


The value of anti-epileptic therapy as a prophylactic factor for seizures in the management of moderate traumatic brain injury

Konstantinos Faropoulos¹, Demosthenes Makris² & George Fotakopoulos^{*,3} 

¹Department of Neurosurgery, Nicosia General Hospital, Nicosia, Cyprus

²Department of Head of Critical Care, University Hospital of Larissa, Larissa, Greece

³Department of Neurosurgery, University Hospital of Thessaly, University Hospital of Larissa, Larissa, Greece

*Author for correspondence: Tel.: +30 262 105 1828; gfortakop@yahoo.gr

Aim: The value of anti-epileptic therapy in the prophylaxis of post-traumatic seizures. **Patients & methods:** All patients received a standard anti-epileptic drug (AED) and were divided into two groups: Group A -with early AED and Group B -with late AED. **Results:** Patients (871/1062) met the inclusion criteria. Multivariate analysis demonstrated that computer tomography findings, headache and prior history of brain head injury were independent risk factors of seizures. Only late post-traumatic seizures (LPTS) was significantly associated with AED ($p < 0.05$). **Conclusion:** Early treatment with AED seems to not affect the incidence of IPTS. In addition, an AED with a mean time of initiation of 7.5 days from the moderate traumatic brain injury occurrence could reduce the IPTS incidence.

Lay abstract: The aim was to study the role of anti-epileptic drugs (AED) as a prophylactic factor for post-traumatic seizures. Patients were divided into two groups: Group A (with early AED). And Group B (with late AED). AED with a mean time of initiation of 7.5 days from the moderate traumatic brain injury occurrence could reduce the late post-traumatic seizure (IPTS) incidence. We believe that an association between the IPTS and AED exists. Both history of brain operation or traumatic brain injury and computer tomography findings like traumatic focal hemorrhagic contusions (temporal), were independent risk factors of IPTS.

First draft submitted: 5 May 2020; Accepted for publication: 14 July 2020; Published online: 2 September 2020

Keywords: anti-epileptic drugs • brain trauma • early seizures • electroencephalogram • late seizures • levetiracetam • moderate traumatic brain injury • post-traumatic seizures • prophylactic anti-epileptic therapy • single post-traumatic seizures

Traumatic brain Injury (TBI) is defined as a disturbance in brain function, or other forms of brain pathology, caused by an external force [1,2]. In the USA, there are approximately 30 million injuries per year, which are referred to Emergency Departments, with 16% of these are being referred to as TBIs [3].

Sometimes, this injury is followed by seizures, which could worsen the patient's outcome and lead to neurologic deterioration or recurrent seizures. Post-traumatic anti-epileptic drugs (AED) are normally utilized to reduce already appearing seizures.

The role of AED in preventing the risk of the development of seizures in people after moderate TBI (mTBI) patients is yet elusive [4]. According to the Brain Trauma Foundation (NY, USA), prophylactic use of anti-epileptic drugs is not advocated as a prophylactic treatment for late post-traumatic seizures (IPTS), even in the case of risk factors [5]. Early post-traumatic seizure (ePTS) does not deteriorate late neurological status [5]. Moreover, anti-epileptic drugs such as levetiracetam are easily used in clinical practice since they do not require blood level counting or loading to reached therapeutic levels.

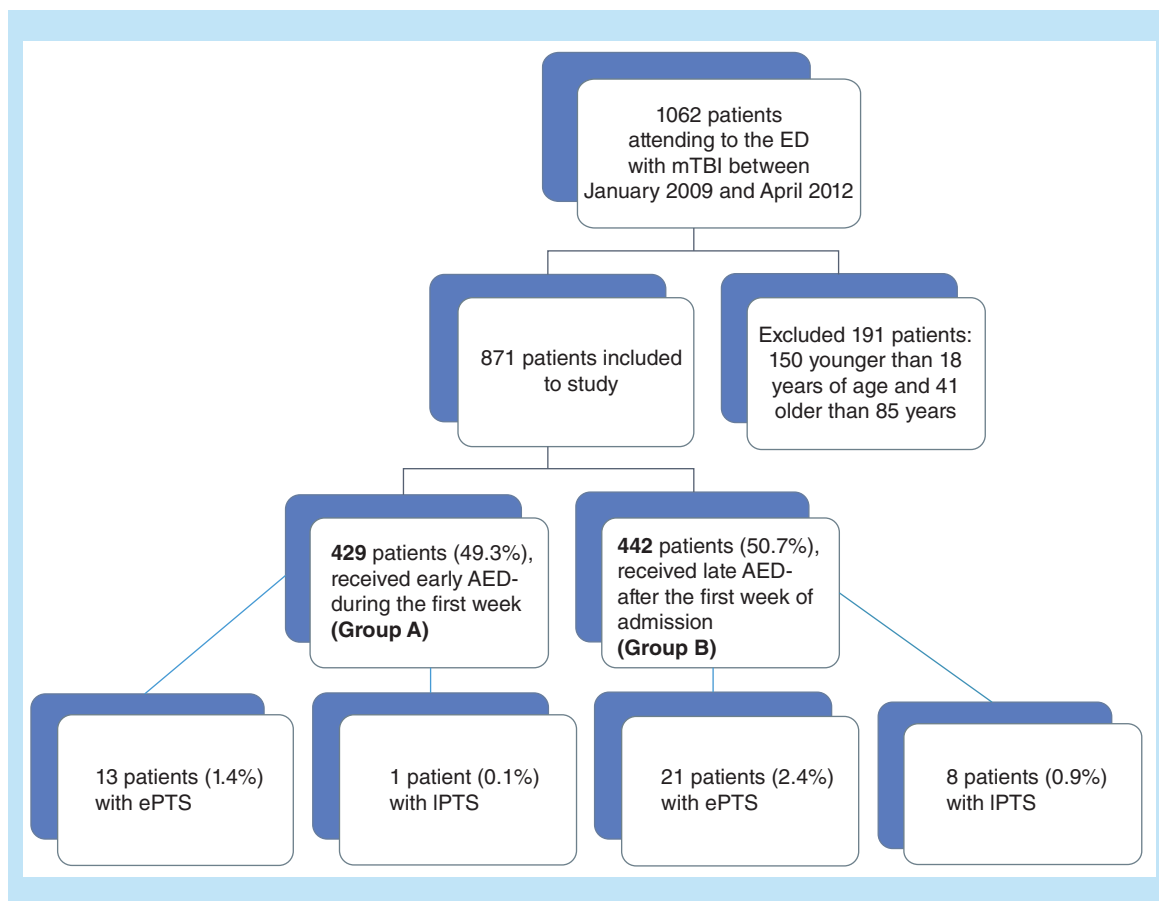


Figure 1. Study selection process. A total number of patients were hospitalized during the study period and were screened for eligibility.

AED: Post-traumatic anti-epileptic therapy; ePTS: Early post-traumatic seizure; IPTS: Late post-traumatic seizure; mTBI: Moderate traumatic brain injury.

In this prospective study, we aimed to record the frequency of PTS (ePTS & IPTS) following mTBI, to identify risk factors among clinical and imaging characteristics related to PTS and to determine if prophylactic anti-epileptic drug therapy reduces the risk of PTS. These data could support the potential use of AED after TBI and thus, they might help guide cognitive rehabilitation scheduling [6].

Patients & methods

Patients

Patients were recruited from the Emergency Department of the University Hospital of Larisa (Greece), between January 2009 and April 2012 (40 months duration). Exclusion criteria included: less than 18 years of age or greater than 85 years, a medical record of dementia, significant premorbid psychiatric or neurological history and recent use of alcohol or drug abuse (Figure 1). If the patients with mTBI (Glasgow Coma Scale [GCS] 9–12) were eligible for the study, they received a standard AED levetiracetam (1000 mg derived in two doses) daily.

Based on the time when the treating physicians decided to prescribe the AED, patients who entered the study were allocated in two groups; Group A- those who started anti-epileptic therapy at early stages (during the first week of admission) or Group B- those who started at late states (after the first week of admission).

Patients were followed for 5 years in total, having scheduled clinic visits at 1, 2 and 5 years after the incident. Informed consent was obtained.

Outcomes

The number of patients experiencing seizures after the first week of admission (IPTs) was the primary outcome in this study.

The number of patients experiencing seizures within the first week of admission ePTS was assessed as a secondary outcome.

Clinical data

Patients were divided into two groups: Group A: with early AED-starting from the very first moment of admission and group B: with late AED – starting 7 days after the incident (a single or/+ multiple seizures). A questionnaire was used to document whether PTS was persistent or and an electroencephalogram was performed to confirm seizures. Moreover, various data were examined as predictor factors, such as the GCS in the moment of admission, chronic smokers, coronary heart disease, medical history of seizures, hypertension, mTBI mechanism (car/motorcycle accident and fall +/- beating), sex, headache age, anticoagulation/antiplatelet treatment, CT scan findings: (traumatic focal hemorrhagic contusions [HCs] in the frontal and temporal lobes or more diffuse punctate HCs, and fractures: convexity or skull base), diabetes, vomiting, stroke incidence, brain surgery or evidence of traumatic brain injury in the past.

CT scan and medical history were utilized for the evaluation of current or/and previous CNS pathology, while alcohol consumption was assessed by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) [7] and drug consumption was assessed by the Drug abuse testing using a 24-h timed urine or serum sample [8]. The proportion of people who experienced disability (partially or fully dependent on others in normal activities of daily living) was assessed according to the Karnofsky performance scale index where those patients who were able to carry on normal activity and to work were scored from 80 to 100; those were unable to work but able to live at home and care for most personal needs, were scored from 50 to 70; and patients who were unable to care for self or requires hospital care, were scored from 0 (dead) to 40.

Statistical analysis

Data are expressed as mean \pm standard deviation (SD). Data were assessed for normality using the Shapiro–Wilkes test. Nominal data were analyzed using Fisher's exact test. Continuous data were analyzed using the Student's *t*-test or the Mann–Whitney U test as appropriate. Variables significantly associated with univariate analysis were then entered into a multivariable analysis model. A $p < 0.05$ was considered as statistically significant. Statistical analyses were performed with the use of Statistical Product and Service Solutions (SPSS) software, version 15 (SPSS Inc., IL, USA).

Results

There were 871 out of 1062 patients (males: 511, 58.6%) who fulfilled study inclusion criteria. From them, 429 patients (49.3%) received early AED (Group A) and 442 (50.7%) received late AED (Group B) (Figure 1). Patients in Group A presented significant differences compared with Group B considering age, GCS on admission, history of brain operation or head injury, headache, traumatic focal HCs in the temporal lobe and skull base fractures (Table 1). In all patients, the electroencephalogram confirmed the seizures. The incidence of seizures (ePTS & IPTs) among the two groups was 3.3% ($n = 29$) and 1.5% ($n = 14$), respectively (Table 2). Multivariate analysis (Table 3) demonstrated that a history of brain operation or head injury and computer tomography (CT) findings: traumatic focal HCs in the temporal lobe were independent risk factors of seizures (both ePTS and IPTs). There was a significant difference between patients with ePTS and those with IPTs only in terms of GCS on admission ($p < 0.05$) (Table 4).

Clinical outcomes are demonstrated in Table 2. Only IPTs was significantly associated with AED ($p < 0.05$). Overall, IPTs was 1% (9/871 patients) and it was higher in Group A when compared with Group B.

Receiver operator characteristic (ROC) analysis determined that 7.5 days duration of AED presented significant predictive value for IPTs (sensitivity of 95% and specificity of 67% [95% CI: 0.545–0.947]), $p = 0.01$ (Table 5 & Figure 2).

Discussion

The cardinal findings of the present study that included patients with mTBI were: PTS incidence was 4.8%; IPTs was 1% and ePTS was 3.8%. IPTs was statistically significant with AED, history of brain surgery or head injury

Table 1. Baseline characteristics of patients suffering moderate traumatic brain injury.

Characteristics	All patients n = 871	Group A: early AED, n = 429 (49.3%)	Group B: late AED, n = 442 (50.7%)	p-value
Age, years	32.8 ± 9.7	26.3 ± 8.6	39.0 ± 5.9	0.001
Sex (male), n (%)	511, (58.6)	261, (29.9)	250, (28.7)	0.200
GCS of admission, mean ± SD	10.6 ± 1.0	11.1 ± 0.9	10.1 ± 0.9	0.001
mTBI Mechanism				
– Car/motorcycle accident, n (%)	553 (63.4)	280 (32.1)	273 (31.3)	0.292
– Fall +/- or beating, n (%)	318 (36.6)	149 (17.1)	169 (19.4)	0.230
History of seizures, n (%)	13 (1.4)	8 (0.9)	5 (0.5)	0.372
Hypertension, n (%)	48 (5.5)	23 (2.5)	25 (2.8)	0.849
Coronary heart disease, n (%)	18 (2.0)	8 (0.9)	10 (1.1)	0.680
Chronic smokers, n (%)	163 (18.7)	83 (9.5)	80 (9.1)	0.637
Diabetes, n (%)	21 (2.4)	10 (1.1)	11 (1.2)	0.879
History of brain surgery or head injury, n (%)	8 (0.9)	7 (0.8)	1 (0.1)	0.030
History of stroke, n (%)	7 (0.8)	4 (0.4)	3 (0.3)	0.722
Anticoagulation/antiplatelet treatment, n (%)	14 (1.6)	9 (1.0)	5 (0.5)	0.291
Headache, n (%)	89 (10.2)	54 (6.1)	35 (4.0)	0.023
Vomiting, n (%)	24 (2.7)	13 (1.4)	11 (1.2)	0.682
RTS, mean ± SD	7.243 ± 0.3	7.342 ± 0.6	7.249 ± 0.7	0.128
CT Findings				
1. Traumatic focal HCs				
– Frontal, n (%)	111 (12.7)	48 (5.5)	63 (7.2)	0.175
– Temporal, n (%)	40 (4.5)	28 (3.2)	12 (2.5)	0.007
– Diffuse punctate HCs, n (%)	510 (58.5)	307 (35.2)	203 (23.3)	0.187
2. Convexity fractures, n (%)				
	108 (12.3)	9 (1.0)	99 (11.3)	0.175
3. Skull base fractures, n (%)				
	102 (11.7)	6 (0.9)	96 (11.2)	0.001

Data are presented as mean ± SD, otherwise is indicated.
p-value for the difference between groups was assessed for Nominal data using the Fisher's exact test and for Continuous data with the Mann-Whitney U-test as appropriate.
AED: Anti-epileptic drug; CT: Computer tomography; GCS: Glasgow Coma Scale; HC: Hemorrhagic contusion; PTS: Patients with post-traumatic seizure; RTS: Revised Trauma Score; SD: Standard deviation; TBI: Traumatic brain injury.

Table 2. Patients' outcomes.

Outcome	Group A, n = 429 (49.3%)	Group B, n = 442 (50.7%)	p-value
ePTS, n (%)	21 (2.4)	13 (1.4)	0.162
IPTS, n (%)	8 (0.9)	1 (0.1)	0.019
Karnofsky performance scale index, n (%)	97.4 ± 9.5	97.7 ± 9.35	0.102

Data are presented as mean ± standard deviation, otherwise is indicated.
ePTS: Early post-traumatic seizure; IPTS: Late post-traumatic seizure.

Table 3. Independent risk factors of seizures (IPTS & early post-traumatic seizure) after multivariable analysis.

Name	p-value	OR	CI (95%) Lower-upper
1. Age	0.324	0.030	0.006–0.019
2. GCS of admission	0.312	0.027	0.103–0.323
3. History of brain surgery or head injury	0.003	0.083	0.572–2.898
4. Headache	0.742	0.009	0.410–0.292
5. CT findings: traumatic focal HCs (temporal)	0.000	0.577	4.995–6.064
6. CT findings: Skull base fractures	0.233	0.035	0.136–0.557

p-value for the difference between groups.
CT: Computer tomography; ePTS: Early post-traumatic seizure; GCS: Glasgow Coma Scale; HC: Hemorrhagic contusion. IPTS: Late post-traumatic seizure; OR: Odd ratio.

and CT findings: traumatic focal HCs (temporal), were independent risk factors of IPTS and AED with a mean time of initiation of 7.5 days from the mTBI incident could reduce the occurrence of IPTS.

Table 4. Comparison between patients with early post-traumatic seizure and with IPTS.

n = 43 with seizures	ePTS, n = 34 (79.0%)	IPTS, n = 9 (20.9%)	p-value
Age, years	49.2 ± 18.3	39.5 ± 22.9	0.468
Sex (male), n (%)	10 (23.2)	3 (6.9)	0.820
GCS of admission, mean ± SD	10.5 ± 0.9	9.7 ± 0.9	0.031
mTBI Mechanism			
– Car/motorcycle accident, n (%)	21 (48.8)	7 (16.2)	0.370
– Fall +/-or beating, n (%)	13 (30.2)	2 (4.6)	0.357
History of seizures, n (%)	1 (2.3)	1 (2.3)	0.301
Hypertension, n (%)	14 (32.2)	3 (6.9)	0.669
Coronary heart disease, n (%)	7 (16.2)	1 (2.3)	0.516
Chronic smokers, n (%)	3 (6.9)	1 (2.3)	0.834
Diabetes, n (%)	9 (20.9)	2 (4.6)	0.795
History of brain surgery or head injury, n (%)	5 (11.6)	1 (2.3)	0.782
History of stroke, n (%)	5 (11.6)	0	–
Anticoagulation/antiplatelet treatment, n (%)	12 (27.9)	2 (4.6)	0.457
Headache, n (%)	6 (13.9)	1 (2.3)	0.637
Vomiting, n (%)	6 (13.9)	2 (4.6)	0.754
RTS, mean ± SD	7.332 ± 0.5	7.334 ± 0.5	0.231
CT Findings			
1. Traumatic focal HCs			
– Frontal, n (%)	20 (46.5)	7 (16.2)	0.294
– Temporal, n (%)	8 (18.6)	7 (16.2)	0.587
– Diffuse punctate HCs, n (%)	29 (67.4)	2 (4.6)	0.934
2. Convexity fractures, n (%)	7 (16.2)	2 (4.6)	0.915
3. Skull base fractures, n (%)	5 (11.6)	0	–
Groups			
Group A	13 (30.2)	1 (2.3)	
Group B	21 (48.8)	8 (18.6)	0.123

Data are presented as mean ± SD, otherwise, it is indicated.
p-value for the difference between groups was assessed for Nominal data using the Fisher's exact test and for Continuous data with the Mann–Whitney U-test as appropriate.
CT: Computer tomography; ePTS: Early post-traumatic seizure; GCS: Glasgow Coma Scale; HC: Hemorrhagic contusion; IPTS: Late post-traumatic seizure; PTS: Patients with post-traumatic seizure; RTS: Revised Trauma Score; SD: Standard deviation; TBI: Traumatic brain injury.

Table 5. Statistical findings for receiver operator characteristic.

	Area	Std Error	CI (95%) Lower–upper	p-value
ePTS	0.726	0.055	0.619–0.834	0.001
IPTS	0.746	0.102	0.545–0.947	0.011

Data are presented as n (%), otherwise is indicated.
ePTS: Early post-traumatic seizure; IPTS: Late post-traumatic seizure; ROC: Receiver operator characteristic; Std: Standard.

According to a study by Wang *et al.* [9], 59.9% of patients were identified as having PTS after TBI. Hence, there is an increased possibility for developing PTS after TBI to patients with severe TBI (patients with low GCS) [10], frontal–temporal lobar contusion and linear skull fracture. In our study, the incidence of PTS in mTBI patients was low 4.8%. Only patients who had previously been operated on or had an injury on the brain and those were diagnosed with temporal lobes focal HCs and skull base fractures during the accident, seemed to develop PTS.

Phenytoin, carbamazepine, sodium valproate and phenobarbitone have been demonstrated to be effective in the treatment of partial or generalized tonic-clonic seizures [11]. Furthermore, Phenytoin is effective in the prevention of ePTS when administered within the first-week post-injury [11]. Notwithstanding, many papers concluded that the use of aforementioned the drugs appears to prevent IPTS [4], regardless of the investigations or the type of injury [11].

On the other hand, some argue that the risk of IPTS occurrence was reduced by AED compared with placebo or usual cure, although the difference was not statistically significant [10]. According to a study by Temkin *et al.*

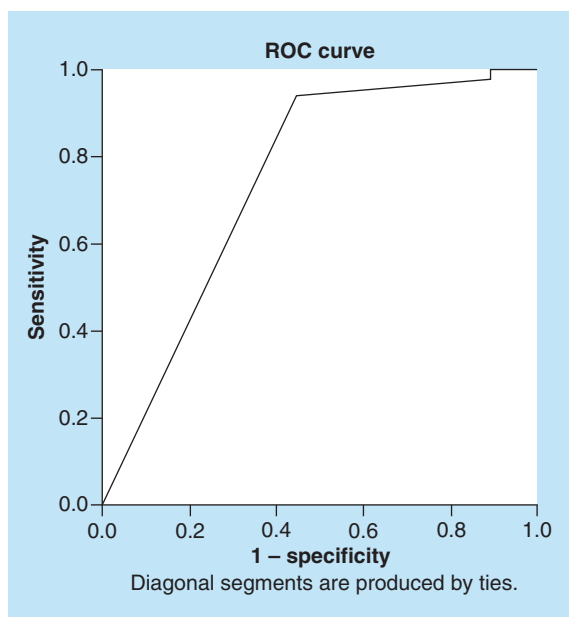


Figure 2. ROC curve is shown with a sensitivity of 95% and specificity of 67% (95% CI: lower-upper [0.545–0.947]; $p = 0.01$) that an AED with a mean time of initiation of 7.5 days from the mTBI incidence could reduce the IPTS.

AED: Post-traumatic anti-epileptic therapy; IPTS: Late post-traumatic seizure; mTBI: Moderate traumatic brain injury; ROC: Receiver operating characteristic.

AED, a valuable result by reducing seizures was achieved during the first week after head injury [12]. Our study demonstrated that only the AED with a mean time of initiation of 7.5 days from the mTBI incidence could reduce the IPTS. Instead, an AED at the very first moment from the event had not any effect in reducing seizures.

In many reports, the prophylactic use of anti-epileptic drugs is not recommended for the prevention of ePTS [13]. Additionally, other studies mentioned that ePTS are not associated with worse outcomes [5]. These different results may be due to the comparatively low or variable incidence of PTS in published series [13]. Our study dialed with mTBI patients and showed no definitive significant difference, between AED and ePTS; $p = 0.162$ (Table 2).

PTS is not generally in attendance of all mTBI cases. Over the last decade, several studies have identified the frequency of AED which accounts for 20% of acquired seizures in the general population [14]. Other studies also have shown unreliable incidence rates [9,15]. The reason for that variability in the occurrence of PTS may be derived by the differences in study design and population, in other words there was no homogeneity in participants, where the pathophysiologic basis for PTS and the expand of the damage may differ considerably. In our study, we included homogenous populations with mTBI and PTS incidence was 4.8% (43/871 patients) – IPTS was 1% (9/871 patients) and ePTS was 3.8% (34/871 patients). IPTS was higher in Group A when compared with Group B ($p < 0.05$), indicating that IPTS could act as an independent factor of AED. Thus, early therapy – during the first week of admission – with AED seems to not affect the incidence of IPTS. ROC analysis demonstrated a value of 7.5 days presented with a sensitivity of 95% and specificity of 67%. This means that the AED with a mean time of initiation of 7.5 days from the mTBI incidence could reduce the IPTS. On the other hand, in this study the incidence of seizures among the groups was 43 (4.9%) as 29 patients (67.4%) were in Group A (patients with early prophylaxis) – 21 patients (48.8%) developed seizure at an early stage and only eight patients (18.6%) showed late epileptic seizure. This probably could be explained: first, from the fact that these patients mainly had a lower GCS – as they divided into Group A were the physician decided early prophylaxis – hence they had a greater possibility to developed seizure or second, probably in the first 7 days, the drug levels in these patients were influenced by many factors caused by TBI.

In previous studies, PTS has been associated with multiple risk factors [16] such as young age, depression, family history, alcohol and factors of increasing damage harshness such as penetrating injuries [17]. Others have been identified as a risk factor for PTS the distraction of the blood–brain barrier [17]. More recently, it has been suggested that genetic factors [18] and people with a history of depression are at high risk of developing PTS [19]. Another interesting point is that most studies focused on severe TBI only [13], while our attention was concentrated in mTBI. On the other hand, our study showed that young age was significantly different ($p = 0.001$) among the groups (Table 1), but multivariable analysis demonstrated that age was not an independent risk factor of seizures ($p < 0.05$; Table 3).

It should be underlined here that some points should be taken into consideration in the explanation of our findings. First, is that a number of patients (6.7 %) who were lost to follow-up. Nevertheless, we believe that this loss was negligent, and were equally distributed in the two groups (3.5 and 3.2 % in Group A and B respectively), thus this population may not have affect our findings. Next, patients over 85 or less than 18-year old were excluded from the study. Older patients were excluded since they frequently present disabilities due to pathological causes or cognitive problems that could obscure TBI related to AED evaluation [20,21]. Young patients (less than 18-year old) also, due to different recovery rates or duration of symptoms when compared with older patients, could disturb the homogeneity in the study population [22–26]. Third, in this protocol, we used only CT studies that may lack sensitivity when damages are small. MRI scan might be more perceptible but was difficult to be applied in such a large scale. Fourth, in our study as we did not perform any measurement for the blood levels of Levetiracetam, perhaps patients with more severe brain injury could have affected Levetiracetam levels by many factors.

Other limitations were that this study uses data from a single-center and may have been underpowered to detect a difference in the primary outcome since the incidence of PTS is very low. A larger cohort could demonstrate a more significant difference in the incidence of early PTS among TBI patients who received prophylaxis and those who did not.

Conclusion

We believe that an association between the IPTS and AED exists. In our study, ePTS incidence in mTBI cases was approximately 3.6% and IPTS was 1%, respectively. Multivariate analysis revealed that both, history of brain operation or head injury and CT findings like traumatic focal HCs (in temporal lobe), were independent risk factors of IPTS. IPTS was higher in Group A when compared with Group B ($p < 0.05$), thus early treatment with AED seems to not affect the incidence of IPTS. But an AED with a mean time of initiation of 7.5 days (i.e., at late stage) from the mTBI occurrence could reduce the IPTS incidence. Future studies including MRI scans as a screening procedure into the emergency departments could be beneficial to determine the existence of traumatic lesions, that cannot be visible using only CT scan.

Future perspective

Future studies including MRI scan as a screening procedure into the emergency departments could be beneficial to determine the existence of traumatic lesions, that cannot be visible using only a CT scan. Our study may be used to measure patients' response to AED and may improve their outcomes. New methods are being developed to quantify injure on images and perhaps improve predictive power.

Executive summary

- We believe that an association between the late post-traumatic seizures (IPTS) and anti-epileptic drug (AED) exists. Both history of brain operation or traumatic brain injury and computer tomography findings such as traumatic focal hemorrhagic contusions (temporal), were independent risk factors of IPTS.
- Early treatment with AED seems to not affect the incidence of IPTS.
- AED with a mean time of initiation of 7.5 days from the moderate traumatic brain injury occurrence could reduce the IPTS incidence.

Author contributions

G Fotakopoulos contributed to the study design, contributed to data collection, and contributed to data analysis and interpretation. D Makris and K Faropoulos contributed to manuscript writing. All authors reviewed the final manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Open access

This work is licensed under the Creative Commons Attribution 4.0 License. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>

References

Papers of special note have been highlighted as: • of interest

- Marr AL, Coronado VG (Eds). *Central nervous system injury surveillance data submission standards–2002*. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, GA, USA (2004). www.cdc.gov/mmwr/preview/mmwrhtml/mm6227a2.htm
- Menon DK, Schwab K, Wright DW *et al.* Demographics and clinical assessment working group of the international and interagency initiative toward common data elements for research on traumatic brain injury and psychological health. Position statement: definition of traumatic brain injury. *Arch. Phys. Med. Rehabil.* 91(11), 1637–1640 (2010).
- Centers for Disease Control and Prevention. Report to congress on traumatic brain injury in the United States: epidemiology and rehabilitation. National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention, GA, USA (2014).
- Thompson K, Pohlmann-Eden B, Campbell LA *et al.* Pharmacological treatments for preventing epilepsy following traumatic head injury. *Cochrane Database Syst. Rev.* 10, 8 (2015).
- Carney N, Totten AM, O'Reilly C *et al.* Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 80, 6–15 (2017).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures management.**
- Ganti L, Daneshvar Y, Ayala S *et al.* The value of neurocognitive testing for acute outcomes after moderate traumatic brain injury. *Mil. Med. Res.* 22, 3–23 (2016).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures management.**
- Wade D, Varker T, Forbes D *et al.* The alcohol use disorders identification test-consumption (AUDIT-C) in the assessment of alcohol use disorders among acute injury patients. *Alcohol. Clin. Exp. Res.* 38(1), 294–299 (2014).
- Küme T, Karakükcü Ç, Pınar A *et al.* [The scope, quality and safety requirements of drug abuse testing]. *Turk. Psikiyatri. Derg.* 28(3), 198–207 (2017).
- Wang H, Xin T, Sun X *et al.* Post-traumatic seizures—a prospective, multicenter, large case study after head injury in China. *Epilepsy Res.* 107, 272–278 (2013).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures management.**
- Temkin NR, Dikmen SS, Keihm J *et al.* Does phenytoin prevent posttraumatic seizures - 1-year follow-up results of a randomized double-blind-study in 407 patients [abstract]. *J. Neurosurg.* 70(2), 314A–315A (1989).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures.**
- Young D, Okada PJ, Sokolove PE *et al.* A randomized, double-blinded, placebo-controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. *Ann. Emerg. Med.* 43, 435–446 (2004).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures.**
- Temkin NR, Dikmen SS, Wilensky AJ *et al.* A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N. Engl. J. Med.* 323(8), 497–502 (1990).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures.**
- Wat R, Mammi M, Paredes J *et al.* The effectiveness of antiepileptic medications as prophylaxis of early seizure in patients with traumatic brain injury compared with placebo or no treatment: a systematic review and meta-analysis. *World Neurosurg.* 122, 433–440 (2019).
- Agrawal A, Timothy J, Pandit L *et al.* Post-traumatic epilepsy: an overview. *Clin. Neurol. Neurosurg.* 108, 433–439 (2006).
- Kazemi H, Hashemi-Fesharaki S, Razaghi S *et al.* Intractable epilepsy and craniocerebral trauma: analysis of 163 patients with blunt and penetrating head injuries sustained in war. *Injury* 43, 2132–2135 (2012).
- Piccenna L, Shears G, O'Brien TJ. Management of post-traumatic epilepsy: an evidence review over the last 5 years and future directions. *Epilepsia Open* 2(2), 123–144 (2017).

17. Tomkins O, Feintuch A, Benifla M *et al.* Blood-brain barrier breakdown following traumatic brain injury: a possible role in posttraumatic epilepsy. *Cardiovasc. Psychiatry Neurol.* 2011, 1–11 (2011).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures.**
18. Darrah SD, Miller MA, Ren D *et al.* Genetic variability in glutamic acid decarboxylase genes: associations with post-traumatic seizures after severe TBI. *Epilepsy Res.* 103, 180–194 (2013).
19. Ferguson PL, Smith GM, Wannamaker BB *et al.* A population-based study of risk of epilepsy after hospitalization for traumatic brain injury. *Epilepsia* 51, 891–898 (2010).
- **Help for a better understanding of the underlying mechanism of post-traumatic seizures.**
20. Marquez de la Plata CD, Hart T, Hammond FM *et al.* Impact of age on long-term recovery from traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89(5), 896–903 (2008).
21. Potapov AA, Krylov VV, Gavrilov AG *et al.* Guidelines for the management of severe traumatic brain injury. Part 3. Surgical management of severe traumatic brain injury (Options). *Zh. Vopr. Neurokhir. Im. N N Burdenko.* 80(2), 93–101 (2016).
22. Chermann JF, Klouche S, Savigny A *et al.* Return to rugby after brain concussion: a prospective study in 35 high-level rugby players. *Asian J Sports Med* 5, e24042 (2014).
23. Field M, Collins MW, Lovell MR *et al.* Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate Athletes. *J. Pediatr.* 142, 546–553 (2003).
24. Terwilliger VK, Pratson L, Vaughan CG *et al.* Additional post-concussion impact exposure may affect recovery in adolescent athletes. *J. Neurotrauma* 33, 761–765 (2016).
25. Covassin T, Elbin RJ, Harris W *et al.* The role of age and sex in symptoms, neurocognitive performance, and postural stability in Athletes after concussion. *Am. J. Sports Med.* 40, 1303–1312 (2012).
26. Majerske CW, Mihalik JP, Ren D *et al.* Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J. Athl. Train.* 43, 265–274 (2008).