JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2019;15(4):468-472 / https://doi.org/10.3988/jcn.2019.15.4.468

Clinical Efficacy and Safety of Injectable Levetiracetam Versus Phenytoin as Second-Line Therapy in the Management of Generalized Convulsive Status Epilepticus in Children: An Open-Label Randomized Controlled Trial

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Background and Purpose There is sparsity of quality evidence for the use of drugs after first-line benzodiazepines in convulsive status epilepticus in children. The aim of the study was to compare the clinical efficacy and safety of intravenous levetiracetam versus intravenous phenytoin as second-line drugs in the management of generalized convulsive status epilepticus in children.

Methods This open-label randomized controlled trial was conducted in the Emergency Department of The Children's Hospital and The Institute of Child Health, Multan, Pakistan over a period of 4 years and 6 months from January 2014 to June 2018. This study included 600 children with generalized convulsive status epilepticus: 300 in the 40 mg/kg levetiracetam group, and 300 in the 20 mg/kg phenytoin group. Cessation of a clinical seizure (seizure cessation rate) within 30 minutes after the end of drug administration was the primary outcome in this study, and the presence or absence of adverse effects was noted as the secondary outcome. Data were analyzed using SPSS (version 20.0).

Results The children in the levetiracetam and phenytoin were aged 3.5±0.2 and 3.4±0.2 years (mean±SD), respectively, their seizure durations before the start of treatment were 25.1±0.6 and 23.8±0.4 minutes, and their treatment efficacies were 278/300 (92.7%) and 259/300 (83.3%). Levetiracetam was significantly more effective than phenytoin (p=0.012), with no significant difference in safety. Adverse events were observed in eight children in the phenytoin group.

Conclusions Levetiracetam is significantly more effective than phenytoin for the treatment of convulsive status epilepticus in children who have failed to respond to benzodiazepines.

Key Words intravenous levetiracetam, intravenous phenytoin, convulsive status epilepticus, children.

INTRODUCTION

In neurology-related emergency situations, convulsive status epilepticus (CSE) remains the most common life-threatening condition among children. The incidence of pediatric CSE is 20 per 100,000 children, with 22% of patients requiring rapid sequence induction and admission to an intensive care unit.[1] Among pediatric CSE patients, 3% to 5% suffer mortality and 34% suffer from neurological sequelae, which result in major long-term demands on acute and chronic health-care and social-care resources.[2]

Amongst the current emergency-care pathways for the management of childhood CSE, the stepwise algorithm advocated in advanced pediatric life support (APLS) is most often

Received January 14, 2019
Revised April 11, 2019
Accepted April 11, 2019

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used in clinical practice. The first-line treatment is two doses of a benzodiazepine administered 10 minutes apart. If the child continues to fit at 10 minutes after the second dose of benzodiazepine, APLS recommends phenytoin (PHT) as the first-choice second-line anticonvulsant. However, if the child is allergic to PHT, has previously not responded to it, or has experienced a serious adverse event, phenobarbital is recommended.[3]

The current standard drug, PHT, is only effective in 60% of CSE patients and it is associated with considerable adverse effects including fatal cardiac arrhythmias and Stevens-Johnson syndrome.[4,5] Levetiracetam (LEV) is a broad-spectrum anticonvulsant that is effective in treating generalized tonic-clonic, focal, and myoclonic seizures.[6] There is considerable anecdotal evidence that intravenous (IV) LEV is safe and effective in the treatment of acute repetitive seizures and both CSE and non-CSE, with reported seizure cessation rates of between 76% and 100%.[7] A systematic review published in 2012 indicated that the efficacy rate ranged from 44% to 94%, and was higher in retrospective studies.[8] Reported IV LEV doses range from 20 to 60 mg/kg, with infrequent and mild adverse effects even at the upper limit of the dose range.[9] Furthermore, LEV can be infused over 5−7 minutes, which suggests that CSE can be stopped more rapidly than with PHY.[10]

It is therefore reasonable to hypothesize that LEV is more effective and safer than IV PHT in stopping CSE. A high-quality randomized controlled trial (RCT) is therefore essential to determine whether PHT or LEV is the ideal drug in CSE.

The objectives of this study were to compare the efficacy and safety of LEV and PHT as a second-line anticonvulsant for the management of childhood CSE.

METHODS

Design

This was an open-label RCT comparing IV LEV and IV PHT in children presenting to an Emergency Department with CSE. The study participants were allocated to the two intervention groups at a ratio of 1:1. The study followed the CONSORT guidelines in reporting the results of the trial.

Setting and participants

The study was conducted in the Emergency Department of The Children's Hospital and The Institute of Child Health, Multan, Pakistan from January 2014 to June 2018. Male and female patients aged 1−14 years with generalized CSE who did not responding to two doses of diazepam (0.2 mg/kg to a maximum of 10 mg, administered 5 minutes apart) were included in the study at 5 minutes after the second dose of diazepam.

The following exclusion criteria were applied:

- Received anticonvulsant treatment other than benzodiazepine for the acute management of CSE.
- On assisted ventilation.
- Having CSE secondary to hypertensive encephalopathy, head injury, chronic kidney, or liver disease and electrolyte derangement (hypoglycemia, hypocalcemia, hypo/hypernatremia, or hypomagnesemia).
- Presence of hypotension symptoms.

Study process and interventions

The study was approved by the ethical committee of The Children's Hospital and The Institute of Child Health, Multan (approval no. CHICH/EC/DR.NUZHAT NOUREEN/25-01-2014/109), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents or guardians of the children prior to their inclusion in the study. A specially designed pro forma reporting form was used to record all information including demographics, date and time of presentation, cause of CSE, study drug allocation and treatment, and efficacy and adverse drug reactions. Children were divided into two groups by random allocation for the selection of second-line drug (i.e., LEV and PHT groups).

LEV was used in a dose of 40 mg/kg (maximum of 500 mg) infused over 15 minutes, while the PHT dose was 20 mg/kg (maximum of 250 mg) given over 30 minutes. Both drugs were diluted in normal saline. Supportive treatment (e.g., antipyretics and antibiotics) was provided simultaneously to both groups according to the hospital protocol. Emergency resuscitation equipment was available and functional to deal with any untoward reaction.

Outcomes

The primary efficacy outcome of the study was clinical cessation of the seizure within 30 minutes following completion of the administered drug infusion (primary efficacy outcome). The seizure activity (increased tone, jerking movements, and level of consciousness) was assessed by a clinical investigator or senior treating physician from the start of administering the study drug until 30 minutes after completing the infusion. The secondary outcome of the study was adverse events or serious adverse events caused by the study drug (primary safety outcome). Adverse reactions were detected by monitoring for changes in baseline arterial blood gases, electrocardiogram, blood pressure, and score on the Glasgow Coma Scale (GCS). These parameters were monitored during drug administration and up to 1 hour after drug administration.

The following adverse effects were monitored in all of the

included patients:

- Respiratory depression, defined as the presence of respiratory acidosis (PCO_2 >45 mm Hg) and hypoxemia (PaO_2 <80 mm Hg) in arterial blood gas after drug administration.
- Cardiac depression, defined as the presence of bradyarrhythmia on an electrocardiogram after drug administration.
- Hypotension, defined as a decrease in blood pressure to the third percentile after drug administration.
- Central nervous system depression, defined as a decrease of ≥3 points in the GCS score from baseline after drug administration.

Sample size

Based on the seizure cessation rates reported by Alvarez et al.[11] and Misra et al.,[12] 152 participants were required to be randomized into each arm for the study to provide a statistical power of ≥90% in detecting a total difference of ≥10% in the seizure cessation rates between LEV and PHT for a significance level (α value) of 0.05. It was initially planned for 300 CSE pediatric patients to be included, but the study duration was subsequently extended and the sample size expanded to 600 in order to further validate the results and allow for dropouts.

Randomization

Patients were allocated randomization codes using a simple randomization technique, with a sealed-envelope system used for randomization. Each of the prepared envelopes included the name of a drug ("PHT" or "LEV" was written on 300 envelopes each). All envelopes were securely sealed and shuffled by a person not involved in the study. These prewritten sealed envelopes containing the drug names were opened at the time of administering the second-line drug for the management of CSE, and the clinical investigator ensured that the drug as specific on each envelope was administered by the clinical staff without bias.

Statistics

Data were analyzed using SPSS (version 20.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were applied to calculate the mean±SD values for age and the duration of seizures. Frequencies and percentages were calculated for qualitative variables such as sex, cause of CSE, and efficacy and safety of IV LEV and IV PHT. The efficacy and safety of the two drugs were compared using the chi-square test. A p value of ≤0.05 was considered to indicate statistical significance.

Registration of clinical trial

This open-label RCT is registered on WHO, International Clinical Trial Registry Platform, through the Iranian Registry of Clinical Trials (IRCT), with an IRCT ID of IRCT201706 14034526N2 (search portal: https://irct.ir/trial/33671).

RESULTS

This study screened 1,024 children, of whom 600 (300 in each group) meeting the inclusion criteria were included. The study flow chart is shown in Fig. 1, and the baseline demographic characteristics are provided in Table 1. Most of the children were younger than 5 years, comprising 234 (78%) of those in the LEV group and 242 (80.7%) of those in the PHT group, while 66 (22%) and 58 (19.3%), respectively, were aged 6–14 years. The male:female ratio was 2.5:1 in the LEV group and 1.7:1 in the PHT group.

LEV and PHT were found to be effective in stopping CSE seizures in 278 (92.7%) and 250 (83.3%) children, respectively (p=0.0128). LEV was found to be safe in all 300 (100%) children, while PHT was safe in 292 (97.3%) children. The safety rate did not differ significantly between the two groups (p=0.122).

Adverse drug reactions were noted in 8 (2.7%) children treated with PHT. Cardiac and respiratory depression were

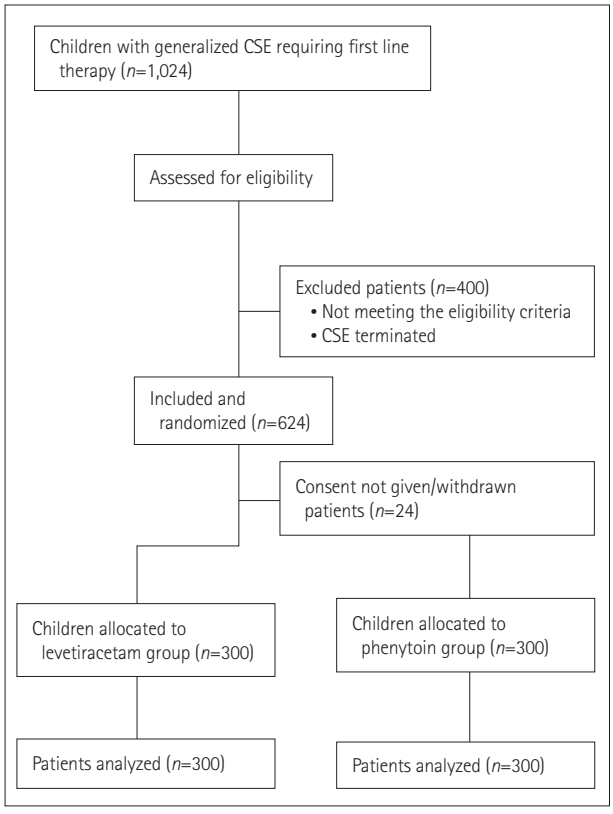

Fig. 1. Study flow chart. CSE: convulsive status epilepticus.

Table 1. Comparison of baseline parameters between the LEV and PHT groups

Variable	LEV group	PHT group	p^*
Age, years	3.52±0.24	3.46±0.22	0.246
Sex			
Male	216 (72.0)	190 (63.3)	0.042
Female	84 (28.0)	110 (36.7)	0.051
Duration of seizures, minutes	25.11±0.66	23.88±0.49	0.124
Cause of convulsive status epilepticus			
Meningitis/encephalitis	130 (43.3)	120 (40)	0.156
Febrile seizures	18 (6)	20 (6.7)	0.345
Epilepsy	52 (17.3)	50 (16.6)	0.256
Cerebral palsy and epilepsy	58 (19.3)	62 (20.7)	0.215
Neurodegenerative disorders and epilepsy	42 (14)	48 (16)	0.143

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

Table 2. Comparison of efficacy and safety of intravenous LEV and PHT

Variable	LEV group (*n*=300)	PHT group (*n*=300)	p^*
Drug efficacy			0.0128
Effective	278 (92.7)	250 (83.3)	
Not effective	22 (7.3)	50 (16.7)	
Drug safety†			0.122
Adverse events	0 (0.0)	8 (2.7)	
Nonserious			-
Cardiac depression	0 (0.0)	2 (0.7)	
Respiratory depression	0 (0.0)	6 (2.0)	
Serious	-	-	-

Data are *n* (%) values.
*Chi-square test, with $p \leq 0.05$ considered significant, †Patients were monitored for acute responses only, which reduced the number of events reported. No serious event was observed during the short study period.
LEV: levetiracetam, PHT: phenytoin.

noted in 2 (0.7%) and 6 (2.0%) children who were treated with PHT, respectively. The efficacy and safety in the two groups are compared in Table 2. No serious adverse events were observed in either study group.

DISCUSSION

Generalized CSE is the most common life-threatening pediatric neurological emergency. However, current treatment protocols acknowledge the lack of robust evidence to guide treatment for CSE after administering first-line benzodiazepines in children.[13] One systematic review regarded phenobarbital, PHT, and paraldehyde as suitable second-line drugs for CSE management.[14]

A few previous small case series have proposed that LEV is a safe and effective antiepileptic for the acute treatment of seizures in children. Bootsma et al.[15] reported that LEV has a good safety profile compared to both older and newer antiepileptic drugs. Reiter et al.[16] demonstrated that IV LEV was effective in managing acute seizures in 79% of their adult patients. Milligan et al.[17] concluded that both LEV and PHT decreased the incidence of postoperative seizures and epilepsy. Our study provides reliable evidence for the efficacy and safety of LEV in managing generalized CSE in children based on data obtained from a large sample.

Chakravarthi et al.[18] conducted a randomized comparison trial of LEV versus PHT in the management of CSE in 44 children. That study found that LEV and PHT were equally effective with regard to both primary and secondary outcome measures, from which it can be concluded that LEV may be an attractive and effective alternative to PHT for managing CSE. Aiguabella et al.[19] assessed the efficacy of IV LEV as an add-on treatment after benzodiazepines plus PHT in CSE in 40 adults in an observational multicenter retrospective study, and found that LEV was effective in 57.5% when used as an add-on therapy and 78.5% when used as the initial second-line treatment.

The appropriate and timely management of CSE is of paramount importance, and so antiepileptic drugs need to be able to immediately control seizures and also have a good safety profile.[20] While the present study has provided further evidence that LEV is an effective and safe drug for the management of CSE in children, there is a need for further prospective studies to validate and justify the role of IV LEV as a second-line antiepileptic drug in this population. The response rates of 92.7% for LEV and 83.3% for PHT in stopping CSE seizures in children are notably higher than those found in previously published series, except for a few retrospective studies.[21,22] This difference might have been due to specific characteristics of the present study population.

While this was one of largest studies to provide clinical-efficacy data for IV LEV and IV PHT in children aged 1−14 years with CSE seizures, it had certain limitations that need to be addressed in future trials, such as 1) only the acute responses related to efficacy and safety of the drugs were studied, which led to underreporting or even no reporting of adverse events and 2) the stopping of electric seizures was not measured in the LEV group due to the unavailability of portable EEG. However, the purpose of this study was to revise or strengthen clinical practices, and its findings will ultimately lead to the strengthening of practices for using IV LEV in particular and PHT infusion as second-line drugs in the management of acute CSE in children.

In conclusion, IV LEV is significantly more effective than IV PHT as a second-line drug for treating CSE in children who have failed to respond to benzodiazepines. Patients who received IV LEV did not show any respiratory, cardiac, or neurological depression, or hypotension.

Author Contributions

Conceptualization: Nuzhat Noureen, Saadia Khan, Imran Iqbal. Data curation: Nuzhat Noureen, Saadia Khan, Moallah Maryam. Formal analysis: Nuzhat Noureen, Asim Khursheed, Syed Muhammad Sharib, Neeta Maheshwary. Investigation: Nuzhat Noureen, Saadia Khan, Asim Khursheed, Imran Iqbal, Moallah Maryam. Methodology: Nuzhat Noureen, Saadia Khan, Asim Khursheed, Imran Iqbal. Project administration: Nuzhat Noureen, Saadia Khan, Asim Khursheed, Moallah Maryam. Supervision: Nuzhat Noureen, Asim Khursheed, Imran Iqbal. Visualization: Nuzhat Noureen, Saadia Khan. Writing—original draft: Nuzhat Noureen, Saadia Khan, Asim Khursheed, Syed Muhammad Sharib, Neeta Maheshwary. Writing—review & editing: Nuzhat Noureen, Syed Muhammad Sharib, Neeta Maheshwary.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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