Section: Pediatric

Original Research Article

COMPARATIVE EFFICACY AND SAFETY OF PHENYTOIN AND LEVETIRACETAM IN PEDIATRIC STATUS EPILEPTICUS: A RANDOMIZED CONTROLLED TRIAL

Loveena[1], Habibullah[2], Siraj Nabi Depar[3], Fozia Baloch[4], Sheeraz Ahmed[5], Zulfiqar Ali Dahri[6]

[1]*WMO, Ruth km pfau Civil Hospital Karachi Pakistan.*
[2]*Senior Registrar Pediatric Surgery, Sindh Institute of Child Health Neonatology Sukkur (SICHN) Pakistan Pakistan.*
[3]*Senior Registrar Pediatric Medicine, People's University of Medical and Health Sciences for Women Nawabshah Pakistan.*
[4]*Associate Professor Pediatric Department, Liaquat University of Medical & Health Sciences Jamshoro Pakistan.*
[5]*Assistant Professor Pediatric Medicine, Sindh Institute of Child Health Neonatology Sukkur (SICHN) Pakistan.*
[6]*Consultant Pediatrician, Institute of Mother & Child Health Nawabshah Pakistan.*

Received *: 19/09/2025*
Received in revised form *: 27/10/2025*
Accepted *: 18/11/2025*

Corresponding Author
Dr. Loveena,
WMO, Ruth km pfau Civil Hospital Karachi Pakistan
Email: loveenasrichand@gmail.com

DOI: 10.70034/ijmedph.2025.4.285

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (4); 1579-1583

ABSTRACT

Background: Objective: To compare the efficacy of intravenous levetiracetam (LEV) versus phenytoin (PHT) as second-line therapy for status epilepticus (SE) in children aged 1 month to 12 years in a tertiary care hospital in Pakistan. **Study Design:** This was a randomized controlled trial. **Place and Duration:** This study was conducted at Ruth km pfau Civil Hospital Karachi from May 2024 to May 2025.

Materials and Methods: Children with SE (n=180) were split into two groups (n=90 each): Group A (LEV) and Group B (PHT). After benzodiazepine failure, participants who met eligibility criteria were assigned to either LEV (Group A: 30 mg/kg loading dose, 30 mg/kg/day maintenance) or PHT (Group B: 20 mg/kg loading dose, 5 mg/kg/day maintenance). The definition of efficacy was the cessation of seizure after 24 hours. Age, seizure type, and efficacy data were collected, and vital parameters were monitored at several time points. Statistical analyses were carried out in SPSS version 25, using chi-square tests ($p<0.05$ as the criterion for significance).

Results: Mean ages were 6.52 ± 2.68 years (Group A) and 6.59 ± 2.72 years (Group B), with most children aged 1-6 years (55.6% vs. 51.1%). Seizure types in Group A: 33.3% generalized tonic-clonic (GTC), 27.8% focal tonic-clonic, 38.9% complex partial; Group B: 26.7% GTC, 18.9% focal tonic-clonic, 54.4% complex partial. Overall efficacy was higher in Group A (91.1%, n=82/90) than Group B (71.1%, n=64/90; p=0.005). For focal tonic-clonic seizures, efficacy was 86% (49/57) in Group A vs. 78% (42/54) in Group B (p=0.118). For GTC, it was 85% (22/26) in Group A vs. 67% (20/30) in Group B (p=0.295).

Conclusion: Levetiracetam demonstrated superior efficacy over phenytoin for convulsive SE in children, though subtype differences were non-significant. Future multicenter studies should assess long-term outcomes.

Keywords: Status Epilepticus, Levetiracetam, Phenytoin, Pediatric, Seizure Control.

INTRODUCTION

Status epilepticus (SE) is defined as a seizure lasting longer than five minutes or recurrent seizures without full recovery of consciousness between episodes.[1] In children, SE often arises from diverse etiologies, including febrile illnesses, structural brain abnormalities, and metabolic disturbances. This contributes to it being one of the top causes of emergency hospitalization globally.[2] SE affects children worldwide with an estimated incidence of 17 to 23 episodes per 100,000 children per annum,

with the highest prevalence rate in children under the age of two years.[3] This corresponds to about 102,000 to 138,000 cases per year among the 600 million children under age 15 worldwide.[3,4] The morbidity is high, with 25-40% of survivors developing epilepsy recurrence, cognitive and behavioral problems, and mortality estimated at 3 to 5% based on etiology.[3] SE is often a result of perinatal insults such as birth asphyxia, neonatal infections, febrile seizures, and head injuries.[5,6] However, in high-income environments, the condition is more frequently associated with structural causes, including brain tumors, traumatic brain injuries, and cerebrovascular events.[6] Children with a family history of seizures also have a significantly higher risk of developing epilepsy themselves.[7]

This condition must be managed immediately, and first-line therapy typically involves benzodiazepines such as lorazepam or midazolam.[8] In case of failure, second-line therapies are necessary. The current American Epilepsy Society and Neurocritical Care Society guidelines prescribe phenytoin (PHT) or fosphenytoin as second-line treatment after benzodiazepine failure, with levetiracetam (LEV) as an alternative option because of its desirable pharmacokinetic profile and reduced cardiac risks.[2,9] The classic hydantoin analog, PHT, stabilizes neuronal membranes by increasing sodium channels' inactivation, and LEV, a protein modulator of synaptic vesicles, has a better safety profile and fewer drug interactions.[9,10]

Multiple randomized controlled trials (RCTs) have compared PHT to LEV as second-line agents in benzodiazepine-refractory SE in children. A multicenter trial of 233 children aged 3 months to 18 years (ConSEPT) reported no significant difference in seizure cessation at 24 hours between LEV (68%) and PHT (68%). However, LEV was associated with fewer intensive care requirements (31% vs. 46%). Likewise, in the ESETT trial, LEV and fosphenytoin (a PHT prodrug) showed similar efficacy in terminating seizures within 60 minutes, with no difference in the primary outcomes.[2] A smaller Indian randomized control trial by Wani et al. showed better 24-hour control with LEV (96% compared to PHT 60%), which they attributed to rapid pharmacokinetics and tolerability.[8] These findings are supported by recent meta-analyses that combine the outcomes of 14 RCTs (2,197 children) and demonstrate that LEV does not increase the number of seizure terminations (odds ratio 1.18), but rather comorbid recurrences (odds ratio 0.60) and adverse events (odds ratio 0.59).=.

Despite these developments, critical research gaps remain, especially in low-resource settings such as Pakistan. Most trials are conducted in high-income nations, where remote etiologies predominate over acute infections and where drugs are a given. This study fills this gap by conducting a randomized controlled trial at a tertiary care hospital in Pakistan to compare the effectiveness of intravenous phenytoin and levetiracetam as second-line interventions for convulsive SE in children aged 1 month to 12 years.

MATERIALS AND METHODS

This RCT was conducted over in our hospital. The study sample consisted of 180 participants, 90 in each group. The sample size was determined using the WHO proportion comparison tools (p1 = 96%, p2 = 59.6%), with a statistical power of 90% and a significance level of 5%. The study included children aged 1 month to 12 years, regardless of gender, who were presented to the pediatric emergency department with SE. We excluded those who were on antiepileptic medications, those who had had previous adverse reactions to phenytoin or levetiracetam, and absence, non-convulsive, or myoclonic SE.

We recruited eligible patients after obtaining the institutional review board authorization. We gathered data from using a pre-structured form and obtained written informed consent from guardians. A computer random number table was used to randomly assign patients to groups based on their arrival order in the emergency room. Once airway stability and ventilation were ensured, an intravenous access was set up. For children in active seizure, an initial slow intravenous dose of 0.1 mg/kg was given, followed by the assigned study drug. In instances where SE had recently resolved without ongoing convulsions, only the designated intravenous agent was administered.

Group A participants received LEV with an IV loading dose of 30 mg/kg, mixed in 50 ml normal saline and infused over 15 minutes. Maintenance followed at 30 mg/kg/day, split into two equal portions every 12 hours. Group B was given PHT, starting with a 20 mg/kg IV loading dose in 50 ml normal saline over 15 minutes, then maintained at 5 mg/kg/day in two divided doses 12 hours apart. Should seizures re-emerge after the loading phase, an extra 10 mg/kg of the same drug was provided over 10 minutes in both groups. In a subsequent recurrence, sodium valproate was administered at 30 mg/kg in 50 ml of normal saline, infused over 15 minutes.

Vital parameters, including Glasgow Coma Scale score, pulse rate, respiratory rate, systolic and diastolic blood pressure, and peripheral oxygen saturation, were recorded at admission and re-evaluated at 30 minutes, 1 hour, 6 hours, 12 hours, and 24 hours of treatment. Close observation of all patients was conducted for the first 24 hours in case of recurrent seizures. A successful seizure management was characterized by the lack of convulsive activity during the 24 hours after the first dose.

Statistical analysis was conducted using SPSS software, version 25. Counts and percentages were used to summarize categorical data, including

treatment success, sex, and SE classification. Continuous measurements, such as participants' age and body weight, were reported as means with standard deviations. The chi-square test was used to compare group efficacy, with a p-value of 0.05 or lower considered statistically significant.

RESULTS

A total of 180 participants were included in the study. In Group A, 50 patients (n=50, 55.6%) were in the 1-6 years age group, and 40 patients (n=40, 44.4%) were in the 7-12 years age group. In Group B, 46 patients (n=46, 51.1%) were in the 1-6 years age group, and 44 patients (n=44, 48.9%) were in the 7-12 years age group. The mean age for Group A was 6.52 ± 2.68 years, while for Group B, it was 6.59 ± 2.72 years. [Table 1]

Table 1: Age Distribution (n=180)

Age (years)	Group A (n=90)		Group B (n=90)	
	No. of patients	*Percentage (%)*	*No. of patients*	*Percentage (%)*
1-6	50	55.6	46	51.1
7-12	40	44.4	44	48.9
Total	90	100	90	100
Mean ± SD	6.52 ± 2.68		6.59 ± 2.72	

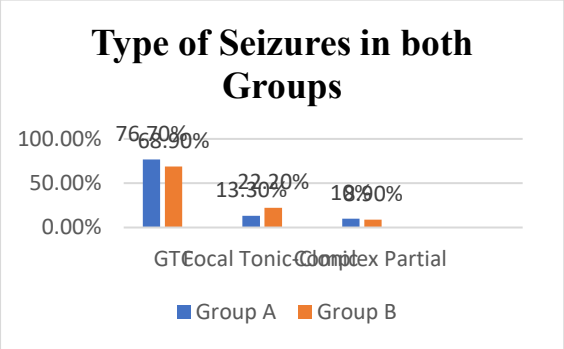

Figure 1: Seizure Types in both groups

In Group A (n=90), 30 patients (n=30, 33.3%) experienced Generalized Tonic-Clonic (GTC) seizures, 25 patients (n=25, 27.8%) had Focal Tonic-Clonic seizures, and 35 patients (n=35, 38.9%) experienced Complex Partial seizures. In Group B (n=90), 24 patients (n=24, 26.7%) had GTC seizures, 17 patients (n=17, 18.9%) had Focal Tonic-Clonic seizures, and 49 patients (n=49, 54.4%) had Complex Partial seizures. [Figure 1]

In group A, 82 patients (n=82, 91.1%) showed efficacy, while 8 patients (n=8, 8.9%) did not respond to treatment. In Group B, 64 patients (n=64, 71.1%) demonstrated efficacy, and 26 patients (n=26, 28.9%) did not. Group A showed a significantly higher response rate compared to Group B, with a p-value of 0.005. [Table 2]

Table 2: Comparison of Treatment Efficacy Between Group A and Group B (n=180)

Efficacy	Group A (n=90)		Group B (n=90)	
	No. of patients	*Percentage (%)*	*No. of patients*	*Percentage (%)*
Yes	82	91.1	64	71.1
No	8	8.9	26	28.9
Total	90	100	90	100
p value				0.005

In Group A, 49 patients (n=49, 54.4%) with Focal Tonic-Clonic seizures showed efficacy, while 8 patients (n=8, 8.9%) did not. In Group B, 42 patients (n=42, 46.7%) showed efficacy, and 12 patients (n=12, 13.3%) did not. For GTC seizures, 22 patients (n=22, 24.4%) in Group A and 20 patients (n=20, 22.2%) in Group B showed efficacy, while 4 patients (n=4, 4.4%) in Group A and 10 patients (n=10, 11.1%) in Group B. [Table 3]

Table 3: Comparison of Treatment Efficacy by Type of Seizure

Type of Seizure	Efficacy	Group A (n=90)		Group B (n=90)		p value
		No. of patients	*Percentage (%)*	*No. of patients*	*Percentage (%)*	
Focal Tonic-Clonic	Yes	49	54.4	42	46.7	0.118
	No	8	8.9	12	13.3	
GTC Seizure	Yes	22	24.4	20	22.2	0.295
	No	4	4.4	10	11.1	

DISCUSSION

This study evaluated the comparative efficacy of intravenous phenytoin versus levetiracetam as second-line treatments for SE in children aged 1 to 12 years. We found a mean age of 6.52 ± 2.68 years in the phenytoin group (n=90) and 6.59 ± 2.72 years in the levetiracetam group (n=90), with a majority of children aged 1-6 years (55.6% vs 51.1%). This

result is quite similar to the ConSEPT trial by Dalziel et al., in which the mean age was 3.1 years, with more than three-quarters of participants under 5 years of age.[11]

In terms of seizure types, group A (LEV) exhibited a higher percentage of GTC seizures (33.3%), focal tonic-clonic seizures (27.8%), and complex partial seizures (38.9%). Conversely, group B (PHT) had fewer GTC (26.7%) and focal tonic-clonic (18.9%) seizures but had more complex partial seizures (54.4%). Our seizure patterns are similar to those reported in various pediatric RCTs, in which GTC events frequently dominate, but focal types, such as complex partial, are variable across groups. In the EcLiPSE trial, Lyttle et al. had reported about 60% GTC seizures overall, the rest focal or mixed, a close match with our combined GTC and focal tonic-clonic rates of 61.1% in PHT and 45.6% in LEV.[12] However, in a smaller Indian RCT of 100 children, Singh et al. reported 50% GTC and 50% focal seizures, all evenly divided between PHT and LEV groups. This contrasts with ours, possibly because they focused on acute non-febrile etiologies.[13]

We found a substantially higher efficacy rate in the LEV group, where 91.1% (n=82/90) had ceased seizures after 24 hours, compared with 71.1% (n=64/90) in the PHT group (p=0.005). Similar findings were reported by Wani et al., who found that LEV was superior, with 96% seizure control at 24 hours compared with 60% with PHT in 60 children, due to LEV's rapid onset and tolerance.[8] Similar efficacy was reported by Kapur et al., with 47% cessation with LEV and 45% fosphenytoin (PHT prodrug) within 60 minutes.[2] Additional support for LEV comes from recent reviews. Jin et al. found LEV to be comparable to PHT/fosphenytoin for seizure management, with lower recurrence and adverse events in 2,197 children.[9] This is challenged by our data, which show that LEV performed better than PHT and that there was no difference in recurrence. Similarly, a 2023 systematic review by Tasya et al. demonstrated a higher cessation rate with LEV (RR 1.10) in Asian cohorts, as in our case, but this may be due to dosing or population-specific factors.[14]

LEV proved to be more effective in controlling both GTC and focal tonic-clonic seizures. In a meta-analysis of 12 trials (2,293 pediatric patients), similar cessation rates (82% with levetiracetam versus 77.5% with phenytoin) were reported across all subgroups, consistent with our findings of non-significant differences in focal and GTC responses.[15] The ConSEPT trial, however, compared our results and found no difference between them, with levetiracetam at 50% and phenytoin at 60% cessation, but excluded convulsive episodes and did not subgroup by type.[11] Overall, the LEV was more effective than PHT in treating pediatric SE.

The main limitation of this study was its open-label design, which could have introduced bias in patient assessments due to a lack of blinding. In addition, the emphasis on 24-hour seizure cessation also neglects long-term consequences, including neurodevelopmental effects or the development of recurrences beyond the original time interval.

CONCLUSION

This research showed that intravenous levetiracetam had a substantially better seizure control rate in children with SE than phenytoin. Levetiracetam showed greater efficacy for both focal tonic-clonic and generalized tonic-clonic seizures, though differences were not statistically significant. Future studies should use blinded, multicenter designs and evaluate long-term outcomes, including neurocognitive effects and recurrence risks.

Funding source

This study was conducted without receiving financial support from any external source.

Conflict in the interest

The authors had no conflict related to the interest in the execution of this study.

Permission

Prior to initiating the study, approval from the ethical committee was obtained to ensure adherence to ethical standards and guidelines.

REFERENCES

1. Newton CR. Epidemiology of status epilepticus in children. Developmental medicine and child neurology. 2021;63(9):1011.
2. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized trial of three anticonvulsant medications for status epilepticus. New England Journal of Medicine. 2019;381(22):2103-13.
3. Gurcharran K, Grinspan ZM. The burden of pediatric status epilepticus: Epidemiology, morbidity, mortality, and costs. Seizure. 2019;68:3-8.
4. Biset G, Abebaw N, Gebeyehu NA, Estifanos N, Birrie E, Tegegne KD. Prevalence, incidence, and trends of epilepsy among children and adolescents in Africa: a systematic review and meta-analysis. BMC Public Health. 2024;24(1):771.
5. Leitinger M, Trinka E, Giovannini G, Zimmermann G, Florea C, Rohracher A, et al. Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. Epilepsia. 2019;60(1):53-62.
6. Migdady I, Rosenthal E, Cock H. Management of status epilepticus: a narrative review. Anaesthesia. 2022;77:78-91.
7. Alyoubi RA, Aljaafari DT, Basheikh MA, Al-Yahyawi NY, Bakry MA, BenHli NM, et al. The etiology and risk factors of convulsive status epilepticus in pediatric patients of tertiary center in Saudi Arabia. Neurosciences Journal. 2021;26(1):26-30.
8. Wani G, Imran A, Dhawan N, Gupta A, Giri JI. Levetiracetam versus phenytoin in children with status epilepticus. Journal of Family Medicine and Primary Care. 2019;8(10):3367-71.
9. Jin L, Jin Z, Wang Z. Levetiracetam versus phenytoin/fosphenytoin for second-line treatment of children with convulsive status epilepticus: an up-to-date meta-analysis and systematic review of randomized controlled trials. Frontiers in Neurology. 2025;16:1580329.
10. Sharawat IK, Murugan VK, Bhardwaj S, Tomar A, Tiwari L, Dhamija P, et al. Efficacy and safety of phenytoin and levetiracetam for acute symptomatic seizures in children with acute encephalitis syndrome: an open label, randomised

controlled trial. Seizure: European Journal of Epilepsy. 2024;118:110-6.
11. Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. The Lancet. 2019;393(10186):2135-45.
12. Lyttle MD, Rainford NE, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. The Lancet. 2019;393(10186):2125-34.
13. Singh K, Aggarwal A, Faridi M, Sharma S. IV levetiracetam versus IV phenytoin in childhood seizures: a randomized controlled trial. Journal of Pediatric Neurosciences. 2018;13(2):158-64.
14. Tasya GA, Djatmiko NI, Rahman FHF, Rahmawati VK. Comparative efficacy of intravenous levetiracetam and phenytoin in status epilepticus: a systematic review and meta-analysis of randomized controlled trials. Medical Journal of Indonesia. 2023;32(1):45-51.
15. Feng Y, Chen Y, Jia Y, Wang Z, Wang X, Jiang L, et al. Efficacy and safety of levetiracetam versus (fos)phenytoin for second-line treatment of epilepticus: a meta-analysis of latest randomized controlled trials. Seizure. 2021;91:339-45.