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Original Article

Multicenter and prospective trial of anti-epileptics for early seizure prevention in mild traumatic brain injury with a positive computed tomography scan

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ABSTRACT

Background: Posttraumatic seizures (PTSs) are a major source of disability after traumatic brain injury (TBI). The Brain Trauma Foundation Guidelines recommend prophylactic anti-epileptics (AEDs) for early PTS in severe TBI, but high-quality evidence is lacking in mild TBI.

Methods: To determine the benefit of administering prophylactic AEDs, we performed a prospective and multicenter study evaluating consecutive patients who presented to a Level 1 trauma center from January 2017 to December 2020. We included all patients with mild TBI defined as Glasgow Coma Scale (GCS) 13–15 and a positive head computed tomography (CT). Patients were excluded for previous seizure history, current AED use, or a neurosurgical procedure. Patients were given a prophylactic 7-day course of AEDs on a week-on versus week-off basis and followed with in-person clinic visits, in-hospital evaluation, or a validated phone questionnaire.

Results: Four hundred and ninety patients were enrolled, 349 (71.2%) had follow-up, and 139 (39.8%) were given prophylactic AEDs. There was no difference between seizure rates for the prophylactic AED group (0.7%) and those without (2.9%; $P = 0.25$). Patients who had a PTS were on average older (81.4 years) than patients without a seizure (64.8 years; $P = 0.02$). Seizure rate increased linearly by age groups: <60 years old (0%); 60–70 years old (1.7%); 70–80 years old (2.3%); and >80 years old (4.6%).

Conclusion: Prophylactic AEDs did not provide a benefit for PTS reduction in mild TBI patients with a positive CT head scan.

Keywords: Anti-epileptic medications, Anti-seizure medicine, Mild traumatic brain injury, Prophylaxis, Seizures

INTRODUCTION

Every year, 42 million people worldwide suffer a mild traumatic brain injury (TBI).[11] The consequences of mild TBI are often underappreciated, with some patients experiencing chronic headaches, cognitive dysfunction, and an inability to return to work.[3,8] Mild TBI accounts for over 75% of TBI and accounts for $17 billion dollars of health care and lost productivity cost in the U.S. alone.[9] The average patient with mild TBI loses an average of 4 weeks of work productivity and nearly one-third of patients have not returned to work at 3 months.[2] Posttraumatic seizures (PTSs) are a common complication after head injury, occurring in up to 25% of brain injury patients.[23,24] PTSs are commonly classified as early (within 7 days of injury) and late (>7 days after injury). An early PTS increases the risk of a late PTS and subsequently the development of epilepsy.[17,21] In severe TBI, prophylactic antiepileptics (AEDs) have been shown to decrease the incidence of early PTS, although it does not lead to improved long-term outcomes.[6,7,21] The Brain Trauma Foundation recommends the use of prophylactic AEDs for early PTS prevention in severe TBI.[5]

The benefits of prophylactic AEDs in mild TBI are unknown[7] and consistent recommendations for prophylactic AEDs do not exist.[10] A recent Cochrane review concluded that there is a low-quality evidence that early treatment with AEDs reduces early PTS among all TBI subtypes.[22] Few studies have specifically evaluated early PTS in mild TBI and existing studies are flawed by their retrospective nature, single-center nature, or lack of randomization.[4,7,14,18] Despite the lack of data for the benefit of prophylactic AEDs, many practitioners routinely prescribe prophylactic AEDs for mild TBI.[13,14,19]

Although there is a lack of evidence for the use of AEDs, mild TBI patients may still benefit from prophylactic AED use. Seizures account for an large portion of emergency room visits and readmissions after TBI.[16] The incidence of PTS among all mild TBI patients, defined as TBI with a GCS of 13–15, is reported ranging from 0.3% to upward of 4%.[4,15,17] Patients with a positive computed tomography (CT) head scan may have increased risk for early PTS, making prophylactic AEDs more effective.

To address this shortcoming, we performed a study to prospectively evaluate the incidence and effectiveness of prophylactic AEDs in mild TBI patients with a positive CT head scan in a prospective and multicenter setting.

MATERIALS AND METHODS

Data collection

Consecutive mild TBI patients older than 18 years old with acute intracranial blood were prospectively collected at two Level 1 trauma centers. Our observational study recruited patients from January 2017 to February 2019 at Mercy Hospital of the University of Pittsburgh Medical Center and from January to December 2020 at Cooper University Hospital. Patients were excluded from this study for a previous seizure history, current use of AEDs (i.e., mood stabilizer or for trigeminal neuralgia), or a neurosurgical procedure before or within 7 days of TBI. Both institutions received approval to complete this study as a quality improvement project.

The primary outcome was the effect of prophylactic AEDs on the rate of early PTS within 7 days of the trauma date. All trauma patients with a GCS 13–15 and intracranial blood on CT head scan received prophylactic AEDs on a week-by-week basis based on the day of admission. Patients who received AEDs at outside facilities before transfer were included in the cohort that received AED prophylaxis. Advanced practice providers, neurosurgery residents, and medical students collected the results but were blinded to the analysis completed by a statistician. Secondary outcomes included risk factors for seizure, overall incidence of early PTS, and a *post hoc* power analysis.

An inpatient seizure was defined as any witnessed seizure activity confirmed by the treating clinical team to be a seizure or a positive EEG, both of which were adjudicated by a neurologist blinded to the study. A positive EEG was defined as the neurologist reading the EEG stating an electrographic seizure occurred. Patients with seizures before arrival at the hospital were prescribed AEDs for therapeutic intent and excluded from this study.

Patient demographic, radiological, and follow-up information was collected by neurosurgery care providers. All patients were screened for alcoholism and an EtOH level was obtained in the emergency room. A neurosurgery resident physician or advanced care provider recorded a GCS for every patient within 24 h of admission. CT head scans were reviewed for the presence of subarachnoid hemorrhage (SAH), subdural hematoma (SDH), epidural hematoma (EDH), contusion, intraventricular hemorrhage (IVH), or skull fracture by a radiologist. Patients were either called or their hospital charts reviewed at 7-day posttrauma, depending on their admission status at the time. All patients were instructed to follow up 30 days after presentation. For patients who did not follow up in the outpatient office, three attempts were made to call the patient and speak with them. Patients were screened for seizures using a modification of a validated questionnaire.[20] Patients with a positive screen were further evaluated for seizures by the treating clinical team.

Statistical analysis

Statistical analysis was performed using *R package* (*version* 3.2.3), MATLAB version 2020b (MathWorks, Natick, MA), and G*Power (version 3.1.9.4) as needed. *P*-values were calculated using Fisher's exact test, Chi-squared test, and Wilcoxon rank-sum test as appropriate. We performed a *post hoc* power analysis assuming two independent study groups and measured Cohen's w effect size for a Chi-squared goodness-of-fit test.[1] $P < 0.05$ was considered statistically significant.

RESULTS

Five hundred and forty-eight patients who presented with a mild TBI and a positive CT head were entered into the study database. Patients were excluded for seizure history (39), craniotomy before or within 7 days of TBI (15), or AED use (4). Four hundred and ninety patients remained after exclusion [Figure 1]. Of these, 349 had follow-up at 7 days (71.2%) with 139 receiving prophylactic AEDs (39.8%). One hundred and thirty-seven patients received levetiracetam (98.6%). One patient in the AED group had a seizure (0.7%), while six in the no AED group had a seizure (2.9%; odds ratio 4.0; 95% confidence interval: 0.5–33.4; $P = 0.25$). The number needed to treat (NNT) was 46.7 to prevent an early PTS with prophylactic AEDs.

Among those with 7-day follow-up, demographic, clinical, and radiographic information is listed in [Table 1]. None of the seven patients with a documented seizure either drank on the day of admission or had a history of alcohol use. All of these patients sustained a ground level fall ($P = 0.64$) and one patient passed away within 7 days ($P = 0.09$), neither of which were significantly different than the nonseizure group. Overall, 74% of patients in our study had a ground level fall. When stratifying by age, falls accounted for 96.5% of injuries in the >80-year-old group, 84.9% in the 70–79 group, 77.2% in the 60–69 group, and 48.7% in the <60 group. Elderly patients, when stratified by age groups, were significantly more likely to fall than patients <60 years old [$P < 0.001$ for each age group >80, 70–79, and 60–69 compared to <60 years old; Table 2]. The radiographic patterns of injury were similar to the nonseizure group for traumatic SAH (tSAH; 57%), SDH; 71%, EDH; 0%, contusion (14%), intraventricular hemorrhage (0%), and skull fracture (0%).

Patients who had a PTS were on average older (81.4 years) than patients without a seizure (64.7 years) regardless of AED use ($P = 0.02$). The seizure rate linearly increased by age groups: <60 years old (0%); 60–70 years old (1.7%); 70–80 years old (2.3%); and >80 years old [4.6%; Figure 2].

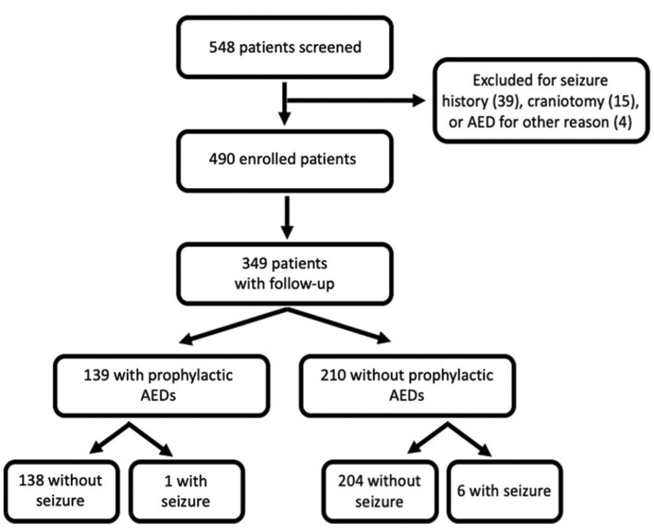

Figure 1: Consort diagram.

Table 1: Demographic information of patients with 7-day follow-up.

Patient characteristics	Without seizure	With seizure	*P*=value
Number of patients	342	7	
Age (years)	64.7	81.4	**0.025**
Mechanism of injury (*n*)			
Fall	251	7	0.641
Motor vehicle	63	0	
Assault	17	0	
Penetrating	1	0	
Other/unknown	10	0	
GCS	14.6	14.4	0.327
Alcoholic (%)	12% (40/342)	0% (0/7)	1
Intoxicated	13% (45/342)	0% (0/7)	0.602
CT characteristics			
tSAH	57% (194/342)	57% (4/9)	1
SDH	50% (171/342)	71% (5/7)	0.448
EDH	4% (12/342)	0% (0/7)	1
Contusion	25% (85/342)	14% (1/7)	0.686
IVH	6% (19/342)	0% (0/7)	1
Skull fracture	18% (60/342)	0% (0/7)	0.610
Died within 7 days (*n*)	4	1	0.097

RED indicates significance

Table 2: Seizure risk stratified by age group.

Age	Seizures (No.)	AEDs	Overall	PTS %	GLF %
>80	4	29	87	4.6	**96.5**
70–79	2	38	86	2.3	**84.9**
60–69	1	15	57	1.7	**77.2**
<60	0	57	119	0.0	48.7

Effect of prophylactic AEDs for early PTS reduction all $P>0.15$ with each age group. When comparing rates of group level fall by age group (i.e., >80, 70–79, and 60–69), **RED** indicates statistical significance ($P<0.001$) compared to<60 age group

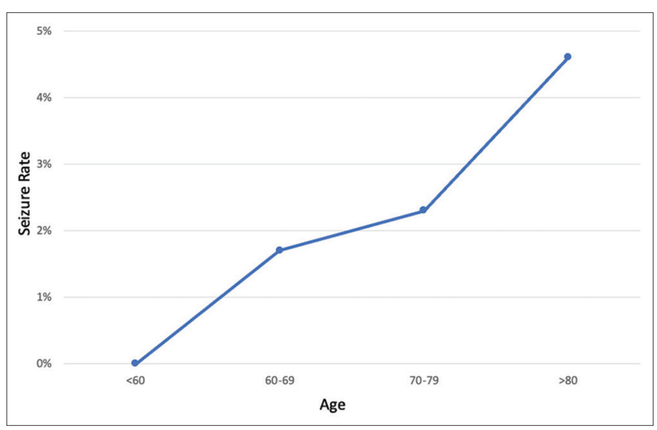

Figure 2: Overall seizure risk stratified by age group.

Among patients >80 years old, the rate of seizures without prophylactic AEDs was 6.9% (0% for those with prophylactic AEDs). The effect of prophylactic AEDs was not significant within any age subgroup.

Although patients were assigned prophylactic AED use on a week-by-week basis, several cofounders were noted when stratifying by prophylactic AED groups. The rates of cerebral contusions (p=0.03) and skull fractures [P = 0.01; Supplementary Table 1] are known risk factors for PTS and were higher in the prophylactic AED group.[10] Despite this, the prophylactic AED group did have an increased seizure risk. tSAH (P = 0.02) was also increased in the prophylactic AED group. GCS was 0.2 points lower (P < 0.01), a clinically insignificant finding.

DISCUSSION

A paucity of data exists in the literature describing the early PTS rates or effectiveness of prophylactic AEDs in mild TBI despite the large prevalence, societal impact, and cost. Neurosurgeons at many centers prescribe prophylactic AEDs in mild TBI[13,14,18,23,25] by extrapolating data from severe TBI to mild TBI.[21] Seizures in mild TBI, however, occur much less frequently than in severe or moderate TBI.[13,18,21,23]

The quality of data for seizure prophylaxis in mild TBI is low.[12] Wat *et al*. performed a systematic literature review and meta-analysis in 2019 of the effectiveness of AEDs for seizure prevention in all TBI subtypes and only identified two retrospective studies that included mild TBI.[23] Two subsequent retrospective papers have reported increased incidence of early PTS in patients without AEDs that did not reach statistical significance.[4,13] All of these studies had low numbers of mild TBI patients (<500 total) and had overall incidence rates of 0.7–3.2%.[4,13]

We completed a multicenter and prospective trial evaluating the effects of prophylactic AEDs in mild TBI to address these shortcomings. Our study failed to find a benefit for prophylactic AEDs in reducing early PTS. We prospectively reported the incidence of early PTS at 2.0% overall, 2.9% without prophylactic AEDs, and 0.7% with prophylactic AEDs. With a NNT of 46.7, providers have a better understanding of the risk-benefit ratio for prophylactic AEDs in mild TBI.

Among our secondary outcomes, we found a significant difference in age between patients who had a seizure and those who did not have a seizure (P = 0.02). The seizure rate linearly increased when stratifying patients by age [Figure 2]. In the era of personalized medicine, prophylactic AEDs for early PTS may not be a one-size-fits all approach and, instead, elderly patients may have a larger benefit. Providers could consider treating patients older than 60 with prophylactic AEDs, as no patients under 60 had an early PTS in our study. Among patients who had a seizure, all had a ground level fall as the mechanism of injury, a low impact mechanism associated with the elderly. Falls accounted for 96.5% of injuries in the >80 age group and decreased in younger patients. With an increasingly ageing population, our study highlights how minor injuries can have increased risks for negative consequences such as TBI and PTS. Effective methods to screen elderly patients for falls may reduce the risks of mild TBI in this patient population.

Our study has several weaknesses. Mainly, on a *post hoc* power analysis, we were underpowered to detect a benefit for prophylactic AEDs based on our effect size. Another weakness is our failure to identify radiographic features correlated with seizures such as brain contusions and skull fractures.[10]

CONCLUSION

In a multicenter and prospective study evaluating the effectiveness of prophylactic AEDs in early PTS for mild TBI patients, we were underpowered to find a benefit for prophylactic AEDs for early PTS rates. Patients who had seizures tended to be older, which can help guide personalized treatment decision.

Data availability

Data will be made available to qualified researchers on request.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY TABLE

Supplementary Table 1: Study confounders by AED prophylaxis groups.

Patient characteristics	AED	Without AED	*P*-value
Number of patients	139	210	
Age (years)	62.3	66.8	0.07
Mechanism of injury (*n*)			
Fall	101	157	0.22
Motor vehicle	24	39	
Assault	6	11	
Penetrating	1	0	
Other/unknown	7	3	
GCS	14.5	14.7	**0.01**
Alcoholic (%)	14%	10%	0.16
Intoxicated	15%	11%	0.25
CT characteristics			
tSAH	65%	52%	**0.02**
SDH	55%	48%	0.19
EDH	4%	3%	0.55
Contusion	31%	21%	**0.04**
IVH	5%	4%	0.45
Skull fracture	24%	13%	**0.01**
Died within 7 days (*n*)	3	2	0.39

RED indicates statistical significance