

Prophylactic effect of sodium valproate in traumatic brain injury patients with early post-traumatic seizures

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Abstract:

Background: Post traumatic seizures has been described as a particularly heterogeneous condition, specifically because of the heterogeneity associated with TBI. Epidemiological studies have found that PTS accounts for 10–20% of symptomatic epilepsy in the general population and 5% of all epilepsies. Seizure activity in the early post-traumatic period after head injury may cause secondary brain damage. Prophylaxis for PTS refers to the practice of administering anti convulsants to the patients following head injury to prevent the occurrence of seizures. **Aim:** The present study was undertaken to evaluate the prevalence of early posttraumatic seizures in TBI and effectiveness of sodium valproate in treating seizures. **Materials and Methods:** It is an observational study conducted at a private hospital and the information from the medical records and charts of medical investigations of the patients were collected and reviewed. **Results:** From a total study population of 200, the incidence of ePTS was found to be 12% (24 patients). The most affected age group was between 18-50years (81.5%). The most common cause of traumatic brain injury among the study population was road traffic accident in 152 patients (76%). After treating with sodium valproate, the incidence of ePTS was zero in all patients previously observed with ePTS. **Conclusions:** The frequency of occurrence of TBI is high among young adults compared to elderly. There are multiple causes for TBI but the most important cause is RTA, among which males are at higher risk of TBI. The incidence of occurrence of early post traumatic seizures was found to be 12% from the study population. Occurrence of PTS is linked to the severity of injury. Use of sodium valproate has reduced the incidence of ePTS in almost all patients.

Key Words: Post traumatic seizures (PTS), early post traumatic seizures (ePTS), traumatic brain injury (TBI), Glasgow coma scale (GCS), Glasgow outcome scale (GOS), Sodium valproate.

I.Introduction

Post traumatic seizures has been described as a particularly heterogeneous condition, specifically because of the heterogeneity associated with TBI.^[1] PTS appearing within first week following TBI are called as early post traumatic seizures.^[2] ePTS are often generalized tonic-clonic convulsive type in comparison to late seizures, which are mostly non-convulsive in nature.^[1] Certain risk factors have been identified that place head injured patients at increased risk for developing post traumatic seizures. These risk factors include: Cortical contusions, Depressed skull fractures, hematoma (subdural, epidural, intracerebral), and Penetrating head wounds.^[3]

Epidemiological studies have found that PTE accounts for 10–20% of symptomatic epilepsy in the general population and 5% of all epilepsies.^[4] In general, the incidence of post-traumatic seizures varies with the time period after injury and population age, as well as the spectrum of severity of the inciting injuries. It ranges from 4% to 53%.^[5] The incidence of post-traumatic seizure in Indian population is 11.4% with higher frequency in severe head injury. Incidence of early and late onset seizure is 2.1% and 2.7% respectively.^[6]

Prophylaxis for PTS refers to the practice of administering anti convulsants to the patients following head injury to prevent the occurrence of seizures.^{[7][8]} Seizure activity in the early post-traumatic period after head injury may cause secondary brain damage as a result of increased metabolic demands, raised intracranial pressure and excess neurotransmitters release. Although concern about the adverse effects of early seizure activity has been the primary therapeutic rationale for the prophylactic use of antiepileptic drugs in the management of acute traumatic head injury,^[9] several clinical trials have demonstrated that antiepileptic drugs are effective in reducing the frequency of acute PTS, but do not alter natural history of late PTS. Phenytoin and Carbamazepine are shown to suppress ePTS. Sodium valproate has been recommended for TBI patients and is proven to have

less side effects.^{[10][11]} The clinical trials reveal that this drug does not reduce late posttraumatic seizures. However, it has been proposed that administration of sodium valproate could prevent the development of early posttraumatic seizures.^[11]

II. Materials & Methods

An observational study was conducted in the Department of Neurosurgery, superspeciality hospital at Hanumakonda city of Telangana state. It is a 150-bedded hospital which is a private hospital. A total of 200 cases were enrolled during the study period of 6 months. All the Patients of both genders above 15years of age diagnosed with traumatic brain injury were included. Data such as demographic details, mode of injury, type of injury, plan of care, incidence of early posttraumatic seizures and the affect of sodium valproate with a loading dose of 10-15mg/kg/day followed by oral sodium valproate dosing based on body weight within the first week after trauma was observed by following the patients for 7 days after the trauma and outcome was obtained from the patient record. Initial GCS was used to assess the severity of injury and GOS to assess the outcome at time of discharge. Patients with history of seizure disorder, paediatric patients, pregnant women with TBI and patients who are unable to comply with the study procedure were excluded.

All the results were analyzed by using Microsoft excel 2007 and Graph Pad Prism software version 7.01. Chi-square test was used to evaluate the associations between patient seizure rate and antiepileptic therapy within 7 days of trauma and P-value were calculated wherever required.

III. Results

During the study period of 6 months a total of 200 patients with TBI were enrolled in the study and their data was reviewed. Among them 167 (83.5%) were male and 33 (16.5%) female. Mean age was 35.7years. The most affected age group was between 18-50years (81.5%) followed by age group > 50 years (14.5%) and age group < 18 years (4%). Male adults were more prone to TBI among the study population.

Of 200 patients, majority 81 (40.5%) were mildly injured followed by moderately injured 63 (31.5%) and severely injured 56 (28%). The most common cause of traumatic brain injury among the study population was road traffic accident (RTA) constituting 152 patients (76%), followed by fall from height 48 patients (24%). Most predominantly observed risk factors were hematoma 92 (46%) followed by fractures 48 (24%), contusions 28 (14%), DBI 26 (13%) and concussion 6 (3%).

Among the study population, 56 patients (28%) were severely injured with poor GCS (≤ 8), 63 patients (31.5%) were moderately injured with moderate grade GCS (9-13) and 81 patients (40.5%) were mildly injured with good GCS (>13). Most of the study population were treated conservatively 162 (81%) and 38 (19%) were undergone surgery, in both conditions male population was predominant.

Of the total study population the incidence of ePTS was found to be 12% (24 patients). Mean age of patients with ePTS was 29.9 years. Among them male were more affected than female. After treating with sodium valproate, the incidence of ePTS was zero in all patients.

Severity of injury and outcome measures were determined by Glasgow coma scale (GCS) and Glasgow outcome scale (GOS).

Table 1: Standard classification of severity based on Glasgow coma scale.^[19]

GLASGOW COMA SCALE		
Severe TBI	Moderate TBI	Mild TBI
GCS ≤ 8	GCS 9-12	GCS ≥ 13

Table 2: Glasgow outcome scale:^[20]

Score	Description
GOS 1	Good recovery
GOS 2	Moderate disability (disabled but independent), no assistance with activities of daily living
GOS 3	Severe disability (conscious but disabled), need assistance with activities of daily living.
GOS 4	Persistent vegetative state
GOS 5	Death

Severity in the TBI patients has been reduced after the treatment with sodium valproate significantly with P-value of <0.00001.

Table 3: Characteristics of study population

Characteristic	No.of Patients (n=200)		Total (%)
Gender			
Male	167		83.5%
Female	33		16.5%
Age (years)	Male	Female	
<18	7	1	8 (4%)
18-50	140	23	163 (81.5%)
50	20	9	29 (14.5%)
Initial GCS			
Severe	53	3	56 (28%)
Moderate	49	14	63 (31.5%)
Mild	65	16	81 (40.5%)
Social history			
Alcoholic	40	2	42 (21%)
Alcohol and smoking	3	0	3 (1.5%)
No social history	124	31	155 (77.5%)
Injury			
Contusion	22	6	28 (14%)
Concussion	6	0	6 (3%)
DBI	25	1	26 (13%)
Hematoma	71	21	92 (46%)
Fractures	43	5	48 (24%)

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Etiology of TBI			
RTA	131	21	152 (76%)
Fall	36	12	48 (24%)
Treatment			
Conservative	136	26	162 (81%)
Operated	31	7	38 (19%)
Status at discharge			
Alive	159	31	190 (95%)
Dead	8	2	10 (5%)
Posttraumatic seizures			
Yes	21	3	24 (12%)
No	146	30	176 (88%)

Characteristics of patients with ePTS. (n=24)

The incidence of ePTS in the study population according to age group <18 years, 18-50 years and >50 years was 12.5% , 83.3% and 4.1% respectively. Among them male population was predominant.

Table 4: Age wise classification of patients with ePTS.

Age (years)	ePTS at admission		Total (%) (n=24)	ePTS at discharge
	Male	Female		
<18	3	0	3 (12.5%)	
18-50	17	3	20 (83.3%)	No seizures present
>50	1	0	1 (4.1%)	

In 24 patients with PTS the major risk factor contributing to the occurrence of seizure was hematoma (33.3%) followed by skull fractures (25%), DBI (20.8%), contusions (16.6%) and the least contributing risk factor is concussions (4.1%)

Table 5: Risk factors contributing to ePTS

Type of injury	No. of patients (n=24)	Total (%)
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	Male	Female	
Contusions	3	1	4 (16.6%)
DBI	4	1	5(20.8%)
Hematoma	8	0	8(33.3%)
Fracture	5	1	6(25%)
Concussional	1	0	1(4.1%)

Outcome in patients with ePTS was measured on basis of initial (at admission) and final (at discharge) GCS. When analysed in 24 patients, 12 patients were in severe and moderate category, except one patient, all the remaining patients recovered well and were categorized into mild group as per final GCS. From this we can say that the severity of injury was decreased from the admission to discharge. There is a significant outcome of the patients who were treated conservatively, and seizure occurrence was zero at the time of discharge.

Table 6: Mode of treatment and outcome in ePTS patients

GCS	Initial (n=24)			Final (n=24)			Statistical analysis
	Conservative	Operated	Total	Conservative	Operated	Total	
Severe	7	1	8	0	1	1	
Moderate	3	1	4	1	0	1	$X^2=16$ $P= 0.000335$
Mild	9	3	12	18	4	22	

Among 24 patients the mortality rate and persistent vegetative state is zero (GOS 1 and 2), (12.5%) patients had severe disability (GOS-3), A total of 87.4% patients had shown a better outcome (GOS 4 and 5) at the time of discharge.

Table 7: Glasgow Outcome Scale (GOS) in ePTS patients at discharge

GOS	No. of patients (n=24)		Total (%)
	Male	Female	
Grade 5	13	1	14 (58.3%)
Grade 4	6	1	7 (29.1%)
Grade 3	2	1	3 (12.5%)
Grade 2	0	0	0
Grade 1	0	0	0

IV. Discussion

Early posttraumatic seizures are thought to result from direct effects of brain damage caused by physical trauma to the brain. The likelihood that a person will develop seizures is influenced by the severity and type of injury, for example those with penetrating injuries and bleeding within the brain confer a higher risk.^[2]

As per current available literature, the Brain Trauma Foundation and American association of neurosurgery (AAN) guidelines recommend administering antiepileptic drugs for the prophylaxis of PTS only during the first week after a moderate or severe TBI. Patients with risk factors would most likely benefit from early PTS prophylaxis.^{[12][13]}

Antiepileptic drugs can prevent early posttraumatic seizures. Phenytoin, Sodium valproate and Carbamazepine have shown protective effect on seizures in early posttraumatic seizures trials. It has been proposed that administration of sodium valproate could prevent the development of early posttraumatic seizures and was confirmed in study conducted by MA Chi-yaan *et al.*,^[2]

In the present study 24 (12%) of the study population showed early post traumatic seizures, in which male were (87.5%) and are at higher risk of TBI than females (12.5%), whereas a study conducted by Rajashekar reballi *et.al.*, have found that 40% of the study population with TBI, developed seizures and they found that there was significant increase in incidence of epilepsy, if there was any radiological abnormality.^[14] In a retrospective study done by Bizhan Aarabi *et.al.*, 2000, found that 32% of patients developed seizures during the course of study.^[15] Compared to the above two studies the present study showed less incidence of posttraumatic seizures.

In the present study the primary cause of TBI is RTAs (76%) and the secondary cause is fall from height (24%) while in a study conducted by Guerrero *et.al.*, found that the primary cause of TBI was falls (39%), motor vehicle accidents (MVAs) (29%) and struck/assaults (23%).^[16]

In the present study we found that patients among age group of 18-50 years at the time of admission were more prone to early seizures 20/200 (10%) in which male were predominant. Of those in the age group of less than 18 years and above 50 years 3/200 (1.5%) and 1/200 (0.5%) patients had early seizures respectively which is in contrast with a clinical research done by Ilmari Asikainen *et.al.*, where children of age 7 years at the time of injury were more prone to early seizures (30.8%). Among the age group 8-16 and older than 16 years (20%) and (8.4%) patients had early seizures respectively.^[17]

Of 200 patients, 81 individuals were with mild head injury (GCS 13-15), among them 12 patients developed seizures. 63 patients were with moderate head injury (GCS 9-12), among them 4 developed seizures and 56 patients were with severe head injury (GCS \leq 8), among them 8 suffered from early posttraumatic seizures during the first week after TBI which is in contrast with the study conducted by Rajashekar reballi and Siva Prasad, where 26 individuals with mild head trauma (GCS 13-15), among them 5 patients developed seizures. 19 patients were with moderate head injury (GCS 9-12), among them 10 patients developed seizures and 5 patients were with severe head injury, among them all the 5 patients developed seizures. The incidence of seizures in those with mild head trauma was significantly less than those with moderate and severe head trauma.^[14]

In our study, 28 patients had contusions, 4 patients developed seizures. Among 6 patients with concussion head injury, 1 patient developed seizures. Among 26 patients with DBI, 5 patients developed seizures. Among 92 patients with hematoma 8 patient developed seizures and among 48 patients with skull fracture, 6 patients developed seizures in the first week following TBI. Indicates the major risk factor contributing to the occurrence of seizure is hematoma 33.3%, followed by skull fractures (25%), DBI (20.8%), contusions (16.6%) and the least contributing risk factor is concussion (4.1%) which is similar to a population based study conducted by Nancy R.Temkin, 783 patients were reviewed and they found that the incidence of ePTS in patients diagnosed with hematoma was (63%), followed by skull fractures was (27%) and patients diagnosed with contusion was (10%)^[18]

Outcome in patients with ePTS was measured on basis of initial (at admission) and final (at discharge) GCS. When analysed in 24 patients, 12 patients were in severe and moderate category, except one patient, all the remaining patients recovered well and were categorized into mild group as per final GCS. From this we can say that the severity of injury was decreased from the admission to discharge. There is a significant outcome of the patients who were treated conservatively, and seizure occurrence was zero at the time of discharge.

V. Conclusion

The frequency of occurrence of TBI is high among young adults compared to elderly. There are multiple causes for TBI but the most important cause is RTA, among which males are at higher risk of TBI. The incidence of occurrence of early post traumatic seizures was found to be 12% from the study population. Occurrence of PTS is linked to the severity of injury. Use of sodium valproate has reduced the incidence of ePTS in most of patients. Majority of the patients were treated conservatively which indicates the effectiveness of the drug.

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