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Use Of Anti-Epileptics For Seizure Prophylaxis After Traumatic Brain Injury In The Pediatric Population

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Abstract

Objective: To determine the frequency of Early Post-Traumatic Seizures (EPTS) in patients receiving anti-epileptic prophylaxis after moderate to severe traumatic brain injury (TBI) in children.

Methods: A Descriptive Case Series was conducted at the Department of Neurosurgery, Shifa International Hospital Islamabad from 26 August 2021 to 25 August 2022. A total of 160 children aged from 2 to 18 years who presented with traumatic brain injury within 24 hours of trauma were included. Patients were given intravenous phenytoin in a loading dose of 20mg/kg with the rate of 1-2mg/kg/min infusion followed by a daily maintenance dose of 5mg/kg twice daily. Patients were clinically monitored for the occurrence of seizures during the first 7 post-traumatic days. Diagnosis of early post-traumatic seizures was made by a consultant neurologist as per operational definitions. All the study-relevant information was noted on the proforma. Data entry and analysis was done using SPSS version 24.0.

Results: In 160 patients mean age and duration of injury were 8.45±4.54 years and 7.91±4.93 hours respectively. Male to female incidence was 92 (57.50%) and 68 (42.50%) respectively. Early post-traumatic seizures were seen in 17 (10.63%) patients.

Conclusion: EPTS occurred in 10.63% of children with moderate to severe TBI despite Phenytoin prophylaxis. In our view, phenytoin prophylaxis should be given to all children with traumatic brain injury to reduce the incidence of early seizures.

Keywords: Early posttraumatic seizures, Phenytoin, Traumatic brain injury.

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1. Introduction

Brain injury resulting from trauma in the paediatric population carries a grave morbidity and mortality.[1] In Developed countries like the USA it's the cause of almost 12% of hospitalizations and mortality with around 2.5 million cases annually.[2,3] Global incidence ranges from 100-500 per one hundred thousand. WHO statistics showed that brain injury surpassed many other diseases by the year 2020. In developing countries, it accounts for almost one-third of all trauma-related deaths. Resulting survivors suffer long-term deprivation in neurocognition, education and quality of life.[4] Post-traumatic seizures can be classified into immediate that is occurring within the first 24 hours, early occurring within 1-7 days of life and late if seizures occur after 7 days of life. Incidence of early and late post-traumatic seizures ranges from 4-25 % and 42 % respectively.[5,6] Chances of recurrence of a second seizure rise to 86% after the first seizure. Early seizures result in increased metabolic demand of the brain and increased neurotransmitter release resulting in cerebral hypoxia which further insults already traumatized brain tissue. Seizure control is important because acute brain insults may add secondary insult to an already traumatic brain. Early seizures are also linked to poor GCS and behavioural abnormalities.[7,8]

Treatment strategies focused on both reducing or preventing secondary brain insult. Prompt identification and control of seizures are needed to reduce and prevent brain hypoxia and insult. Children aged less than 2 years suffering from severe brain injury defined as GCS of<8, non-accidental trauma are more at risk of early post-traumatic seizures. The presence of cerebral oedema, depressed skull bone fracture and haemorrhage in parenchyma are also predisposing factors for seizures. Clinicians should advise strict EEG monitoring to identify subclinical seizures thus helping in the identification of high-risk groups. Early post-traumatic seizures result in a prolonged stay in the paediatric intensive unit and poor functional and neurocognitive outcomes associated with severe injury measured by GCS.[9,10]

Prophylactic use of anti-epileptic drugs during the first 7 days is protective against early seizures. A lower incidence of seizures was observed in patients who received anti-epileptic prophylaxis.

A study by Chung et al. reported EPTS in 17% of pediatric patients with moderate to severe traumatic brain injury receiving anti-epileptics prophylaxis.[11] While Another study by Kolf et al. reported EPTS in 9.0% of pediatric patients receiving post-traumatic anti-epileptic seizures prophylaxis.[12]

This research aimed to determine the frequency of early post-traumatic seizures in children receiving prophylactic anti-epileptic phenytoin after moderate to severe traumatic brain injury. The rationale of the study is that acute seizures during early post-traumatic brain injury not only acutely insult the brain but also result in secondary damage to brain tissue. Seizures on already traumatized brains lead to poor Glasgow outcome scores, behavioural abnormalities, poor cognition and motor disabilities as long-term sequelae. Study results will not only help in determining the frequency of seizures but also measure the actual burden they put on traumatic brain injury in our local population. Very few studies have been conducted on our local population, especially among the paediatric age group.

The objective of the study is to determine the frequency of early post-traumatic seizures (EPTS) in patients receiving anti-epileptic prophylaxis after moderate to severe traumatic brain injury (TBI) in pediatric patients.

Operational Definitions:

Moderate to Severe Traumatic Brain Injury (TBI): The diagnosis of moderate to severe TBI was made based on the post-resuscitation Glasgow coma scale (GCS). Patients having a GCS score ≤12 were labelled as having moderate to severe TBI.

Early Post-Traumatic Seizures (EPTS): The diagnosis was made on clinical assessment. Patients who developed symptoms such as impaired awareness, aberrations of mental function, falls and generalized convulsive movements within 7 days after TBI were labelled as having EPTS.

2. Materials & Methods

It was a Descriptive Case Series with Non-probability consecutive sampling carried out at the Department of Neurosurgery, Shifa International Hospital Islamabad from 26 August 2021 to 25 August 2022. A total of 160 patients were included in the study. This sample size was calculated using the following formula; $N= Z_{\alpha/2}^2 X P(100-P) / e^2$. Where P is the expected frequency of EPTS=9.0%[9]. And e is the desired margin of error=4.5%. All patients presenting in the emergency department of both genders aged 2 to 18 years with moderate to severe TBI and having a duration of injury ≤48 hours were included in the study. Patients with penetrating head injuries and known Epileptics were excluded from the study. Approval was taken from hospital IRB and Ethical Committee reference No 215/21-28/21, and data collection was started. A written consent was taken from each patient before including him/her in the study. Data regarding baseline study variables such as age, gender, and duration of brain injury was collected for each child. Patients were given intravenous phenytoin in a loading dose of 20mg/kg with the rate of 1-2mg/kg/min infusion followed by a daily maintenance dose of 5mg/kg twice daily. Patients were clinically monitored for the occurrence of seizures during the first 7 post-traumatic days. Diagnosis of early post-traumatic seizures was made by a consultant neurologist as per operational definitions. All information relevant to the study was noted on a proforma. Data was entered and analysis was done using SPSS version 24.0. For quantitative variables like age and duration of trauma at the time of admission, mean and standard deviation were used. For gender and early post-traumatic seizures frequency and percentage were calculated. Effect modifiers such as age, gender and duration of injury were controlled through stratification. To determine the association of age, gender and duration of injury association with early post-traumatic seizures post stratification chi-square test was applied. A p-value of equal or less than 0.05 was considered significant.

3. Results

A total of 160 patients were included in the study with a mean age of 8.45±4.54 years. The minimum age was 1 year and the maximum age was 18 years (Table 1).

Table 1: Descriptive Statistics of Age

Variable (N=160)	Age(Years)
Mean	8.45
S.D.	4.54
Minimum	01.00
Maximum	18.00

The mean duration of injury was 7.91±4.93 hours. The minimum duration of injury was 2 hours and the maximum was 24 hours (Table 2).

On the frequency of gender, there were 92 (57.50%) males and 68 (42.50%) females (Figure 1).

Table 2: Descriptive Statistics of Duration of Injury

Variable (N=160)	Duration of Injury (Hours)
Mean	7.91
S.D.	4.93
Minimum	02.00
Maximum	24.00

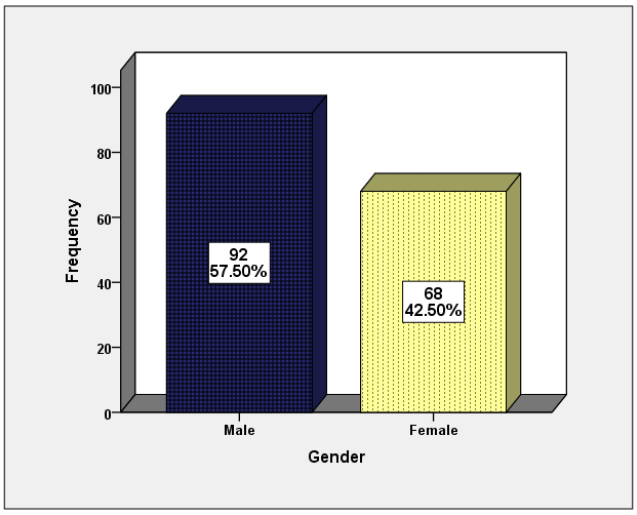

Figure 1: Frequency of Gender

Of the 160 patients included in the study, 17 (10.63%) patients developed early post-traumatic seizures (Figure 2).

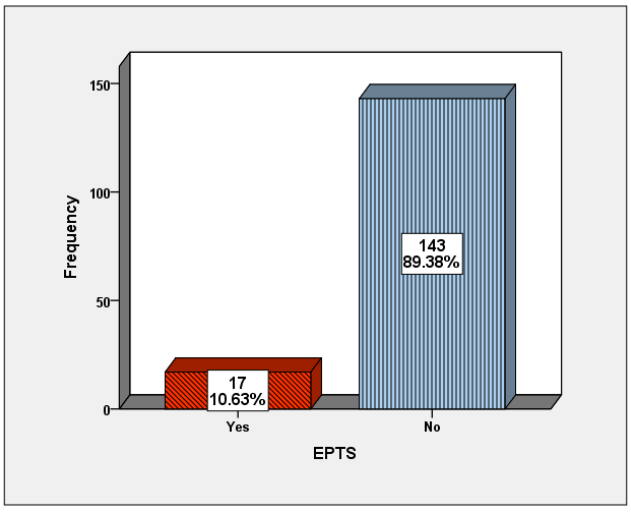

Figure 2: Frequency of Early Post Traumatic Seizures

Stratification of age was performed. In pediatric patients aged 1-7 years, 10 (12.5%) patients developed early post-traumatic seizures while in patients aged 8-18 years, 7 (8.8%) patients developed early post-traumatic seizures with a p-value of 0.422 (Table 3).

Table 3: Stratification of Age, Gender, Duration of Injury to Determine the Association of Age with Frequency of Early Post Traumatic Seizures

Variable		EPTS		P-value
		Yes (N=17)	No (N=143)	
Age Group	1-7 Years	10 (12.5%)	70 (87.5%)	0.422
	8-18 Years	07 (8.8%)	73 (91.3%)	
Gender	Male	17 (18.5%)	75 (81.5%)	<0.001
	Female	00 (0.0%)	68 (100.0%)	
Duration of Injury	2-6 Hours	06 (8.0%)	69 (92.0%)	<0.311
	7-24 Hours	11 (12.9%)	74 (87.1%)	

Regarding gender, 17 (18.5%) male patients developed early post-traumatic seizures and none of the females developed early post-traumatic seizures, with a p-value of <0.001 (Table 3).

Regarding the duration of injury, 06 (8.0%) patients developed early post-traumatic seizures (EPTS) having a duration of injury of 2-6 hours while 11 (12.9%) patients developed early post-traumatic seizures having a duration of injury of 7-24 hours with a p-value of 0.311 (Table 3).

4. Discussion

A total of 160 patients were included in the Study. The mean age of patients included in this study was 8.45±4.54 years. The mean duration of injury was 7.91±4.93 hours. Males to female incidence was 92 (57.50%) and 68 (42.50%) respectively. 17 (10.63%) patients developed EPTS. The frequency of EPTS in patients of TBI receiving phenytoin prophylaxis was 10.63%.

For the prevention and treatment of seizures occurring during or after any neurosurgical procedure, phenytoin is approved by the FDA. In the cerebral cortex, phenytoin promotes sodium efflux and prevents hyperexcitability of neurons by stabilizing the threshold. It carries a unique pharmacokinetics due to which it requires therapeutic monitoring.

Khattak k et al carried study at the Department of Neurosurgery at Ayub Medical College on the role of phenytoin in post-traumatic brain injury in the prevention of seizures. They included 163 patients. Male to female incidence was 122(74.8%) and 41(25.2%) respectively. The incidence of seizures in patients who received Phenytoin versus group not

receive was 9.89% and 23.11% respectively with statistically significant differences (p-value of 0.018). They concluded that early post-traumatic brain seizures are common after brain injury and phenytoin has a role in decreasing the frequency of seizures. These findings are consistent with our study results.[13]

Samara et al carried systemic review and meta-analysis on post-traumatic seizures and the role of prophylactic anti-epileptic drugs in controlling early and late-onset seizures. They included ten studies and a total of 4621 patients with traumatic brain injury. The mean incidence of early seizures was 8%. They concluded that anti-epileptics have a role in controlling early post-traumatic seizures. [14] These are all consistent with our study results. Yachad N et al carried out a study on the pharmacological management of post-traumatic brain injury and the prophylactic role of anti-epileptic drugs. They gave anti-seizure drugs to 44 patients admitted to the emergency department and found that the incidence of seizures decreased with prophylactic anti-epileptic drug usage. All these findings are consistent with our study results. [15]

Shu Ling C et al conducted a multicenter study on post-traumatic seizures. They analyzed 313 children and concluded that early post-traumatic seizures are common among children with moderate to severe brain injury. They also stressed on prophylactic usage of anti-epileptic in such cases.[16] Meghan J Kolf et al conducted a study on paediatric patients with severe brain injury and the prophylactic role of anti-epileptics in preventing seizures. Results found that among those who received prophylaxis, only 4(9%) patients developed seizures. These findings are consistent with our study results in the prophylactic role of antiepileptic in seizure control in traumatic brain injury.[12]

Oyemolade TA et carried out a prospective randomized double-blinded trial on the efficacy of phenytoin effect in reducing the incidence of seizures in traumatic brain injury. They included 94 patients and divided them into a treatment group and a control group. Male-to-female incidence was 77 and 17 with a ratio of 4.5:1 respectively. Demographic and clinical profiles were similar in both groups. The treatment group received phenytoin for 48 hours prophylactically. Results found that the incidence of seizures in the Phenytoin group versus the control group was 2.1% and 21.3% respectively with a significant p-value less than 0.01. They recommended phenytoin usage as prophylaxis in traumatic brain injury. These findings are consistent with our study results.[17]

Wat R et carried systemic review and meta-analysis on the prophylactic role of anti-epileptics in post-traumatic brain injury. They included three randomized control trials and six observational studies and included 4412 patients with traumatic brain injury. They observed that a significant protective effect was seen with prophylactic anti-epileptic drugs and phenytoin was the most commonly used drug in such cases. These findings are consistent with our study results. Brain Trauma Foundation recommended phenytoin usage as seizure prophylaxis in post-traumatic brain injury. American Academy of Neurology and Brain Trauma Foundation in the years 2003 and 2007 issued guidelines regarding post-traumatic brain injury and anti-epileptic prophylaxis. They recommended post-traumatic seizure prophylaxis during the first seven days after brain trauma. [18, 19]

Jones KE et al researched the comparison of phenytoin versus levetiracetam prophylaxis in controlling seizures in brain injury. The results found that both drugs have equal efficacy in treating seizures. However, phenytoin has superior efficacy because patients in the levetiracetam group had a higher incidence of abnormal EEG with a significant p-value of 0.003. They concluded that phenytoin prophylaxis reduces seizure risk in brain injury. These are all consistent with our study results. [20] Nancy R et al carried study on phenytoin effectiveness in controlling seizures occurring after traumatic brain injury and included 404 patients with head injury. They gave a loading dose of phenytoin within 24 hours of trauma and blood levels of the drug were maintained in the therapeutic range. Patients who received phenytoin versus the placebo group had seizure incidences of 3.6% and 14.2% respectively. They concluded that it has beneficial effects in controlling seizures. [21]

Ryan J MacGinn et al conducted a systemic review and meta-analysis on the prophylactic role of anti-epileptics phenytoin and levetiracetam in controlling seizures after brain injury. They assessed both primary outcomes in terms of seizure control and secondary outcomes in terms of mortality and hypotension. After screening of 487 research papers 5 were reviewed and found no difference between phenytoin and levetiracetam efficacy in controlling seizures. [22]

Wang BC et al carried out a systemic review on the comparative efficacy of antiepileptic drugs in

traumatic brain injury. They included 11 studies and included 2450 patients following brain injury and they received different anti-epileptic drugs prophylactically. They observed that prophylactic anti-epileptic drugs reduce early seizures with phenytoin (ORs=0.43 & 0.71;95%Cis=0.18-1.01 and 0.23-2.20). They found that phenytoin had a superior efficacy in controlling early post-traumatic seizures, especially in the paediatric population. They recommend the use of anti-epileptic prophylaxis in traumatic brain injury. These findings are consistent with our study results. [23]

Limitations of the study are a small sample size and a single-centre study with shorter follow-up. Large multicenter studies should be done with longer follow-ups to determine the effectiveness of phenytoin prophylaxis for the control of seizures after brain trauma.

5. Conclusion

EPTS occurred in 10.63% of children with moderate to severe TBI despite Phenytoin prophylaxis. In our view, phenytoin prophylaxis should be given to all children with TBI to reduce the incidence of EPTS.

CONFLICTS OF INTEREST- None

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Contributions:

A.K - Conception of study
- Experimentation/Study Conduction
A.K, S.T.M - Analysis/Interpretation/Discussion
A.K, S.T.M, H.A, A.T, H.M - Manuscript Writing
S.T.M - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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