Original Article

Comparison of Phenytoin versus Levetiracetam in Early Seizure Prophylaxis after Traumatic Brain Injury, at a Tertiary Care Hospital in Karachi, Pakistan

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Abstract

Aims: The aim of the study was to compare the efficacy of phenytoin and levetiracetam for seizure prophylaxis in patients with severe traumatic brain injury (TBI). **Subjects and Methods:** A randomized controlled trial was conducted over a period of 6 months, at a tertiary health care center in Karachi, Pakistan. Patients with TBI were divided into two groups. Patients in Group A were given phenytoin, whereas Group B patients received levetiracetam. The first dose of the drugs was given within 24 h of injury and continued for 7 days. Data were collected using a predesigned pro forma. All the patients who were in a state of persistent coma, had altered mental status, or had clinical signs of seizures underwent a 1-h electroencephalographic (EEG) recording to observe the seizures, the first EEG was done on the 1st day posttrauma and a second one was done on day 7 of drug use, both the EEGs were compared for changes. We also analyzed the patients according to their duration of antiepileptic drug therapy, length of hospital stay, and complications during therapy. **Results:** One hundred and forty (117 males and 23 females) patients who presented with TBI having a mean age of 29.48 ± 16.24 years were part of the study. The most prevalent cause of brain injury was road traffic accidents in 72.85% patients. There was no significant relationship between the antiepileptic drug used with the initial EEG (P = 0.313) and seizure activity (P = 0.502). However, a significant correlation of the antiepileptic drug used was found with EEG (P = 0.002) and seizure activity (P = 0.014) on follow-up. Patients who took levetiracetam had decreased the incidence of abnormal EEG and seizure activity on follow-up. There was not any correlation between GCS both initially (P = 0.845) and on follow-up (P = 0.104) with the antiepileptic drug used. **Conclusion:** The incidence of abnormal EEGs and seizure activity in patients with TBI is the same for both levetiracetam and phenytoin for the initial 7 days post-TBI; however, the incidence of seizures is lower for patients who used levetiracetam on the subsequent follow-up.

Keywords: *Levetiracetam, phenytoin, posttraumatic seizure, prophylaxis, traumatic brain injury*

Introduction

Traumatic brain injury (TBI) is an insult or trauma to the brain caused by external mechanical forces, whereas head injury is a generic term referring to injuries affecting not only the brain but also other structures of the head. In the UK, about 6 out of 100,000 people suffering from TBI die every year.[1] A trauma-induced structural injury or physiological disruption of brain function as a result of application of an external force is indicated by the new onset or worsening of at least one of the following clinical signs, immediately following the event: (1) any period of loss of or a decreased level of consciousness, (2) any loss of memory for events immediately before or after the injury (posttraumatic amnesia), (3) any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, and alteration of consciousness/mental state), (4) neurological deficits (weakness, loss of balance, changes in vision, praxis, paresis/plegia, sensory loss, and aphasia) that may or may not be transient, and (5) intracranial lesion.[2] Severe brain injury results in loss of consciousness for >6 h and a Glasgow Coma Scale (GCS) of 3–8. Complication of severe brain injury includes seizures or seizure-like activity. They can be early (occurring in <7 days of injury) or late (occurring after 7 days of injury) posttraumatic seizures (PTS). A study revealed increased incidence of development of posttraumatic epilepsy (PTE) in patients who had PTS.

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PTE is defined as recurrent seizures >7 days following injury. According to a study by Carney *et al*., in patients with severe TBI, the rate of clinical PTS may be as high as 12%, whereas that of subclinical seizures detected on electroencephalography may be as high as 20% to 25%. The risk factors for early PTS include GCS score of ≤10; immediate seizures; posttraumatic amnesia lasting longer than 30 min; linear or depressed skull fracture; penetrating head injury; subdural, epidural, or intracerebral hematoma; cortical contusion; age ≤65 years; or chronic alcoholism.[3] Hence, PTS should be prevented to avoid PTE disorders, to decrease the associated morbidity and mortality rate.[4] The Brain Trauma Foundation recommended the use of anticonvulsants such as phenytoin and valproate to prevent early seizures but not late seizures because of the side effects associated with the chronic use of these medications. Other anticonvulsants such as phenobarbital and carbamazepine are generally avoided because of adverse effects and pharmacodynamic profile.[5] In our study, we compare the efficacy of phenytoin and levetiracetam for the seizure prophylaxis in patients with severe TBI at our institute in Karachi, Pakistan.

Subjects and Methods

The type of study is a prospective randomized controlled trial, conducted over a period of 6 months, from September 2015 to February 2016, at a large public tertiary health care center in Karachi, Pakistan. Nonprobability purposive sampling was used to calculate the sample size. Inclusion criteria were TBI patients admitted to the hospital having a time of injury to the presentation of <24 h, GCS scores of 9–12 (moderate), 13–15 (mild), and age >18 years. Exclusion criteria included any previous history of brain injury, brain tumor, cerebral infarct or spontaneous intracerebral hemorrhage, hemodynamically unstable patients, GCS scores of <5 and age <18 years, known hypersensitivity to any anticonvulsant, any treatment, or condition contraindicated for the drugs used in the study. The study was approved by the hospital Ethics Committee. After taking fully informed consent from the patients or in case of unconscious patients and their next of kin, patients with severe TBI were randomly divided into two groups A and B with an equal number of patients in each group by a random allocation software. Group A patients were given phenytoin for seizure prophylaxis, whereas Group B patients received levetiracetam for the first 7 days after severe TBI. Data were collected using a predesigned pro forma in both the groups and included various variables such as age, gender, complete medical history, clinical examination, GCS score, loss of consciousness, duration of loss of consciousness, type of brain injury sustained, Marshal CT classification, any events such as fever, raised ICP, hypotension, arrhythmia, anemia, and thrombocytopenia, various laboratory tests such as complete blood count and liver function tests, mortality, time from injury to presentation, occurrence of seizures, and electroencephalographic (EEG) characteristics. Patients were initiated on a protocol of intravenous (IV) levetiracetam monotherapy or phenytoin for early seizure prophylaxis based on standardized hospital-wide clinical protocols. Therapy was initiated within 24 h of injury. Phenytoin was given as an IV loading dose of 15–20 mg/kg, followed by a dose of 4–8 mg/kg (IV/oral) divided into three doses per day, titrated to achieve therapeutic blood levels. Levetiracetam was given as a 1000 mg IV loading dose, followed by a dose of 500–1,000 mg (IV/orally) twice daily. All the patients who were in persistent coma, had altered mental status, or clinical signs of seizures underwent a 1-h EEG recording. Once on the 1st day posttrauma and a second time on day 7 of drug use, both the EEGs were compared for any changes or epileptic fits. The EEG findings for each patient were labeled as normal or abnormal based on focal abnormal waveforms. Abnormal EEG findings were classified as: (i) status epilepticus, (ii) seizure activity, or (iii) seizure tendency. The EEGs exhibiting epileptiform activity (intermittent sharp waves or periodic lateralized discharges) without capturing electrographic seizures were categorized as demonstrating seizure tendency. If a patient underwent >1 EEG examination within the 7-day monitoring period, the most abnormal result was used for categorical stratification for that patient. Occurrence of early PTS in both groups on the basis of EEG was compared. We also analyzed the patients according to their duration of antiepileptic drug therapy, length of hospital stay, and complications during therapy.

Statistical analysis

Data were analyzed using IBM SPSS (IBM Corporation, Armonk, New York 10504-1722, United States) version 23.0 for Windows. Continuous variables such as age are expressed as mean and standard deviation, whereas categorical variables such as gender are given in frequency and percentage. Data analysis was done to determine if there are any significant differences between the two cohorts with respect to abnormal EEG findings, seizure activity, and seizure tendency with epileptiform activity. Chi-square test was utilized to compare the two medication groups in terms of their age, gender, and GCS scores, and Fisher's exact test was utilized to determine any differences in the two groups in terms of the EEG findings, seizure activity, tendency, and epileptiform activities, respectively. $P < 0.05$ was considered to be statistically significant.

Results

The study population consisted of 140 patients of whom 117 were males and 23 were females having a mean age of 29.48 ± 16.24 years. The most prevalent cause of brain injury was road traffic accidents in 72.85% patients, for other details refer to Table 1. We failed to determine a significant relationship between the antiepileptic drug used with the

initial EEG (P = 0.313) and seizure activity (P = 0.502) in between the two drug groups. However, a significant correlation of the anti-epileptic drug used was found with EEG (P = 0.002) and seizure activity (P = 0.014) on subsequent follow-up; patients who took levetiracetam had decreased incidence of abnormal EEG and seizure activity on follow-up. There was no significant correlation between the GCS score both initially (P = 0.845) and on follow-up (P = 0.104) with the antiepileptic drug used. The above-mentioned P values were derived by comparison of two groups based on the anti-epileptic drug given to prevent PTS. Group A patients who were given phenytoin had increased incidence of abnormal EEG and seizures, whereas Group B patients who took levetiracetam had decreased incidence of abnormal EEG and seizures on follow-up. However, initial EEG, seizure activity, initial GCS scores, and follow up GCS scores were not affected by the choice of drug used [Table 2].

Table 1: Various characteristics such as mode of injury, type of brain injury, and loss of consciousness after injury in the patient population

Mode of injury	Loss of consciousness		Classification of brain injury			Total	*P*
	Yes	No	Mild	Moderate	Severe		
RTA	72	30	21	71	10	102	0.690*
Fall	23	7	6	23	1	30	
Assault	6	2	1	7	0	8	
Total	101	39	28	101	11	140	

*P value indicates that there is no significant correlation between mode of injury and type of brain injury. RTA – Road traffic accident

Discussion

TBI is the leading cause of long-term disability in children and young adults worldwide. According to a study, incidence of moderate-to-severe TBI in the rural population (73/100 000 person/years) is 2–5 times greater than in the urban population (31/100 000 person/years).[6] Males between the age of 14 and 24 seem to be the group most commonly affected by TBI. Females have lesser frequencies and better outcomes of TBI as compared to males.[7] It is suggested that the better outcome in females may be due to lower levels of lipid peroxidation due to the antioxidant effects of estrogen and progesterone.[8] The effects of TBI on the brain are numerous, and they can be divided into external and internal effects. Some cranial outcomes of TBI are scalp hematoma, hemorrhagic contusion, herniation, and midline shifts of the brain.[9] Blood–brain barrier is formed by astrocytes, and its function is to maintain ion concentrations, regulation of flow of elements into the brain, and protection of the brain from foreign elements circulating in the bloodstream. TBI compromises this protective effect of the blood–brain barrier, leading to damage of the brain parenchyma.[10]

Table 2: Correlation of electroencephalographic findings, seizure activity, and Glasgow Coma Scale score (initially and on follow up) with the drug used

EEG findings	Phenytoin		Levetiracetam		*P*
	Yes	No	Yes	No	
Initially					
Abnormal EEG	34	36	40	30	0.313
Seizure activity (24-48 h)	32	34	38	32	0.502
On follow up					
Abnormal EEG	16	43	4	60	0.002*
Seizure activity (7-10 days)	16	50	6	63	0.014*

Drug	EDH	SDH	SAH	ICH	DAI	Marshal classification	Mean initial GCS	Mean follow-up GCS	*P*
Phenytoin	15	20	27	1	6	I: 4 II: 43 III: 22 IV: 1	11.23	13.84	For initial GCS: 0.845#
Levitracetam	22	20	23	0	8	I: 12 II: 33 III: 22 IV: 3	11.17	14.26	For follow up GCS: 0.104#
Total	37	40	50	1	14	I: 16 II: 76 III: 44 IV: 4			

*P value indicates that EEG and seizure activity on follow-up has a statistically significant correlation with the drug used; #P value indicates no significant correlation between GCS (initially and on follow up) with the drug used. GCS – Glasgow Coma Scale; EDH – Epidural hematoma; SDH – Subdural hematoma; ICH – Intracerebral hematoma; EEG – Electroencephalographic; SAH – Subarachnoid hemorrhage; DAI – Diffuse axonal injury

The neurologic insults that occur in the brain after any injury can be divided into primary and secondary insults. The primary injury (diffuse or focal) initiates a series of reactions which culminate in cell death, whereas secondary injury occurs as a response of neurons to the primary injury. Hence, the secondary injuries can be modified to improve the outcome of traumatic brain injuries and to reduce the morbidity and mortality rate. They are usually ischemic in nature and include cerebral edema, hematomas, hydrocephalus, intracranial hypertension, vasospasm, metabolic derangement, excitotoxicity, calcium ion toxicity, infection, and seizures.[11] According to a study by Wang *et al*., 59.9% of patients were identified as having PTS after TBI. Hence, there is a high incidence of PTS after TBI, the risk factors being frontal–temporal lobar contusion, linear skull fracture, and severity of TBI measured by initial GCS.[12]

A number of studies have been done to determine the drug of choice for PTS prophylaxis. One of the studies showed an increased tendency of seizures on EEG for patients taking phenytoin, but there was not any difference in actual seizure activity. An increased risk for gastrointestinal upset and deterioration of neurologic status is also associated with phenytoin use. In the study by Gregg Vk, those patients treated with levetiracetam showed an improvement in GCS scores, however, the reliability of results cannot be determined because of the small sample size in their study.[13] Another study showed that levetiracetam is as effective as phenytoin in preventing early PTS, but it is associated with increased frequency of abnormal EEG findings.[14] Another study showed a decreased incidence of early PTS in children with the use of phenytoin.[15] Guidelines issued by the Brain Trauma Foundation, published in 2007, and the American Academy of Neurology, published in 2003, support the results of this study. According to these guidelines, PTS prophylaxis should be provided for the initial 7 days only, and the most appropriate drug for this purpose is phenytoin. Phenytoin has been approved by the Food and Drug Administration for the control of generalized tonic–clonic and complex partial seizures and the prevention and treatment of seizures occurring during or after neurosurgery.[16] Our study showed a decreased tendency of seizures and abnormal EEG on follow-up with the use of levetiracetam. A number of studies reveal results in favor of levetiracetam owing to its relatively safer side effect profile and improved long-term outcomes.[17] The use of levetiracetam rather than phenytoin in acute TBI is associated with better 6-month cognitive outcomes.[18] Use of levetiracetam also enhances higher integrative mechanisms of the brain. In fact, levetiracetam has been shown to improve a range of cognitive abilities including visual short-term memory, working memory, motor functions, psychomotor speed and concentration, and fluid intelligence.[19,20]

Conclusion

According to the results of our study, the incidence of abnormal EEGs and seizure activity in patients with TBI is the same for both levetiracetam and phenytoin for the initial 7 days posttrauma; however, the incidence of seizures is lower for patients who use levetiracetam on the subsequent follow-up. Hence, levetiracetam is a better option for PTS prophylaxis overall, and it is well tolerable and has a smaller side effect profile.

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Conflicts of interest

There are no conflicts of interest.

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