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Clinical study

The use of antiepileptic medication in early post traumatic seizure prophylaxis at a single institution

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ABSTRACT

Background: Current international guidelines for traumatic brain injury (TBI) recommend the use of phenytoin for the prevention of early post traumatic seizures (PTS) when the benefits are thought to outweigh the risks. In practice however, alternative antiepileptic drugs (AEDs) such as levetiracetam and valproate are being used as they are believed to have a more favourable risk profile. This is despite there being insufficient evidence to support their efficacy. The purpose of this study was to identify which AED was prescribed to patients presenting with a TBI at a single institution, and to determine the rate of early PTSs.

Methods: This was a retrospective case-note review study done at the Flinders Medical Centre including patients admitted from May 2013 to June 2017. All patients with traumatic intracranial haematomas were included. Patients were excluded if they had seizures prior to presentation to hospital or died within 24 h of injury. The primary outcomes were rate of early PTSs and the type of prophylactic AED prescribed.

Results: During this study period, 610 patients presented with a mild, moderate or severe traumatic brain injury. Overall, 16% of patients were prescribed an AED, with more than 90% of these patients being prescribed levetiracetam. Overall, the rate of early PTSs for patients prescribed AEDs was 2.9% compared with 3.5% for patients not prescribed AEDs (OR 0.83 CI 0.24–2.85 p = 1).

Conclusions: This study showed that levetiracetam was the most commonly prescribed AED. It also demonstrated no statistically significant difference in the rate of early PTSs in patients with TBI, with or without prophylactic AEDs. This is in keeping with other contemporary studies, and therefore the routine administration of prophylactic AEDs may need to be re-examined.

1. Introduction

Traumatic brain injury (TBI) in Australia is estimated to cost 8.6 billion dollars per year and is responsible for 107 admissions per 100,000 population per year [7]. Post traumatic seizures (PTSs) are a recognised complication of TBI. PTSs are divided into early, occurring within seven days, or late if occurring beyond seven days post injury. The incidence of early PTSs is variable and has been estimated to occur between 2.8% and 25% of blunt TBIs [9,10,12].

Seizure prophylaxis is the practice of administering antiepileptic drugs (AEDs) with the intention of preventing PTSs. It is believed that seizures may exacerbate secondary injury through increasing cerebral metabolic demands, increasing intracranial pressure and augmenting cerebral oedema. These acute derangements in physiology can lead to herniation and death [2,3]. In addition, it has been shown that early PTSs increase the risk of late PTSs [17]. Therefore, preventing early PTSs has been a topic of research over the past few decades.

Research published by Temkin et al in 1990 established the practice of prescribing prophylactic phenytoin for the first seven days post injury as they were able to demonstrate a significant reduction in the rate of early PTSs in patients prescribed prophylactic phenytoin, compared to a 'control' group of patients (3.6% vs 14.2% p < 0.001) [17]. These results are what form the foundation of the guidelines published by the Brain Trauma Foundation.

The 2016 guidelines published by the Brain Trauma Foundation do not recommend routine prophylaxis with phenytoin or valproate for prevention of late PTSs. However, the guidelines recommend that phenytoin may be used to decrease the rate of early PTSs when it is thought the overall benefit outweighs the risks associated with treatment. Furthermore, it states there is insufficient evidence to recommend levetiracetam over phenytoin with regards to efficacy and side effects [2].

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Despite this lack of evidence levetiracetam has become a commonly prescribed AED used in PTS prophylaxis in many centres. This is likely due to the ease of dosing, no requirements for serum level monitoring, and the perception of a more favourable side effect profile [7].

In addition, there are some contemporary studies challenging the efficacy of early PTS prophylaxis, demonstrating no clinical benefit or a potential negative cognitive effect with poorer functional patient outcomes [1,4,5].

The purpose of this study was to identify prescribing practices regarding antiepileptic medications for patients presenting with a TBI at a single institution, and to determine the rate of early PTSs and compare it with the literature.

2. Methods

2.1. Data collection

This was a retrospective case-note review study conducted at the Flinders Medical Centre including patients admitted from May 2013 to June 2017. Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) (OFR 159.17).

The case notes of all patients with a discharge diagnosis of intracerebral haematoma at the Flinders Medical Centre between May 2013 and June 2017 were included for review. Diagnosis was determined by the ICD 10 code assigned to the patient on discharge and was assigned to the patient by the doctor responsible for the patients care. This diagnosis was then assigned the appropriate ICD 10 code by medical administration staff. A single author reviewed patient discharge summaries and patients with non-traumatic haematomas were excluded. This included haemorrhagic stroke, aneurysmal subarachnoid haemorrhage and haemorrhagic metastases. This was done to ensure an accurate dataset as the ICD 10 codes did not characterise intracerebral haematomas as traumatic or non-traumatic. The remaining patients had their case notes reviewed.

Patients were excluded if: age under 18, death within 24 h of presentation, PTS prior to hospital presentation, seizure resulting in TBI, or patients presenting with isolated chronic subdural haematoma.

The primary outcomes measured were early (within 7 days of injury) PTS after admission to hospital and the type of AED prescribed. A seizure was defined as any witnessed seizure activity by any healthcare staff, confirmation by a physician was not required. Use of electroencephalogram to confirm suspected seizure activity was not employed. As previously mentioned, patients with suspected seizure activity prior to hospital presentation were prescribed AEDs with therapeutic intent, as oppose to prophylactic.

The secondary outcome measures associated with early PTS included: type and location of traumatic intracranial haemorrhage, mechanism of injury, TBI grade, if an operation was required, and operation type. Data on patient characteristics were collected and included: length of stay, gender, age, time of injury, secondary traumatic injuries, past history of seizures, presence of impact seizure, seizure prior to presentation to hospital, time to antiepileptic administration, GCS at scene and post resuscitation, time to operation, death within seven days, cause of death and anti-coagulant use.

TBI grade was calculated using post resuscitation GCS prior to being transferred to ward, ICU or operating theatre. Patients with GCS between 3 and 8 were classified as severe, between 9 and 12 were classified as moderate, and 13 to 15 were classified as mild.

At the study institution a standardised protocol for managing TBI does not exist. However, the accepted treatment is for patients with severe TBI to be prescribed prophylactic AEDs routinely. Whereas, patients with moderate and mild TBI are only prescribed prophylactic AEDs on an individualized basis.

Data was collected by the first author and reviewed independently by the second author with discrepancies being discussed in a consensus meeting.

2.2. Statistical analysis

Statistical analysis was performed using IBM SPSS, version 24 (IBM, Armonk, NY). Categorical and discrete data was analysed using Fisher's exact or Chi-square tests as appropriate. Continuous data was analysed using an independent samples *t* test and Wilcoxon-rank sum test as appropriate. All confidence intervals were reported to 95%.

3. Results

A total of 2124 patients were discharged from the study centre with an intracranial haematoma during the study period of May 2013 to June 2017. 1496 patients were excluded because of a non-traumatic haematoma aetiology, and an additional 18 patients were excluded for having PTS prior to admission. This resulted in a total of 610 patients, with 495 mild TBI, 49 moderate TBI, and 66 severe TBI. The average age was 71 years, and approximately 58% were males. The flowchart of patient selection is shown in Fig. 1.

4. Primary outcome

4.1. Rate of early post traumatic seizure

Overall early PTSs were observed in 21 (3.4%) patients in the study group of 610 patients. A total of 102 patients were prescribed AED prophylaxis, while 508 patients were not prescribed any prophylaxis. In the 508 patients who were not prescribed prophylaxis, a total of 18 patients (3.5%) had early PTSs. Whereas, in the 102 patients who were prescribed AED prophylaxis, a total of 3 patients (2.9%) had early PTSs.

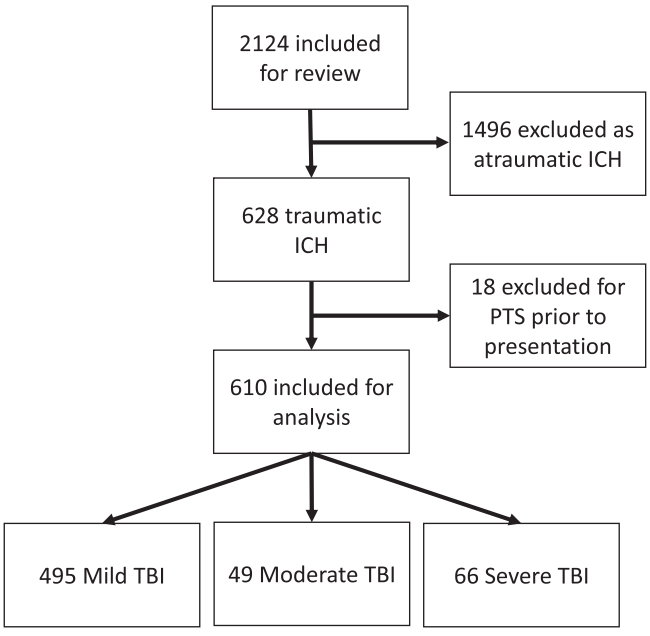

Fig. 1. Flowchart demonstrating patients involved in the study at all stages. Intracranial haematoma (ICH), traumatic brain injury (TBI), posttraumatic seizure (PTS).

Within the 495 patients who suffered a mild TBI, 450 of them received no AED prophylaxis whereas the other 45 were prescribed AED prophylaxis. A total of 13 early PTSs occurred in the 450 patients who were not prescribed prophylaxis. This represented an early PTS rate of 2.8%. For the remaining 45 patients who were prescribed AED prophylaxis, 1 patient had an early PTS, representing a rate of 2.2%.

There was a total of 115 patients who suffered a moderate or severe TBI. Out of them, 7 patients (6%) had an early PTS. Of the 115 patients in the group, 58 patients were not prescribed AED prophylaxis, whereas 57 were prescribed prophylaxis. In the no prophylaxis group of 58 patients, a total of 5 patients (8.6%) had an early PTS. Whereas, 2 of the 57 patients (3.5%) who were prescribed prophylaxis, had an early PTS. These results are demonstrated in Table 1.

4.2. Prescribed prophylactic antiepileptic drugs

Overall 102 (17%) patients in the study group were prescribed PTS prophylaxis and 508 (83%) patients were not. In the study group levetiracetam alone was the most common AED, prescribed to 93 (91%) patients. Phenytoin alone was prescribed in 4 (4%) patients, valproate in 2 (2%) patients, and phenytoin loading followed by regular levetiracetam in 3 (3%) patients. All patients received the first dose of AED on day 0 of admission, with a regular weight based dosing schedule being prescribed for the first 7 days based on the type of AED prescribed.

Within the 495 patients suffering a mild TBI, 45 were prescribed prophylaxis. Levetiracetam was the most commonly prescribed in 41 patients, with 2 patients being prescribed valproate and 2 patients being loaded with phenytoin and then commenced on regular levetiracetam. There were 57 patients prescribed AED prophylaxis in the 115 patients suffering moderate or severe TBI. Levetiracetam was the most commonly prescribed, observed in 52 patients. 4 patients were prescribed phenytoin alone, and 1 patient was prescribed phenytoin loading followed by regular levetiracetam.

The 3 patients with 1 mild, 1 moderate, and 1 severe TBI, who were prescribed a prophylactic AED and suffered an early PTS were all prescribed levetiracetam.

There was no statistically significant difference in the rate of early PTSs in patients prescribed prophylactic AEDs compared to those who were not (OR 0.83 CI 0.24–2.85 p = 1). Sub-group analyses by TBI grade did not demonstrate any evidence to support a difference in rate of early PTSs either, mild TBI (OR 0.76 CI 0.098–5.98 p = 1), moderate or severe TBI (OR 0.39 CI 0.072–2.07 p < 0.438).

5. Secondary outcomes

5.1. Intracranial injuries

In the study cohort of 610 patients, there were 283 different combinations/types of intracranial injuries. The most common intracranial injury was a left fronto-parietal acute subdural haematoma occurring in 22 patients (3.6%). Followed by, a parafalcine acute subdural haematoma in 21 patients (3.4%), and a right fronto-parietal acute subdural haematoma in 20 patients (3.3%).

The pattern of intracranial injuries was similar for patients with mild TBI and for moderate or severe TBI. In the 495 patients suffering a mild TBI, parafalcine acute subdural haematoma was the most common occurring in 20 patients followed by, left fronto-parietal acute subdural haematoma, left frontal traumatic subarachnoid haemorrhage, and right frontal traumatic subarachnoid haemorrhage, each occurring in 18 patients. In the 115 patients suffering a moderate or severe TBI, the most common intracranial injury was right fronto-temporo-parietal acute subdural haematoma, and left fronto-parietal acute subdural haematoma, each occurring in 4 patients.

5.2. Intracranial injury pattern

Examining the intracranial injury pattern after grouping it by laterality (unilateral vs bilateral) and by type (acute subdural haematoma vs extradural haematoma vs traumatic subarachnoid haemorrhage etc) shows that for the study cohort of 610 patients the most common injury pattern is unilateral acute subdural haematoma, occurring in 171 patients (28%). The other common patterns of injury include unilateral traumatic subarachnoid haemorrhage in 91 patients (14.9%), unilateral acute subdural haematoma + unilateral traumatic subarachnoid in 43 patients (7%), and unilateral contusion in 39 patients (6.4%).

Within the 495 patients suffering mild TBI, unilateral acute subdural haematoma was the most common pattern occurring in 147 patients (29.6%). The other common patterns were similar to the overall study cohort with unilateral traumatic subarachnoid haemorrhage occurring in 90 patients (18%), and unilateral contusion occurring in 36 patients (7.3%).

Within the 115 patients suffering moderate or severe TBI the most common injury was unilateral acute subdural haematoma occurring in 24 patients (20%). The other common injury patterns were unilateral acute subdural haematoma plus unilateral traumatic subarachnoid haemorrhage occurring in 13 patients (11.3%), bilateral contusions in 5 patients (4.3%), unilateral acute subdural haematoma plus unilateral traumatic subarachnoid haemorrhage plus unilateral contusion in 5 patients (4.3%), and unilateral intracerebral haematoma in 4 patients (3.4%). This is shown in Fig. 2.

5.3. Intracranial injury location

Grouping the intracranial injury pattern into location by either extra-axial, intra-axial, or both demonstrates that for the 610 patients in the study cohort, the most common injury location was an extra-axial lesion, occurring in 410 patients (67%). Intra and extra-axial lesions occurred in 112 patients (18%) and intra-axial lesions occurred in 88 patients (13%).

Table 1
Rate of early PTS prophylaxis in patients prescribed prophylactic antiepileptic drugs grouped by severity of traumatic brain injury.

TBI Grade		Early post traumatic seizure		Total
		No seizure	Seizure	
Mild TBI	No prophylaxis	437	13	450
	Prophylaxis prescribed	44	1	45
Total		481	14	495
Moderate or Severe TBI	No prophylaxis	53	5	58
	Prophylaxis prescribed	55	2	57
Total		108	7	115

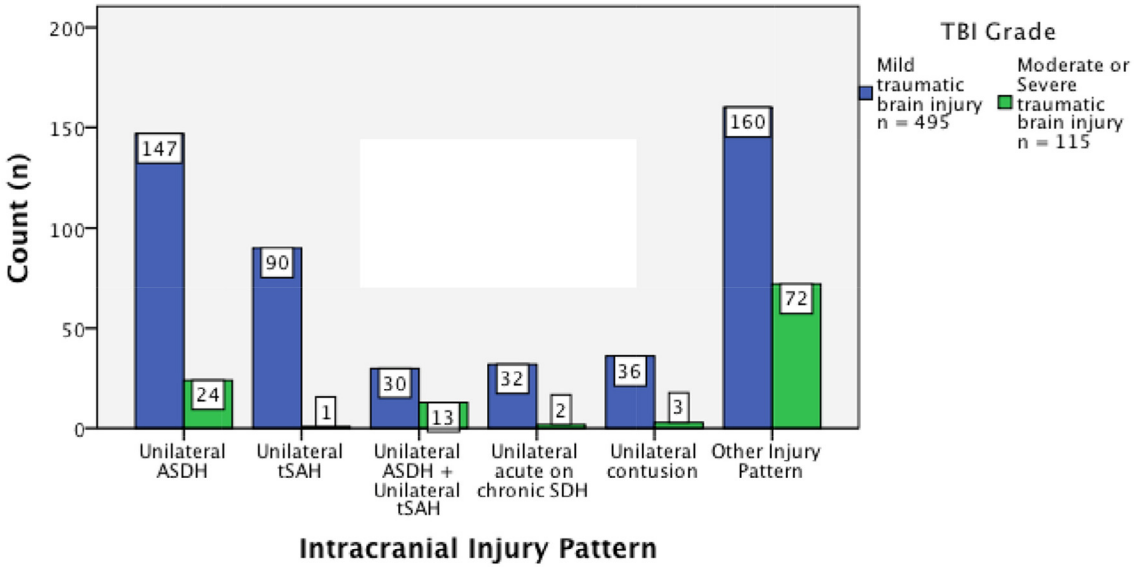

Fig. 2. Bar chart displaying the intracranial injury pattern for all patients grouped by the severity of traumatic brain injury.

Within the 495 patients suffering a mild TBI, 352 patients (71%) had extra-axial lesions, 69 (14%) had intra-axial lesions and 74 (15%) had both intra and extra-axial lesions. Of the 115 patients suffering a moderate or severe TBI, 58 (50%) had an extra-axial lesion, 19 (16%) had intra-axial lesions and 38 (33%), had both intra and extra-axial lesions. This is shown in Table 2.

There was a statistically significant difference between the mild TBI patients and the moderate or severe TBI patients with a higher proportion of extra-axial lesions in the mild TBI group ($\chi^2 = 18.11$ df 1 $p < 0.0001$, Proportion 20.7%, 95% CI 10.8–30.4), and a higher proportion of combined intra plus extra-axial lesions in the moderate to severe TBI group compared to mild TBI ($\chi^2 = 20.4$ df 1 $p < 0.0001$ proportion 18.1%, 95% CI 9.5–27.5). There was no difference in the proportions of intra-axial lesions between the groups ($\chi^2 = 0.511$ df 1 $p = 0.47$ proportion 2.6%, 95% CI −3.9 to 10.9).

In patients with mild TBI, at least 55% of patients had a subdural haemorrhage, 7% had intracerebral haematoma, and 18% had cortical contusions. In patients with moderate or severe TBI, at least 68% had a subdural haemorrhage, 20% had an intracerebral haematoma, and 27% had cortical contusions.

5.4. Rates of early post traumatic seizures and intracranial injury location

Comparing the rate of early PTSs with the location of the patient's intracranial lesion demonstrated that of the 21 patients out of the study cohort who had early PTSs, 17 patients (80%) had an extra-axial lesion. 2 patients had an intra-axial lesion, and 2 patients had both intra and extra-axial lesions.

Examining this by TBI grade shows that out of the 495 patients with a mild TBI, 14 patients had an early PTS. 13 of these occurred in patients with extra-axial lesions and 1 occurred in a patient with an intra-axial lesion.

Out of the 115 patients with moderate or severe TBI, 7 patients had an early PTS. 4 occurred in extra-axial lesions, 1 in intra-axial lesions and 2 in combined intra plus extra-axial lesions.

Further comparison with whether AED prophylaxis was prescribed shows that in the no prophylaxis group with mild TBI there was a total of 450 patients. In this group the most common location for intracranial injury was extra-axial, occurring in 326 patients (72%). Intra-axial, and combined intra and extra-axial lesions occurred in 61 (14%), and 63 patients (14%) respectively. In this cohort there was a total of 13 seizures, 12 occurred in patients with extra-axial lesions, and 1 occurred in an intra-axial lesion. The rate of early PTSs for patients not provided AED prophylaxis, suffering a mild TBI and had an extra-axial lesion was 3.6%, and for intra-axial lesions was 1.6%. No patients with combined intra and extra-axial lesions suffered an early PTS.

Examining the 115 patients with moderate or severe TBI shows that there were a total of 58 patients not prescribed AED prophylaxis. In this group the most common intracranial injury location was extra-axial, occurring in 32 patients (55%), followed by both intra and extra-axial in 16 patients (28%), and intra-axial in 10 patients (17%). In this group, there was a total of 5 PTSs with 3 occurring in patients with extra-axial lesions (9.3%), 1 intra-axial lesion (10%), and 1 combined intra and extra-axial lesion (6.2%). The remaining 57 patients with moderate or severe TBI were prescribed AED prophylaxis. In this group the most common injury location was extra-axial lesions, occurring in 26 patients (45%), followed by 22 combined intra and extra-axial lesions (38%) and 9 intra-axial lesions (15%). In this group there was a total of 2 seizures with 1 occurring in a patient with an extra-axial lesion

Table 2
Table of intracranial injury location grouped by severity of traumatic brain injury.

		TBI Grade		Total
		Mild TBI	Moderate or Severe TBI	
Intracranial injury location	Extra-axial lesion	352	58	410
	Intra-axial lesion	69	19	88
	Intra and Extra-axial lesion	74	38	112
Total		495	115	610

(3.8%) and another in a patient with a combined intra and extra-axial lesion (4.5%).

Examining all the patients who had early PTSs and had been prescribed AED prophylaxis, regardless of TBI grade, shows that there was a total of 3 patients who had an early PTS. Of these patients, 2 had extra-axial lesions, and 1 had a combined intra and extra-axial lesion. Of the two patients with an extra-axial lesion 1 had a mild TBI while the other had a moderate to severe TBI. The 1 combined intra and extra axial lesion occurred in a patient with a moderate or severe TBI. This data is demonstrated in Table 3.

5.5. Time to early post traumatic seizures

The majority of early PTSs occurred before day 4. However, there were 2 patients who had early PTSs at day 7. Both of these patients suffered a mild TBI, but only one had been prescribed AED prophylaxis.

5.6. Extracranial injuries

In the study cohort of 610 patients the most common extracranial injury patterns were skull or facial fractures in 96 patients (16%), thoracic injuries in 18 patients (3%), or spinal fractures in 13 patients (2%). There was only 1 mild TBI patient who presented with a depressed skull fracture.

5.7. Mechanism of injury

In the study cohort of 610 patients the most common observed mechanism of injury was fall from standing height, occurring in 448 patients (73%). The other common mechanisms of injury were, motor vehicle accident in 41 (7%), fall from over 3 m in 30 (5%) and pushbike accident in 25 (4%). In patients suffering a mild TBI, a fall from standing height (77%) represented the most common mechanism of injury.

Of the 115 patients who suffered a moderate or severe TBI, 66 (57%) were admitted with a fall from standing height. There were 18 patients who were involved in a motor vehicle accident, 8 patients involved in a motor bike accident and 6 assaults. There was 1 severe TBI patient who presented with a penetrating missile injury secondary to a gunshot wound.

5.8. Operation type

Overall 84 patients, of the total 610 patients, received an operation. The most common operation was unilateral frontal and parietal burrholes, occurring in 22 patients. Examining the operation type by the TBI grade reveals that all 22 unilateral frontal and parietal burrhole procedures were performed on patients with mild TBI in a delayed fashion. In the 115 patients suffering a moderate or severe TBI, there was a total of 17 primary hemicraniectomies, 1 secondary hemicraniectomy and 1 bifrontal craniectomy. The most common operations in patients with moderate or severe TBI were primary hemicraniectomy alone in 14 patients (12%), craniotomy and evacuation of haematoma in 9 patients (8%), and insertion of ICP monitor in 6 patients (5%). No patients with mild TBI received a craniectomy.

5.9. Operation type and early post traumatic seizures

Comparing operation type and rate of early PTSs showed that of the 14 early PTSs occurring in mild TBI, 12 occurred in patients who did not receive an operation. The other 2 occurred in patients who underwent craniotomy and evacuation of haematoma. Of the 7 patients who had an early PTS in the moderate or severe TBI group, 5 patients did not receive and operation and 2 underwent a craniotomy and evacuation of haematoma.

5.10. Patient characteristics

5.10.1. Anticoagulant or antithrombotic medication

Nearly half of included patients (48%) used anticoagulant or antithrombotic medication. There was weak evidence that patients using anticoagulant/antithrombotic medication were more likely to die within 7 days of presentation (3.6 $p < 0.057$).

Table 3
Table of location of intracranial injury compared with rates of early post traumatic seizures grouped by severity of traumatic brain injury and whether prophylactic antiepileptic drugs were prescribed.

AED prophylaxis prescribed	TBI Grade			Early post traumatic seizure		Total
				No seizure	Seizure	
No prophylaxis	Mild TBI	Intracranial Injury Location	Extra-axial lesion	314	12	326
			Intra-axial lesion	60	1	61
			Intra and Extra-axial lesion	63	0	63
		Total		437	13	450
	Moderate or Severe TBI	Intracranial Injury Location	Extra-axial lesion	29	3	32
			Intra-axial lesion	9	1	10
			Intra and Extra-axial lesion	15	1	16
		Total		53	5	58
	Total	Intracranial Injury Location	Extra-axial lesion	343	15	358
			Intra-axial lesion	69	2	71
			Intra and Extra-axial lesion	78	1	79
		Total		490	18	508
Prophylaxis prescribed	Mild TBI	Intracranial Injury Location	Extra-axial lesion	25	1	26
			Intra-axial lesion	8	0	8
			Intra and Extra-axial lesion	11	0	11
		Total		44	1	45
	Moderate or Severe TBI	Intracranial Injury Location	Extra-axial lesion	25	1	26
			Intra-axial lesion	9	0	9
			Intra and Extra-axial lesion	21	1	22
		Total		55	2	57
	Total	Intracranial Injury Location	Extra-axial lesion	50	2	52
			Intra-axial lesion	17	0	17
			Intra and Extra-axial lesion	32	1	33
		Total		99	3	102

5.10.2. Length of stay

The average length of stay was 11 days. A greater length of stay was observed for higher grade TBI, mild 9 days, moderate 17 days, and severe 21 days. There was strong evidence to suggest that increased length of stay correlated with moderate or severe TBI ($t = 5.86$ 128df CI 7.3–14.8 $p < 0.001$).

6. Discussion

The results of this study indicate that levetiracetam is the most frequently prescribed AED at this institution being prescribed 91% of the time. The overall rate of early PTSs for patients in the study cohort was 3.4%. More significantly, the rate of early PTSs for patients with moderate or severe TBI who did receive prophylactic AEDs was 3.5% compared to 8.6% for those who did not receive prophylaxis. This result was not statistically significant.

6.1. Phenytoin and early post traumatic seizures

In the literature there are six studies [1,3,15–17,19] that assessed the efficacy of phenytoin in preventing early PTSs compared to controls. Four [3,15–17] were able to demonstrate a significant reduction in rates of early PTSs for patients given prophylactic phenytoin.

One of the four studies that demonstrated a significant reduction in the rate of early PTSs in patients prescribed prophylactic phenytoin was conducted by Temkin et al. [17] in 1990. This study established prophylactic phenytoin for early PTS prevention as a component in the management of TBI. They reported a rate of early PTSs for patients prescribed phenytoin of 3.4%, which is similar to our results and those reported in the literature. However, they reported an early PTS rate of 14.3% in patients who were not prescribed AEDs. This is significantly higher than other similar studies (2.2–8.1%) and the rate observed in our study (8.6%).

It is important to note that there are several significant differences between the patients included in the study by Temkin et al. [17] and our moderate or severe TBI patients such as: mean age (34 vs 62), AED prescribed (100% phenytoin vs 91% levetiracetam) depressed skull fractures (17% vs 0.8%), penetrating head injury (8% vs 0.8%), subdural haemorrhage (38% vs 68%), cortical contusions (49% vs 27%). Both cohorts had a similar occurrence of intracerebral haematoma (20%). The difference in AED prescribed is unlikely to be strongly related given that other studies have not demonstrated significant differences between levetiracetam and phenytoin, therefore the differences in patient and intracranial injury patterns are likely contributing to the differences in results.

Firstly, it is well established that there are certain risk factors for PTSs such as penetrating head injuries, depressed skull fractures, intra-axial lesions such as cortical contusions and intracerebral haematomas [18,11]. The increased epileptogenic factors in Temkin's patients may explain the higher rates of early PTS in the non-prophylaxis group.

Secondly, patients with a younger age have less age-related cerebral atrophy and may therefore be more susceptible to intra-axial injury as opposed to subdural haemorrhage, which tends to occur in older populations.

Finally, a factor that may account for these differences could be that Temkin's study was conducted between 1983 and 1987. Our review was conducted 30 years later on patients treated between 2013 and 2017, over which time primary prevention of TBI has significantly improved.

There are several other studies in the literature that have failed to replicate similar results to Temkin. A prospective observational study by Khor et al. [12] examined the rate of early PTSs in 522 patients prescribed prophylactic AEDs at an American institution and compared them to patients not prescribed prophylactic AEDs at a Chinese institution. Information on intracranial injury location was not available but 20.9% of patient received a craniectomy which is similar to our 16.5%. They demonstrated no statistical difference in either patient cohorts with regards to severity of injury or a difference in the rate of early PTSs.

A randomised controlled trial by Young et al. [19] with 244 patients assessed the rate early PTSs in patients prescribed prophylactic phenytoin compared to placebo. The study was unable to demonstrate a significant difference in the rate of early PTSs, with a rate of 3.7% in both groups. Penetrating missile injuries occurred in approximately 12% of patients with at least 50% having a severe TBI (GCS < 8). The mean age of included patients was 25 and at least 47% were operated on within 24 h, although the type of operation is not defined. Therefore, although the patients in this study appeared to have a high severity of injury comparable to Temkin's study they were unable to show a difference in rates of early PTSs.

Another study by Bhullar et al. [1] demonstrated no difference in rate of early PTSs between a cohort of 93 patients who were either prescribed prophylactic phenytoin or placebo. All patients included had severe TBI with at least 58% of patients having an intracerebral haematoma.

It is likely that these studies have been unable to reproduce the results of Temkin et al. [17] because the rate of early PTSs in the placebo group is too similar to the rate of early PTSs in the prophylaxis group. The decreased rate of early PTSs in the no prophylaxis group may be due to differences in the included patients and the severity of their epileptogenic factors. Similarly, as each of these studies occurred over different time periods it may be influenced by the change in primary prevention for TBI.

6.2. Levetiracetam and phenytoin in early post traumatic seizures

There are no studies comparing levetiracetam to placebo. There are four [6,8,10,13] studies that have compared phenytoin with levetiracetam. All of these studies demonstrated no significant difference in the rate of early PTSs for patients prescribed either AED. This created the assumption that levetiracetam is as effective as phenytoin. One [8] of these studies had a large sample size of 813 patients and reported an early PTS rate of 1.5% for patients prescribed either levetiracetam or phenytoin. Importantly, this paper was unable to demonstrate a difference in the rate of complications associated with either AED. This challenges the perception that levetiracetam has a more favourable side effect profile compared to phenytoin. The three [6,10,13] other smaller studies reported an early PTS rate between 0% and 2.1% for phenytoin and 0% and 5% for levetiracetam.

6.3. Neurobehavioural effects of antiepileptic drugs

Two studies have assessed the neurobehavioral effects of prophylactic AEDs for early PTS prevention in TBI patients. A study by Dikmen et al. [5] randomised patients to prophylactic phenytoin or placebo for 12 months post TBI and observation of both groups for a further 12 months. This study demonstrated significant negative cognitive effects at 1 month post injury in the patients treated with phenytoin compared to placebo (78% vs 47%). At 12 and 24 months there was a trend towards better cognitive functioning in the placebo group, although these results were not significant. Although it is not standard practice to prescribe prophylactic AEDs for 12 months, it is important to note that patients with moderate or severe TBI have significant cognitive impairments. Any additional cognitive damage, even from 7 days of AEDs, may have significant effects on their rehabilitation potential in the acute stage.

In our patient cohort, AEDs were only prescribed for 7 days, similar to what has been done in other studies.

Another study by Demkin et al. [4] randomised 279 patients suffering a TBI to early PTS prophylaxis with either 1 month of valproate, 6 months of valproate or 1 week of phenytoin. They demonstrated no significant positive or negative neuropsychological effects from prophylactic valproate and also demonstrated no difference in the rate of early PTSs. Therefore, despite the negligible neuropsychological side effects, valproate could not be recommended for early PTS prophylaxis as it had no therapeutic benefit. There are no other studies that have specifically assessed the efficacy of valproate compared to placebo for the prevention of early PTSs. Valproate was only prescribed to 2 patients in our study therefore its efficacy cannot be accurately assessed using our results.

6.4. Functional outcome in patients with early post traumatic seizures

One study by Lee et al. [14] has assessed the outcomes of patients suffering early PTSs. This study prospectively examined 3340 patients between 1984 and 1995 with severe TBI (GCS < 8) who were not prescribed prophylactic AEDs. Patients were excluded if they had penetrating injuries, depressed skull fractures or a history of seizures before the injury. Patients only received AEDs as a treatment after they had seizures, and for the purposes of the study were not included in further analysis. The average age of patients included was 34 years and at least 85% of injuries were caused by motorcycle accidents or traffic injuries to pedestrians. They demonstrated no difference in neurological recovery at 6 months between patients with or without early PTSs. The significance of this result is that the outcome of patients with severe TBI does not appear to be affected whether or not they have an early PTS. This means that there may be no benefit in administering prophylaxis.

6.5. Operation type

In our review all 22 patients who received frontal and parietal burrholes had also suffered a mild TBI. The likely explanation is that these patients had operations in a delayed fashion once their subdural haemorrhage had liquified. All 19 decompressive craniectomies, 2 external ventricular drains and 7 out of the 8 of ICP monitors were carried out in patients with moderate or severe TBI. The rate of early PTSs was similar between patients who received an operation and those who did not, however our small sample is likely affecting the significance of these results.

6.6. Risk factors for post traumatic seizures

Risk factors for PTSs have been described in the literature [11,18]. Interestingly, in our cohort these risk factors have not been associated with increased rates of early PTSs with similar rates between extra-axial and combined extra and intra-axial. There were no patients with a moderate or severe TBI and an intra-axial lesion in our study with an early PTS. It is likely that this is due to our small sample size.

Overall, the results of our study demonstrate that the most commonly prescribed AED in our institution is levetiracetam. The perception that levetiracetam has lower rates of adverse events compared to phenytoin, is not demonstrated in the literature. However, it is possible that the use of levetiracetam is related to its easier use.

The results regarding rate of early PTSs in moderate or severe TBI from our study appear to be in keeping with other contemporary studies in the literature. However, the patients included in our review had fewer risk factors for seizures, which may have affected our results. In addition, it is possible that other contemporary studies were unable to replicate results similar to Temkin et al. [17] because their patients were not as severely injured. This also makes drawing accurate comparisons between each study difficult due to the heterogeneity of the patient cohorts. Given our review was conducted on patients recently treated at a trauma centre, it may represent a more modern demographic of patients that present with TBI. Patients included in our review were older, had higher rates of falls and subdural haemorrhage, with decreased rates of high-risk epileptogenic features such as penetrating head injuries and depressed skull fractures. It is possible that this may affect any future studies that aim to examine the efficacy of early PTS prevention.

There appears to be conflicting evidence regarding the neurocognitive effects of AEDs in patients with moderate or severe TBI. Finally, there is no evidence to demonstrate any long-term detriment in patients having early PTSs. Therefore, it appears that the practice of prophylactic AEDs for prevention of early PTSs in patients with moderate or severe TBI should be re-examined as it may be ineffective and/or may have no impact on the patient's neurological recovery.

6.7. Limitations

This study has several limitations that are mainly due to its retrospective nature. A major limitation relates to accurate detection of early PTSs in patients who were not prescribed prophylactic AEDs. At the study institution a standardised protocol for managing TBI does not exist. However, the accepted treatment is for patients with severe TBI to be prescribed prophylactic AEDs routinely. Whereas, patients with moderate and mild TBI are only prescribed prophylactic AEDs on an individualized basis. Patients who are receiving palliative treatment, have sustained non-survivable injuries or who are being maintained on life support for organ donation do not receive prophylactic AEDs. However, as these patients would not have died within 24 h of presentation they would have been included in data collection. These patients would not receive frequent routine observations, and therefore seizure activity may have been missed. This could have resulted in an under-reporting of the early PTS rate in patients who were not prescribed AEDs.

Due to the studies retrospective nature it was difficult to determine why some patients did not receive AED prophylaxis, as was determining why a particular AED was prescribed instead of another. It is common practice at the study institution for all patients with a severe TBI to receive AED prophylaxis as a component of neuroprotective treatment. Patients with mild or moderate TBI are prescribed AED prophylaxis at the discretion of the treating clinician. This is usually done by assessing the intracranial injury type and location and determining the risk for post-traumatic seizures. Unfortunately, this rationale is rarely documented, which makes it difficult to study. This may explain the differences in the type of AED prescribed as well as why some patients did not receive AED prophylaxis.

A limitation due to sampling error may have occurred during our study. Given that this was a case note review it heavily relied on the ICD 10 codes assigned to the patient. It is possible that the incorrect code may have been assigned to some patients, resulting in their case not being included in analysis. This potential error was addressed in the methodology by the primary author reviewing all intracranial haematomas and then selecting the patients with a traumatic aetiology for inclusion in the study. Another potential error relating to ICD 10 codes is related to the staff involved in assigning the discharge diagnosis. At this institution a discharge diagnosis is assigned by a doctor on the treating team. The diagnosis is then assigned the appropriate ICD 10 code by administrative

staff. This does reduce the potential bias by removing the financial gain from ICD 10 code that is occurring in a variety of institutions around the world.

A limitation encountered by most studies investigating rates of early PTS is that only clinically detectable seizures were recorded. As in most other studies, patients in this study were not routinely monitored with continuous EEG. Therefore, the true rate of convulsive and non-convulsive seizures could not be determined, potentially resulting in an under reporting of rates of early PTS.

7. Conclusion

In conclusion, the overall rate of early PTSs in patients with moderate or severe TBI who did receive prophylactic AEDs at our institution was 3.5%. The rate of early PTSs in patients with moderate or severe TBI who did not receive prophylactic AEDs was 8.6%, but this was not found to be statistically different. Levetiracetam was the most frequently prescribed AED at our institution. This study adds to the contemporary literature calling for the practice of prescribing prophylactic AEDs for the prevention of early PTSs to be re-examined.

8. Ethics approval

For this type of study formal consent is not required.

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Informed consent

This article does not contain any studies with human participants performed by any of the authors.

Declaration of Competing Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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