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Effectiveness of Levetiracetam Versus Phenytoin in Acute Management of Childhood Seizures

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ABSTRACT

Objective: To compare the antiseizure efficacy of Levetiracetam versus Phenytoin in acute management of childhood seizures.
Study Design: Quasi-experimental Study
Place and Duration of Study: Pediatric Unit, Combined Military Hospital, Abbottabad, Pakistan, from Aug 23 to Jan 24.
Methodology: Pediatric patients (0-28 days, 2 months-5 years, and 6-12 years age) presenting with acute seizures or first fit of life not yet attributed to any underlying cause were included in the study. Employing a non-probability consecutive sampling technique, 70 patients were recruited in Group-L, who received Levetiracetam, and 70 patients in Group-P who received phenytoin. Recorded parameters included demographics, cardiovascular parameters, duration of seizure, recurrence of seizures in 24 hours, and duration of sedation.
Results: A total of 140 patients were recruited with a male-to-female ratio of 3.2:1. Efficacy of both drugs as revealed by seizure duration with a median value of 7.3(5.4-14.5) minutes in Group-L as compared to 14.2(9.7-17.5) minutes in Group-*P* (*p*-value 0.001). Recurrence of seizures during 24 hours was observed in 03(4.3%) patients in Group-L as compared to 05(7.1%) patients in Group-P (*p*-value 0.466). Comparison of side effects among groups revealed that bradycardia, hypotension, and arrhythmia events occurred more in Group-P as compared to Group L. At the same time, the duration of sedation was significantly greater in Group-L compared to Group-P (*p*-value 0.001).
Conclusion: Levetiracetam and phenytoin are both effective in acute pediatric seizures with a better safety profile of Levetiracetam as compared to phenytoin.

Keywords: Anticonvulsants, Levetiracetam, Pediatrics, Phenytoin, Seizures

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INTRODUCTION

Childhood seizures are one of the most encountered emergencies that can affect the growth and development of the brain. Electrolyte imbalances, hypoxic ischemic encephalopathy, infections, metabolic disorders, syndromes, intracranial hemorrhage, post trauma are the common causes that can precipitate seizures.[1]

The reported prevalence of childhood seizures is 0.12% with a mortality of 4%.[2] The prevalence of neonatal seizures varies according to gestational age, ranging from 0.02% to 0.12%. The highest prevalence is at 24 weeks GA. The greatest impact of seizures on mortality is at 33–36 weeks GA.[3] Pediatric age group has immature brains with a propensity to develop dysregulated electrical activity in response to minor homeostatic changes in the body. Hypoxic ischemic encephalopathy and intracranial hemorrhage remain the most common causes of seizures in term and preterm neonates, yet most seizures are subclinical.[4] Prompt management and acute intervention in childhood seizures are pivotal in decreasing long-term cognitive and developmental abnormalities. Recent advances have led to effective therapeutic modalities achieving earlier control of seizures and decreasing the rate of morbidity and mortality.[5]

Seizure control pathway is implemented globally to achieve a standard acute management where seizures lasting more than 5 minutes is treated by a 1st line antiepileptic (Diazepam/Midazolam/ Phenobarbitone). 2 doses of 1st line drugs 5 mins apart in case of recurring seizures, followed by a loading dose of either Levetiracetam or Phenytoin as a single loading dose. Seizures lasting more than 15 minutes (status epilepticus) is treated by multi-drug loading as well as maintenance dosage. In this study, we have picked these two drugs, Levetiracetam and Phenytoin to compare their efficacy and side effects as they are widely used in equal potency. Our results will help us to have insight into the drug with a better safety profile and efficacy.

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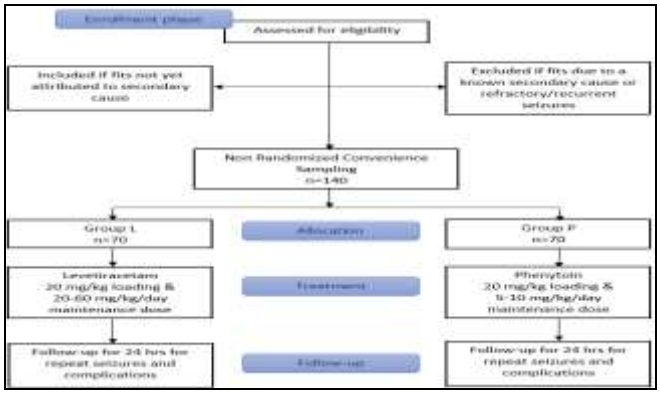

Figure: Patient Flow Diagram

The molecular effects of Levetiracetam lead to anti-inflammatory, GABAergic, neuroprotective, antioxidant, and anti-epileptic effects, resulting in earlier control of childhood seizures.[6] Phenytoin is a conventionally used antiepileptic that increases the refractory period of sodium channels and prevents the transmission of impulses.7 In addition, it increases the concentration of inhibitory neurotransmitters like Gamma Amino Butyric Acid (GABA) and stabilizes the cell membrane, leading to an antiepileptic mechanism. Slurred speech, vomiting, nystagmus, bradyarrhythmia's, and AV blocks are acute side effects of Phenytoin. Whereas cerebral dysfunction, dyskinesia, and gingival hyperplasia are the long-term complications associated with phenytoin.[8]

This study was conducted to comprehensively compare the anti-seizure efficacy of Levetiracetam and Phenytoin in the acute management of childhood seizures, with particular emphasis on their ability to rapidly control seizures, prevent recurrence within the first 24 hours, and assess their associated safety profiles and treatment-related adverse effects.

METHODOLOGY

This quasi-experimental trial was undertaken at the Pediatric Department, Combined Military Hospital, Abbottabad, Pakistan, after obtaining approval from the ethical review committee of the hospital (ERC Num CMH-Atd-ETH-151-Paeds-24). The study duration was 06 months, commencing from Aug 23 to Jan 24.

The WHO sample size calculator was used for the estimation of sample size. In a study conducted by Besli GE et al., the efficacy of levetiracetam in childhood seizures was observed in 78% of the patients compared to 58% in patients receiving phenytoin.8 With 95% power of the study and a significance level of 5%, a sample size of n=140 was calculated. Employing a non-probability consecutive sampling technique, 70 patients were recruited in Group-L, who received injections of Levetiracetam 20 mg/kg, and 70 patients were included in Group-P, who received 20mg/kg intravenous Phenytoin.

Inclusion Criteria: Pediatric patients, neonates, and children (0-28 days, 2 months to 5 years, and 6-12 years of age) of either gender, presenting with acute focal/ generalized tonic clonic seizures (seizure duration less than 10 minutes, which were controlled with a single drug loading dose) were included in the study.

Exclusion Criteria: Patients with recurrent/refractory seizures secondary to an underlying cause (seizure duration greater than 15 mins which required more than one loading dose of drugs) were excluded.

Patients with acute focal/ generalized tonic-clonic seizures were received in the pediatric emergency unit of the hospital. Patients were placed in lateral position. Airway, breathing, and circulatory support were provided as per seizure treatment protocol. An intravenous line of appropriate size was established using a sterile technique. Non-invasive monitoring, including blood pressure, pulse oximetry probe, electrocardiographic electrodes, and temperature probe, was attached to the patients. Blood samples were obtained in aseptic specimen bottles for performing baseline investigations, including complete blood picture, random blood sugar, serum urea, serum electrolytes, and liver function tests. First-line anti-epileptics, Midazolam and Phenobarbitone, were given according to the initial seizure control pathway regime in age-appropriate dosage. Patients from Group-L received a 20 mg/kg loading dose in 20 mins followed by a maintenance dose of 20-60 mg/kg/day, while patients from Group-P received a 20 mg/kg loading dose in 20 mins followed by a maintenance dose of 5-10 mg/kg/day 12 hourly. Recorded parameters included demographic characteristics of patients, blood pressure, and heart rate at presentation, followed by every 15-minute interval for 01 hour and then hourly monitoring. Any decrease in heart rate of greater than 20% of the baseline was recorded as bradycardia, while a decrease in blood pressure reading of greater than 20% from the baseline was recorded as hypotension. During the treatment period, any rhythm other than a sinus rhythm was recorded as an arrhythmia. The duration of sedation in each patient was recorded on a stopwatch and recorded in minutes. All patients were

admitted and followed up for a period of 24 hours, and any recurrence of seizures was recorded. Rescue treatment of Levetiracetam (Group-L) or Phenytoin (Group-P) in the same loading dose was administered on recurrence of seizures. Seizures that could not be controlled with monotherapy were excluded from the trial and were treated with multiple antiseizure drugs.

Data entry and analysis were performed using Statistical Package for Social Sciences (SPSS) software version 23.0. Frequencies and percentages were used for qualitative variables, while quantitative variables were computed using mean and standard deviation. Chi-square test for qualitative variables and Mann-Whitney U test for continuous variables following a non-normal distribution. A *p*-value of ≤0.05 is considered significant.

RESULTS

Out of 140 patients, 76.4% were males, while 23.6% were female patients with a male-to-female ratio of 3.2:1. The median age of the patients in Group-L was 53.0(48.0-66.0) months, as compared to 57.0(49.0-78.0) months in Group-P. Median weight in Kilograms (kgs) was recorded as 16.0(12.0-22.0) kgs in Group-L versus 16.0(13.0-23.0) kgs in Group-P. Baseline characteristics of the patients are shown in Table-I. The efficacy of both drugs, as revealed by seizure duration among the groups, was comparable with a median value of 7.3(5.4-14.5) minutes in Group-L as compared to 14.2(9.7-17.5) minutes in Group-P (*p*-value 0.001). In both groups, seizures were effectively controlled 24 hours after treatment, and only 03(4.3%) patients in Group-L, as compared to 05(7.1%) patients in Group-P had repeated seizures in 24 hours (*p*-value 0.466). Treatment efficacy among the groups is shown in Table-II. A comparison of side effects between the groups revealed that bradycardia, hypotension, and arrhythmia events occurred more in Group-P as compared to Group-L. At the same time, the duration of sedation was significantly greater in Group-L compared to Group-P (*p*-value 0.002), as shown in Table-III.

DISCUSSION

This quasi-experimental trial was conducted to compare the efficacy of Levetiracetam versus Phenytoin in the acute management of childhood seizures. The study concluded that seizure control was achieved earlier in Levetiracetam group as compared to phenytoin, with a median of 7.3(5.4-14.5) mins versus 14.2(9.7-17.5) mins (*p*-value 0.001).

Table-I: Demographic Characteristics among Groups (n=140)

Variables		Group-L (n = 70)	Group-P (n =70)	*p*-value
Gender n (%)	Male	49(70.0%)	58(82.9%)	0.073
	Female	21(30.0%)	12(17.1%)	
Age in months Median (IQR)		53.0(48.0-66.0)	57.0(49.0-78.0)	0.143
Weight in Kgs Median (IQR)		16.0(12.0-22.0)	16.0(13.0-23.0)	0.637

Table-II: Efficacy of Treatment among Groups (n=140)

Variables		Group-L (n =70)	Group-P (n =70)	*p*-value
Seizure Duration in mins Median (IQR)		7.3(5.4-14.5)	14.2(9.7-17.5)	0.001
Repeat Seizure in 24 hours (%)	Yes	03(4.3%)	05(7.1%)	0.466
	No	67(95.7%)	65(92.9%)	

Table-III: Complications among Groups (n=140)

Variables		Group-L (n = 70)	Group-P (n =70)	*p*-value
Hypotension	Yes	01(1.4%)	08(11.4%)	0.023
	No	69(98.6%)	62(88.6%)	
Bradycardia	Yes	0 (0.0%)	03(4.3%)	0.080
	No	70(100.0%)	67 (95.7%)	
Arrhythmias	Yes	0 (0.0%)	02(2.9%)	0.154
	No	70(100.0%)	68(97.1%)	
Duration of Sedation in mins Median (IQR)		155.5 (125.7-184.5)	135.5 (123.0-152.0)	0.002

**IQR - Interquartile Range*

A study by Vignesh *et al.,* concluded that the outcome of the efficacy of Levetiracetam in children with status epilepticus was that the resolution of symptoms was faster with Levetiracetam than with phenytoin. But recurrence rate showed no significant difference.[9] In our study, seizure control was achieved within a 15-min period after commencement of the infusion. These were supported by Samra et al., which showed achievement of seizure control within 15 mins in 94% of patients when levetiracetam was given as compared to 89% after infusion of phenytoin.[10] Another cross-sectional study by Wani *et al.,* concluded that a combination of levetiracetam and phenytoin is 70% efficacious in infants presented with status epilepticus.[11] This is in comparison to our study, which excluded patients going into status epilepticus and required multi-drug seizure control. Similarly, in our trial, the recurrence of seizures 24 hours post-treatment was observed in 05(7.1%) patients in Group-P as compared to 03(4.3%) in Group-L. Zahid *et al.,* in his study revealed similar results by administration of levetiracetam or phenytoin in achieving seizure control over 24 hours; in this study, both drugs were used as second-line drugs.[12]

A recent prospective comparative study by AlMulihi *et al.,* concluded that phenytoin has a better

efficacy than Levetiracetam in neonates with hypoxic ischemic encephalopathy. Phenytoin alone controlled seizures in 73.3% of cases, while Levetiracetam controlled seizures alone in 63.3% of cases.[13] Whereas our study aimed at assessing the efficacy of both drugs separately in the pediatric age group, which included. The emphasis on neonatal and pediatric seizures separately has great importance in terms of differences in etiology, management, and outcome. Hence, future studies targeting specific age groups and plausible causes are suggested. Another meta-analysis by Fiani *et al.,* with a comparison between Levetiracetam and Phenytoin, revealed that when Levetiracetam was administered to pediatric patients, only 10% of the patients had episodes of recurrence as compared to 15.6% in patients receiving phenytoin. Incidence of seizure termination in 24 hours was observed in 76.9% with levetiracetam as compared to 70.5% with phenytoin, revealing the effective antiepileptic activity of both the drugs.[14]

We have limited data from Pakistan on the efficacy of Levetiracetam and Phenytoin in seizure control and management. This calls for more elaborate studies on individual drugs and study populations to assess efficacy and their possible side effects. Phenytoin has long been used as a traditional antiepileptic, as compared to Levetiracetam, which is a newer drug with fewer side effects. This fact has also been studied by Dar *et al.,* reinforcing the findings of the literature.[15]

Trails like Ramesh *et al.,* have been conducted to establish the efficacy and safety of the two drugs, and no consensus was established as to which antiepileptic to prefer.[16] In our trial, the demographics showed a male predominance with a male-to-female ratio of 3.2:1, which was similar to the results concluded from a cross-sectional study of McGinn *et al.,* in children presenting with seizures, with a male-to-female ratio of 1.3:1.[17] The comparison of cardiovascular effects, including hypotension, arrhythmia, and bradycardia in Group-P was comparatively greater than in Group L. In our results, hypotension was significantly greater in phenytoin Group 08(11.4%) as compared to 01(1.4%) patients in Group-L (*p*-value 0.023). Like our results, Dell *et al.,* revealed similar results with greater cardiovascular side effects with phenytoin as compared to Levetiracetam.[18] As the results from our trial revealed a better safety profile with fewer cardiovascular incidents in Levetiracetam as compared to Phenytoin, several studies concluded that levetiracetam has a better safety profile with lesser chances of hypotension and arrhythmias as compared to phenytoin. Hughes *et al.,* explained that Levetiracetam does not depend on cytochrome p450 for its metabolism as compared to phenytoin with linear pharmacokinetics and no requirement of drug monitoring as compared to phenytoin thus providing a better safety profile in comparison.[19] However, the sedation time after infusion was significantly greater in Group-L as compared to Group-P with a *p*-value of <0.01.

In our study, we plan to follow up with patients for a longer period, which may provide a better insight into the long-term side effects of the drugs. A trial conducted by Nazir *et al.,* revealed that when patients were followed for a period of 03 months, 14.28% of the patients had a recurrence of seizures after initial treatment with phenytoin as compared to 28.57% of the patients after receiving levetiracetam. This revealed longer protection from seizures with phenytoin as compared to levetiracetam.[20]

In our study, we followed the patients for a period of 24 hours, and the effect of treatment depending on the type of seizures and separate age groups was not assessed; however, we derived the fact that both levetiracetam and phenytoin were effective treatment modalities for addressing childhood seizures in acute setting.

LIMITATIONS OF STUDY

In our study, we followed the patients for a period of 24 hours only and the effect of treatment, depending on the type of seizures and separate age groups was not assessed. Treating physicians were not blinded to the study.

CONCLUSION

Levetiracetam and phenytoin are both effective in the acute management of childhood seizures with a better safety profile of levetiracetam as compared to phenytoin.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RK & AI: Data acquisition, data analysis, critical review, approval of the final version to be published.

TW & MG: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AAA & HE: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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