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Phenytoin as Post-Traumatic Seizures Prophylaxis in Head Trauma Patients

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ABSTRACT

Introduction: Post-traumatic seizures can occur as a complication of head injury, whether it is immediately after the head injury to months or years after. Phenytoin is an anti-epileptic drug that has been used widely as a prophylaxis of posttraumatic seizures.
Method: The study was conducted retrospectively using medical records of head trauma patients in hospitals in 2020-2022 on 54 samples treated up to seven days post-trauma. Samples were obtained which then analyzed by medical records, looking at the patient's identity, patient diagnosis, seizure symptoms, and history of anti-seizure drugs.
Result: Patients given phenytoin prophylaxis [22 (40.7%)] who did not have seizures [18 (33.3%)] were more than patients who had seizures [4 (7.4%)]. Similar results occurred in patients without phenytoin prophylaxis [32 (59.3%)], more patients with no seizures [30 (55.6%)] than those with seizures [2 (3.7%)].
Conclusion: The usage of phenytoin is still not routinely given to post-traumatic head patients at RSIJ Cempaka Putih. The administration is carried out on a case-by-case basis assessment must be carried out in determining the use of phenytoin as a seizure prophylactic so that the benefits outweigh the side effects. For further research, it is recommended to conduct EEG examination on head trauma patients to determine the diagnosis of post-traumatic seizures / epilepsy and conduct further seizure evaluation.
Keyword: Post-trauma seizure; Phenytoin; Prophylaxis; Head Trauma; Jakarta Islamic Cempaka Putih Hospital

1. Introduction

Head injuries due to trauma are still the leading cause of death and disability in the world, causing socioeconomic losses. Every year about 10 million cases occur in the world. Post-traumatic seizures can occur as one of a series of complications of head injury immediately after the event to months or years after [1]. This condition can lead to morbidity and greatly reduce the quality of life of patients. Identification and prevention are the first priorities in the management of post-traumatic head seizures using several anti-seizure alternatives by considering the dose and side effects. A group of doctors in Hippocrates' day observed patients with seizures on the right side of the body after brain injury to the left temporal lobe, and attributed poor patient outcomes. Arthur Elvidge, a neurosurgeon from England in 1939 divided post-traumatic head seizures based on the period of attack, namely: early phase seizures (immediate seizure) occur <24 hours posttraumatic, early seizures (early seizure) occur ≤ 1 week posttrauma, late seizures (late seizure) > 1 week post-traumatic without provocation so that it can be referred to as epilepsy, and posttraumatic epilepsy is defined as recurrent seizures >1 weeks posttraumatic with no other cause than a previous head injury. It combines early-phase and early-phase seizures into posttraumatic epilepsy(2). The incidence of post-traumatic epilepsy in patients in hospitals is 3-5%, which represents 10-20% of epilepsy in the general population. A retrospective study in 1980 of 2,747 head trauma patients experienced decreased consciousness and seizures with an incidence of 2.1%, and as many as 75%

occurred within the first 24 hours. In pediatric patients, early seizures are more likely to occur regardless of the severity of brain injury than in adult individuals. The Vietnam Head Injury Study (VHIS) states that in the military population, patients with penetrating brain injuries have an incidence of post-traumatic seizures of 4.3% [2,3]. Post-traumatic epilepsy is often generalized, focal or focal with secondary generalizations, depending on the location of the lesion and age. In children <5 years with a history of post-trauma, temporal lobe mesial epilepsy may appear as a result of hippocampal sclerosis [4,5].

Head trauma causes a series of cellular and molecular activities, divided into primary and secondary damage, as well as self-repair mechanisms. The mechanism of posttraumatic seizures of the head in early phase and late phase seizures has some differences. Tissue deformation and compression of brain tissue occurs from a few seconds to minutes after a mechanical injury to the brain that results in production of glutamate and calcium influx. This causes excitotoxic injuries seen from mitochondrial damage and energy depletion, edema in the neurons and glials, leading to cell death. Vascular disorders and the blood-brain barrier also play a role in the primary injury. In moderate and severe head injuries, cortical structure damage occurs, especially in the hippocampus. Seizures that occur in this phase are the result of acute injury and are not epileptic in nature. Primary injuries can be prevented preventively such as by using helmets on motorcyclists. Secondary injuries resulting in seizures are caused by inflammatory chains, growth factor response, edema, mitochondrial dysfunction, oxidative stress caused by free radicals and reactive oxygen, and delayed cell death. The "self-repair" mechanism is useful in functional repair, but it can also initiate seizures (the process of axon growth and synapse reorganization) especially in the late phase which can be categorized as post-traumatic epilepsy. Neuroprotective therapy is recommended to increase the benefits of the "self-repair" process and prevent secondary brain injury [6,7].

Phenytoin is an anti-epileptic drug that is recommended as a prophylactic agent for early phase posttraumatic seizures that are easily available, not effective in preventing late-phase seizures. Other anti-seizure drugs such as levetiracetam have also shown lower tolerability and neurological side effects [8,9]. Some studies suggest posttraumatic seizure prophylaxis using phenytoin had no significant effect on early-phase seizures compared to placebo, so this remains controversial [10,11]. Therefore, This study aims to determine the usage of phenytoin as a prophylaxis of post-traumatic seizures in head trauma patients at Jakarta Islamic Hospital Cempaka Putih.

2. Method

A retrospective study of medical records was conducted on neurosurgery patients at Jakarta Cempaka Putih Islamic Hospital for the period January 2020 – August 2022 with inclusion criteria for head trauma patients caused by traffic accidents or domestic accidents who were handled and operated on at Jakarta Cempaka Putih Islamic Hospital and treated for at least one week post-trauma. Head trauma patients who died or were referred before seven days of treatment were not included in the study. A total of 54 research samples were obtained which then analyzed by medical records, looking at the patient's identity, patient diagnosis, seizure symptoms, and history of anti-seizure drugs.

3. Result

3.1 Sample Characteristics

Based on the results of the distribution of sample data (Table.1), it was found that there are 36 male patients (66.7%), more than female patients (18 patients, 33.3%). The largest sample age group is the age group of 10-19 years with 14 patients (25.9%) and followed by the age group of 20-29 years with 10 patients (18.5%), and the age group of 70-79 years with 2 patients (7.4%) is the least (Fig.1).

Table 1. Gender and Causes of Head Trauma

Gender	Number of patients	%
Male	36	66.7
Female	18	33.3

Causes of Trauma		
Traffic accidents	42	77.8
Domestic accident	12	22.2
Total	54	100

The most causes of trauma in this study were caused by traffic accidents amounting to 42 cases (77.8%) followed by domestic accidents such as falls at home or around the workplace amounting to 12 cases (22.2%).

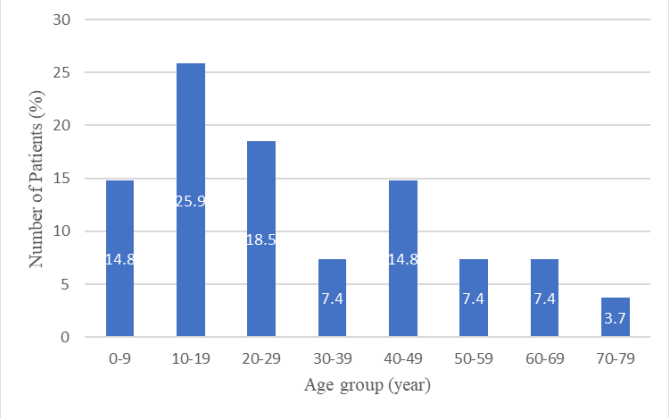

Figure 1. Age Group in Head Trauma Patients

3.2 Type of Head Injury

The severity of head injuries is divided by level of consciousness as measured by the Glasgow coma scale (GCS). Head injuries based on GCS are divided into three, namely: mild, moderate and severe brain injuries. Mild brain injury if the level of consciousness based on GCS is 14-15, moderate brain injury GCS between 9-13 and severe brain injury GCS between 3-8. This level of awareness does not depend on the type of abnormality or lesion that occurs in the brain [12].

Table 2. Head Injuries Classification

Type of Head Injury	**Number of Patients**	**%**
Minor Head Injury	22	40,7
Moderate Head Injury	28	51,9
Severe Head Injury	4	7,4
Total	54	100

In this study, moderate head injuries were the most head injuries (Table.2) with 28 cases (51.9%), followed by minor head injuries as many as 22 cases (40.7%), and severe head injuries as many as 4 cases (7.4%). Patients who had seizures were 6 people, 4 people had minor head injuries and 2 people had moderate head injuries. Types of head injuries based on a clinically established diagnosis and CT-scan of the head are divided into several types of intracranial hemorrhage namely epidural hemorrhage (EDH), subdural hemorrhage (SDH), intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH). In one individual, multiple lesions can occur in the form of more than one type of intracranial hemorrhage or one type of intracranial hemorrhage in more than one brain area. Intracranial hemorrhage may also be accompanied by fractures of the cranial or maxillofacial bones.

Table 3. Types of Intracranial Hemorrhage

Intracranial Hemorrhage	Number of Cases	%
EDH	38	67,9
SDH	8	14,3
ICH	10	17,9
SAH	2	3,6
Total	58	100

In this study, the most cases of intracranial hemorrhage (Table.3) were EDH with 38 cases (67.9%) followed by ICH with 10 cases (17.9%). Multiple intracranial hemorrhages were also found in this study as many as 18 cases where there were multiple lesions and the same lesions but in different brain regions. There are multiple cranial fractures that accompany head injuries such as os fractures. Frontal, Os. parietal, as well as Os. Occipital (Table.4).

Table 4. Type of Head Injury Comorbidities

Comorbidities	Number of Cases
Multiple Intracranial hemorrhages	18
Skull base fracture	4
Os. Frontal fracture	4
Os. Parietal fracture	4
Os. Occipital fracture	2

3.3 Effectiveness of Phenytoin as Posttraumatic Seizure Prophylaxis

Based on data obtained from 54 medical records of head trauma patients at Jakarta Islamic Hospital Cempaka Putih for the period January 2020-August 2022, it was found that 22 patients (40.7%) were given phenytoin with varying doses according to the assessment of the doctor in charge with a dose of ± 20 mg/kg, with maximum dose of 300-2000 mg/day. Seizures persisted in 4 patients (7.4%) given phenytoin and 18 patients (33.3%) showed no early-stage seizures (occurring ≤1 week posttraumatized).

In the group of patients who were not given phenytoin, there were 32 patients (59.3%), as many as 2 patients (3.7%) had seizures and 30 patients (55.6%) did not have seizures (Table 5). Based on these data, an analysis of the relationship between phenytoin use and post-traumatic seizure prophylaxis using the Fisher test obtained *p value* of 0.211.

Table 5. Comparison of the Effectiveness of Phenytoin As A Prophylaxis of Posttraumatic Head Seizure

		Early Phase Seizure		Total
		Seizure	No Seizure	
Phenytoin given	Number of case	4	18	22
	%	7.4	33.3	40.7
No phenytoin given	Number of case	2	30	32
	%	3.7	55.6	59.3
Total		6	48	54
%		11.1	88.9	100

4. Discussion

In the Southeast Asia and the Western Pacific, head injuries from motor vehicle accidents are still the highest compared to other countries and are more common in lower-middle countries [13]. In this study, the proportion of male patients (66.7%) was more than female (33.3%), and the highest age group in head trauma patients was 10-19 years (25.9%) and followed by the age group of 20-29 years (18.5%). This is in line with retrospective research conducted in South Korea, namely sex differences in head trauma patients are

significantly different at the age of puberty to middle age. At that age, men more often experience head trauma due to lack of attention to road safety or because of work. Likewise, at the age of > 65 years there were no significant sex differences in head trauma patients, but 2/3 of female patients with head trauma were more often found at the age of >75 years caused by domestic accidents such as falls at home [13,14].

Head injuries, especially severe head injuries can cause posttraumatic seizures and increase the increase in intracranial pressure and affect blood pressure and oxygen distribution. Severe head injury has a 29x greater tendency to appear in the general population with severe head trauma, which has any of the signs: brain contusion (based on abnormal neurological tests or surgical observation), intracranial hemorrhage, or post-traumatic amnesia or unconsciousness >24 hours. Early seizures occur when head trauma occurs up to two weeks after injury, occurring in 2.1% with risk factors for age <15 years and severe head injury. In this study, moderate head injuries were the most head injuries with 28 cases (51.9%), followed by minor head injuries with 22 cases (40.7%), and severe head injuries with 4 cases (7.4%). A total of 2 patients who had seizures had moderate head injuries and 4 people who had seizures had minor head injuries. This is not in line with other studies, where severe head injury increases risk factors for early-phase seizures. In some cases of minor head injuries, there can be a misdiagnosis of post-traumatic head seizures in children due to a history of focal or general seizures that are not known or conveyed to the hospital, so that when a minor head injury occurs, epilepsy occurs that is not caused primarily by the head injury with normal CT-scan of the head and electroencephalography (EEG) results [15,16,17].

Another study conducted on 137 head injury patients found the incidence of end-phase seizures was 13.1% and increased in low GCS (3-8), single lesions in the temporal or frontal, the presence of early-phase seizures (up to four weeks from injury), and the presence of focal EEG abnormalities 1 month after injury. The study conducted by Englander et al, investigating the incidence of EPT in 647 head trauma patients explained an increased risk of seizures in the presence of multiple or bilateral contusions, dural penetration, the need for brain surgery in patients more than once, subdural hematoms requiring evacuation, and midline shifts > 5mm [(16,17)]. The use of phenytoin is recommended if an early-stage seizure has been obtained rather than as a post-traumatic seizure prophylactic [(10,11)]. However, a meta-analysis of 11 randomized controlled trials showed phenytoin significantly reduced early-phase post-traumatic seizures compared to placebo, but not significantly reduced late-phase seizures [18].

5. Conclusion

The usage of phenytoin is still not routinely given to post-traumatic head patients at RSIJ Cempaka Putih. The administration is carried out on a case-by-case basis assessment must be carried out in determining the use of phenytoin as a seizure prophylactic so that the benefits outweigh the side effects. For further research, it is recommended to conduct EEG examination on head trauma patients to determine the diagnosis of post-traumatic seizures / epilepsy and conduct further seizure evaluation.

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Conflict of Interest

The authors declare no conflicts of interest in preparing this article.

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