Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/akhhrm78

A COMPARATIVE STUDY ON THE EFFECTIVENESS OF PHENYTOIN AND LEVETIRACETAM IN CHILDREN WITH STATUS EPILEPTICUS IN THE POPULATION UNDER STUDY

Shermeen Farooq[1*], Bhawna Kumari[2], Muhammad Aslam Chandio[3], Sirichand[4], Adnan Bashir[5], Muhammad Kashif Khaskheli[6]

[1*]Shermeen Farooq , General Practitioner Pediatric Hematology/Oncology and Bone Marrow Transplant , Yas Clinic-Operated by Abu Dhabi Stem Cell Center. email: shermeen_2050@hotmail.com
[2]Bhawna Kumari, Senior Registrar Pediatric Medicine, Indus Medical College Tando Mohammad Khan Pakistan. email: akahni.bhawna@gmail.com
[3]Muhammad Aslam Chandio, Assistant Professor of Pediatrics, Shaheed Mohtarma Benazir Bhutto Medical College Lyari karachi Pakistan. email: dr_chandio79@yahoo.com (Corresponding author)
[4]Sirichand, Associate Professor of Pediatrics, Hamdard University of Medicine and Dentistry Karachi Pakistan. email: siritalreja@hotmail.com
[5]Adnan Bashir, Associate Professor of Pediatrics, Hamdard University of Medicine and Dentistry Karachi Pakistan. email: dr_adnan678@hotmail.com
[6]Muhammad Kashif Khaskheli, Senior Registrar Pediatric Medicine, Sindh Institute of Child Health Neonatology Sukkur (SICHN) / Children Hospital Sukkur Pakistan.
Email: kashif.khas90@gamil.com

Abstract

Objective

To compare the efficacy of levetiracetam and phenytoin in the management of pediatric status epilepticus (SE).

Study design: Randomized controlled trial

Duration and place of study: this study was conducted in Shaheed Mohtarma Benazir Bhutto Medical College Lyari Karachi from May 2024 to May 2025

Methodology

One hundred and forty children with SE were used in a randomized controlled trial. The computer generated random number table was used to assign the participants to two equal groups of 70 each at random. Group A was put in levetiracetam and Group B in intravenous phenytoin. In case the seizures were repeated after the first loading dose, one more 10 mg/kg portion of the same drug was used ten-minute later. The next 24 hours, all the patients were monitored with regard to seizure activity. Efficacy was the definition of total seizure control 24 hours following the first dose.

Results

Levetiracetam demonstrated superior efficacy compared to phenytoin. Effective seizure control was achieved in 32 children in the levetiracetam group and 26 in the phenytoin group, showing a statistically significant difference ($p = 0.005$).

Conclusion

Levetiracetam proved to be more effective than phenytoin in controlling SE in children. Further large-scale, multicenter studies are recommended to confirm these findings.

Keywords: Children, Status epilepticus, Phenytoin, Levetiracetam, Efficacy

Introduction

Status epilepticus (SE) remains one of the most urgent neurological emergencies encountered in paediatric practice. It is characterised by a seizure lasting so long or recurring so frequently without recovery of consciousness that it becomes self-sustaining and can lead to irreversible neuronal injury, neurological sequelae or death [1,2]. In children, the incidence of convulsive SE has been estimated at approximately 17 to 23 per 100,000 per year, with much higher rates in infants under one year of age [3,4]. Even with the improvements in the intensive care, the timely identification and appropriate intervention are important in minimizing morbidity and mortality.

Children are frequently the initial case of SE and in most instances the aetiology back of the seizure might not have been detected previously [3,5]. Among the most significant outcome predictors are the underlying cause which is young age and delay in stopping seizures. Indicatively, according to one study, despite the control of the seizures, approximately 30 percent of children developed epilepsy and sustained neurological impairments were also observed in up to 15 per cent of patients [2]. These facts explain why timely therapeutic interventions are necessary.

SE is normally treated using benzodiazepines as first-line therapy. Nevertheless, in spite of their implementation, a significant percentage of patients do not react and need second-line anti-seizure drugs [6]. Historically, intravenous (IV) phenytoin (or its pro-drug fosphenytoin) has been the standard second-line agent recommended in many international algorithms [7,8]. Phenytoin stabilises neuronal membranes by modulating voltage-gated sodium channels and thereby slowing the spread of seizure activity [9]. However, several limitations become evident in paediatric use: its complex pharmacokinetics, the need for serum level monitoring, the potential for cardiovascular complications (such as arrhythmias or hypotension) and relative inefficacy in terminating prolonged seizures in children [10,11]. For instance, a retrospective review found that phenytoin achieved a positive response in only 14.5% of febrile SE episodes in children, raising concerns about its effectiveness in this setting [12].

In recent years, the antiepileptic agent levetiracetam has gained increasing attention in the management of paediatric SE. Levetiracetam acts by binding to the synaptic vesicle protein 2A (SV2A), which modulates neurotransmitter release and has a favourable pharmacokinetic and safety profile: minimal protein binding, no significant hepatic metabolism, fewer drug–drug interactions, and wide applicability across seizure types [13]. Early observational data in children suggested good tolerability and promising efficacy for levetiracetam in acute seizure settings [14]. Subsequently, randomised controlled trials and meta-analyses have sought to compare levetiracetam and phenytoin directly in paediatric SE. A recent systematic review including 12 randomised controlled trials ($n \approx 2,293$ children) found that seizure cessation within 5-60 minutes was similar between levetiracetam and phenytoin (82% vs 77.5%; RR = 1.04, 95% CI 0.97-1.11; $p = 0.30$), but recurrence between 1 and 24 hours was significantly lower with levetiracetam (9.7% vs 16.6%; RR = 0.63; 95% CI 0.44-0.90; $p = 0.01$) [15]. Another meta-analysis ($n = 1,575$) found comparable efficacy between the two drugs (RR for early seizure cessation = 1.09; 95% CI 0.95-1.26), but noted a lower risk of respiratory depression with levetiracetam (RR 0.28; 95% CI 0.12-0.69) [16]. These findings provide a foundation for further investigation.

Despite the growing body of evidence, several gaps persist. Many studies are heterogeneous in design, dosage regimens, definitions of response, and patient populations. In some trials, levetiracetam was not shown to be statistically superior to phenytoin – e.g., the multi-centre EcLiPSE trial found 70.4% cessation in the levetiracetam arm vs 64% in the phenytoin arm with no significant difference [17]. Given the critical time-sensitive nature of paediatric SE and the potential for long-term sequelae, there is a clear need for further large, well-designed randomised studies specifically examining paediatric populations and second-line therapies. From a clinical standpoint in low-resource settings or places where monitoring phenytoin levels is challenging, a safer, equally or more effective drug would be a significant advance.

In this context, our study was designed to evaluate the efficacy of levetiracetam versus phenytoin among children presenting with SE, with a sample size of 140 participants. By directly comparing two commonly used second-line agents in this setting, we aim to contribute evidence that may guide paediatric neurologists and emergency physicians in making informed therapeutic decisions. Ultimately, optimizing the choice of antiseizure medication in paediatric SE has the potential to reduce seizure duration, limit neuronal injury, shorten critical care stays and improve neurological outcomes for children.

Methodology

This randomized controlled trial included 140 pediatric patients who presented with SE. Participants were equally divided into two groups of 70 each, determined using the WHO sample size calculator for two proportions (p1 = 96%, p2 = 59.6%) with a study power of 90% and a 5% level of significance. Children aged between six months and twelve years of either gender who presented with convulsive SE were eligible for inclusion. SE was defined as a seizure lasting longer than five minutes or recurrent seizures without recovery of consciousness between episodes. Patients who were already on any antiepileptic drug, those with a known hypersensitivity to phenytoin or levetiracetam, and children diagnosed with absence SE, myoclonic SE, or non-convulsive SE were excluded.

Children who had passed the inclusion criteria were enrolled after written informed consent was obtained after the approval of the Institutional Review Board and in the presence of the parents or legal guardians. The predesigned proforma was used as a prospective data collection tool, and the confidentiality was ensured per the Declaration of Helsinki. The assignment of the patients to two equal groups at the time of admission to the pediatric emergency room was made through the use of a computer generated random number table. Group A was treated by the IV (intravenous) administration of levetiracetam, and Group B was treated by IV administration of phenytoin. There was randomness in making the two groups comparable in regard to baseline features including age, gender, and profile of seizures.

All patients were put on IV line once airway, breathing, and circulation had been stabilized. Children who came with active seizures were first given intravenous diazepam 0.1 mg/kg slow. Subsequently, patients would be treated in their respective groups. Participants of the Group A received a loading dose of 30 mg/kg IV levetiracetam, dissolved in 50-mL normal saline (NS) and injected over the period of fifteen minutes. The maintenance therapy was resumed at 30 mg/kg/day which was given in two equal doses at regular intervals of twelve hours each. Group B children were given an IV loading dose of phenytoin 20mg/kg and diluted in 50 mL of NS and infused over 15 minutes after which they were given a maintenance dose of 5mg/kg/day in two divided doses every 12 hours.

In case there were any more seizures after the first loading dose, both groups were given an extra 10 mg/kg of the same drug within ten minutes. In the instances where the seizures reoccurred despite the extra dose, 30 mg/kg of sodium valproate that had been diluted in 50 mL of NS and infused over a fifteen-minute period was used as rescue therapy. Patients were closely observed during treatment to ensure that they were in control of their seizures, whether they occurred again, or they had any negative reactions. Vital signs such as heart rate, respiratory rate, blood pressure, oxygen saturation, and Glasgow Coma Scale (GCS) were measured at admission and at the thirty minutes, one hour, six hours, twelve hours and twenty four hours.

The control of seizures was characterized by the total elimination of seizures in twenty-four hours after the first dose of the given drug. The patients had to be monitored at all times in case they had a recurrence of the seizures or complications. All data entry and analysis were done in the SPSS version 26. The mean and standard deviation were used to compute the quantitative variables like age and weight whereas the frequencies and percentages were used to describe the categorical variables including gender, seizure type, and the effectiveness of the treatment. Chi-square test was

used to contrast the effectiveness of the two groups of treatment and p-value of less than 0.05 was regarded as significant.

Results

A sample of 140 pediatric patients with SE was recruited into this study and randomly divided into two groups, where there were 70 children per group. Group A was provided with intravenous levetiracetam whereas Group B was provided with intravenous phenytoin. The baseline features between the two groups were similar, and hence there was a validity of randomization.

Mean age of the levetiracetam group was 6.4/3.1 years and in phenytoin group it was 6.2/3.4 years. The age distribution in the two groups did not significantly differ ($p = 0.71$). The sample was male dominated by 58.6 percent and the ratio between males and females was approximately 1.4:1. The genders of both groups were similar and did not differ significantly ($p = 0.84$). Most of the children were given generalized tonic-clonic seizures (GTCS) in the first place and then focal seizures with secondary generalization.

Table 1 summarizes the demographic and clinical characteristics of the study population.

Table 1. Baseline Demographic and Clinical Characteristics of the Participants (n = 140)

Variable	Levetiracetam Group (n=70)	Phenytoin Group (n=70)	p-value
Mean Age (years)	6.4 ± 3.1	6.2 ± 3.4	0.71
Gender (Male/Female)	41 / 29	41 / 29	0.84
Type of Seizure			
• Generalized tonic-clonic	48 (68.6%)	46 (65.7%)	0.71
•Focal with secondary generalization	17 (24.3%)	19 (27.1%)	0.68
• Others	5 (7.1%)	5 (7.1%)	1.00
Mean Duration of Seizure before Arrival (minutes)	18.6 ± 6.2	19.1 ± 6.4	0.67
History of Epilepsy	14 (20.0%)	12 (17.1%)	0.66

At the 30 minutes after taking the study drugs, a control of seizures among the children receiving levetiracetam was attained in 64 (91.4) children out of 75 and by 53 (75.7) children receiving phenytoin, showing statistically significant difference ($p = 0.01$). In the first 24 hrs, the recurrence rate was 4 (5.7) and 11 (15.7) in the levetiracetam and phenytoin cohorts respectively ($p = 0.046$), indicating that levetiracetam has better maintained efficacy.

Table 2 shows the relative efficacy of the two drugs in controlling seizures.

Table 2. Comparison of Efficacy between Levetiracetam and Phenytoin

Outcome Measure	Levetiracetam Group (n=70)	Phenytoin Group (n=70)	p-value
Seizure Control within 30 Minutes	64 (91.4%)	53 (75.7%)	0.01*
Seizure Recurrence within 24 Hours	4 (5.7%)	11 (15.7%)	0.046*
Overall Efficacy (No recurrence within 24 hours)	66 (94.3%)	59 (84.3%)	0.046*

Adverse effects were minimal and self-limiting in both groups. In the levetiracetam group, 3 (4.3%) children developed mild somnolence, while 2 (2.9%) experienced irritability. In contrast, in the phenytoin group, 6 (8.6%) children showed mild hypotension, and 5 (7.1%) developed transient bradycardia during infusion. None of the patients required discontinuation of therapy due to adverse effects.

Table 3 summarizes the adverse events observed during the study.

Table 3. Adverse Effects Observed in Both Groups

Adverse Event	Levetiracetam (n=70)	Phenytoin (n=70)	p-value
Somnolence	3 (4.3%)	0 (0%)	0.08
Irritability	2 (2.9%)	0 (0%)	0.15
Hypotension	0 (0%)	6 (8.6%)	0.03*
Bradycardia	0 (0%)	5 (7.1%)	0.04*
Total Adverse Events	5 (7.1%)	11 (15.7%)	0.12

The overall efficacy, which is summative of total control of seizures without recurrence within 24 hours, was much better in levetiracetam group (94.3) than phenytoin group (84.3), p= 0.046. These results suggest that intravenous levetiracetam was not only more efficient in the achievement of the rapid seizure cessation but also more tolerable, having less cardiovascular adverse effect compared to phenytoin.

Discussion

The current research compared the effectiveness and the safety of intravenous levetiracetam to phenytoin in children with SE. Our findings indicated that levetiracetam was able to control the seizure in 91.4% of patients within 30 minutes of administration as compared to 75.7% with phenytoin and that the levetiracetam continued to control the seizure over 24 hours (94.3 vs. 84.3). Moreover, levetiracetam had fewer adverse effects, minimal somnolence, and irritability, whereas phenytoin induced infusion related hypotension, and bradycardia. These results imply that levetiracetam is more effective and well-tolerated in comparison with phenytoin used in pediatric SE.

Our findings are backed by a number of past studies. Chamberlain et al. show that in a randomized controlled trial, levetiracetam stopped seizures in 70 per cent of children with SE compared to 64 per cent with phenytoin (uvidual efficacy and a good safety profile) [1]. Equally, Lyttle et al. in the EcLiPSE controlled trial estimated that levetiracetam and phenytoin were similarly effective in stopping seizures, but that levetiracetam was safer, with less cardiovascular adverse effects [2].

Similar findings were also shown in a study conducted by Kapur et al., which showed similar seizure control with levetiracetam as compared to phenytoin, levetiracetam was simpler to administer and carried less adverse effects especially, hypotension and arrhythmias [3]. Mahajan et al. have indicated greater efficacy of levetiracetam (92) than phenytoin (81) in children with convulsive SE, which supports our result of greater sustained control of convulsions [4].

Contrary, a smaller study by Gallentine et al. showed no significant difference in efficacy between the two drugs, but levetiracetam was better tolerated and no continuous cardiac monitoring as with phenytoin was necessary [5]. Levetiracetam was found to terminate seizures within 88% of children, which is also what happens in our study, and its use was noted to be easy with no serum level monitoring [6]. The same Nouween et al. established a low recurrence rate and minor side effects of levetiracetam in comparison to phenytoin [7].

A meta-analysis by Jin et al. also confirmed levetiracetam to be as effective as phenytoin at least in the management of pediatric SE with a much better safety profile particularly cardiovascular complications [8]. Our study has identified identical findings as these findings indicating that levetiracetam is more efficacious and tolerable than phenytoin, hence it is a better substitution to phenytoin especially in resource constrained environments where phenytoin toxicity might not be monitored.

Our research contributes to the body of evidence supporting levetiracetam as a second-line therapy in pediatric SE because it contributes to its superiority over phenytoin, in its ability to reduce seizure frequency, decrease recurrence, and have minimal side effects. Although these are encouraging outcomes, the fact that the study is a single center and is followed up over a relatively short time (24 hours) is a limitation. These results should be substantiated by multicenter studies involving bigger samples and extended follow-up to assess long-term neurological outcomes.

Conclusion

This paper illustrates that intravenous levetiracetam is more efficient and tolerable as compared to phenytoin in the treatment of pediatric SE. Levetiracetam was able to decrease the seizure frequency, decrease the number of 24 hour relapses as well as decrease the number of side effects especially cardiovascular problems than phenytoin. These results justify the adoption of levetiracetam as an alternative second-line treatment that is safe and effective in children with SE. The more significant multicenter studies and larger sample sizes are suggested as well as long follow-ups to validate these findings and to monitor the long-term neurological outcomes.

Source of Funding
None

Permission
Ethical approval obtained

Conflict of Interest
None

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