ORIGINAL ARTICLE

EFFICACY OF PHENYTOIN IN PREVENTION OF EARLY POST-TRAUMATIC SEIZURES

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Background: The use of anti-epileptic drugs for prophylaxis of early post-traumatic seizures after traumatic brain injury has been very promising. The objective of this study was to determine the outcome of phenytoin in prevention of early post-traumatic seizures in moderate to severe traumatic brain injuries and to compare the frequency of seizures in moderate to severe traumatic brain injury, with phenytoin started within 12 hours and after 12 hours of injury. **Methods:** This cross-sectional study was conducted at Department of Neurosurgery, Ayub Medical Institute, Abbottabad from April to October, 2015. All the patients with moderate to severe head injury presenting within 48 hours of injury were included in this study in consecutive manner. Patients were started on phenytoin and observed for early post-traumatic seizures. **Results:** A total of 163 patients were included in this study with a mean age of 24.69±10.186 years. One hundred and twenty-two (74.8%) were males and rest of 41 (25.2%) were females. A total of 26 (16%) patients had early post-traumatic seizures. 9.89% patients in whom phenytoin was started within 12 hours had seizures, while 23.11% patients in whom phenytoin was started after 12 hours of injury had seizures, the difference being statistically significant (*p*-value .018). **Conclusion:** Frequency of early post-traumatic seizures is high in patients with moderate to severe head injured patients. Anti-epileptics like phenytoin should be started within 12 hours for seizure prophylaxis.

Keywords: Phenytoin; Seizures; Early post-traumatic seizures; Prophylaxis; Brain injury; Head injury

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INTRODUCTION

Traumatic brain injury (TBI) is one of the majors causes of mortality and morbidity in today's urbanized world. The global incidence rates ranging from 91–546 per 100,000 population.[1] The annual incidence is more than 2.5 million in the United States, and of which about 12% results in hospitalization or death.[2]

WHO statistics indicate that TBI will surpass many other diseases and would lead as a major cause of death and disability by the year 2020.[3]

Traumatic brain injury (TBI) is a devastating and multifaceted disease state. In developing countries, the rate of traumatic brain injury is growing, accounting for one quarter to one third of all accidental deaths. Traumatic Brain injury is a leading cause of disability and death affecting people during the most productive period of their life with highest incidence in age group of 15–30 years and males are the major sufferers.[4]

Traumatic brain injury leads to many undesired problems and impediments including epilepsy. The definition of epilepsy requires the occurrence of at least one unprovoked seizure. Depending on the time delay, from the TBI to the occurrence of the first seizure, post-TBI seizures have been categorized into immediate (within 24 hours), early (1–7 days), or late seizures (more than 7 days). Thus, when TBI is associated with one unprovoked late seizure it qualifies for diagnosis of PTE.[5,6]

The incidence of early post-traumatic seizures after civilian brain traumatic injury is 4–25% whereas the incidence of late post-traumatic seizures can be as high as 42%.[7]

After the first late seizure, 86% of patients have been reported to develop a second seizure within 2 years. This strongly suggests the development of an epileptogenic process.[8] Early posttraumatic seizures pose a serious threat to already insulted brain tissue by increasing metabolic requirements, raised intracranial pressure, cerebral hypoxia, and/or excessive release of neurotransmitters.[9,10]

The control of early post-traumatic seizure is of paramount importance because these acute insults may add secondary damage to the already insulted brain. Post-traumatic seizure is associated with poor Glasgow outcome score (GOS) and higher incidence of behavioural abnormalities on follow up. Early post-traumatic seizures are also linked with enlarged incidence of late post-traumatic seizures.[11]

Prophylactic use of anti-epileptic drugs like phenytoin during the first seven days after injury

have been found to be protective against early post-traumatic seizure.[12]

Although convincing results have been seen as regards the lower incidence of early post-traumatic seizures in patients who were on drug prophylaxis. Yet little work has been done as to how early the anti-epileptics can be started. And how efficacious can be the early start of anti-epileptic prophylaxis. Keeping this in mind, this study was planned to access the efficacy of phenytoin in prevention of early post-traumatic seizures in moderate to severe traumatic brain injury and to compare the prophylactic effect of phenytoin started within 12 hours and after 12 hours of injury.

MATERIAL AND METHODS

This cross-sectional study was conducted in department of Neurosurgery, Ayub Medical College, Abbottabad from April to October 2015. Study was started after taking permission from hospital ethical review board. All the patients of either gender, with moderate to severe head injury presenting within 48 hours of head injury were included in this study in a consecutive manner. Patients above 50 years and below 5 years were excluded. Patient with penetrating head injuries, known epileptics and patients with deranged electrolytes, liver functions and renal functions were also excluded. Patients reported to have a seizure after the injury were also not included in the study.

Sample size was 163 in each group. Sample size is calculated using WHO software for sample size determination in health studies using the formula of estimating the proportion with absolute precision and the following assumptions.

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 for evaluation of head injury. All the patients were started on phenytoin on admission. Phenytoin was started in a loading dose of 20 mg/kg intravenously over sixty minutes followed by maintenance dose of 50 mg/kg/day in two divided doses. Patients were clinically observed during first seven post-traumatic days for occurrence of seizures. Patients presenting with 12 hours of head injury were placed in one group while the patients presenting after 12 hours were placed in the other.

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 predesigned *proforma*.

All data were processed and analysed on SPSS-14.0. Descriptive statistics are used to calculate mean standard deviation for quantitative variables like age and GCS at presentation. Frequency and percentages are presented for all categorical variables like gender and efficacy. Efficacy in both the groups is stratified among age, gender, severity of brain injury to see the effect modifications. Chi square test is used at 5% significance level to see the difference with respect to outcome variables in patients presenting within 12 hours and those presenting after12 hours.

RESULTS

A total of 163 patients were included in this study. Age of the patients ranged from 6 to 48 years mean of 24.69±10.186 years. Out of total 163 patients 122 (74.8%) were males and rest of 41 (25.2%) were females. A total of 13 (8%) patients were in age group of 5–10 years, 54 (33.1%) were in age group of 11-20 years, 52 (31.9%) patients in age group of 21–30 years, 22 (13.5%) patients each in age group of 31–40 years and 41–50 years.

A total of 90 (55.2%) patients presented after history of fall, 57 (35%) had history of road traffic accident and rest of 16 (9.8%) had history of assault. In severity of head injury, a total of 80 (49.1%) patients had moderate head injury and rest of 83 (50.9%) patients had severe head injury.

CT-scan of the patients revealed that 43 (26.4%) had extradural hematoma, 34 (20.9%) each had acute subdural hematoma and depressed skull fracture, 23 (14.1%) had sub-arachnoid haemorrhage, 20 (12.3%) patients had diffuse axonal injury and only 9 (5.5%) patients had intracerebral bleed.

A total of 91 (55.8%) patients were started on IV phenytoin within 12 hours of head injury and rest of 72 (44.2%) were started after 12 hours of head. A total of 26 (16%) patients were observed to have early post-traumatic seizures and rest of 137 (84%) were seizure free after starting phenytoin.

Frequency of patients with seizures in different age groups is shown in table-1. The difference of frequency of patients with seizures among the age groups were found to be statistically insignificant with *p*-value of .395.

A total of 19 (15.5%) males and 7 (17.1%) females were found to have seizures. The difference of frequency of seizures in either gender was again found to be statistically insignificant with a p-value of .821 as shown in table-2.

A total of 16 (17.8%) patients with Fall, 6 (10.5%) with RTA and 4 (25%) were observed to have early post-traumatic seizures. The difference again being statistically insignificant with a *p*-value

of .293. (Table-3). Out of 80 patients with moderate head injury 8 (10%) had early post-traumatic seizures while 18(21.7%) patients out of 83 with severe head injury had the seizures. The difference in the frequency of seizures among moderate and severe head injured patients being statistically significant with a *p*-value of .042.

Table-4 presents the frequency of seizures among patients with different CT findings which shows that there is no statistically significant different in the frequency of early post-traumatic seizures among patients with different CT findings (*p*-value .155). A total of 9 (9.89%) patients out of 91 patients in whom phenytoin was started within 12 hours of brain injury had seizures, while 17 (23.11%) patients out 72 patients in whom phenytoin was started after 12 hours of injury had seizures. The frequency of seizures among both these groups was found to be statistically significant with a *p*-value of .018, as tabulated in table-5.

Table-1: Frequency of seizures in different age groups.

		Age Groups					*p*-value
		5–10 years	11–15 years	21–30 years	31–40 years	41–50 years	
Seizures observed	Yes	3	10	10	2	1	.395
	No	10	44	42	20	21	
Total		13	54	52	22	22	

Table-2: Frequency of seizures observed among either gender

		Gender		Total	*p*-value
		Male	Female		
Seizures observed	Yes	19	7	26	.821
	No	103	34	137	
Total		122	41	163	

Table-3: Frequency of seizures observed among patients with different modes of injury

		Trauma Type			Total	*p*-value
		Fall	Road Traffic Accident	Assault		
Seizures observed	Yes	16	6	4	26	.293
	No	74	51	12	137	
Total		90	57	16	163	

Table-4: Seizures observed *CT findings cross tabulation

Seizures observed		CT Findings						Total	*p*-value
		Extradural hematoma	Subdural hematoma	Depressed skull fracture	Sub-arachnoid haemorrhage	Diffuse Axonal Injury	Intracereb ral bleed		
	Yes	9	1	7	2	5	2	27	.155
	No	34	33	27	21	15	7	137	
Total		43	34	34	23	20	9	163	

Table-5: Frequency of seizures in patients started on phenytoin within 12 hours and after 12 hours of traumatic brain injury

		Group		Total	*p*-value
		Started with 12 hours	Started after 12 hours		
Seizures observed	Yes	9	17	26	.018
	No	82	55	137	
Total		91	72	163	

DISCUSSION

Seizure prophylaxis in neurosurgical patients has been experienced with promising outcomes.[13] The causes for the seizure prophylaxis include the patients with raised intracranial pressure with or without the presence of an abnormal supratentorial focus. In such patients the injured neural tissue or the mas lesion may act as epileptogenic focus The same aims of prophylaxis holds true for the patients with TBI, in which the probability of seizures are increased with dreadful consequences of seizures in terms of outcome.[14]

The use of medication for the seizure prophylaxis is known to decrease the incidence of seizures during the first 7 days, yet, it has not been noted to decrease the late post-traumatic seizures. But these drugs used for the prophylaxis of seizures are not without their side-effects, anti-epileptics should therefore not be approved unless there is documented clinical or EEG evidence of seizures for the seizure prophylaxis in long term. There is a general consensus among the neurosurgeons and neurologists that seizure prophylaxis should be done in cases of moderate to severe TBI.[15]

Various drugs like phenytoin, phenobarbital, carbamazepine and valproic acid, are effective for the prevention of early PTS. A meta-analysis review, using Cochrane-pooled data confirmed that prophylactic treatment with phenytoin was effective in cases of TBI.[16,17]

Hence, on the basis of this evidence, prophylaxis against seizures is a part of standard therapy in the acute phase of moderate or severe TBI. According to Brain Trauma Foundation and the American Academy of Neurology recommendation the most commonly used prophylactic agent is Phenytoin. [15]

In a study by Sundararajan K *et al*, a total of 18% patients in neurosurgical ICU were found to have seizure activity even when they were on prophylactic medications, similarly in our study 16% of patients were observed to have seizures even with seizure prophylaxis.[18]

Chan *et al* documented that 7.0% of their patients developed early post-traumatic seizures. Their study was similar to our study in a way the diagnosis of the seizure was based on based on clinical symptomatology and features. Of these patients Chan *et al* reported that 90.9% had generalized tonic-clonic seizures, whereas 0.9% had focal seizures.[19]

Debenham S documented that 5.4 % had early PTS and 2.3 % while on prophylaxis and 3.1% while not on prophylaxis, 1.9% before reaching the hospital and 1.2% prior to phenytoin administration while in hospital. They documented a delay of administration of AED of 5 hours. This may be a reason of lower frequency of early PTS in this study population.[20] In our study one group received the AED within 12 hour of trauma and the other group received after 12 hours, the time delay being the fact that these patients reached our neuro-trauma centrelate. We observed that the group which received AED within 12 hours had the frequency of 10.97%, while 30.90% patients in whom AED was started after 12 hours of injury had seizures. The result was statistically significant with a *p*-value of .018.

Limitations of this include that patients were not put on continuous EEG monitoring. We had to rely on clinical manifestations of the seizure activity. A few studies suggest that there can a difference in the clinical versus EEG assessment. The incidence of acute post-TBI seizures has been reported to be as low as 2% versus ~22% in patients on continuous EEG monitoring.[22]

The other limitation of this study being that the plasma levels of the AED were not monitored because of the financial constraints. Another limitation being the limited number of patients enrolled in the study and the study being a single study trial.

Keeping in view the better of response of patients started don AED within 12 hours of TBI, further multicentre studies need to be conducted which can pave way for starting the AED early even at the site or at the time of primary resuscitation.

CONCLUSION

Frequency of early post-traumatic seizures is high in patients with moderate to severe head injured patients. Anti-epileptics like phenytoin should be started within 12 hours for seizure prophylaxis

AUTHORS' CONTRIBUTION

NG, SAK: conceived the idea, data collection, write up. HAK, GM, AAK, IK: literature search, data analysis. AA: supervised the study, write-up and proof read the manuscript.

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