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ORIGINAL PAPER

The Incidence of Early Seizures in Non-Severe Traumatic Brain Injury Patients and the Efficacy of Prophylactic Antiepileptic Drugs

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Abstract

The incidence of early seizures (ES) in traumatic brain injury (TBI) ranges between 1 and 7%. However, the incidence of ES after a non-severe TBI (NSTBI) with traumatic hemorrhage (TH) is unknown. Moreover, the data about seizure prophylaxis (SP) in this population remains inconclusive. We aim to determine the incidence of ES in NSTBI and the efficacy of SP. We retrospectively reviewed all adult patients with NSTBI with evidence of a TH on presentation from 2015 to 2018 at Methodist University Hospital in Memphis TN. Patients with history of epilepsy or receiving antiseizure medications (ASM) were excluded. We collected demographic data, the type, severity, and mechanism of injury; the need for neurosurgical intervention (NSI); ES; and SP use. A total of 633 patients met our inclusion criteria; 94.4% had mild TBI; mean age was 70.5 years (SD 16.9); 55.0% were males; and 49.1% had subdural hematoma (SDH). Same level fall was the most common mechanism of injury in 79%. Forty patients (6.3%) had ES. After excluding seizures on presentation, 22 of 310 (7.1%) patients had an ES in the SP group (16 clinical) vs 5 of 310 (1.6%) in the non-prophylaxis group (all clinical) ($P=0.001$). Levetiracetam as SP was used in 83.5%. Patients with combined SDH and traumatic subarachnoid hemorrhage or with multicompartment hemorrhage were more likely to have ES than SDH alone ($p=0.02$ and 0.001, respectively). NSI was not a predictor for ES in our cohort. The incidence of ES (clinical and electrographic) in NSTBI with TH patients in our cohort is higher than previously reported in those with non-severe TBI. ES were reported more in the SP group, which might indicate a clinical selection bias giving more moderate TBI and multicompartmental hemorrhage patients receiving ASM for SP. However, prospective studies are required to further determine the predictors of ES in non-severe TBI and the effect of ASM for SP on outcomes and reducing ES in NSTBI patients.

Keywords Traumatic brain injury · Seizure prophylaxis · Post traumatic seizure

Introduction

In the United States, traumatic brain injury (TBI) is a serious public health concern that results in death and disability for thousands of people each year [1]. Post traumatic seizures (PTSs) are a recognized complication of TBI. PTSs

Topical Collection on *Medicine*

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are divided into early (ES), occurring within 7 days of brain injury, or late if occurring beyond 7 days post injury [2]. The International League Against Epilepsy defines post traumatic epilepsy (PTE) as one or more unprovoked seizures more than 7 days out of injury. Current recommendations for use of prophylactic antiseizure medications (ASM) as per the Brain Trauma Foundation (BTF) are only for early PTSs in the setting of severe TBI. The incidence of early PTS in severe TBI can be as high as 12% [3]. Prophylactic use of ASM is not recommended for prevention of late PTSs, even if risk factors are present [3–5].

PTSs have the potential of causing detrimental consequences including secondary brain injury, longer length of stay, chronic epilepsy, and even death [6], thus making early onset PTSs a strong predictor of adverse outcome in TBI patients. Mortality associated with generalized status epilepticus is high even in mild TBI. Still, the incidence of early PTS in non-severe TBI (NSTBI) with traumatic hemorrhage (TH) and the use of seizure prophylaxis (SP) in them is unknown. In this study, we sought to determine their incidence and the effect of SP on their outcome.

Methods

This is a single-center retrospective study conducted at the Methodist University Hospital in Memphis TN, USA. All adult patients who presented to the hospital from 2015 to 2018 with blunt NSTBI and computed tomography (CT) findings of epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intracerebral hemorrhage, and diffuse axonal injury were reviewed. All patients who had history of epilepsy or were taking ASM were excluded from the study. The study population was evaluated for clinical or electrographic seizures for the first seven post-admission days.

Other baseline characteristics that were collected include demographic data, type, severity and mechanism of injury, and the need for neurosurgical intervention. Primary outcomes measured were the occurrence of clinical or electrographic seizures in the first 7 days of TBI and the efficacy of seizure prophylaxis if given in preventing seizures.

Statistical Analysis

Baseline characteristics and descriptive statistics are presented as mean and standard deviations for continuous variables and as counts with percent for counts. Group comparisons were tested with a *t*-test for continuous variables and Fisher's exact test for categorical variables. The analysis was performed using R version 3.5.3, with a p-value < 0.05 considered statistically significant.

Results

A total of 834 subjects were screened, and we excluded those who met the criteria of severe TBI after review, patients without data regarding prophylaxis, patients who met the clinical criteria of mild TBI but had no evidence of TH on initial CT scan, and those with history of epilepsy and/or on ASM prior to admission were excluded. A total of 633 patients met these inclusion criteria. Seizures were present in 13 patients on presentation (2.1% of cases) who were further excluded resulting in a final study cohort of 620 patients.

Characteristics for the cohort who presented without seizures are in the accompanying table for the entire sample and based on whether they received prophylaxis. In the cohort, 94.4% had mild TBI, mean age was 70.7 (16.9), and 55.0% were males with no significant differences based on receiving prophylaxis (Table 1).

Early seizures developed in 22 of 310 (7.1%) patients who received prophylaxis, 16 of which were clinical. In the No prophylaxis group, 5 of 310 (1.6%) had seizures, all of which were clinical ($P = 0.001$). Levetiracetam as SP was used in 83.5%, while Phenytoin was used in 55 patients, and the rest of the prophylaxis group used another ASM mainly lacosamide. Patients with combined SDH and traumatic subarachnoid hemorrhage or with multicompartment hemorrhage were more likely to have ES than SDH alone ($p = 0.02$ and 0.001, respectively). NSI was not a predictor for ES in our cohort. SDH was the most common diagnosis in 49.7% of patients, though there were significant differences in the distribution of diagnoses based on receiving prophylaxis.

Discussion

Post traumatic seizures can occur early or late after brain injury. Seizures can increase cerebral metabolic demand, increase intracranial pressure, and increase cerebral edema. Early seizures have a higher risk of developing post traumatic epilepsy later in life.

SP has been routinely used to prevent early seizures in the acute phase after severe TBI [4]. In this study, we tried to determine if the use of SP would be beneficial in preventing seizures in non-severe TBI with TH. Another question which we tried to answer was to find the incidence of early seizures in this group of patients given the variability and the wide spectrum definition of TBI in general. Also, we believe that given the extensive use of electroencephalogram EEG monitoring in our center, our incidence of seizures will likely be higher than what

Table 1 Baseline characteristics with incidence of seizures in "No prophylaxis" group and "Prophylaxis" group

	All patients	No prophylaxis	Prophylaxis	*P* value
No. of patients	620	310	310	
Age	70.7 (16.9)	71.0 (16.1)	70.4 (17.7)	0.67
Gender				0.08
Female	279 (45.0%)	151 (48.7%)	128 (41.3%)	
Male	341 (55.0%)	159 (51.3%)	182 (58.7%)	
Diagnosis				0.0005
SDH	308 (49.7%)	143 (46.1%)	165 (53.2%)	
SDH + tIVH	1 (0.2%)	0 (0.0%)	1 (0.3%)	
EDH	18 (2.9%)	3 (0.1%)	14 (4.5%)	
tSAH	109 (17.6%)	76 (24.5%)	33 (10.6%)	
DAI	10 (1.6%)	6 (1.9%)	4 (1.3%)	
SDH + tSAH	72 (11.6%)	30 (9.7%)	42 (13.5%)	
Multicompartment	42 (6.8%)	15 (4.8%)	27 (8.7%)	
tSAH + contusions	24 (3.9%)	11 (3.5%)	13 (4.2%)	
tIVH	1 (0.2%)	1 (0.3%)	0 (0.0%)	
tICH	35 (5.6%)	25 (8.1%)	10 (3.2%)	
GCS				0.08
Mild	585 (94.4%)	298 (96.1%)	287 (92.6%)	
Moderate	35 (5.6%)	12 (3.9%)	23 (7.4%)	
Seizures	27 (4.4%)	5 (1.6%)	22 (7.1%)	0.001

was previously reported including non-convulsive seizures. The incidence of ES was 7.1% in patients receiving SP while it was 1.6% in the non-prophylaxis group of patients. Overall incidence of early seizures in our cohort with non-severe TBI with TH was 6.3% which is within the previously studied range for TBI in general regardless of the severity [3, 7]. However, it is higher than what was previously reported in patients with mild TBI only. And this is likely related to including those with electrographic seizures in our cohort and the use of EEG monitoring. Also, it is likely related to limiting our study to those who met the clinical criteria of mild TBI with a TH on their initial scan.

The patients who received ASM for SP were selected as per the treating clinician. This was usually done by the clinical assessment of the treating physician based on the type of intracranial injury and determining the risk for PTSs. There is no such documented protocol in our center for non-severe TBI to help selecting those for SP and that makes it difficult to study as to why some patients received ASM for SP while some did not. Levetiracetam was the ASM of choice in our cohort largely because of the better side effect profile, easier administration, and availability. We found that the incidence of seizures was higher in the SP group. This could indicate a selection bias here by the treating clinician. However, the incidence of seizures was in line with previously documented studies [7, 8]. This partly also could be related to the fact that SP group had more SDH, SD with tSAH, and multicompartmental TH which we found to be more predictive of ES. However, there was no statistical difference in all the subgroups. In addition, the SP group had more moderate TBI compared to the no SP 7.4% vs 3.9% respectively which was not statistically different as well.

ES were more likely to occur in patients who had multicompartmental TBI (SDH with tSAH etc.) rather than SDH alone. Neurotrauma in traumatic brain injury causes disruption of the blood–brain barrier causing neuronal hyperexcitabilty [9]. This leads to an epileptogenic focus and thus can explain the likelihood of ES in multicompartmental TBI which also reflects the degree of severity of the injury and the force, at times due to underlying coagulopathy. Neurosurgical intervention however was not found to be a predictor of early seizures in our study; this might be related to the variability in the neurosurgical intervention used to treat this patient cohort of NSTBI which varies between burr holes, subdural drains, external ventricular drains, craniotomy, and craniectomy. Those different surgical interventions carry variable risks of seizures which in this group are most likely related to the underlying injury rather than the intervention.

Our study is novel as there are not much data about the incidence of seizures in non-severe TBI, but it has some limitations. Firstly, despite the large sample size, it is a single-center retrospective study. Secondly, the decision of starting ASMs prophylactically was based on the clinician evaluation and we do not have documented protocol in non-severe TBI indicating a possibility for selection bias. Thirdly, EEG monitoring was not used in all the cohort, and it was used more in those patients with severe injury and those who

were suspected to have non-convulsive seizures giving the fluctuation in the clinical exam. Thus, the true rate of the non-convulsive seizures was not determined and could be far higher than that documented.

Conclusion

Overall, the incidence of ES in our cohort of non-severe TBI with TH was found to be 6.3% which is higher than what was previously reported in the non-severe TBI but falls within similar rates for all TBI patients regardless of the severity. However, we found more ES in those patients receiving ASM for SP. Therefore, more prospective studies are needed to assess the efficacy of these drugs and the practice for prescribing the ASM for SP needs to be reexamined.

Author Contribution Rashi Krishnan: UTHSC, Memphis TN; Designed and conceptualized the study, interpreted the data, drafted the manuscript for intellectual content

Yasser Khorchid: UTHSC, Memphis TN; Interpreted the data, revised the manuscript for intellectual content

Juan Goyanes: UTHSC, Memphis TN; Major role in the acquisition of data

Abhi Pandhi: UTHSC, Memphis TN; Major role in the acquisition of data

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Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate The retrospective study is in accordance with the ethical standards.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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