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ORIGINAL ARTICLE

Preventing epilepsy after traumatic brain injury: A propensity score analysis

Jaw-Horng Liou[a,b], Yen-Lin Chang[a], Hsu-Tung Lee[c,d], Ming-Fen Wu[a], Yu-Chi Hou[b], Wen-Shyong Liou[a,b,*]

[a]Department of Pharmacy, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; [b]School of Pharmacy, China Medical University, Taichung, Taiwan, ROC; [c]Department of Neurosurgery, Neurology of Institute, Taichung Veterans General Hospital, Taichung, Taiwan, ROC; [d]Cancer Prevention and Control Center, Taichung Veterans General Hospital, Taichung, Taiwan, ROC

Abstract

Background: Due to the potential consequences of post-traumatic epilepsy (PTE) exacerbating secondary injury following traumatic brain injury (TBI), the use of antiepileptic drugs (AEDs) is an accepted option for seizure prophylaxis. However, there is only a paucity of data that can be found regarding outcomes surrounding the use of AEDs. The purpose of this retrospective study is to evaluate whether the prophylactic administration of AEDs significantly decreased the incidence of PTE, when considering the severity of TBI.

Methods: All trauma patients who had been newly diagnosed with TBI from January 1, 2010 to December 31, 2017 were retrospectively analyzed. Statistical comparisons were made using the chi-square test, Mann-Whitney *U* test, and Cox regression modeling. After excluding any exposed subjects with no appropriate match, patients who had received AED prophylaxis were matched by propensity score with those who did not receive AEDs. All of the TBI populations were followed up until June 30, 2018.

Results: We identified 1316 patients who met the inclusion and exclusion criteria in our matched cohort through their propensity scores, where 138 patients had been receiving prophylactic AEDs and 138 patients had not. Baseline characteristics were similar in gender, age, Glasgow Coma Scale (GCS) scores, and risk factors of PTE including skull fracture, chronic alcoholism, subdural hematoma, epidural hematoma, and intracerebral hematoma. After adjusting for those risk factors, the relative incidence of seizure was not statistically significant in either of the groups ($p = 0.566$).

Conclusion: In our cohort analysis, AED prophylaxis was ineffective in preventing seizures, as the rate of seizures was similar whether patients had been receiving the drugs or not. We therefore concluded that the benefits of routine prophylactic anticonvulsant therapy in patients with TBI need to be re-evaluated.

Keywords: Anticonvulsants; Brain injuries, traumatic; Epilepsy, post-traumatic

1. INTRODUCTION

Traumatic brain injury (TBI) brings upon many consequences including mortality, various disabilities, and neurological deficits, while also being identified as a major cause of adult post-traumatic epilepsy (PTE).[1–5] Epilepsy has been classified into both early PTE (occurring in the first 7 days of trauma) and late PTE (occurring >7 days after experiencing trauma). Depending on the severity of the initial TBI and various study designs, the prevalence of PTE has shown itself to have extensive differences.[6–8] The cumulative incidence rate of PTE after TBI over the past 30 years is 2% for mild injuries, 4% for moderate injuries, and more than 15% for severe injuries.[6]

The consequences of epilepsy include hanging awareness/behavior, abnormal movements, and social disability, all of which can cause both personal and social burdens. Patients who suffer from PTE are also strongly associated with a high risk of mortality, compared with TBI patients who have not experienced PTE.[9,10]

In a randomized study, TBI patients were administered phenytoin (PHE) versus a placebo over the course of 1 year, with analyses performed during a 2-year follow-up.[11] Although it had no impact on late PTE, treatment with PHE decreased the early seizure rate significantly, dropping it from 14.2% down to 3.6% ($p < 0.001$). Based heavily on this result, the Traumatic Brain Injury Guidelines from the Brain Trauma Foundation recommends administering PHE for the purpose of decreasing the incidence of early PTE.[12]

Due to the incidence rates of PTE and concern about its possible consequences, many hospitals have initiated routine prophylactic administration of antiepileptic drugs (AEDs) following TBI. However, the use of these drugs may be prescribed for >7 days, which is above the guideline's recommendation.[12,13] Unfortunately, the available evidence on seizure prophylaxis with AEDs remains insufficient.[14] In addition, there are other notable risk factors which need to be considered when evaluating epilepsy following TBI, including cortical contusion, skull fracture, chronic alcoholism, post-traumatic amnesia, subdural hematoma (SDH), epidural hematoma (EDH), intracerebral hematoma (ICH), and most importantly, the severity of the

*Address correspondence. Dr. Wen-Shyong Liou, Department of Pharmacy, Taichung Veterans General Hospital, 1650, Taiwan Boulevard Section 4, Taichung 407, Taiwan, ROC. E-mail address: wlschna.liou@gmail.com (W.-S. Liou).

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patient's TBI, all of which would complicate the consequences of TBI.[15–17] However, the severity of a patient's TBI is not included in most of the available claim data (such as the National Health Insurance claim data in Taiwan). Therefore, it is reasonable to consider having the severity of TBI be included in order to evaluate the consequences of TBI. The Glasgow Coma Scale (GCS), for example, has been used extensively to classify TBI into various levels of severity and prognosis.[12,18]

The purpose of this observational study was to evaluate whether clinical routine prophylactic administration of AEDs will affect the incidence of PTE (early, late, or cumulative), once the severity of a patient's TBI has been considered, as well as evaluating other important risk factors.

2. METHODS

2.1. Patient population and data source

Patients with newly diagnosed TBI during both inpatient and emergency settings from January 1, 2010 to December 31, 2017 were included in this study, which was held within a medical center in Central Taiwan. Patients were excluded if they had had a previous diagnosis of TBI, brain tumor, stroke, epilepsy, or had previously received AEDs prior to the diagnosis of TBI. We also excluded patients who had died or had a history of epilepsy prior to using AEDs during hospitalization for newly diagnosed TBI. Patient follow-up began on the date of their first TBI diagnosis and ended on the date of PTE or the end of the study (June 30, 2018). The study was approved by the Institutional Review Board of Taichung Veterans General Hospital, Taiwan.

In this retrospective, population-based, 8-year cohort study, we obtained delinked data, including patient demographics (age, gender), GCS score, history of seizures, and mortality, from the electronic medical record database. The severity of TBI was grouped according to each patient's GCS score which was determined on the closed date of their TBI diagnosis after admission, where a score of 13 to 15 was categorized as mild TBI, a score of 9 to 12 as moderate TBI, and a score of 3 to 8 as severe TBI. The codes of the ninth and tenth editions of the *International Classification of Diseases*, Clinical Modification (ICD-9-CM and ICD-10), were applied to define the diagnosis of TBI, brain tumor, stroke, and epilepsy which needed to be identified within the population. The PTE-related risk factors, which included cortical contusion, skull fracture, chronic alcoholism, SDH, EDH, and ICH, were also collected.

2.2. Statistical analysis

The data are expressed as counts and proportions for categorical variables, as well as mean and standard deviation for continuous variables. The chi-square test, Fisher's exact test, and Mann-Whitney *U* test were used for categorical and continuous variables, in order to compare the characteristics between the TBI patients who had or had not been administered AEDs. For assessment on the effect of prophylaxis on the hazard ratio (HR) of seizure occurrence, 95% confidence intervals (CI) were calculated in both univariate and multivariate Cox regression models, which were then adjusted for potential confounders (Table 1). Statistical significance was defined as a p value of <0.05. All analyses were performed using SPSS version 22.0 (IBM, New York, NY, USA).

After excluding patients who possessed no GCS score data, there remained 1316 patients enrolled in this study. We matched age, gender, GCS. and potential confounders including chronic alcoholism, cortical contusions, skull fractures, SDH, EDH, and ICH by their propensity scores, in order to acquire a one-to-one ratio with patients who did or did not receive any AED prophylaxis. To better understand the effect of AEDs prophylaxis in the different severity levels of TBI patients, we also stratified the prophylaxis group (n = 209) from the overall population who had provided GCS score data (n = 1316) into three different severity groups by using the initial definition of GCS score groups and subsequently used the same propensity score approach to match the non-AED groups. The primary outcomes were the incidence of PTE and overall mortality. The secondary outcome was overall mortality rate.

Table 1

Demographics of traumatic brain injury patients (n = 1316)

	Non-prophylaxis (n = 1107)	Prophylaxis (n = 209)	Total (n = 1316)	*p*
Baseline characteristics				
Gender[a]				<0.001**
Female	507 (45.8%)	52 (24.9%)	559 (42.5%)	
Male	600 (54.2%)	157 (75.1%)	757 (57.5%)	
Age[b]	40.3 ±23.1	53.2 ±24.1	42.4 ±23.8	<0.001**
Age[a]				<0.001**
≤65	903 (81.6%)	128 (61.2%)	1031 (78.3%)	
>65	204 (18.4%)	81 (38.8%)	285 (21.7%)	
Initial GCS score[b]	14.2 ±2.1	12.7 ±3.3	14.0 ±2.4	<0.001**
Initial GCS score[a]				<0.001**
13-15	990 (89.4%)	140 (67.0%)	1130 (85.9%)	
9-12	66 (6.0%)	41 (19.6%)	107 (8.1%)	
3-8	51 (4.6%)	28 (13.4%)	79 (6.0%)	
Risk factor for PTE				
Cortical contusion[a]	0 (0%)	0 (0%)	0 (0%)	...
Skull fracture[a]	100 (9.0%)	44 (21.1%)	144 (10.9%)	<0.001**
Chronic alcoholism[c]	0 (0.0%)	1 (0.5%)	1 (0.1%)	0.159
Subdural hematoma[a]	62 (5.6%)	74 (35.4%)	136 (10.3%)	<0.001**
Epidural hematoma[c]	4 (0.4%)	9 (4.3%)	13 (1.0%)	<0.001**
Intracerebral hematoma[a]	90 (8.1%)	72 (34.4%)	162 (12.3%)	<0.001**
Outcome				
PTE[a]	20 (1.8%)	16 (7.7%)	36 (2.7%)	<0.001**
PTE group (n = 36)[c]				0.024*
Early PTE	6 (30.0%)	0 (0%)	6 (16.7%)	
Late PTE	14 (70.0%)	16 (100%)	30 (83.3%)	
Death[a]	34 (3.1%)	15 (7.2%)	49 (3.7%)	0.007**

Continuous data are expressed as mean ± SD.
Categorical data are expressed in number and percentage.
GCS = Glasgow Coma Scale; PTE = post-traumatic epilepsy.
[a]Chi-square test.
[b]Mann-Whitney *U* test.
[c]Fisher's exact test.
*$p < 0.05$; **$p < 0.01$.

3. RESULTS

The flow chart of patient selection is presented in the Fig. 1. There were 3973 patients who met the TBI diagnosis criteria in this retrospective cohort study. This total came about after the exclusion of all patients who provided no GCS score data, as well as the 209 patients who had had AEDs prophylaxis and the 1107 patients who had experienced no AED prophylaxis. The mean age of the subjects was 42.4±23.8 years and 57.5% were male, with the majority of TBI patients suffering from mild TBI (85.9%). The median of the initial GCS score assessment timing was 0 (range: 0–7 days). The overall seizure rate was 2.7%, and the all-cause mortality rate was 3.7%. Other than chronic alcoholism, all characteristics were significantly different statistically (Table 1). A total of 276 patients were included for further analysis after propensity score matching was completed. The number of subjects in the AED prophylaxis group

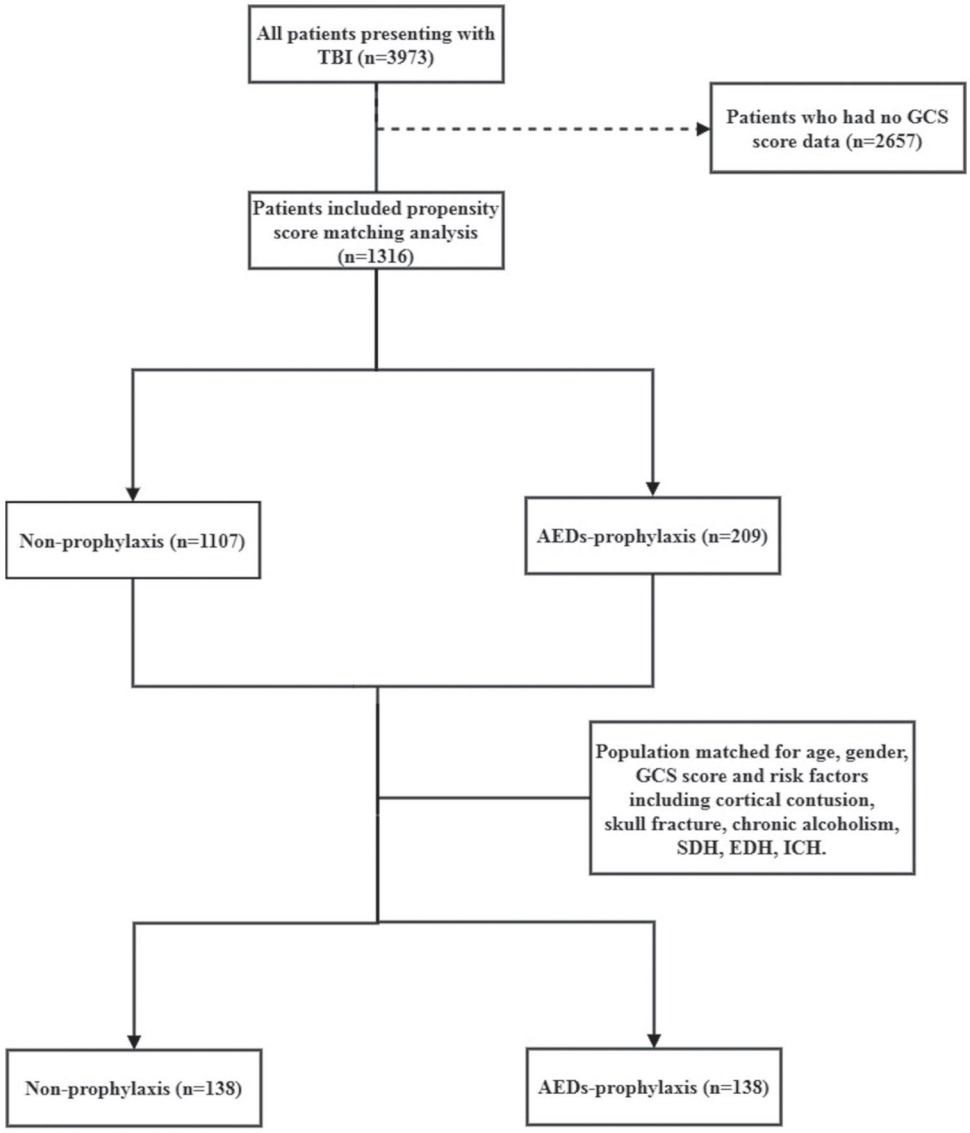

Fig. 1 Flowchart for subject selection. AEDs = antiepileptic drugs; EDH = epidural hematoma; GCS = Glasgow Coma Scale; ICH = intracerebral hematoma; SDH = subdural hematoma; TBI = traumatic brain injury.

(PP group) and non-prophylaxis group (NP group) was squared. Baseline characteristics were not statistically significant between the two groups (Table 2). AED prophylaxis did not offer any statistical difference in the seizure rates between the two groups (3.6% vs 5.1%, respectively; $p > 0.05$). Because there were no patients in the prophylaxis group who had experienced early PTE, the AED prophylaxis effect can only provide an estimation on overall incidence (Table 2). After adjusting for age, gender, severity of injury, and potential risk factors, the incidence of seizures between the two groups was not statistically different ($p = 0.566$). In the AED prophylaxis group, the result revealed that a longer duration of administration was not a significant predictor of seizure risk ($p = 0.417$). Similarly, all-cause mortality was also not significantly different in those receiving prophylactic AEDs (Table 3). The administration of preventive AEDs did not offer any benefit to PTE, regardless of the severity of TBI (Table 4).

4. DISCUSSION

This retrospective cohort analysis has revealed that the administration of prophylactic AEDs after TBI is not associated with a significant change in seizure incidence or all-cause mortality. Our results show that early PTE did not occur in the AEDs prophylaxis group, either in moderate or severe head injury group. This was compatible with the findings that PHE decreased the incidence of early post-traumatic seizures as seen in a previous study.[11] However, we were not able to differentiate the results on what impact AEDs prophylaxis has on early and late PTE attacks in multiple variates analysis, due to the reason that early PTE did not occur in the AEDs prophylaxis group. In this study, we regard both early and late PTE to be one PTE indicator representing the overall incidence rate. Our results were consistent after adjusting for potential confounders, including severity of injury (by GCS groups), previous cortical contusions, skull fractures, chronic alcoholism, SDH, EDH, and ICH ($p = 0.566$). The duration of AEDs administration did not affect seizure occurrence.

Table 2

Demographics of traumatic brain injury patients after propensity score matching (n = 276)

	Non-prophylaxis (n = 138)	Prophylaxis (n = 138)	Total (n = 276)	*p*
Baseline characteristics				
Gender[a]				1.000
Female	38 (27.5%)	38 (27.5%)	76 (27.5%)	
Male	100 (72.5%)	100 (72.5%)	200 (72.5%)	
Age[b]	52.7 ±24.3	52.8 ±24.1	52.8 ±24.2	0.987
Age[a]				1.000
≤65	82 (59.4%)	83 (60.1%)	165 (59.8%)	
>65	56 (40.6%)	55 (39.9%)	111 (40.2%)	
Initial GCS score[b]	13.5 ±3.0	13.4 ±2.9	13.4 ±3.0	0.755
Initial GCS score[a]				0.725
13-15	110 (79.7%)	110 (79.7%)	220 (79.7%)	
9-12	16 (11.6%)	13 (9.4%)	29 (10.5%)	
3-8	12 (8.7%)	15 (10.9%)	27 (9.8%)	
Risk factor for PTE				
Cortical contusion[a]	0 (0%)	0 (0%)	0 (0%)	...
Skull fracture[a]	23 (16.7%)	23 (16.7%)	46 (16.7%)	1.000
Chronic alcoholism[c]	0 (0.0%)	1 (0.7%)	1 (0.4%)	1.000
Subdural hematoma[a]	32 (23.2%)	32 (23.2%)	64 (23.2%)	1.000
Epidural hematoma[c]	1 (0.7%)	1 (0.7%)	2 (0.7%)	1.000
Intracerebral hematoma[a]	43 (31.2%)	43 (31.2%)	86 (31.2%)	1.000
Outcome				
PTE[a]	5 (3.6%)	7 (5.1%)	12 (4.3%)	0.768
PTE group (n = 12)[c]				0.152
Early PTE	2 (40.0%)	0 (0.0%)	2 (16.7%)	
Late PTE	3 (60.0%)	7 (100.0%)	10 (83.3%)	
Death[a]	9 (6.5%)	10 (7.2%)	19 (6.9%)	1.000

Continuous data are expressed as mean ± SD.
Categorical data are expressed in number and percentage.
GCS = Glasgow Coma Scale; PTE = post-traumatic epilepsy.
[a]Chi-square test.
[b]Mann-Whitney *U* test.
[c]Fisher's exact test.

Table 3

Effect of antiepileptic drugs prophylaxis used on post-traumatic epilepsy and mortality in traumatic brain injury patients (n = 276)

	Univariate analysis		Model adjusting for GCS score, gender, age, and risk factors[a]	
	HR 95% CI	*p*	HR 95% CI	*p*
PTE				
AED administration	0.63 (0.18-2.24)	0.478	0.17 (0.02-1.36)	0.096
AED duration (n = 138)	1.00 (1.00-1.01)	0.428	1.00 (1.00-1.01)	0.417
Death				
AED administration	1.03 (0.41-2.59)	0.955	1.06 (0.42-2.68)	0.902
AED duration (n = 138)	1.00 (1.00-1.01)	0.809	1.00 (1.00-1.01)	0.196

AED = antiepileptic drugs; GCS = Glasgow Coma Scale; HR = hazard ratio; PTE = post-traumatic epilepsy.
[a]Risk factors included skull fracture, subdural hematoma (SDH), epidural hematoma (EDH), and intracerebral hematoma (ICH).

Table 4

Effect of antiepileptic drugs prophylaxis used on post-traumatic epilepsy in different severity levels of traumatic brain injury patients (n = 418)

	Univariate analysis		Model adjusting for GCS score, gender, age, and risk factors[a]	
	HR (95% CI)	*p*	HR (95% CI)	*p*
GCS 3-8 (n = 56)				
Non AED-prophylaxis	Ref.		Ref.	
AED-prophylaxis	6.58 (0.79-54.65)	0.081	3.56 (0.39-32.23)	0.259
GCS 9-12 (n = 82)				
Non AED-prophylaxis	Ref.		Ref.	
AED-prophylaxis	67.35 (0.05-89 557.36)	0.251		
GCS 13-15 (n = 280)				
Non AED-prophylaxis	Ref.		Ref.	
AED-prophylaxis	1.01 (0.29-3.48)	0.990	1.06 (0.30-3.67)	0.931

AEDs = antiepileptic drugs; GCS = Glasgow Coma Scale; HR = hazard ratio.
In the group with GCS scores from 9 to 12, we omitted data because the sample size was too small to estimate correctly.
[a]Risk factors included skull fracture, subdural hematoma (SDH), epidural hematoma (EDH), and intracerebral hematoma (ICH).

This phenomenon has also been seen in other studies. The efficacy of routine prophylactic use of AEDs in patients with TBI did not reveal any significant differences when compared with patients who had been given a placebo during randomized control trials.[11,19] Previous retrospective studies and systematic reviews which specifically evaluated prophylactic AED therapy failed to demonstrate a clear benefit on the prophylactic use of AEDs after TBI.[20,21] A Cochrane systematic review also found insufficient evidence to support the routine use of prophylactic AEDs.[14]

Due to their therapeutic effect, AEDs may be affected by different AED choices and dosage; we therefore analyzed 181 patients who were administered the same AEDs throughout the entire study period as taken from the original population (n = 1,316). The median of each AED daily dose was slightly lower than the defined daily doses, after considering different dosage forms and oral bioavailability. This may be due to the majority of the TBI patients having CGS scores which were categorized as minor injury. After comparing the patients' prescribed PHE, carbamazepine, valproic acid, and levetiracetam with the non-AED prophylaxis group, we found no statistical difference in the risk of PTE occurrence. Some randomized controlled trials and cohort studies have evaluated the pharmaceutical effects of PTE control in TBI patients and found a similar trend that the results were not statistically different.[22–26] In our study, we integrated all of the AEDs which patients had been given prior to a seizure attack into one group, regardless of which drugs or dosage forms were administered.

PTE may reduce the available oxygen to the brain, change the brain's metabolic status, and raise the pressure within the intracranial space causing damage.[27] Thus, people who suffer more severe head trauma are more likely to be given anticonvulsant medications as a precaution against seizures.[28] The incidence rate of PTE increases with the severity of TBI.[29] Severe TBI patients tend to use AED prophylaxis for both clinical and practical considerations. However, the lack of TBI severity data may make it difficult to avoid selection bias.

Although the severity of TBI remains an important risk factor, few retrospective cohort studies consider it and adjust its data into their analyses, which may inappropriately present skewed results, due to the better prognosis given to mild TBI patients.[20,30] Other retrospective cohort study subgroup analysis has mentioned that patients with more severe TBI suffer a higher incidence of PTE, but these studies have failed to adjust the severity of TBI on odds ratio analyses.[31] In a population-based study with Taiwanese TBI patients from the National Health

Insurance Research (NHIR) database, the author observed that PTE patients who were prescribed more AEDs were associated with a higher mortality risk than those who had been administered none or only one AED.[32] However, this study was not able to obtain the severity levels of TBI for this to be adjudicated. Therefore, these results may be inconclusive.

Whether patients with TBI receive AEDs prophylaxis or not is based on a clinical judgment, where it is difficult to avoid selection bias. In this study, we performed a propensity score methodology to match both groups using related confounders, particularly on the severity of TBI through use of their GCS score. We believe this method could have reduced the possibility of selection bias in this retrospective cohort study, thus increasing the reliability of the results. In addition, due to the retrospective study design, we were able to follow up the eligible cases until either the date of PTE or the end of study, which allowed us to have a more complete tracking time. In this study, we excluded more than half of the patients due to the fact that they did not have a GCS score. However, to ensure research quality, we did analyze patients who had dropped out from our study population and found that they had experienced no difference in seizure incidence (study population vs drop-out population = 4.3% vs 2.3%, respectively; $p = 0.065$). After analyzing the effect of the AEDs prophylaxis in different severity groups of TBI patients, and determining that there was no statistical difference, it is reasonable to conclude that AEDs administration did not provide any additional benefits for PTE, regardless of the severity of TBI.

There were several limitations which should be addressed in this study. First, we were not able to access a patient's medical records if they were seeking medical care for a seizure attack which occurred outside of our hospital. Therefore, the incidence of PTE could be underestimated. Second, we enrolled only patients with TBI who were receiving either emergency or inpatient care. Thus, the overall number of patients may be underestimated. However, patients with TBI who were receiving outpatient care may have only been experiencing mild TBI, which may not have affected the overall results of this study. Finally, there were no patients in the prophylaxis group who had experienced early PTE, which limits the ability to assess the differences between early and late PTE prophylaxis. All of these limitations indicate that the sample size should be expanded for the purpose of further investigation. The NHIR in Taiwan includes details of each patient's medical records which help to identify the severity of TBI. A long-term cohort study using Taiwan's NHIR database should be conducted in order to clarify the effects of AEDs prophylaxis in TBI, considering the severity of the condition.

In conclusion, we have observed that the administration of prophylactic AEDs after TBI is not associated with a significant change in seizure incidence or all-cause mortality. Considering the higher cost which AEDs prophylaxis incurs, without offering any additional benefits, the use of AEDs prophylaxis in patients with TBI needs to be re-evaluated. A further long-term cohort study using Taiwan's NHIR database, implemented with a sufficient sample size, needs to be performed in order to clarify the benefits of AED prophylaxis in TBI patients.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

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