

ORIGINAL ARTICLE

COMPARISON OF EFFICACY OF PHENYTOIN AND LEVETIRACETAM FOR PREVENTION OF EARLY POST TRAUMATIC SEIZURES

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Background: The incidence of early post-traumatic seizures after civilian traumatic brain injury ranges 4–25%. The control of early post-traumatic seizure is mandatory because these acute insults may add secondary damage to the already damaged brain with poor outcome. Prophylactic use of anti-epileptic drugs have been found to be have variable efficacy against early post-traumatic seizures. The objective of this study was to compare the efficacy of Phenyton and Levetiracetam in prevention of early post-traumatic seizures in moderate to severe traumatic brain injury. **Methods:** This randomized controlled trial was conducted in department of Neurosurgery, Ayub Medical College, Abbottabad from March, 2012 to March 2013. The patients with moderate to severe head injury were randomly allocated in two groups. Patients in group A were given phenytoin and patients in group B were given Levetiracetam. Patients were followed for one week to detect efficacy of drug in terms of early post traumatic seizures. **Results:** The 154 patients included in the study were equally divided into two groups. Out of 154 patients 115 (74.7%) were male while 29 (25.3%) were females. Age of patients ranges from 7–48 (24.15±9.56) years. Ninety one (59.1%) patients had moderate head injury while 63 (40.9%) patients had severe head injury. Phenyton was effective in preventing early post traumatic seizures in 73 (94.8%) patients whereas Levetiracetam effectively controlled seizures in 70 (90.95%) cases (*p*-value of .348). **Conclusion:** There is no statistically significant difference in the efficacy of Phenyton and Levetiracetam in prophylaxis of early post-traumatic seizures in cases of moderate to severe traumatic brain injury.

Keywords: Phenyton; Levetiracetam; Seizures; Post-traumatic; Epilepsy; Trauma; Head injury

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INTRODUCTION

Traumatic brain injury (TBI) is a common cause of mortality and morbidity with global incidence rates ranging from 91–546 per 100,000 population. In developing countries the rate of traumatic brain injury is on rise, accounting for one quarter to one third of all accidental deaths. The traumatic brain injuries are highest in age group of 15–30 years and males are the predominant sufferers.¹

The mechanical forces in head injured patient result in compression and shearing of neuronal and vascular tissue at the time of impact. A series of pathological events may further lead to brain injury. These secondary causes are amenable to intervention and may be worsened by physiological insults.²

Trauma is an important cause of epilepsy. The incidence of post-traumatic epilepsy ranges from 2–50%.³ Post-traumatic epilepsy can be divided into three groups: immediate seizures, occurring within 24 hours; early seizures, occurring within 7 days; and late seizures, occurring after 7 days of injury. The incidence of each after civilian Traumatic brain injury ranges from 14%, 4–25% and 9–42% respectively.⁴ Severe traumatic brain injury results in seizures in 2–12% of patients with closed head injury and in 50% of cases with penetrating injuries. Moderate traumatic brain injury patients have a slightly increased risk of

post-traumatic epilepsy including early post-traumatic seizures.^{4,5}

The control of early post-traumatic seizure is mandatory because these acute insults may add secondary damage to the already damaged brain.⁶ Post-traumatic seizure is associated with poor Glasgow outcome score (GOS) and higher incidence of behavioral abnormalities on follow up. Early post-traumatic seizures are also associated with increased incidence of late post-traumatic seizures.⁷ Early post-traumatic seizures are associated with poor case mortality rate. The case mortality rate being 27.9% and 19.2% in patients with and without early post-traumatic seizures.⁷

Prophylactic use of anti-epileptic drugs have been found to be protective against early post-traumatic seizures, Various drugs like Carbamazepine, Valproic, and Phenobarbitone have been used for prevention of early post-traumatic seizures, but predominantly phenytoin is being used.^{8,9} Levetiracetam is a new anti-epileptic drug with better tolerability and lower frequency of worsened neurological status. The rate of early seizures has been reported to up to 16% of patients receiving prophylactic phenytoin.¹⁰ Other studies report the incidence of early seizure to be 8%, 4.5% and 4.2% with phenytoin prophylaxis.¹¹ The rate of early

seizures in patients receiving prophylactic Levetiracetam has been documented to be as high as 8.3%.⁹⁻¹¹

The objective of the currently designed study was to compare the efficacy of Levetiracetam with phenytoin in the prevention of early post traumatic seizures. The rationale behind doing this study is that the available literature has provided variety in the success of both drugs in preventing early post traumatic seizures and this study will provide us with first hand and local evidence the best drug in prevention of post traumatic seizures.

MATERIAL AND METHODS

This randomized controlled trial was conducted at department of Neurosurgery, Ayub Medical College, Abbottabad, from March 2012 to March 2013. All the patients of either gender with moderate to severe traumatic brain injury with age group of 5–50 years were included in this study by consecutive (non-probability) sampling technique.

Sample size was 77 in each group. It was calculated using 16%¹⁰ proportion of early onset seizures with Phenytoin and 2.5%¹¹ proportion of early onset seizures with Levetiracetam after traumatic brain injury, 95% confidence interval and 90% power of the test using WHO sample size calculations. Patients presenting after 12 hours of traumatic brain injury, known epileptics on the basis of history and medical records, patients with deranged electrolytes. ($\text{Na}^+ > 145$ mEq/L, $\text{K}^+ > 5.0$ mEq/L) and deranged renal functions (Creatinine > 1.4 mg/dl, Urea > 50 mg/dl), and patients with history of seizure before presentation to our hospital were excluded from the study. Patients who underwent surgery and those who died during the first week of admission were also excluded from the study. All these afore-mentioned conditions act as confounders and if included would have introduced bias in the study results.

Approval was obtained from hospital's ethical committee before starting the study. Patients were included in the study through OPD/ER department in a consecutive manner. All patients who presented with moderate to severe head injury were enrolled in the study after taking their informed written consent. All patients were admitted in the Neurosurgery department and neurosurgical ICU of the hospital for further evaluation. After taking detailed history, complete general physical, systemic and neurological examination was done. GCS of the patients were assessed and the patients with moderate and severe head injury were included in the study. All patients were subjected to X-rays and CT-scans of skull for evaluation of head injury. Laboratory investigations like serum electrolytes, urea, and

creatinine were performed from the hospital laboratory.

All patients were randomly allocated in two groups by lottery method. Patients in group A were subjected to Phenytoin, starting in a loading dose of 20 mg/kg intravenously over sixty minutes followed by maintenance dose of 5 mg/kg/day in two divided doses. Patients in group B were subjected to LEV, starting in a loading dose of 20 mg/kg intravenously over sixty minutes followed by maintenance dose of 10-20 mg/kg/day in two divided doses. All the patients were followed till 7th day of injury to detect efficacy of drug in terms of early post traumatic seizures.

All the above mentioned information including name, age, gender, type of trauma and observation of any seizure during the first seven days of trauma was recorded in a pre-designed *pro forma*.

All data were processed and analyzed on SPSS-16.0. Chi square test was used to compare efficacy in both the groups while keeping *p*-value of ≤ 0.05 as significant.

RESULTS

Total of 154 patients were divided equally into the two groups. Out of the total 154 patients 115 (74.7%) patients were male while the rest of 29 (25.3%) were females. Age of the patients ranges from 7–48 years with a mean of 24.15 ± 9.56 years. Majority of the patients were from Manshehra district, i.e., 50 (32.5%), followed by 41 (26.6%) from Abbottabad, 27 (17.5%) from Kohistan and 16 (10.4%) from Azad Kashmir. Majority of the patients in our study population sustained head injury after fall, i.e., 82 (53.2%), followed by road traffic accidents that accounted for 64 (41.6%) patients and only 8 (5.2%) had history of assault as a cause of head injury.

Ninety one (59.1%) patients had moderate head injury (GCS of 8–13) while rest of 63 (40.9%) patients had severe head injury (GCS of 3–7). Out of the 82 patients that sustained injury after fall, 49 had moderate head injury while 33 had severe head injury. Similarly out of 64 patients who had RTA, 35 had moderate head injury and 29 had severe head injury. Out of the eight patients that had history of assault, 7 had moderate head injury and 1 had severe head injury.

In group A there were 60 (39.0%) males and 17 (11.0%) females while in group B there were 55 (35.7%) males and 22 (14.3%) were females. In group A 45 (29.2%) patients sustained head injury after fall from a height, 29 (18.8%) after RTA and 3 (1.9%) after assault where as in group B 37 (24%) had history of fall, 35 (22.7%) had RTA and only 5 (3.2%) had history of assault. Forty eight (31.2%) patients in group A had moderate head injury while 29 (18.8%) had severe head injury, while in group B, 43 (27.9%)

had moderate head injury and rest of 34 (22.1%) had severe head injury.

In group A 73 (94.8%) remained fit free during the first seven days after the head injury while 4 (5.19%) had early post-traumatic seizures. In group B 70 (90.95%) patients were free of any seizure while 7 (9.1%) had seizure during the first seven days after head injury while being on LEV for the prevention of early post-traumatic seizures, as summarized in table-8. Hence PHY was effective in preventing early post traumatic seizures in 73 (94.8%) patients while in 4 (5.19%) patients it failed to prevent seizures. Whereas LEV effectively controlled seizures in 70 (90.95%) cases and in remaining 7 (9.1%) cases it was ineffective. (Table-1).

The difference in the efficacy of the drugs during the study period was found to be insignificant after using Chi square test to compare efficacy in both the groups while keeping *p* value of ≤ 0.05 as significant. Severity of injury and the efficacy of drugs in both of the groups also didn't show any statistically significant correlation with a *p*-value of 0.113 for the group receiving PHY and a *p*-value of 0.942 for the group receiving LEV. (Table-2). Similarly type of trauma and gender didn't show any significant correlation with the efficacy of the drugs, with a *p*-value of 0.540 and 0.572 respectively. (Table-3&4)

Table-1: Efficacy of drugs in the two groups

			Drug efficacy		Total	<i>p</i> -value
			No	Yes		
Study group	PHY	Count	4	73	77	.348
		% of Total	5.19%	94.8%	50.0%	
	LEV	Count	7	70	77	
		% of Total	4.5%	45.5%	50.0%	
Total		Count	11	143	154	
		% of Total	7.1%	92.9%	100.0%	

Table-2: Cross table showing the efficacy of phenytoin and levetiracetam drugs in moderate and severe TBI

			Drug efficacy		Total	<i>p</i> -value
			Yes	No		
PHY	Severity of injury	Moderate	47	1	48	.113
		Severe	26	3	29	
	Total	73	4	77		
LEV	Severity of injury	Moderate	39	4	43	.942
		Severe	31	3	34	
	Total	70	7	77		

Table-3: Efficacy of drugs in patients with different mode of injury

			Drug efficacy		Total	<i>p</i> value
			Yes	No		
Type of trauma	Fall	Count	77	5	82	.540
		% of total	50.0%	3.2%	53.2%	
	RTA	Count	58	6	64	
		% of total	37.7%	3.9%	41.6%	
	Assault	Count	8	0	8	
		% of total	5.2%	.0%	5.2%	
Total		Count	143	11	154	
		% of total	92.9%	7.1%	100.0%	

Table-4: Efficacy of drugs in either gender

			Drug efficacy		Total	<i>p</i> value
			Yes	No		
Gender of Patients	Male	Count	106	9	115	.572
		% of Total	68.8%	5.8%	74.7%	
	Female	Count	37	2	39	
		% of Total	24.0%	1.3%	25.3%	
Total		Count	143	11	154	
		% of Total	92.9%	7.1%	100.0%	

DISCUSSION

Prophylaxis against the seizures in different neurosurgical problems has been used for quite long time.¹² Seizures encountered in neurosurgical patients are commonly because of high intracranial pressure or because of any irritating supra-tentorial lesion which may be damaged brain, tumor bleed or any other mass. Same holds true for the TBI, in which the chances of seizures are increased with dire consequences of seizures in terms of outcome.¹³

Use of anti-convulsants in the settings of traumatic brain injury is recommended during first seven days after injury, though during this time they prevent early post-traumatic seizures, but they don't prevent late post-traumatic seizures. Although the use of anticonvulsants may have beneficial effect by preventing early post-traumatic seizures which predispose the patients to late post-traumatic seizures. On the other hand seizure prophylaxis drugs are not without their side-effects therefore long-term use of prophylaxis is not recommended unless there is documented clinical or EEG evidence of seizures. Some surgical neurologists recommend anti-epileptics in certain high-risk groups, such as those with severe TBI.^{14,15} Chan *et al* also recommend the use of prophylactic anti-epileptics for the prophylaxis of seizures in first seven days after the TBI.¹⁶

PHY has been proved to be efficacious in different types of seizures including partial and generalized seizures.¹⁷ Since PHY is the most studied drug in the setting of traumatic brain injury so it is frequently used for the prophylaxis of early post-traumatic seizures, but, it has several side effects like hypersensitivity syndrome, skin irritation or phlebitis when extravasation occurs, and most importantly hypotension or arrhythmia when administered intravenously.¹⁸ PHY induces hepatic cytochrome P450 system and because of that it is prone to many potential drug interactions. PHY also has a narrow therapeutic index, and minimal to low supplement in dose can cause disproportionately large increases in plasma drug levels. Hence plasma levels should be monitored in order to evaluate whether the plasma concentrations are within therapeutic levels or not. We in our study due to financial constraints and because of non-availability of resources in our local setup couldn't get the serum of both the drugs during the

study period. PHY is documented to temporarily effect the plasma cortisol levels by decreasing its levels, hence it may aggravate the acute adrenal hyporesponsiveness which is commonly encountered in the patients with severe traumatic brain injury. In patients with subarachnoid hemorrhage PHY has been associated with impaired functional and cognitive recovery.¹⁹ The newly developed AEDs that are devoid of hepatic metabolism, such as LEV and gabapentin, are therefore now recommended for seizure prophylaxis.²⁰ Yet the use of LEV is not without drawbacks. LEV has faster systemic clearance and the terminal elimination half-life is documented to be shorter in patients in neuro-critical centers. Hence, higher and, or frequent dosing may be required to achieve target plasma concentrations.²¹

In our study over 74% of the patients were male and patients had a mean age of 24.15 years. These results coincides with results from other regional and international studies which show a predominance of male gender in cases of head injury.²² Sunay YM *et al*,²³ observed a male to female ratio of 3.1:1, which closely correlates with the results of our study that we had male to female ration. Similarly Prashant G *et al*²⁴ also showed that males are the predominant sufferers in cases of head injury, which may be because of more outdoor activities of males. Igun GO *et al* and Sunay YM *et al* both showed road traffic accidents as the most common cause of head injury while our study showed that fall from height (53%) was the most common cause of head injury which is because of our setup is a hill station, and fall from hill and roofs of houses in children less than 10 years are the most common cause of head injury. Our study showed that 8.8% of patients with assault presented with head injury, that is close to the percentages of assault in head injury seen by Bavid and Igun, which is 4.7% and 3% respectively.^{20,25}

Haltiner AM *et al* in their secondary analysis of data of prospective double-blind placebo-controlled study in which 404 patients received either PHY or placebo for prophylaxis of early post-traumatic seizures. They concluded that the incidence of post-traumatic fits during the first week after the trauma can be effectively reduced by use of PHY without any significant drug related effects.²⁶

Up till now several researchers have compared the efficacy of PHY and LEV and their safety profile in various patient populations, though the numbers are small and results are varying.^{11,27} Jones *et al* in their study revealed no significant difference in the efficacy of PHY and LEV for early post-traumatic seizure prophylaxis ($p=0.556$) though the patients in LEV group had higher incidence of abnormal EEG findings.²⁸ These findings strongly coincide to the

findings of our study which revealed no statistically significant difference in efficacy of the two drugs.

Szaflarski *et al* regarding the long-term effects of both have however showed an improved long-term outcomes of patients receiving LEV as compared to those receiving PHY.¹⁰

LEV treated patients have been shown to have lower complications and short neurosurgical intensive care stay. Hence some authors recommend LEV for older patients and patients having different brain space occupying lesions or strokes.²⁹

Apart from trauma newer anti-epileptic drugs are being increasingly used in other neurosurgical settings as well. A retrospective study that compared the safety efficacy of LEV and PHY when used as monotherapy for prophylaxis of seizures in patients operated for supra-tentorial neurosurgery showed that LEV had significantly fewer early adverse reactions with higher retention rate in patients who were in follow up for 1 year.³⁰ The cost of a seven days course of PHY and plasma PHY levels was \$37.50, whereas the cost of LEV for the same duration has been documented to be \$480.00 and since the literature review noted PHY to be as effective as LEV in preventing early post-TBI seizures (even more effective in sub-clinical cases). Hence, Cotton BA *et al* advocated PHY to be more cost-effective than LEV.³¹ But Kazerooni documented that LEV is potentially more cost-effective than PHY for early post-traumatic seizure prophylaxis if the payer's willingness-to-pay is greater than \$360.82 per additional successful seizure prophylaxis regimen during 7 days after the trauma.³² Though studies are supporting the use of LEV for seizure prophylaxis in the settings of trauma, yet the documented results are limited, so multi-centre trials are needed to clarify the guidelines regarding the use of anti-epileptic drugs for the prevention of early PTS.³³

There are a few limitations of the study. First being the open labelled nature of the trial. Secondly, we lacked 24 hours EEG monitoring of the patients and lack of plasma level monitoring. Thirdly there was an element of inter-observer bias since the patients were monitored by different observers during their hospital stay.

CONCLUSION

It can be concluded that there is statistically no significant difference in the efficacy of PHY and LEV in prophylaxis of early post-traumatic seizures in the setting of moderate to severe TBI. Since LEV has better safety profile, it can be used as monotherapy for the seizure prophylaxis. Despite many unwanted PHY side effects, its use is still supported by level-I evidence. Further multicenter trials need to be

conducted to chalk out guidelines for the LEV in the settings of traumatic brain injury.

AUTHORS' CONTRIBUTION

SAK: conceived the idea, literature search, write-up and data collection, AA, AA, EAKA write-up, literature search, GM, KKZ, SA: data collection, write-up, SNB: supervised the study, write-up, and proof read the manuscript.

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