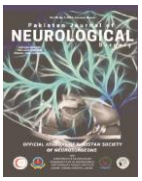

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Original Article

Management of Post Traumatic Epilepsy in Pediatric Population in Pakistan

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ABSTRACT

Objective: To investigate the efficacy of seizure prophylaxis in the prevention of early and late-onset seizures after the traumatic brain injury known as post-traumatic epilepsy (PTE).

Material and Methods: A retrospective study was performed on children aged 0 to < 12 years who were presented to a level 1 trauma center during the six months with the diagnosis of mild to severe TBI. Data included is of 66 patients from Children's Hospital, Lahore. It was analyzed according to a patient's demographic data, mechanism of injury, clinical and radiological presentation, management, and follow-up. History of seizures was tracked through guardian referral or staff witnesses.

Results: Among 66 pediatric cases of acute brain injury from June 2019 to December 2019, 45 were males (68%) and 21 were females (32%) with a male to female ratio of 2:1. The mean age in our study was 3.8 years. 60% of children were managed under observation, 30% of children required medical pharmacological treatment, 9% of children needed surgical intervention, and 13% of children required artificial ventilation. Overall mortality is 4.5%. In our study, we found a considerable relationship between residual neurological deficits and severity of injury ($p = 0.3$), there is no noteworthy relationship between mechanism of injury and outcome ($p = 0.5$). The mean length of stay was 3.9 days but 60% of patients had stayed less than 3 days.

Conclusion: Analyzing the underlying mechanisms of post-traumatic epilepsy can lead us to propose effective treatments to prevent seizures following traumatic brain injury.

Keywords: Traumatic Brain Injury (TBI), Post Traumatic Seizures (PTS), Post Traumatic Epilepsy (PTE), anti-convulsant drugs, anti-epileptic drugs (AEDs), Hematoma, Road traffic accident (RTA)

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INTRODUCTION

Traumatic brain injury (TBI) is considered a leading cause of pediatric mortality and neurological impairment throughout the globe. It consists prominently of two components, a primary phase caused by acute effects of

immediate external impact to the brain parenchyma and a secondary phase mediated by a strong immune reaction, neuronal death, and oxidative stress along with raised neuron formation. The immune response leads to raised glial activity, the release of inflammatory modulators, blood-brain barrier disruption, and the influx of peripheral lymphocytes and leukocytes. All these processes in conjugation decrease the inhibitory synaptic activity in turn lowering the seizure threshold, increases the chances of PTE.[1]

PTE refers to repetitive and unprovoked post-traumatic seizures (PTS) that take place approximately 1-week post-TBI; seizures occurring in the first week after post TBI are stimulated by the head injury and are called early PTS whereas those after 1 week are an indication of PTE and are known as late PTS.[2] PTE has a profound effect on the quality of life, often manifested as anxiety, depression, stigma, cognitive decline, and even social isolation. While prediction, treatment, and optimal management of PTE remain a challenge for clinicians.[3] A better understanding of complex pathophysiology and safer treatment options based on fundamental neurophysiological processes are needed to address the issue.[4]

In the case of children, patients with GCS ≤ 8 poor prognoses are associated with PTE.[5] Identification of patients with a moderate or severe head injury is important for further management and follow-up because of the risk of developing PTE and its serious implications on quality of life. We evaluated the incidence and predisposing factors for developing PTE in a group of children hospitalized at our medical center with mild, moderate, or severe head injury.[6] Post-traumatic seizures are a common complication of TBI. Approximately 20% of patients in the intensive care unit (ICU) and about 25% to 50% of patients chronically face this complication. Post-traumatic seizures cause secondary brain injury due to a rise in intracranial pressure (ICP) and metabolic crisis. This happens especially when the injured brain is vulnerable to secondary injury thus leading to worse outcomes.[7] Generally, different medicines are suggested to overcome early or late PTS without a very clear understanding or listing of their side effects. Three main factors that were associated with an increased frequency of late epilepsy are early post-traumatic seizures (occurring within the first week), hematoma in the brain, or a depressed skull fracture. Many studies show that Glasgow Coma Score (GCS) <10 and a penetrating head wound are also related to the post-traumatic seizures.[8] However, evaluation of PTS requires a competent understanding of the various type of seizures as they can range from simple to complex seizures including generalized or status epilepticus. Head injury is divided into the following categories mild, moderate, and severe depending upon the Glasgow coma scale.

Literature shows remarkable variation in the incidence of PTE which also depends upon the injury severity. 4% of the cases with mild injury hospitalization whereas 50% cases account for severe TBI in children. Epilepsy can be primary or secondary.[9] Primary epilepsy is related to genetic abnormalities while secondary epilepsy can occur after brain tumors, strokes, head injury, previous central nervous system infections, or brain damage during delivery while PTE accounts for nearly 20% of secondary epilepsy.[10] Within the first 12 months after injury, about 80% of patients develop PTE. More than 90% of the patients report seizures by the end of the subsequent year.[8] One research shows that after the first late-onset fits (more than 1 week from injury), the second episode of fits was reported in 86% of the patients within 2 years.[11] PTE is 2 times more common in post-traumatic patients who got depressed at the time of discharge.[12] Qualitative research has proven that an accurate baseline assessment is crucial, and serial assessments are also needed, because neurological status may change with time, sometimes rapidly. Mostly, GCS

has turned out to be authentic and is potent enough for the detection of clinically important alternations in the neurological condition. It is also easy to be used by a range of health care professionals.[13]

MATERIALS AND METHODS

Study Design and Settings

Descriptive case series was conducted at Children Hospital and The Institute of Child Health, Lahore.

Inclusion Criteria

Children of both genders < 12 years were included who were found with TBI reporting to the neurosurgical emergency department. Cases of TBI managed with or without surgery were included.

Exclusion Criteria

Patients with polytrauma and patients with medical illness.

Data Collection

Children aged 0 to < 12, who came to level 1 trauma center of children hospital for 6 months after the diagnosis of severe to mild TBI were subjected to retrospective chart review. The included data is of 66 patients from Children's Hospital, Lahore. It was analyzed according to a patient's demographics, mechanism of injury, mode of injury, clinical and radiological presentation, treatment, and follow-up. Staff witnessing and referral of the guardian were used to monitor the presence of seizures. Following metrics were considered among children with TBI: age, gender, mechanism of injury, diagnosis, occurrence of loss of consciousness, vital signs, and GCS score.

Head trauma was divided into two groups: (1) severe; lack of consciousness > than 24 hours, focal neurological signs, early fits (within the first week), depressed skull fracture, intracranial hematoma or brain contusion (radiologically or surgically diagnosed), and (2) mild-moderate in the remainder; where patients were examined by CT scan within 24 – 48 hours from the time of trauma. CT scan helped us divide diagnosis into six groups: normal, brain edema, intracranial extracerebral hematoma (subdural or epidural), focal hypodensity, intracerebral hemorrhage, intracerebral hemorrhage associated with extracerebral hematomas.[6]

RESULTS

Gender and Age Information

We included a total of 66 children after TBI from June 2019 to December 2019, with 45 males (68%) and 21 females (32%) with a male to female ratio of 2:1.in our study mean age is 3.8 years.

Table 1: TBI Severity and Mode of Injury.

TBI Severity	Percentage
Moderate	12%
Severe	21%
Mild	66%
Mode of Injury	**Percentage**
RTA	9%
Fall from Stairs	18%
Fall from Height	72%

Clinical Information

Out of 66 cases of TBI, 66% were mild, 12% moderate, and 21% severe TBI (Table 1). In general, falls from height are the most frequent cause of TBI then falls from stairs and RTA. On clinical examination loss of consciousness (LOC) was present in 36 children, vomiting in 39, ENT bleeding in 14, and fits in 8, external injuries in 6, while 38 children presented with a normal level of consciousness (Table 2).

Table 2: Clinical Examination.

Mode of Presentation	Number
LOC	36

Vomiting	39
ENT Bleed	14
Fits	8
External Injuries	6

Findings from CT Scan

CT scan findings showed no abnormality in 18% of patients, extradural hematoma (EDH) in 22.7%, subdural hematoma (SDH) in 9%, a subarachnoid hemorrhage in 12%, fractured skull in 53%, and contusion in 12% as the radiological injury patterns. We observed the patients for a certain period and found that PTS existed in 30%. However, we didn't find multiple episodes of seizures, and therefore, the propensity to develop PTE could not be confirmed.

Clinical Management

Out of 66 children, 60% of children were managed under observation, 30% of children required medical pharmacological treatment i.e. valproic acid and levetiracetam (25%) were used more frequently than phenytoin 4%. 9% of children required surgical intervention, and 13% of children required mechanical ventilation (**Table 3).**

Table 3: Clinical Management.

Management	Percentage
Observation	60%
Conservative	30%
surgery	9%
Mechanical Ventilation	13%

The overall mortality rate was 4.5%. Among the survivors (n = 63), 58 (88%) were discharged with no residual deficit, 6(9%) had hemiparesis, 6 (9%) had seizures (PTE – was recovered in a one-year follow-up), 2 (3%) had hydrocephalus, and 2 (3%) had speaking difficulty.

In this study, we found a considerable correlation among residual neurological deficits and severity of traumatic brain injury and no noteworthy interrelation among mode of injury and outcome. Mean hospital stay was 4 days but 60% of children had stayed less than 3 days.

DISCUSSION

Our primary goal was to minimize the exploitation of AEDs in PTE patients but to ensure that we need a mechanism for early detection of PTE. When we discuss the quality of life of a PTE patient, child, or adult, we tend to ask how frequent the seizures will be and can the risk factors be efficiently predicted to reduce the PTE.[9] The answers are much needed but are still not well defined, thus the prevention mechanism cannot be aligned. The occurrence of seizures among PTE patients is not related to any particular metric or variable. Generally, the predictive factors for PTE are the severity of TBI, the presence of intracranial bleeding, and early post-traumatic seizures.[9] Age, results from neuroimaging and treatment methods have shown to be independent risk factors of PTE from early data, however, some reports claim that age does not cause a significant difference in the possibility of developing late PTS. Despite the differences in the definition of severity, one study presented severity of TBI to be associated with the highest risk of PTE. Thus, the predisposing factors after severe TBI for PTE should be further evaluated. There is some evidence that suggests that the risk of PTE may also be dependent upon the type of the PTS, with focal or partial seizures having more frequency of recurrence as compared to generalized seizures. It would be recommended to have more information about the predisposing factors which includes the type of seizures for PTE as well because such information holds important treatment inference.

We have included the Independent risk factors for post-traumatic seizures (PTS) and post-traumatic epilepsy (PTE) that may help in the clinical diagnosis of TBI patients.[2] Risk factors for PTS are acute subdural hematoma, younger age,

brain contusion, and increased injury severity. Other important risk factors include dural penetration, depressed skull fracture, intracranial hematoma, and altered level of consciousness or amnesia for more than one day.[8] Skull fractures and hematomas are mostly present in case of severe TBI. Skull fracture and hemorrhage are responsible for the elevation in inflammation and excitation of neurons which brings down the threshold for seizures. In the case of severe TBI, even after 8 days neuroinflammation remains upregulated which can partially lead to the progression of late-onset seizures. The presence of early seizures may make patients more susceptible to the development of PTE. From some of the experimental data and previous studies, one can assume that young are more susceptible to early seizures, and adults to late seizures. Similarly, older age may also increase the risk for PTE. Gender overall does not appear to influence risk for PTE.[8]

Current treatment options for seizures are Phenytoin which causes an elevation in the refractory period resulting in reversible inhibition of action potential. In the case of severe TBI, a reduction from 14.2% to 3.6% in the incidence of early seizures was found to be associated with Phenytoin.[8] Phenytoin should only be brought into use within the first 48 h after the injury as a randomized control trial depicted a tendency towards increased mortality when applied at later time points.[8]

Levetiracetam operates differently as compared to most seizure medicines. It works in combination with SV2A protein which mediates the release of neurotransmitters in the brain. The actual mechanism causing the decrease in seizures is not known entirely.[14] 20 to 40% of people had at least a 50% decrease in their seizures in most cases where levetiracetam was given along with other seizure medicines. The recommended daily dose for infants and children is based on weight and age.[15]

In our study, the impact of seizure prophylaxis after the traumatic brain injury was evaluated. As international institutes recommend the use of PTS prophylaxis only in the first 7 days of TBI, our clinical research shows that locally the usage/ prescription is much more than the standard principal. Many new anticonvulsants are being forwarded in the pharma regarding PTS, however phenytoin is more common than the rest and because its side effects are much widely discussed, doctors prefer its use over the other alternatives. One research includes a double-blind study of 404 patients with severe head injury randomized to receive phenytoin or placebo within 24 hours of injury and to be continued for 1 year. They found that phenytoin reduced the incidence of early PTS but not thereafter. This study appears to be a justified method of preventing prophylactic anticonvulsants post the first week in the majority of cases.[1] Levetiracetam is showing efficacy in comparison to phenytoin but studies indicate a possibility of increased seizure tendency in patients and are similarly recommended for the only first week after TBI. Thus, anticonvulsant therapy can be helpful in the early PTS but the success of the medication in late PTS or otherwise total prevention of seizures in patients is unclear. Mostly, for late seizures, a long-term anticonvulsants therapy is suggested.[15]

We have observed that if the usage of prophylaxis is prescribed without a complete understanding of the patient's condition, it may lead to more harm than help. The anti-convulsants success rate is still unknown and therefore clinicians should be more careful in proposing medical solutions to kids or adults with TBI history. The misuse of AEDs and the impact it can have on a TBI patient recommends that more focus is required to be put towards the cause and prevention of PTS and PTE. To study the different processes of molecular, cellular, and neural origin happening post-TBI, several models have been established. The relevance of these processes to epileptogenesis is also a focus of interest.[12] The

initiation of these processes takes place at the time of injury while the progression happens in hours, days, and even years. The progression of TBI to epilepsy involves the spontaneous reaction of the brain to the injury which causes loss of cells. In addition, imbalance of excitatory and inhibitory neurotransmission due to alternations in a neural organization and increased permeability of the blood-brain barrier are also involved. The similarities observed in the molecular events of TBI and epilepsy were a confirmation of similarities in the regulated genes as studied in models [12] Not much information is available regarding gene regulation in children. The contribution of inflammation in epileptogenesis in TBI is now gaining attention, especially concerning the age-related differences. These differences between pediatric and adult TBI are attributed to be the result of variation in neuroinflammation according to brain development.[12] We have observed the probability of more vulnerability to epileptogenesis in younger patients due to a "window of susceptibility" for inflammation in the developing brain.

For example, slower interhemispheric transfer time was revealed as a potent corpus callosum-related biomarker to be associated with worse prognosis in children with moderate or severe TBI in a recent study.[15] Contrast in the definition and characterization of TBI severity makes it abstruse to generalize. In a recent report, PTE has been defined as "an occurrence of two or more seizures post > 24 hours TBI". As instantaneous seizures have not been included in this definition, therefore, it excludes the overstated evaluation of the frequency of PTE. Inclusion of early PTS, which is defined by researchers as the occurrence of seizures between 24hrs to 1-week post insult, is a point of argument as it can cause misjudgment of the PTE prevalence. This cause and effect relationship between early PTS and PTE in moderate-severe TBI is not completely understood; therefore, including these seizures for a wider context of PTE appears to be appropriate.[13-16]

CONCLUSION

In this study, we characterized factors correlating with a higher possibility of developing posttraumatic epilepsy in children after head trauma. Patients with early post-traumatic seizures are commonly treated with anticonvulsive drugs like levetiracetam for one week. Our study indicates that very few pediatric cases (less than 9%) required any pharmacological help. International recommendation at present is only to use antiepileptics for early PTS prophylaxis, however, our local approximation is that 60% of PTE cases are being prescribed AEDs by clinicians in Pakistan. We emphasize the need for regular monitoring of PTS and PTE patients to keep them off of long-life medication. Increasing the overall understanding and detection of PTE will help in developing selective therapeutic options for PTE and the prevention of late-onset seizures.

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Additional Information

Disclosures: Authors report no conflict of interest.
Ethical Review Board Approval: The study was retrospective.
Human Subjects: Consent was obtained by the patient in this study.
Conflicts of Interest:
In compliance with the ICMJE uniform disclosure form, all authors declare the following:
Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Lubna Ijaz	1. Study design and methodology.
2.	Faiq Sheikh	2. Paper writing and data calculations.
3.	Jamal Nasir	3. Data collection and calculations.
4.	Rabia Saleem	4. Analysis of data and interpretation of results etc.
5.	Fakiha Sheikh	5. Literature review and referencing.
6.	Noman Saleem, Laeeq-ur-Rehman	6. Analysis of data and quality insurer.