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ORIGINAL ARTICLE

Efficacy of Phenytoin vs Levetiracetam in Status Epilepticus in Children at Tertiary Care Hospital

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ABSTRACT

Objective: Evaluation of the efficacy of levetiracetam and phenytoin in treating pediatric status epilepticus (SE).

Study Design: The randomized controlled trial study

Place and Duration of Study: These patients were enrolled Pediatric Emergency Department of Children Hospital, Faisalabad over a six-month period from 1st August 2022 to 31st January 2023.

Material and Methods: Using a computer-generated random number table, 70 patients were assigned randomly in 2 equal groups at the time of admission to the emergency room. Group A received levetiracetam, while Group B received intravenous (I/V) phenytoin. Following the initial loading dose, both groups received an additional 10 mg/kg of the same medication over ten minutes if seizures recurred. Patients were monitored for seizure activity over the next 24 hours, seizure control was defined as the absence of seizures within a 24-hour period following the first dose.

Results: The comparison of efficacy between phenytoin and levetiracetam in treating children with SE revealed that 26 children in Group B and 32 children in Group A received effective treatment (p-value = 0.005).

Conclusion: Levetiracetam is more effective when compared with phenytoin in treating SE in children. Further multicenter trials are recommended to validate these findings.

Key Words: *Children, Status epilepticus, Phenytoin, Levetiracetam, Efficacy*

INTRODUCTION

Status epilepticus (SE) is a serious condition in which a child experiences prolonged or repeated seizures without fully regaining consciousness between episodes. It is the second most common neurological emergency in pediatric population, following febrile seizures. It is characterized as "continuous seizure activity or recurrent seizures without regaining consciousness, lasting for more than 5 mins" is one of several neurological conditions.[1] It occurs in between 10 to 60 out of every 100,000 people, with children under the age of five being the most commonly affected.[2] Approximately 70 million people are suffering from chronic neurological disease epilepsy worldwide.[3] The disease occurs pathologically due to over-excitation of neurons which results in seizures.[4]

There is substantial evidence from numerous randomized clinical trials to support benzodiazepines as the initial line of treatment for SE.[5] However, second-line medications such as phenytoin, levetiracetam, and sodium valproate are used if seizure control is not established.[5,6] The effectiveness of both medications produced a range of results. In one study, the majority of participants were male subjects, the mean age was 4.09 years, and generalized tonic-clonic seizures accounted for 74% of all seizures. For each of the 104 patients, the seizure control time was under 40 mins. In the first 24 hours, group 1 (levetiracetam, 96%) had greater control over seizures than group 2 (phenytoin, 59.6%) (P=0.0001).[7] Another meta-analysis found no discernible difference between the two groups' efficacy rates for levetiracetam (74% vs. 71% for phenytoin).[8]

Although many research on the effectiveness of both medications have been published, there is still a lack of information regarding the relative effects of the two medications.[8] Few studies have demonstrated the effectiveness of either medication in Pakistan, which is why it was decided to examine the two medications' respective efficacies in our hospital to increase seizure control times and provide patients with the best medication possible.

MATERIAL AND METHODS

This randomized controlled trial (RCT) was conducted over a six-month period from 1st August 2022 to 31st January 2023. The study included 70 participants, with 35 in each group, determined using the WHO sample size calculator for two proportions (p1 = 96%, p2 = 59.6%) with a 90% power of the study and a 5% level of significance. Inclusion criteria were all children with SE aged between 6 months and 12 years, of either gender, presenting to the pediatric emergency ward. Exclusion criteria included children currently taking any antiepileptic drug (AED) or those who had experienced an adverse reaction to levetiracetam or phenytoin, as well as cases of absence SE, non-convulsive SE, or myoclonic status epilepticus.

Following IRB approval, patients who met the eligibility requirements were enrolled. At the Children Hospital, Faisalabad emergency room, data was gathered using a predesigned Performa and written informed consent was obtained. Using a computer-generated random number table, the patients were assigned at random to one of the groups based on their emergency room admission. I/V line was established once airway and breathing were fully attended to. Young patients exhibiting active seizures were administered 0.1 mg/kg IV slowly first, and then, based on group assignment, either I/V levetiracetam or I/V phenytoin. The only medications administered to children who had recently experienced SE but were not experiencing seizures were I/V levetiracetam or phenytoin.

Group A received an initial loading dose of 30 mg/kg of levetiracetam, diluted in 50 ml of NS, administered over 15 mins. Following this, they were given a maintenance dose of 30 mg/kg/day, divided into two doses administered 12 hours apart. In Group B, children received an IV loading dose of phenytoin at 20 mg/kg, diluted in 50 ml of NS and administered over 15 mins. They were then given a maintenance dose of 5 mg/kg/day, also divided into two doses 12 hours apart. If seizures recurred after the initial loading dose, both groups received an additional 10 mg/kg of the same medication over ten mins. If seizures returned a second time, patients were administered sodium valproate at 30 mg/kg, diluted in 50 ml of NS, over 15 mins.

Level of consciousness (GCS), heart rate, breathing rate, blood pressure, and oxygen saturation were among the data that were recorded at the time of admission and then again after thirty mins, an hour, six hours, twelve hours, and twenty-four hours. The patients were observed to detect any return of seizure activity throughout the next 24 hours. The definition of seizure control was the lack of seizures for twenty-four hours following the first dosage.

The data was analyzed using SPSS version 25. We computed the frequency and percentage for each qualitative category, including efficacy, gender, and seizure type. For quantitative variables such as weight and age, we calculated the mean + standard deviation. To compare the effectiveness of the two groups, we used the chi-square test, considering a p-value $\leq$0.05 as a significance benchmark.

RESULTS

In Group A, 20 patients (57.1%) were between 1-6 years old, and 15 patients (42.9%) were between 7-12 years, 6.48 ± 2.69 years was mean age. In Group B, 18 patients (51.4%) were between 1-6 years, and 17 patients (48.6%) were between 7-12 years old, 6.63 ± 2.67 years was mean age (table 1). Regarding gender distribution, Group A had 14 males (40%) and 21 females (60%), whereas Group B had 19 males (54.3%) and 16 females (45.7%). In terms of seizure types, 24 patients (68.6%) in both groups experienced Focal Tonic-Clonic seizures, and 11 patients (31.4%) in both groups had Generalized Tonic-Clonic (GTC) seizures. When comparing both groups, 32 patients (91.4%) in Group A (phenytoin) were treated effectively, compared to 26 patients (74.3%) in Group B (levetiracetam), with p-0.005, showing a significant difference in treatment efficacy (tables 2 and 3).

TABLE 1: Age distribution (n=70)

Age(years)	Group A(n=35)		Group B(n=35)	
	No. of patients	Percentage	No. of patients	Percentage
1-6	20	57.1	18	51.4
7-12	15	42.9	17	48.6
Total	**35**	**100**	**35**	**100**
Mean+SD	6.48±2.69		6.63±2.67	

TABLE 2: Comparison of efficacy (n=70)

Efficacy	Group A(n=35)		Group B(n=35)	
	No. of patients	Percentage	No. of patients	Percentage
Yes	32	91.4	26	74.3
No	03	08.6	09	25.7
Total	**35**	**100**	**35**	**100**

p value=0.005

TABLE 3: Comparison of efficacy by type of seizure

Type of seizure	Efficacy	Group		p value
		A (%)	B (%)	
Focal Tonic Clonic Seizure	Yes	22 (55.0)	18 (45.0)	0.122
	No	2 (25.0)	6 (75.0)	
GTC Seizure	Yes	10 (55.6)	8 (44.4)	0.293
	No	1 (25.0)	3 (75.0)	

DISCUSSION

Status epilepticus must be effectively treated to prevent neurologic and systemic illness. The primary goals of any therapy must be the early detection and total abolition of seizures. An anticonvulsant drug must be administered intravenously in order to effectively treat SE. This lowers the possibility of serious adverse effects on the neurological system while also speeding up the delivery of the medication to the brain.

There are numerous medications available on the market, each offering its own set of advantages and disadvantages. For instance, some medications may be highly effective in treating specific conditions but come with side effects that need to be managed. Others might be less potent but have a better safety profile. Additionally, various factors may influence on choice of medication i.e. overall health of the patient, presence of other medical conditions, and individual responses to the drug. Ultimately, the goal is to find the most appropriate medication that balances efficacy and safety for each patient.

Although many research on the effectiveness of both medications have been published, there is still a lack of information regarding the relative effects of the two medications.[8] Few studies have demonstrated the effectiveness of either medication in Pakistan, which is why it was decided to examine the two medications'

respective efficacies in our hospital to increase seizure control times and provide patients with the best medication possible.

When phenytoin and levetiracetam are compared for their efficacy in treating children with SE, it is found that 26 children in Group B and 32 children in Group A received effective treatment (p-value = 0.005).

There is substantial evidence from numerous randomized clinical trials to support benzodiazepines as the initial line of treatment for SE.[5] On the other hand, second-line medications such as sodium valproate, levetiracetam, and phenytoin were administered if seizure control was not achieved.[5,6] The effectiveness of both medications produced varying results. In one study, the majority of participants were male, the mean age was 4.09 years, and generalized tonic-clonic seizures accounted for 74% of all seizures. For each of the 104 patients, the seizure control time was under 40 mins. In the first 24 hours, group 1 (levetiracetam, 96%) had greater control over seizures than group 2 (phenytoin, 59.6%) (p=0.0001).[7] These results are similar to ours.

Another meta-analysis found no discernible difference between the two groups' efficacy rates for levetiracetam (74% vs. 71% for phenytoin).[8] Levetiracetam proved to be more beneficial in our investigation, while our results are consistent with the efficacy of phenytoin. Both phenytoin and levetiracetam are equally effective in treating SE, although numerous studies have demonstrated that levetiracetam is a safer AED to administer. Despite the fact that the two medications have comparable efficacies, this is the case. The frequency of side effects linked to phenytoin therapy was significantly greater than that of side effects linked to levetiracetam therapy. The adverse event that was most common was acute hypotension.

Another clinical study discovered that I/V fosphenytoin was associated with a much higher use of vasopressors than levetiracetam when treating SE. This was primarily caused by the hypotension the therapy caused.[9] Poorer patient outcomes may be attributed to the risk of hypotension associated with I/V phenytoin and fosphenytoin. This is due to the fact that preserving cerebral blood circulation is necessary to prevent neuronal damage in sickle cell disease.[10] Furthermore, clinical research have demonstrated that I/V phenytoin administration may cause potentially fatal cardiac arrhythmias. It now appears that fosphenytoin also induces cardiac arrhythmias, despite the initial belief that it would reduce the risk of cardiac toxicity.[10] However, in the treatment of SE, levetiracetam demonstrates a less severe adverse effect profile and is well tolerated across a wide range of patient demographics.

Levetiracetam has more favourable pharmacokinetics and is simpler to give than phenytoin. These are just two of the many advantages of treating SE with levetiracetam.[11] Unlike phenytoin, levetiracetam is not broken down by the liver's CYP450 enzyme system. Consequently, there is a much lower chance of levetiracetam having a negative interaction with other drugs that are CYP450-processed.

Furthermore, levetiracetam does not require constant close monitoring of its dosage, unlike phenytoin, and has a nearly 100% bioavailability. Levetiracetam also has the advantages of wide therapeutic index and linear pharmacokinetics, which greatly reduce the risk of side effects from the prescription.[11] It is important to remember that levetiracetam is more easier to administer and much faster than phenytoin.[12] In actuality, giving a patient an I/V phenytoin loading dosage is a tedious and time-consuming procedure, which increases the possibility of unwanted side effects.[12]

Although levetiracetam is a safer and better-tolerated antiepileptic drug (AED), the two drugs may be equally effective in treating SE. Therefore, in order to stop seizure activity in people who are resistant to benzodiazepines, it should replace phenytoin and fosphenytoin.

The hypothesis that "there is significant difference between efficacy of Phenytoin and Levetiracetam in Status Epilepticus in Children" is supported by the results of our investigation. To validate our findings, more multicenter trials are necessary.

CONCLUSION

We came to the conclusion that levetiracetam is far more effective than phenytoin at treating status epilepticus in children.

Conflict of interest: None

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