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The efficacy of Levetiracetam compared to Phenytoin in prevention of post-traumatic seizures. A prospective cohort study from a low-middle-income country

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Keywords
traumatic brain injury, post-traumatic seizures, Levetiracetam, Phenytoin, developing countries

ABSTRACT

Objectives: To compare the efficacy of Levetiracetam (LEV) versus Phenytoin (PHY) in the prevention of post-traumatic seizures in a low-middle-income country.

Materials and Methods: A prospective cohort study was conducted from 25th December 2021 to 24th June 2022 at the Pakistan Institute of Medical Sciences, Islamabad, Pakistan. A total of 140 patients presented with traumatic brain injury, both male and female, aged between 15 to 60 years were included. Patients with a history of epilepsy, acromegaly or hypogonadism, history of brain tumour or abscess were excluded. LEV was given to group A patients as a 1000 mg intravenous (IV) loading dose, followed by a dose of 500-1000 mg (orally) twice daily. PHY was given to group B patients as an IV loading dose of 15-20 mg/kg, followed by an oral dose of 4-8 mg/kg divided into three doses per day. All the patients were followed and the efficacy of the drugs was noted.

Results: The mean age of patients in groups A and B was 43.69 ± 9.05 SD years and 43.07 ± 9.46 SD years, respectively. The majority of the patients i.e., 108 (77.1%) were between the ages of 41 to 60 years. Out of the total 140 patients, 87 (62.1%) were males and 53 (37.9%) were females with male to female ratio of 1.6:1. LEV had an efficacy of 63 (90%) and PHY had an efficacy of 46 (65.7%) in this study, both having a p-value of 0.0005.

Conclusion: According to the results of this study, LEV is superior to PHY at preventing post-traumatic seizures.

INTRODUCTION

Traumatic brain injury (TBI) has an incidence rate of 91 to 546 per 100,000 people worldwide, making it a common cause of mortality and morbidity. TBI is more common in underdeveloped countries, accounting for one-quarter to one-third of all accidental deaths. Traumatic brain injuries are more common in those aged 15 to 30, and men are the most common victims.1,2 Mechanical forces in head injured patients at the time of impact may affect neuronal and vascular

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tissue function. A chain of pathologic events can have a negative impact on the patient's neurologic state and worsen their clinical outcomes.1

The two basic mechanisms that cause primary injury are contact (such as a head-on collision with an object or the brain impacting the interior of the skull) and acceleration-deceleration. The primary effects of contact can include injuries to the scalp, skull fractures, and brain surface contusions. Unrestricted head movement causes primary injury from acceleration-deceleration, which results in shear, tensile, and compressive strains.2 These forces can cause intracranial hematoma, diffuse vascular injury, and cranial nerve and pituitary stalk damage. Contusions are swollen areas of brain tissue. They are most commonly found on the frontal lobe poles, inferior frontal lobes, the cortex above and below the operculum of the sylvian fissures, and the lateral and inferior temporal lobes.3

Seizures are common in patients who have suffered a head injury and are frequently associated with adverse outcomes.2 Controlling post-traumatic seizures is essential because these acute insults can exacerbate secondary brain injuries, altering intracranial pressure, rebleeding, and oxygen delivery to cerebral tissue.3 Prophylactic antiepileptic drugs (AEDs) are commonly used to reduce the risk of seizures.4

LEV received medical approval in 1999, whereas PHY received approval in 1953.5 In the past, PHY was the drug most frequently recommended for seizure prophylaxis. LEV, on the other hand, is a more recent antiepileptic drug with substantially less adverse effects than PHY and fewer drug-drug interactions, as well as a simple dosing regimen.6 Although PHY often works in most situations, it also has a high frequency of detrimental consequences and is significantly impacted by several other drugs.7 According to a study conducted by Younus SM et al, the efficacy of LEV in contrast to PHY was determined to be 91.30% and 75.76%, respectively.8

In local practices, PHY is the most commonly used drug, and LEV has recently been introduced. The ease of administration of LEV, as well as the lack of drug level monitoring, contribute to its increased use. PHY has also been linked to a number of adverse effects, including cutaneous hypersensitivity and CYP-450 induction, which LEV does not have. That is why this study was designed to compare these two drugs in order to find the better agent among them for the prevention of post-traumatic seizures. Although there have previously been many studies on this subject, they are currently unavailable in our area, and there is a need for such research in our population. Our study will provide empirical evidence for a better drug for the management of post-traumatic seizures in order to reduce mortality and morbidity of population.

Materials and Methods

Study design: A prospective cohort study.

Setting: Department of Neurosurgery, Pakistan Institute of Medical Sciences, Islamabad, Pakistan.

Duration of study: 25th December 2021 to 24th June 2022.

Sample size: Sample size of 140 (70 in each group) cases was calculated by using World Health Organization (WHO) calculator with 5% level of significance, 80% power of study and taking efficacy of LEV as 91.30% and PHY as 75.76%.

Sample technique: Non-probability consecutive sampling.

Sample selection

a. Inclusion Criteria:

- All patients who presented with traumatic brain injury.
- Duration of trauma ≤24 hours.
- Age 15-60 years of both genders.

b. Exclusion Criteria:

- Patients with history of epilepsy (assessed on history and medical record).
- Patients with acromegaly or hypogonadism (as there may be seizures in these conditions that interfered with our results).
- Patients with history of brain tumour or abscess (assessed on history and medical record) as it may be a cause of seizures and interfered with our results).

Data collection procedure

Following approval from the institutional ethical committee, 140 (70 in each group) patients admitted to the Department of Neurosurgery, Pakistan Institute of Medical Sciences, Islamabad, Pakistan who met the inclusion criteria were chosen. For inclusion in the study, informed consent was obtained from each patient's attendant. All cases were divided into two groups. LEV was given to group

A patients as a 1000 mg IV loading dose, followed by a dose of 500-1000 mg (orally) twice daily. PHY was given to group B patients as an IV loading dose of 15-20 mg/kg, followed by an oral dose of 4-8 mg/kg divided into three doses per day. All patients were followed, and efficacy was determined. On a predesigned proforma, all data were recorded.

Data analysis procedure

Statistical Package for Social Sciences (SPSS) version 25.0 was used for statistical analysis. The mean and standard deviation for age, trauma duration, and Glasgow Coma Scale (GCS) score were presented. Gender and efficacy (yes/no) were presented in the form of frequency and percentage. The chi-square test was used to compare the efficacy of both groups, and a p-value of ≤0.05 was considered significant. Age, gender, duration of trauma, and GCS score were all stratified. The post-stratification chi-square test was used to determine their effects on efficacy, and a p-value of ≤0.05 was considered significant.

Results

The age range in this study was from 15 to 60 years with mean age of 43.32 ± 9.26 SD years. The mean age of patients in group A was 43.69 ± 9.05 SD years, and 43.07 ± 9.46 SD years in group B. The majority of the patients i.e, 108 (77.1%) were between 41 to 60 years of age as shown in Table-I. Out of these 140 patients, 87 (62.1%) were males and 53 (37.9%) were females with male to female ratio of 1.6:1 (Table-II). The average duration of trauma was 14.78 ± 4.79 hours (Table-III). The average GCS was 11.68 ± 1.48 (Table-IV). As shown in Table-V, the efficacy of LEV was seen as 63 (90%) and that of PHY as 46 (65.7%) with a p-value of 0.0005. Table-VI depicts efficacy stratification based on age, gender, trauma duration, and GCS score.

Table 1. Age distribution in both the study groups.

Age (years)	Group A (n=70)		Group B (n=70)		Total (n=140)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
15-40	15	21.4	17	24.3	32	22.9
41-60	55	78.6	53	75.7	108	77.1
Mean ± SD	43.69 ± 9.05		43.07 ± 9.46		43.32 ± 9.26	

Table 2. Gender distribution in both the study groups.

Gender	Group A (n=70)		Group B (n=70)		Total (n=140)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
Male	43	61.4	44	62.9	87	62.1
Female	27	38.6	26	37.1	53	37.9

Table 3. Distribution of patients according to duration of injury in both the study groups.

Duration (hours)	Group A (n=70)		Group B (n=70)		Total (n=140)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
≤12	17	24.3	24	34.3	41	29.3
13-24	53	75.7	46	65.7	99	70.7
Mean ± SD	15.23 ± 4.72		14.16 ± 5.03		14.78 ± 4.79	

Table 4. Distribution of patients according to GCS in both the study groups.

GCS	Group A (n=70)		Group B (n=70)		Total (n=140)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
10-12	47	67.1	52	74.3	99	70.7
13-15	23	32.9	18	25.7	41	29.3
Mean ± SD	11.83 ± 1.51		11.56 ± 1.47		11.68 ± 1.48	

Table 5. Comparison of the efficacy of LEV versus PHY in prevention of post-traumatic seizures.

Comparison between LEV and PHY on the basis of efficacy		Group A		Group B	
		No. of patients	%age	No. of patients	%age
Efficacy	Yes	63	90	46	65.7
	No	7	10	24	34.3

Table 6. Stratification of efficacy with respect to age, gender, duration of trauma and GCS score.

Parameters		Group A (n=70)		Group B (n=70)		P-value
		Efficacy		Efficacy		
		Yes	No	Yes	No	
Age (years)	15-40	15 (100%)	0 (0%)	11 (67.4%)	6 (35.3%)	**0.011**
	41-60	48 (87.3%)	7 (12.7%)	35 (66%)	18 (34%)	**0.009**
Gender	Male	40 (93%)	3 (7%)	25 (56.8%)	19 (19.2%)	**0.0001**
	Female	23 (85.2%)	4 (14.8%)	21 (80.8%)	5 (19.2%)	**0.667**
Duration of trauma (hours)	≤12	16 (94.1%)	1 (5.9%)	15 (62.5%)	9 (37.5%)	**0.020**
	13-24	47 (88.7%)	6 (11.3%)	31 (67.4%)	15 (32.6%)	**0.009**
GCS score	10-12	43 (91.5%)	4 (8.5%)	33 (63.5%)	19 (36.5%)	**0.001**
	13-15	20 (87%)	3 (13%)	13 (72.2%)	5 (27.8%)	**0.237**

Discussion

Anti-epileptic drug (AED) prophylaxis is frequently used in the management of patients with brain injury because certain sub-groups have been shown to benefit from seizure prophylaxis.9 The drug PHY has been shown to be significantly more effective than placebo in preventing post-traumatic seizures during the first 7 days (risk ratio, 0.27; 95 percent confidence interval, 0.12 to 0.62).10 However, PHY displays a wide array of side effects including induction of the hepatic cytochrome P450 system, cutaneous hypersensitivity reactions and inducing drug-drug interactions.11,12 LEV, on the other hand, is a newer non-enzyme inducing AED with far fewer potential side effects.13 Furthermore, unlike PHY, it does not necessitate close monitoring via serial blood sampling due to a wider therapeutic index. However, it is significantly more expensive than PHY.14

There is disagreement about the efficacy of LEV versus PHY in seizure prevention. Various trials have yielded disparate results in terms of the relative efficacy of the two drugs. In our study, the efficacy of LEV was 63 (90%) and that of PHY was 46 (65.7%) with p-value of 0.0005. According to a study done by Younus SM et al., the efficacy of LEV compared to PHY was found to be 91.30% and 75.76%, respectively.8 Jones et al. found no significant difference in efficacy between PHY and LEV for early post-traumatic seizure prophylaxis (p=0.556), despite the fact that patients in the LEV group had a higher incidence of abnormal EEG findings.15 Regarding the long-term effects of both, Szaflarski et al. found that patients receiving LEV had better long-term outcomes than those receiving PHY.16

One study found that patients taking PHY had an increased tendency to have seizures on EEG, but

there was no difference in actual seizure activity. PHY use is also associated with an increased risk of gastrointestinal upset and neurologic deterioration. The patients treated with LEV improved their GCS scores in Gregg Vk's study, but the reliability of the results cannot be determined due to the small sample size in their study.17 Another study found that using PHY reduced the incidence of early post-traumatic seizures in children.18

Guidelines issued by the Brain Trauma Foundation in 2007 and the American Academy of Neurology in 2003 support the provision of post-traumatic seizure prophylaxis for the first 7 days only, with PHY being the most appropriate drug for this purpose. The Food and Drug Administration has approved PHY for the treatment of generalized tonic-clonic and complex partial seizures, as well as the prevention and treatment of seizures that occur during or after neurosurgery.19

Our study found that using LEV reduced the likelihood of seizures and abnormal EEGs. A number of studies show that LEV is superior due to its lower risk of side effects and better long-term outcomes.20 In acute TBI, the use of LEV rather than PHY is associated with better 6-month cognitive outcomes.21 LEV also improves the brain's higher integrative mechanisms. In fact, studies have shown that LEV improves a variety of cognitive abilities, including visual short-term memory, working memory, motor functions, psychomotor speed and concentration, and fluid intelligence.22,23

A previous meta-analysis compared seizure rates with LEV to those treated with PHY in patients with TBI who were at increased risk of seizures.24 The findings suggested that different TBI patients may have a different underlying tendency to seizures, which may be associated with different functional outcomes when using an AED. The use of AEDs may aid in the prevention of post-traumatic seizures. Seizure prevention medications, on the other hand, are not without side effects. Aside from the debate over the efficacy of LEV and PHY, there are serious human side effects. Four of the studies reported side effects, and there were no significant differences in terms of side effects. This finding is consistent with previously reported rates of PHY side effects versus LEV.25

The incidence of seizures seven days after a TBI in patients receiving PHY and LEV was assessed in a retrospective observational study by Kruer et al. The study also described the selection of AEDs in clinical practice. Patients under the age of 18 were barred from participating in the study. 89 of the 109 patients were given PHY, while 20 were given LEV. In total, two patients, one from each group, had post-traumatic seizures. Kruer et al. concluded that following the approval of IV LEV, there was a trend favouring LEV for seizure prevention.26 Radic et al.27 conducted a separate retrospective cohort study to compare the efficacy and risk of using LEV versus PHY for seizure prophylaxis following an acute or subacute subdural hematoma diagnosis. A total of 124 patients were assigned to the PHY group, while 164 were assigned to the LEV group. There was no significant difference in clinical and/or electrographic seizure risk, but the LEV group had a lower risk of adverse events. When compared to PHY users, LEV was associated with an increased risk of electrographic seizures during hospitalization and a decreased risk of adverse drug effects in subjects with a midline shift of >0 mm. So, according to Radic et al., LEV is associated with a lower risk of adverse drug effects.

The goal of Chakravarthi et al.28 was to compare the safety and efficacy of IV LEV versus IV PHY in the treatment of status epilepticus. In this study, 44 patients were randomly assigned to either PHY or LEV treatment. The primary endpoint was successful clinical seizure activity termination within 30 minutes of drug administration. Secondary endpoints included seizure recurrence within 24 hours, drug-related adverse effects, mortality during hospitalization, and the need for ventilatory assistance. LEV only controlled status epilepticus in 13 patients compared to 15 patients who took PHY. In terms of outcome measures, this study concluded that LEV is as effective as PHY. LEV is popular because of its ease of administration and lack of continuous monitoring. In the treatment of status epilepticus, LEV is an appealing alternative to PHY. Khan et al.29 conducted a separate randomized controlled trial to compare the efficacy of PHY and LEV in the prevention of early post-traumatic seizures in patients with moderate-to-severe TBI. The 154 patients in this study were divided into two equal groups. In 73 patients, PHY was effective in preventing post-traumatic seizures, while LEV effectively controlled seizures in 70 cases. The researchers concluded that there is no statistically significant difference between PHY and LEV in the

prevention of early posttraumatic seizures in patients with moderate-to-severe TBI.

Noureen et al.30 compared the clinical efficacy and safety of IV LEV versus IV PHY as second-line drugs in the treatment of paediatric status epilepticus. In this open-label, randomized controlled trial, 300 children with status epilepticus received LEV, while another 300 received PHY. LEV was effective in 278/300 cases, while PHY was effective in 259/300 cases. In addition, eight children in the PHY group experienced adverse events. The study concluded that LEV is far more effective than PHY in treating paediatric status epilepticus. Besli et al.31 recently published a study comparing the efficacy and safety profile of LEV and PHY as second-line treatment agents in children with convulsive status epilepticus and acute repetitive seizures. LEV was given to 141 of the 227 patients, while PHY was given to 86. In children with convulsive status epilepticus, LEV was effective in 77.6% of cases, while PHY was effective in 57% of cases. However, there was no statistically significant difference between LEV and PHY efficacy rates for acute repetitive seizures (55.8% vs. 58.8%, respectively). The study concluded that LEV appears to be as effective as PHY in treating children with acute repetitive seizures, but it is more effective in treating children with convulsive status epilepticus.

Conclusion

LEV is more effective than PHY at preventing post-traumatic seizures, according to this study's findings. Therefore, in order to lower the morbidity and mortality of these particular individuals, we advise using LEV as a main therapy agent in the prevention of early post-traumatic seizures in traumatic brain injury.

Abbreviations

LEV: Levetiracetam
PHY: Phenytoin
IV: Intravenous
TBI: Traumatic brain injury
AED: Antiepileptic drug
AEDs: Antiepileptic drugs
WHO: World Health Organization
SPSS: Statistical Package for Social Sciences
GCS: Glasgow Coma Scale
EEG: Electroencephalography

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