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ORIGINAL ARTICLE

Effect of Antiepileptic Drugs (Valproate vs Phenytoin) in Patients of Traumatic Brain Injury

Alamgir Khan[1], Muhammad Nawaz[2], Juwayria Omar[3]

[1] Post graduate Resident FCPS Neurosurgery, PIMS Hospital Islamabad
[2] Post graduate Resident MS Neurosurgery, PIMS Hospital Islamabad
[3] Assistant professor Community Medicine, Fazaia Medical College, Air University, Islamabad

ABSTRACT

Objective: To determine the effect of Valproate as compared to Phenytoin in patients with traumatic brain injury to prevent early seizures.

Patients and Methods: This randomized controlled trial (RCT) was conducted at Pakistan Institute of Medical sciences (PIMS) Islamabad from March to September 2015. A total of 100 cases of traumatic brain injury were enrolled in this study; which were randomly divided into two groups A and B. Gender distribution was similar in both A & B groups, with 36 (72%) males and 14 (28%) females. Consecutive (non-probability) sampling technique was used. Group A patients received Valproate as anti-epileptic agent, while in group B, Phenytoin was given. In group A there were 45 (90%) patients with no seizures, 1 (2%) with simple partial, 1(2%) with complex partial and 3 (6%) with generalized tonic clonic seizures. In group B there were 40 (80%) patients with no seizures, 1 (2%) with simple partial, 5(10%) with complex partial and 4 (8%) with generalized tonic colonic seizures. In group A seizures were low (10 %) as compare to group B (20%), with statistically insignificant difference (p= 0.161).

Results:

Conclusion: In this study, Valproate was found to be effective as a prophylactic anti-epileptic agent as compared to phenytoin. New drugs need to be studied on larger scale to find more effective and safe drug for Prophylactic use in post-traumatic seizures.

Key words: Phenytoin, Post-traumatic Seizures Traumatic Brain Injury, Valproate.

Author`s Contribution
[1] Conception, synthesis, planning of research and manuscript writing Interpretation and discussion
[2] Data analysis, interpretation and manuscript writing, [3] Active participation in data collection.

Address of Correspondence
Alamgir Khan
Email: @yahoo.com

Article info.
Received: June 3, 2018
Accepted: July 29, 2018

Cite this article. *Khan A, Nawaz M, Omar J. Effect of Antiepileptic Drugs (Valproate vs Phenytoin) in Patients of Traumatic Brain Injury. JIMDC.2018; 7(3):183-188*

Funding Source: *Nil*
Conflict of Interest: *Nil*

Introduction

Throughout the world, traumatic brain injury (TBI) is a great health and socio-economic burden.[1] Besides being one of the major contributor to death and disability, it puts burden of huge costs on individuals and society.[2] Every year worldwide an estimated 10 million people are affected by traumatic brain injury (TBI). Surgical care is primary option of treatment. TBI results in conditions such as epilepsy which need constant medical and supportive care.[3,4] The frequency of early seizures in post-traumatic brain injury ranges from 4-25%.[5,6] Trauma is responsible for 20% of symptomatic epilepsy in the general population and 5% of all epilepsy. Early post-traumatic seizures occur in more than 20% of patients in the intensive care unit and are related to secondary brain injury and even worse patient results [4] After trauma, seizures can occur early (within 1 week) as well as late (1 week to years, post injury).[7] Early seizures, occurring within first 24 hours post trauma are third in line of post-traumatic seizures

category. Due to secondary brain damage in early post-traumatic seizures it is related to high morbidity and mortality rates.[5]

Besides contusion on CT Scan, pre-hospital hypoxia, young age, severe TBI, acute epidural, subdural or intracerebral hemorrhage, open depressed skull fracture with parenchymal injury and penetrating brain injury, all increase the risk of seizures early after injury.[8] Electrographic seizures can result in increased intracranial pressure, late increases in intracranial pressure (ICP) that is after 96 hours can increase mortality rate. Continuous use of electroencephalography (EEG) to spot seizures may result in better ICP control.[4,9]

Glasgow scale (GCS) is used to classify head injury into grades; mild head injury is classified between score of 13 to 15, whereas GCS score of 9 to 12 is defined as moderate head injury. Some investigators consider GCS of 13 as moderate head injury; the point in favor of this change is that prognosis of patients with GCS 13 is similar to moderate GCS score category.[10-12] The terms cerebral concussion and mild TBI are used under similar considerations in medical literature, whereas concussion is almost always taken as lightest form of cerebral lesion. Post traumatic seizures are mostly witnessed after head injury of severe nature and the prevalence of post-traumatic seizures decreases substantially to below 5% in cases of mild to moderate head trauma. Most common cause of post traumatic seizure after head injury is observed as presence of intracranial hematoma. Approximately 50% occurs within initial 24 hours of event; 25% occurs within first hour.[13,14] Early seizures elevate risk of post-traumatic epilepsy four times to > 25%.[14]

However, among patients with depressed skull fracture and intracerebral hematoma; up to 30% patients can suffer from early seizures.[14,15] Study results done on patients with mild TBI have reported presence of early seizures in 5-10% patients. Similar study which included mild head injury cases who underwent CT scan brain and CT was normal; still seizures were reported in such patients in early period.[15-17]

Time interval has proved to be important criteria for presence of post traumatic seizures. The more the time passes lesser is the incidence of post traumatic early seizures. 50% of early post-traumatic seizures occurred within initial 24 hours and 25% occurred within initial first hour.[18]

It has been observed that, mostly type of seizures is dependent on time duration. Mostly seizures occurring within 24 hours of trauma (72 to 84 percent) were of generalized tonic clonic variety.[17] The later seizure begins with head injuries; it is more likely to be focal in onset; 50% of seizures occurring after 24 hours are simple partial (pure motor) or focal convulsions.[19]

Complete medical assessment should be done in all patients presenting with mild TBI or any concussion. Immediate assessment of patients involves thorough neurologic and mental status examination. Neurological findings need early neuroimaging and neurosurgical evaluation. Mild TBI and concussion can sometimes be missed both by patients and para-medical staff, especially when history shows absence of loss of consciousness.[25] Studies have shown that > 80% of patients with past history of concussion did not realize the nature of injury leading to such condition.[20,21]

When CT scan and MRI are compared, MRI is more sensitive in finding and pointing out minor locations with contusion or petechial hemorrhage, axonal injury and small extra-axial hematomas.[17,22,23]

Administering an Anti-epileptic drug (AED) within 24 hours of injury and maintaining high therapeutic levels is protective and decreases the risk of early seizures by up to 73%.[24,25] Phenytoin, Carbamazepine and Valproate are commonly used AEDs in reducing the risk of early seizures.[26] Now a days it has been recommended that AEDs should be prescribed to all such patients as they have significant risk of status epilepticus or aggravation of a systemic injury. Such practice of prescribing antiepileptic drugs has prophylactic role as well as recurrent seizures can result in heavy cerebral blood flow resulting in increased intracranial pressure and brain edema leading to comatose state of the patient. Prophylactic use of all such drugs has been advocated even in patients who haven't suffered from early seizures but are at high risk for early fits due to presence of intracerebral hemorrhage, brain edema or ventricular compression, it has been advocated that treatment given in AED decreases the occurrence of early fits and can be used due to high risk for secondary complications.[27,28]

Seizures which occur > 7 days' post head trauma are considered as post traumatic epilepsy which indicate towards permanent structural and physiologic changes inside brain parenchyma. It has been established that anticonvulsants are beneficial in the first 7 days after injury.[29] Studies have shown that tonic and tonic-clonic seizures are dependent on voltage gated sodium channels and this knowledge has resulted in acknowledging the fact that drugs like Carbamazepine and Phenytoin inhibit sodium channels voltage gated channels which can be effectively used for such fits control. Advantage of Valproate over other AEDs is that it is available in both intravenous and oral form, has less adverse effects (cognitive), is economical and levels can be determined easily. The main purpose of this trial was to determine effect of valproate as compared to phenytoin as prophylaxis in patients with traumatic brain injury to prevent early seizures. This will help in better management of the patients and devise a plan for proper prophylaxis of seizures. This will, in turn, help in better outcome of the patients with brain contusion.

Patients and Methods

This randomized controlled trial was carried out at Pakistan Institute of Medical sciences (PIMS) Islamabad from March to September 2015. Study permission was taken from the hospital's ethical committee. Calculated sample size was 50 patients in each group. It was computed through raosoft software by taking the least proportion of early seizures in post-traumatic brain injury ranging from 4-25% with 95% confidence interval and 5% margin of error.[6,7] All patients with age range of 18-60 years, having head injury, who presented to Neurosurgery department, PIMS were included. Neonates with head injuries, diagnosed case of epilepsy, patients with space occupying lesion of the brain, patients with previous history of brain surgery, head injury patients who were pregnant and all patients with any co-morbidities were excluded from study. A written informed consent was administered to the patient or caretakers in case of unconscious patients. All the patients were divided in two groups: Group A was comprised of patients having traumatic brain contusion with Valproate cover.

Group B patients had traumatic brain contusion with Phenytoin cover. Both groups were observed from second to seventh day for the occurrence of seizures. Data was collected through a proforma. Demographic characteristics of the patients were recorded and relevant examination was carried out. Computerized Tomography (CT) scan of the head was done on all patients with head injury. Types of seizure, whether focal or generalized were recorded. Data were entered and analyzed on SPSS 17. Mean and standard deviation were measured for the numerical values like age and GCS, whereas categorical variables like gender, mode of trauma, CT scan brain findings, location of the contusion, and type of seizures and day of seizures after head injury were measured as frequency and percentage. Occurrence of early seizures was compared between the two groups using chi-square. p-value of ≤ 0.05 was considered statistically significant. Results were presented in graphical or tabulated forms.

Results

Total of 100 patients having TBI were randomly divided into two equal groups. In group A mean age was 42.5 ± 8.3 years. In group B mean age was 43.5±7.5 years. Proportion of male and female was equal in both groups. In group A as well as in group B main cause of head injury was road accident, 66% and 74% respectively followed by fall from height In group A and B, the minimum GCS at arrival was 8 and 7 respectively. Mean GCS in group A was 12.62±1.68. In group B mean GCS was 12.36± 2.06. In both groups, large number of patients (56%) were in category of 13-15 GCS. In group A, main area of head injury was temporal (38%) while in group B it was parietal 34% (Table 1). In group A, there were 90% patients with no seizures while in group B patients with no seizures were 80%. But this difference was insignificant (p=0.161) (Figure 1).

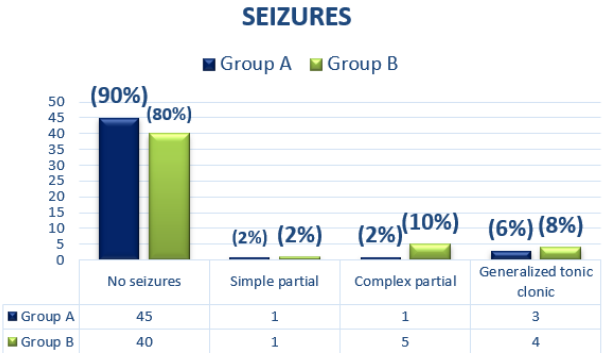

Figure 1: Distribution of cases according to type of seizures (n=100)

Table 1: Baseline characteristics of patients (n=100)		
Variables	**Group A (n=50)**	**Group B (n=50)**
Age (years)		
Mean±SD	42.5±8.3	43.5±7.5
Range	22-57	27-58
Gender;	**n(%)**	**n(%)**
Male	36(72)	26(72)
Female	14(28)	14(28)
Cause of injury, n(%)		
Road accident	33(66)	37(74)
Fall from height	12(24)	8(16)
Assault	2(4)	2(4)
Fire injury	2(4)	2(4)
Others	1(2)	1(2)
GCS category; n(%)		
4-8	2(4)	3(6)
9-12	20(40)	19(38)
13-15	28(56)	28(56)
Head injury; n(%)		
Frontal	13(26)	14(28)
Temporal	19(38)	14(28)
Parietal	14(28)	17(34)
Occipital	2(6)	4(8)
Cerebellum	1(2)	1(2)

Discussion

Review articles have been written based on randomized controlled trials to see effect of prophylactic antiepileptic drugs in traumatic head injury for cessation of fits. The findings of these trials reported that prophylactic use of antiepileptic drugs can be done in high risk patients during initial week after trauma.[30,31] Phenytoin has been commonly and thoroughly studied drug for the prophylaxis of PTS. There have been very few or no studies on Phenobarbital, Valproate and Carbamazepine use due to their complications and pharmaco-dynamic property, it has not proved to be beneficial using these agents as compared to Phenytoin.[32]

Use of Phenytoin for prophylaxis of early PTS is recommended by Brain Trauma Foundation as well. The guidelines say that Valproate has shown same effectiveness as compared to Phenytoin. The FDA approved use of Phenytoin for prevention and stoppage of complex partial seizures and generalized tonic–clonic state as well as for the prevention and treatment during and after neurosurgery seizures.

In a study which was conducted on 244 blunt and penetrating TBI patients (intracranial hematoma; depressed skull fracture of frontal, temporal or parietal regions; major focal deficit or unconsciousness for > 6 hours). Patients in group A category; were administered Phenytoin and group B category patients were given placebo for 7 days. The mean number of seizures was 2.8 in phenytoin and 5.0 in placebo group (p = 0.06).[33]

Another study included 214 TBI patients with blunt and penetrated injuries. Group A patients were administered phenytoin with initial dose of 11 mg/kg i.v. and then followed by 13 mg/kg intramuscularly once per day and group B patients were administered placebo for 18 months. This study also showed no difference between Phenytoin vs. Phenobarbital in terms of frequency of PTS (12.9% vs. 10%, respectively). There was also no difference in late PTS between placebo and phenytoin groups (10.8% and 12.9%, respectively).[34]

A randomized control double blind trial was conducted by Temkin and colleagues. This RCT included 379 TBI patients with moderate or severe injuries. Patients were selected in first 24 hours of TBI and were randomized to either Phenytoin or Valproate. The study revealed that frequency of early PTS was similar among the Phenytoin and Valproate groups (1.5% versus 4.5%, respectively). These findings are continuous with the current study results.[35]

A randomized double blind study included 279 moderate to severe TBI patients who were given either Phenytoin or Valproate within 24 hours after TBI were evaluated at 1, 6, and 12 months for neuropsychological effects from either medication. At any point, no difference in neuropsychological or cognitive measures was seen among the groups.[36]

Conclusion

Valproate was found to be effective as a prophylactic anti-epileptic agent as compared to Phenytoin, however this difference was statistically insignificant. Seizure is a common phenomenon seen in patient after traumatic brain injury. Antiepileptic drugs have been used frequently to prevent or stop these seizures but with little effect. New

larger scale studies are needed to find an effective and safe drug for prophylactic use in post-traumatic seizures.

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