ORIGINAL ARTICLE

EFFICACY OF LEVETIRACETAM VERSUS PHENYTOIN AS A SECOND-LINE ANTIEPILEPTIC DRUG IN THE MANAGEMENT OF BENZODIAZEPINE-REFRACTORY STATUS EPILEPTICUS AMONG CHILDREN

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Background: Status Epilepticus (SE) is a life-threatening neurological emergency requiring appropriate therapy to terminate seizure activity. SE is managed with supportive measures and ultra-short-acting benzodiazepines. However, limited data is available in the paediatric population regarding the next best option when this fails. This study aimed at finding new data to recommend levetiracetam or phenytoin as the second-line option. **Methods**: One hundred and thirty-seven patients with status epilepticus were randomized into two groups; group-I was given IV Levetiracetam (LEV) at 20 mg/kg/dose over 5 minutes followed by a maintenance dose of 20mg/kg/dose BID, whereas Group II received phenytoin at 20mg/kg IV loading dose followed by a maintenance dose of 5–8 mg/kg/day divided BID. The primary outcome was seizure cessation, defined as the termination of the apparent convulsion 30 min after the administration of phenytoin or levetiracetam. Secondary outcomes were the use of different anti-convulsants for continued management, admittance to critical treatment, and severe adverse events (including mortality, Stevens-Johnson syndrome, rash, airway problems, cardiovascular instability, extravasation, and severe agitation). Data was recorded via a clinical proforma and was analyzed by SPSS software version 25. All numerical data were expressed in mean±SD forms, and frequency was determined for qualitative baseline data. Secondary outcomes were tested through the $\chi 2$ test, A p-value of ≤ 0.05 was considered statistical significance. **Results**: Levetiracetam terminated seizures in 94% of children compared to 77% in those treated with phenytoin. The mean time to seizure termination was 19.94±3.76 minutes for the LEV Group as compared to 23.791±9.1 min for the PHT group. (p=0.046). Regarding safety, a profile study shows LEV has fewer and less severe side effects compared to Phenytoin. **Conclusion**: Levetiracetam is a safe, well-tolerated, and effective treatment as a second-line antiepileptic drug in the management of status epilepticus.

Keywords: Antiepileptic drug; Epilepsy; Levetiracetam; Phenytoin; Seizures; Status epilepticus.

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INTRODUCTION

Status Epilepticus (SE) is a medical emergency requiring urgent patient evaluation and management to avoid significant brain damage. SE, by International League Against Epilepsy (ILAE), is defined as a condition in which either the failure of the processes responsible for seizure cessation or the initiation of mechanisms leading to abnormally-prolonged seizures. ILAR has used the term "t_1" to describe a time at which therapy should be initiated, a "t_2" after which convulsive activity leads to long-term sequelae. It is one of the most common neurological emergencies in children and has a mortality rate of about 20%.[1,2]

As the duration of the seizure activity is increased, it becomes more challenging to terminate this. Mortality and morbidity associated with a prolonged seizure are also directly proportional to its duration. Patients with a status epilepticus of shorter duration have a better prognosis than those with prolonged seizures.[3] Therefore, rapid termination of the seizure activity is vital to avoid long-term neurological sequelae. Status epilepticus is currently treated with Advanced-Paediatric-Life-Support (APLS) algorithm, which has a step-wise approach to managing such patients. After the patient's initial stabilization, the pharmacological treatment is initiated with an ultra-short-acting intravenous benzodiazepine such as lorazepam, midazolam or diazepam. A second dose of benzodiazepine is given after 10 minutes if seizure activity is not controlled.[4]

Use of second-line of drugs like phenytoin, fosphenytoin, levetiracetam, phenobarbital or valproate is recommended in a benzodiazepine-refractory status epilepticus (BRSE). Failure of second-line therapy necessitates the use of rapid sequence induction and intubation of the patient. Phenytoin is usually recommended as the second-line therapy for the management of SE. However, there is an absence of a high-quality randomized clinical trial with sufficient precision that supports the use of a particular second-line treatment.[5] A large multicenter trial, The Established SE Treatment Trial (ESETT), studied the efficacy and safety of different antiepileptic medications and found that both of these are effective in almost 50% of the patients with SE.[6] Moreover, various safety concerns have been raised regarding the development of hypotension, fatal arrhythmias and Steven Johnson syndrome while using phenytoin.[6,7]

Due to an urgent need to control BRSE, there remains a need for a good quality study that can help recommend a second-line agent for BRSE. We have designed this study to determine whether levetiracetam or phenytoin is a more effective second-line option for children with status epilepticus. Efficacy of levetiracetam and phenytoin in terms of seizure termination rates and safety profiles in our population is lacking. This study will help us in evaluating the effectiveness as second line drugs in terms of termination of status epilepticus among children.

MATERIAL AND METHODS

After taking approval from the ethical review board (Ref # 60 dated 23rd May 2020) and informed consent from the patients, this prospective, non-blinded, randomized clinical trial was conducted at the Paediatrics department of Jinnah hospital Lahore from November 2020 to May 2021. 134 subjects with age ranging from 1 to 13 years presenting with new-onset convulsive SE, refractory to two doses of ultra-short-acting benzodiazepine, were enrolled in the study. Exclusion criteria was allergic to phenytoin or levetiracetam, non-convulsive SE and patients already intubated before treatment or taking some antiepileptic drugs.

A sample size of 134 (67 in each group) was determined with the WHO Sample Size calculator version 2.0 with 95% confidence and a 5% margin of error and 80% power of study with ratio of sample size B:A of 1 using following formula:

$$n = \frac{\left\{ Z_{1-\frac{\alpha}{2}} \sqrt{2\underline{P}\left(1-\underline{P}\right)} + Z_{1-\beta} \sqrt{P_1\left(1-P_1\right) + P_2\left(1-P_2\right)} \right\}^2}{\left(P_1 - P_2\right)^2}$$

P_0 = Probability of seizures control in Group I (Levetiracetam) = 96.2

P_1 = Probability of seizures control in Group I Phenytoin group = 79.0

(From study of Wani *et al*)[9]

Stabilization and resuscitation of the patients were performed concomitantly. Intravenous midazolam was administered at 0.2mg/kg and repeated, if required, after 5 minutes. Patients' refractory to midazolam were allocated into Phenytoin or Levitiracetam groups in a simple random way by a random number table. Patients in Phenytoin-group (PHT group) received phenytoin at a dose of 20 mg/kg via intravenous route over 20 minutes diluted with 0.9% sodium chloride to a maximum concentration of 10 mg/ml followed by a maintenance dose of 5–8 mg/kg/day divided BID. Patients in the Levetiracetam group (LEV group) were injected with levetiracetam at 20 mg/kg over 5 minutes, and diluted to a maximum of 50 mg/ml with 0.9% sodium chloride followed by a maintenance dose of 20 mg/kg/dose BID. Intravenous routes for both drugs were used to avoid confounding. If seizures persisted beyond 30 minutes of starting this therapy, continuous midazolam infusion was started as per hospital policy. The primary outcome was the seizure cessation rate after starting the drug given IV Levetiracetam (LEV) at 20 mg/kg/dose over 5 minutes followed by a maintenance dose of 20 mg/kg/dose BID, whereas Group II received phenytoin at 20mg/kg IV loading dose followed by a maintenance dose of 5–8 mg/kg/day divided BID

Seizure cessation, in this study, was defined as the termination of the apparent convulsion 30 min after the administration of phenytoin or levetiracetam. Seizure-cessation was not achieved if fits continued, reoccurred within 30 minutes, or a third-line treatment was required within 30 minutes. Secondary outcomes were the use of different anti-convulsants for continued management, admittance to critical treatment, and severe adverse events (including mortality, Stevens-Johnson syndrome, rash, airway problems, cardiovascular instability, extravasation, and severe agitation). Data was recorded via a clinical proforma and was analyzed by SPSS software version 25. All numerical data were expressed in mean±SD forms, and frequency was determined for qualitative baseline data. Secondary outcomes were tested through the $\chi 2$ test.

RESULTS

A total of 300 children were assessed for eligibility, 134 of whom satisfied the criterion for inclusion (67 in each group). Table 1 presents the demographic basis. A total of 67 (50%) of the patient from the LEV group and 67 (50%) in the PHT group were under the age of 5.

The Comparison of Primary outcomes (efficacy) between LEV and PHT groups is presented in table-2. Seizure cessation rates were 94% (63/67) in the LEV group compared to 77% (53/67) in the PHT group. The rate difference was 17% (CI 95% and p= 0.046). The mean time to seizure termination was 19.94 minutes for the LEV Group (SD 3.76) as compared to 23.791 min for the PHT Group (SD 9.1), and the p-value is 0.046. Similarly, three patients (4.5%) in the LEV group required another drug compared to 15 (22%) in the PHT group. ICU admission due to cardiopulmonary disease is 0 for the LEV group compared to 1 (1.5%) case for ICU admission for the PHT group. No death was reported in either group. A total of six adverse events (8.9%) were reported in the LEV group as compared to 9 (13.5%) for the PHT group. There were 11(16.4%) recurrent seizures in the next 24 hours for the PHT group compared to 0 recurrent episodes for the LEV group. (Table-3)

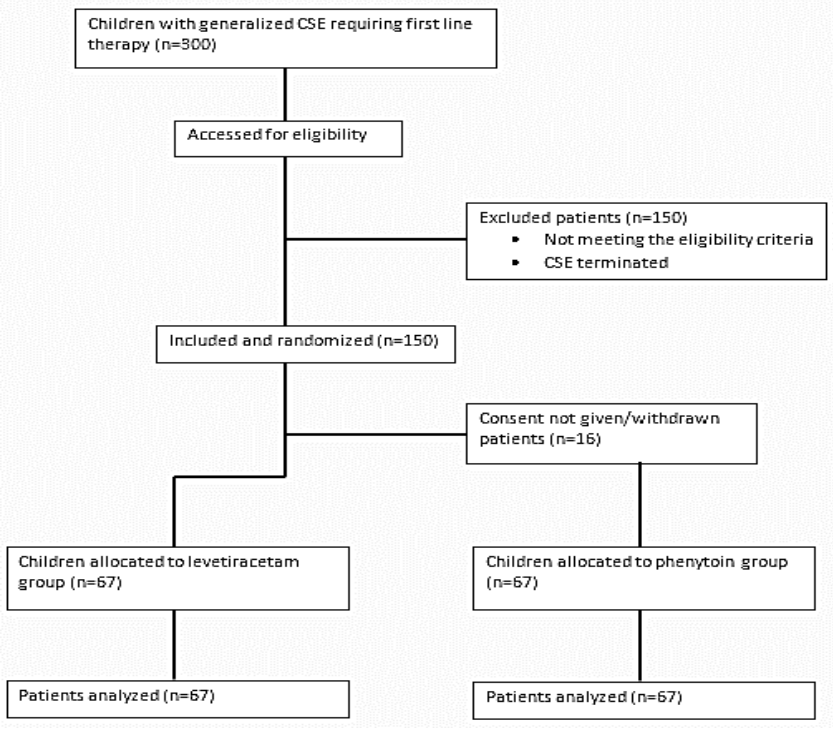

Figure-1: Study flow chart

Table-1: Descriptive Statistics of LEV and PHT Groups

Variable	LEV group (n=67)	PHT group (n=67)	p^*
Age, years			
smaller than two years	15 (22.4%)	16 (23.9%)	0.838
greater than two years	52 (77.6%)	51 (76.1%)	
Sex			
Male	45 (67.1%)	48 (%)	0.574
Female	22 (32.9%)	19 (%)	
Cause of convulsive status epilepticus			
Meningitis/encephalitis	13 (19.3%)	17 (71.6%)	0.673
Febrile seizures	19 (28.3%)	14 (28.5%)	
Epilepsy	22 (32.9%)	18 (26.9%)	
Cerebral palsy and epilepsy	8 (12.0 %)	9 (13.5%)	
Neurodegenerative disorders and epilepsy	3 (4.5 %)	4 (6.0 %)	
Stroke with Epilepsy	2 (3.0%)	5 (7.5%)	

Data are frequency (%) values. *Chi-square test, with $p \leq 0.05$ considered significant. LEV: levetiracetam, PHT: phenytoin.

Table-2: Comparison of primary outcomes (efficacy) between LEV and PHT groups

Seizure cessation within 30 minutes	LEV group (n=67)	PHT group (n=67)	p^*
Yes	63 (94.0%)	52(77.6%)	0.046
No	4 (6.0 %)	15 (22.4 %)	
*Chi-square test, with $p \leq 0.05$ considered significant. LEV: levetiracetam, PHT: phenytoin.			

Table-3: Comparison of secondary outcomes (Safety) between LEV and PHT groups

Variable	LEV group (n=67)	PHT group (n=67)	p^*
Seizures termination in minutes	19.940 ± 3.76	23.791 ± 9.10	0.046
Use of another drug	3 (4.5%)	15(22.9%)	0.002
ICU admission due to cardiopulmonary disease	0	01(1.5%)	0.001
Death	0	0	0
side effects	6 (9.0%)	9 (13.5%)	0.411
Recurrent seizure in the next 24 hours	0 (0.0%)	11(16.4%)	0.001
Data are mean±SD or *n* (%) values. *Chi-square test, with $p \leq 0.05$ considered significant. LEV: levetiracetam, PHT: phenytoin.			

DISCUSSION

In this randomized clinical trial, we compared the efficacy of LEV and PHT as a second-line antiepileptic drug (AED) in benzodiazepine refractory SE. We found that the efficacy of intravenous LEV for termination of convulsive activity was higher as compared to PHT. This response rate is significantly higher than those described in the previous studies. Gulser Esen Besli *et al*. conducted an RCT on 277 children aged one month to 18 years in Turkey. They found that the efficacy of LEV in seizure cessation was 77.6% compared to 57.7% in phenytoin in convulsive status epilepticus (p=0.011). However, they found no differences in the efficacy of the two drugs in treating acute repetitive seizures.[8]

Several studies conducted in a Pakistan and India showed higher efficacy of levetiracetam as a second line of the drug in the management of status epilepticut. A study conducted by Gowhar Wani *et al*. on 104 children with ages ranging from 1–12 years in the Indian population demonstrated a higher efficacy of 96% in patients treated with LEV compared to 59.6% in PHT (p=0.000).[9] Another study conducted in Multan, Pakistan, compared the efficacy of LEV and phenytoin in the management of SE in 600 children. The Authors revealed an efficacy of 92.7% with LEV compared to 83.3% with PHT. However, the dose used in this study (40 mg/kg) was higher than in our study (20 mg/kg).[10] Multicenteric studies with higher sample sizes are needed to confirm this variation in the efficacy of levetiracetam in different nations.

The time to the cessation of seizures (TCS) is shorter after administering levetiracetam than phenytoin 19.94±3.76 vs. 43.79±9.10 minutes p=0.046). This contrasts with the findings published previously. Jaideep Kapur *et al*. reported a median TCS from the start of drug administration of 10.5 minutes with LEV and 11.7 minutes with fosphenytoin.[6] Another study found a TCS of 6.02 with the Lev group and 5.65 min with the PHT group (p=0.71).[9] The difference in infusion time may explain this variation.

Moderate-quality evidence suggested that levetiracetam was not significantly superior to phenytoin in seizure cessation in patients with established status epilepticus.[11–13] Phenytoin is contraindicated in patients with a history of hypersensitivity to phenytoin, other hydantoins, or any inactive ingredient in phenytoin.[14,15]

Various side effects with intravenous phenytoin use have been reported in the literature, including hypotension, arrhythmias, thrombophlebitis, extravasation injury and Steven Johnson syndrome.[8–10] In our study, nine patients from the PHT group (13%) and six from the LRV group (8.9%) reported developing adverse effects. No death was reported in either group. Kapur and Appleton *et al* reported a much lower risk of adverse effects in LEV (3.2%), and 0.7% respectively.[6,7]

This is the first local study conducted in regional settings that compared the efficacy and safety of LEV and PHT in treating BRSE in the paediatric population. The purpose of the study was to provide further evidence to revise the clinical guidelines. However, this study had several limitations. The first one was the use of unblinding while choosing a second-line antiepileptic as this increases the chances of biased; however, it was used so that treating physicians can appropriately use medications in case of refractory seizures. Another drawback of the study was using clinical criteria to determine the cessation of seizure activity. Electroencephalographic (EEG) tracing is more valuable in determining the seizure termination and can detect non-convulsive seizure activity. However, the unavailability of portable EEG in the emergency setting forced us to use clinical criteria. Lastly, drug levels were not done due to financial constraints and the dose given according to those described in the literature.

CONCLUSION

Levetiracetam is a safe, effective, well-tolerated antiepileptic drug that can be used as a second line for treating convulsive status epilepticus. However, more studies with larger sample sizes are needed before a change in clinical practice can be recommended.

Conflict of interest: None

AUTHORS' CONTRIBUTION

BN: Study design, literature search, write-up. MA: Study design, data collection, write-up. MAQ: Methodology, data analysis, proofreading.

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