (7.3%)
Hypertensive emergency	3 (7.3%)
Meningitis	3 (7.3%)
HIE sequalae	2 (4.8%)
IEM	2 (4.8%)
ICSOL	1 (2.4%)
Systemic lupus erythematosus	1 (2.4%)
Subdural empyema	1 (2.4%)
Lead toxicity	1 (2.4%)
Cryptogenic	4 (10%)

within 24 hours was observed for 7 (35%) patients in LEV and 8 (38.1%) in PHT. This observation was not statistically significant (P-value = 1). The median duration of seizure-free interval in case of seizure recurrence in LEV is 8 hours (IQR 11.5) and 3.5 hours (IQR 6.75) in PHT. The need for crossover of study drugs was present in 3 (15%) in LEV and 2 (9.5%) in PHT. Need for intubation at admission was there for 1 patient in both the groups. The requirement for intubation after 24 hours was present in 5 (25%) in LEV and 5 (23.8%) in PHT. The need for PICU admission was there for 7 (35%) in LEV and 6 (28.6%) in PHT. The median duration of mechanical ventilation was observed to be 10 days (IQR=17) in LEV and 6 days (IQR=10) in PHT. Seizure recurrence during hospital stay was present in 11 (55%) in LEV and 13 (61.9%) in PHT. The final outcome of the enrolled patients who were discharged in LEV was 15 (75%) and 5 (25%) died, whereas in PHT, it was 15 (71.4%) and 6 (28.6%), respectively. There was no statistical significance noted in any of the above measured parameters. The functional status of the children in both the groups is detailed in Figure 2. No adverse events were documented in both the groups during the study period.

Discussion

In our study, it was noted that the most common age group who presented with status epilepticus was 12 months to ≤5 years. Comparable findings were noted in study conducted by Tamil Selvan *et al.*[7] and Gulati *et al.*[8] It was noted that males (56%) were more commonly affected when compared to females (44%), which was similar to other Indian studies.[9-11] However, no definite causal relationship was found in literature for this male preponderance. The most common seizure type was generalized tonic-clonic that was observed in our study, which was in par

Table 2: Outcome analysis

Outcome	Levetiracetam group	Phenytoin group	*P*
Duration of seizure at presentation			
≤5 min	5 (25%)	5 (23.8%)	*P*=0.87
5-≤30 min	10 (50%)	12 (57.1%)	
>30 min	5 (25%)	4 (19%)	
Past history of seizure			
Yes	6 (30%)	3 (14.3%)	*P*=0.28
No	14 (70%)	18 (85.7%)	
Family history of seizure			
Yes	1 (5%)	1 (4.8%)	*P*=1
No	19 (95%)	20 (95.2%)	
Developmental delay			
Yes	3 (15%)	3 (14.3%)	*P*=1
No	17 (85%)	18 (85.7%)	
Clinical cessation of seizure in 5 min			
Yes	17 (85%)	19 (90.5%)	*P*=0.66
No	3 (15%)	2 (9.5%)	
Time taken to terminate seizure after initiation of study drugs (min)	3.0 (IQR–2)	4.0 (IQR–2)	*P*=0.04
Recurrence of seizure in 24 h			
Yes	7 (35%)	8 (38.1%)	*P*=1
No	13 (65%)	13 (61.9%)	
Duration of seizure-free interval in case of seizure recurrence (h)	8 (IQR-11.5)	3.5 (IQR-6.75)	*P*=0.49
Need for crossover of drugs			
Yes	3 (15%)	2 (9.5%)	*P*=0.66
No	17 (85%)	19 (90.5%)	
Need for intubation at the time of admission			
Yes	1 (5%)	1 (4.8%)	*P*=0.1
No	19 (95%)	20 (95.2%)	
Need for intubation after 24 h			
Yes	5 (25%)	5 (23.8%)	*P*=1
No	15 (75%)	16 (76.2%)	
Need for admission in PICU			
Yes	7 (35%)	6 (28.6%)	*P*=0.74
No	13 (65%)	15 (71.4%)	
Length of mechanical ventilation (days)	10 (IQR–17)	6 (IQR–10)	*P*=0.22
Seizure recurrence during hospital days			
Yes	11 (55%)	13 (61.9%)	*P*=0.76
No	9 (45%)	8 (38.1%)	
Final outcome of enrolled patients			
Discharge	15 (75%)	15 (71.4%)	*P*=1
Death	5 (25%)	6 (28.6%)	
Glasgow outcome score			
Death	5 (25%)	6 (28.6%)	*P*=0.87
Persistent vegetative state	1 (5%)	1 (4.8%)	
Severe disability	1 (5%)	3 (14.3%)	
Moderate disability	2 (10%)	2 (9.5%)	
Good recovery	11 (55%)	9 (42.9%)	

with Niloy *et al.*[11] and Gulati *et al.*[8] The most common symptom noted in the patients with SE was fever seen in 24 (59%) patients. Similar findings were noted by Vignesh *et al.*[5] In our study, the most common etiology for SE was documented to be break through seizures, which is due to noncompliance of medications (17%), followed by acute encephalitis syndrome (14.6%) and then febrile seizure (10%) and cryptogenic (10%). These findings were similar to Wani *et al.*[12] Around 30% in LEV group and 14.3% in PHT group had past history of seizure in our study, and this result was statistically insignificant. This finding was comparable to the study done by Senthil *et al.*,[13] which showed that 36% of patients in Fosphenytoin group and 28% of patients in LEV group had past history of seizure. Other factors such as family history and developmental delay in our study were comparable with those of Senthil *et al.*,[13] which was not statistically significant.

It was noted that 85% of patients in LEV group and 90.5% in PHT group had clinical cessation of seizures 5 minutes after completion of study drug infusion, which was statistically insignificant. Comparable findings were seen in study conducted by Singh *et al.*,[14] EcLIPSE study,[4] Vignesh *et al.*,[5] and Senthil *et al.*,[13] where there was no statistically significant noted. The

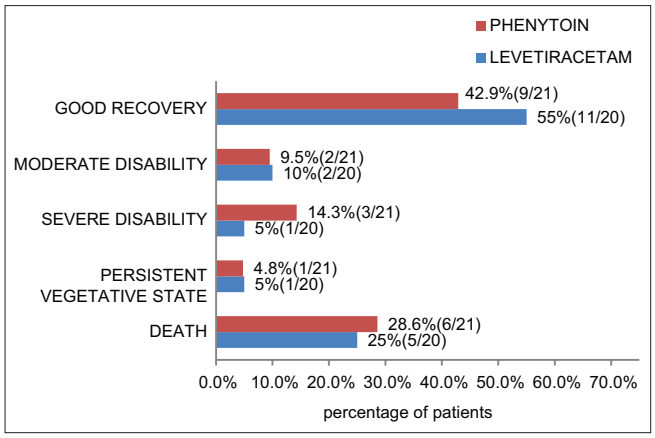

Figure 2: Functional status at discharge

median time taken to terminate seizures after initiation of LEV was 3 minutes and that after initiation of PHT was 4 minutes, which was statistically significant (P-value = 0.04). These findings were comparable with Senthil *et al.* and EcLIPSE study.[4] A study by Sharma *et al.* observed that the mean time to terminate seizures was 2.6±1.5 minutes in PHT group and 3.4±1.2 minutes in LEV group, which was statistically significant.

In our study, 35% of LEV and 38.1% in PHT group had seizure recurrence within 24 hours. Recurrence of seizures was more in PHT group, although it was statistically insignificant. The median duration of seizure-free interval was observed to be 8 hours in LEV group and 3.5 hours in PHT group, which was not statistically significant. Similar findings were found in Senthil *et al.*[13] Sharma *et al.*[15] found that the seizure-free interval is lesser in PHT, which was also statistically not significant. Need for crossover of the drugs was seen in 15% of LEV group and 9.5% in PHT group, which was statistically insignificant. Similar findings were seen in EcLIPSE study.[4]

The need for intubation at the time of presentation was seen in 1 patient in both the groups, which did not show any statistical significance, which was in par with EcLIPSE study.[4] It was noted that 25% patients in LEV and 23.8% in PHT group required intubation during hospital admission, which was statistically insignificant, which was in par with other studies. It was observed that 35% of patients in LEV group and 28.6% in PHT group needed PICU admission, which was not statistically significant, which was comparable with the ConSEPT study.[6] In EcLIPSE study, LEV group had a greater number of PICU admission, but it did not show any statistical significance. Vignesh *et al.*[5] observed PHT group had increased requirement for PICU, which was statistically significant.

The mean length of mechanical ventilation was 13 days in LEV and 15 days in PHT group, which was not statistically significant. Comparable results were obtained by Vignesh *et al.*[5] Mortality in LEV group was 25% and that in PHT group was 28.6%, which was statistically insignificant, which was comparable with Gujjar AR *et al.*[16] and Selvan T *et al.*[7] The overall mortality rate in our hospital was higher than that of the other studies as our institution is a referral center with a poor literacy rate and lack of awareness of timely hospitalization and accessibility would be the contributing factor. The functional status of study patients was assessed by Glasgow outcome score, in which 55% had good recovery in LEV and 42.9% in PHT group had good recovery at the time of discharge [Figure 2]. Comparable results were obtained in study conducted by Vignesh *et al.*

Limitations of the study

This study was not blinded. We were not able to complete the enrollment, which led to reduction in estimated power. The presence or absence of seizures was not confirmed with an electroencephalogram (EEG). This approach is consistent with clinical practice because an EEG is generally not available on an emergency basis. Drug levels of LEV and PHT was not done due to financial constraints.

Conclusions

There was no difference in aborting seizure in both the groups. Similarly, no significant findings were observed between recurrence of seizure within 24 hours, requirement of PICU stay, requirement of intubation at admission, and mortality rate in both the groups. The efficacy and safety of LEV and PHT are comparable as second-line anticonvulsants in SE.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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