SEIZURE PROPHYLAXIS IN PATIENTS WITH TRAUMATIC BRAIN INJURY (TBI)

SUMMARY

Post-traumatic seizures (PTS) are common complications of TBI. Early PTS are linked to a high incidence of late PTS and chronic epilepsy. CT scan is a useful modality in identifying the probability of late PTS. EEG is a promising, but currently underdeveloped technique for the prognostic evaluation of PTS. Pharmacoprophylaxis of early PTS includes phenytoin, levetiracetam, and carbamazepine. Pharmacoprophylaxis of late PTS is not routinely recommended. Valproate and phenobarbital are not acceptable agents in the prophylaxis of PTS.

RECOMMENDATIONS

- **Level 1**
  - ➤ Phenytoin is effective in decreasing the risk of early PTS in patients with severe TBI.
  - ➤ No antiepileptic prophylaxis prevents late PTS.
  - ➤ PTS prophylaxis in patients with mild or moderate TBI is not routinely recommended.

- **Level 2**
  - ➤ Levetiracetam is a safe and effective alternative to phenytoin for early PTS prophylaxis.
  - ➤ Routine prophylaxis of late PTS is not recommended.

- **Level 3**
  - ➤ Levetiracetam for 7 days is preferred for early PTS prophylaxis.
  - ➤ Prolonged antiepileptic therapy (> 7 days) should be determined by expert consultation.

INTRODUCTION

Traumatic Brain Injury (TBI) is the most common cause of death in North America for individuals between the age of 1 and 45, accounting for 1.1 million emergency department visits and one hospitalization per 1,000 people each year(1-3). Among all patients with head trauma who seek medical attention, 2% develop post-traumatic seizures (PTS), and in those with moderate to severe brain trauma, 8.5% develop PTS (3,9). Approximately 12% of patients with severe TBI will develop PTS, however, this risk may approach 50% when seizure activity is diagnosed by electroencephalography (EEG) (4,5). Exposure to penetrating missile injuries is associated with a PTS rate as high as 50% (6-8).

PTS may cause secondary brain injury asa result of increased metabolic demands, increased intracranial pressure, compromised cerebral oxygen delivery, and excess neurotransmitter release. The following are risk factors for the development of PTS (9,10):

EVIDENCE DEFINITIONS
- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS
- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

- Alcoholism
- Younger age
- Penetrating injuries
- Intracranial hemorrhage
- Severity of injury
- Length of posttraumatic amnesia
- Loss of consciousness
- Focal neurologic deficits
- Depressed skull fracture
- Cerebral contusions
- Retained bone and metal fragments
- Lesion location

Early seizures after traumatic and non-traumatic brain insults have been found to be predictive of subsequent epilepsy development (11,12). While a seizure during the first week after injury (early PTS) is associated with subsequent late PTS (after the first week postinjury), late PTS is correlated with an even higher rate of recurrence. Prompt and effective prophylaxis of both early and late PTS is crucial to the reduction of seizure recurrence rates as well as the morbidity of recurrent seizures.

When selecting appropriate medical management, it is important to differentiate between (13):
- Early PTS: 0-7 days after injury
- Late PTS: more than 7 days after injury

The severity of TBI can be estimated as (4,14,15):
- Mild: loss of consciousness or post-traumatic amnesia less than 30 minutes or GCS 13-15
- Moderate: loss of consciousness or post-traumatic amnesia for 30 minutes to 24 hours or a skull fracture or GCS 9-12
- Severe: brain contusion or intracranial hematoma or a loss of consciousness or post-traumatic amnesia for more than 24 hours or GCS 3-8

TBI may be assessed radiographically using the Marshall Computed Tomography (CT) Classification for Head Injury (16) (Table 1).

Table 1: Marshall CT Classification

Category	Definition
Diffuse Injury I	- No visible intracranial pathology seen on CT
Diffuse Injury II	- Cisterns are present with midline shift 0-5 mm and/or lesion densities present - No high- or mixed-density lesion >25 mL - May include bone fragments and foreign bodies
Diffuse Injury III	- Cisterns compressed or absent with midline shift 0-5 mm - No high- or mixed-density lesion >25 mL
Diffuse Injury IV	- Midline shift > 5 mm - No high- or mixed-density lesion >25 mL
Diffuse Injury V (Evacuated mass lesion)	- Any lesion surgically evaluated
Diffuse Injury VI (Non-evacuated mass lesion)	- High- or mixed-density lesion >25 mL - Not surgically evacuated

TBI may also be classified via the Rotterdam scale, developed to overcome limitations in the Marshall CT Classification. It predicts six month mortality based on score, as indicated below (17) (Table 2):

Table 2: Rotterdam CT scale

Predictor value	Score
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift or shift ≤5 mm	0
Shift >5 mm	1
Epidural mass lesion	
Present	0
Absent	1
Intraventricular blood or subarachnoid hemorrhage	
Absent	0
Present	1
Sum score	**Total + 1**

Risk of Six Month Mortality by Rotterdam CT scale

- Score 1: 0%
- Score 2: 7%
- Score 3: 16%
- Score 4: 26%
- Score 5: 53%
- Score 6: 61%

The use of antiepileptic drugs to treat patients who have developed post-traumatic epilepsy is an accepted standard of care. However, there is substantial variability among clinicians in the practice of PTS prophylaxis. Two surveys of neurosurgeons reported that a majority prescribed antiepileptic drugs for seizure prophylaxis at least some of the time, although the indications, choice of drug, and duration of treatment varied widely (18,19). Similar variability was seen in the care of head injured patients referred to a rehabilitation center (20).

This review systematically analyzes available literature and proposes recommendations for seizure prophylaxis in TBI patients.

LITERATURE REVIEW

Imaging Modalities in PTS prophylaxis
Electroencephalography (EEG)
Several methods have been suggested to improve identification and monitoring of PTS onset. EEG was proposed as a potential method of prediction and early prophylaxis. Studies do not clearly associate EEG findings with early or late PTS (21-24). Vespa et al. (Class II study) employed continuous EEG monitoring to establish the incidence of convulsive and non-convulsive seizures in the ICU during the initial 14 days post-injury (25). In 52% of patients, the seizures were non-convulsive and diagnosed on the basis of EEG studies alone. Another study by Vespa (Class II) assessed the usefulness of continuous EEG monitoring in ICU patients for determining prognosis after TBI (26). Percentage of alpha variability (PAV) was found to be a sensitive and specific method of prognosis to indicate outcomes in patients with moderate to severe TBI within 3 days of injury. Ronne-Engstrom et al. (Class II study) established the presence of certain epileptiform activity on EEG in TBI patients, which in 67% of cases was a seizure (27). Jones et al. (Class II study) utilized 1 hour EEG monitoring for comparing phenytoin vs. levetiracetam monotherapy for PTS prophylaxis in patients with severe TBI. They concluded that clinical seizures are difficult to identify through observation or physical examination in the early stages after severe TBI. In addition, TBI itself along with sedative and neuromuscular blockade agents used in the ICU may mask seizure activity. Routine use of

EEG monitoring to discern abnormal EEG patterns was encouraged. Based on the evidence outlined above, EEG appears to be an attractive option of early seizure onset detection and prophylaxis, especially in the ICU setting. However, more studies are needed to precisely determine EEG patterns related to PTS onset and establish a treatment protocol.

Computed Tomography
Englander et al. (Class II study) found that CT scan findings and neurosurgical procedures performed were the most useful factors in identifying moderate to severe TBI patients at highest risk for late post traumatic seizures (28). The following factors had the highest cumulative prognostic probability for late PTS onset: biparietal contusions (66%), dural penetration with bone and metal fragments (62.5%), multiple intracranial operations (36.5%), multiple subcortical contusions (33.4%), subdural hematoma with evacuation (27.8%), midline shift greater than 5mm (25.8%), or multiple or bilateral cortical contusions (25%). Initial GCS score was associated with the following cumulative probabilities for development of late PTS at 24 months: GCS score of 3 to 8, 16.8%; GCS score of 9 to 12, 24.3%; and GCS score of 13 to 15, 8.0%. Initial injury severity as measured by GCS score alone was not associated with higher cumulative risk for late PTS. Debenham et al. (Class III study) supported these claims by identifying positive CT findings as a primary decision-making parameter in administering phenytoin prophylaxis to patients with mild TBI (15). He also identified a Marshall category of IV or more as an important factor suggesting need for anticonvulsant prophylaxis. Age and initial GCS score were not identified as factors affecting the development of PTS. CT scan can be successfully implemented in the decision making process on PTS prophylaxis in TBI patients.

Early PTS Pharmacoprophylaxis in Patients with TBI
Pharmacoprophylaxis against early seizures following TBI is recommended currently in the 2016 Trauma Brain Foundation Guidelines and endorsed by the American Association of Neurologic Surgeons Joint Section on Neurotrauma and Critical Care, the World Health Organization's Committee on Neurotrauma, and the Congress of Neurologic Surgeons. According to the most recent Trauma Brain Foundation Guidelines, anticonvulsants are indicated to decrease the incidence of early PTS. However, early PTS is not associated with worse outcomes (29,30). The limitation of these guidelines is their focus on adults with severe TBI (GCS 3-8).

Phenytoin
Although several antiepileptic drugs are available for early PTS prophylaxis in the setting of severe TBI, phenytoin is used most commonly (31). Two class I studies assessed the efficacy of phenytoin for PTS prophylaxis in patients with severe TBI. Temkin et al. demonstrated a significantly lower rate of early PTS development among the group who received prophylaxis compared to the placebo group with a relative risk (RR) of 0.25 (32). Young et al. evaluated a similar phenytoin regimen in a smaller but similar cohort and found no significant difference (33). However, the rate of early seizures reported in this study (3.7%) was much lower than the rates reported in other studies and the 95% CI (0.27 – 3.58) was very wide suggesting insufficient power to detect a statistical difference. To arrive at a definitive conclusion, Chang et al. pooled the data from two Class 1 studies and demonstrated a significantly lower rate of early seizures among the pooled prophylaxis group compared to the pooled control group with a RR of 0.37 (95% CI 0.18 to 0.74) (31). Additionally, one class III study evaluated phenytoin and showed a significant difference in PTS risk reduction (RR 0.24, 95% CI 0.06-0.98) (21). Controversially, a more recent retrospective cohort study of 93 patients with blunt severe TBI (class 3) found no difference between phenytoin prophylaxis and no antiepileptic drug treatment in early seizure rates, length of stay in ICU, days on the ventilator, or TBI-related mortality. The treatment group had significantly worse functional outcome at discharge based on Glasgow score (2.9 vs. 3.4, $p < 0.01$), and longer hospital stays (36 vs. 25 days, $p = 0.04$) (34). However, further randomized trials are needed to verify these results, and they cannot apply to penetrating traumas.

- Dosing
  In most instances, phenytoin is administered intravenously with a loading dose of 17 mg/kg intravenous infusion over 30-60 minutes, followed by a maintenance dose of 100 mg given three times daily, either intravenously or orally for a total of seven days. In appropriate patients, an oral loading dose of 300 mg orally can be given every 6 hours for a total of three doses (900 mg), followed by the same maintenance dose as described above (15).

- Serum levels
Testing of serum phenytoin levels was performed in all studies outlined above. Temkin et al. reported 97% of phenytoin-treated patients to have levels in or above the therapeutic range on the first day after injury and 57% to maintain such levels at 1 week (32). All patients with early seizures had therapeutic levels on the day of their first seizure. Young et al. observed that more than 78% of patients maintained therapeutic levels through the first week although only 60% of those who had an early seizure had a therapeutic level immediately afterward (33).

- Adverse effects
Phenytoin traditionally has been linked to serious adverse events including Stevens-Johnson syndrome, anticonvulsant hypersensitivity syndrome, purple glove syndrome, and induction of the hepatic cytochrome P450 system, causing significant drug-drug interactions and necessitating the need for frequent laboratory monitoring of serum levels (34,35). However, few adverse effects specifically occurring within the first week of phenytoin therapy were reported in the studies outlined above. Temkin et al. reported that 5.2% of patients stopped phenytoin and 9.2% stopped placebo in the first week owing to patient request or idiosyncratic and other reactions (32). Additional analysis of side effects in the same cohort has been published separately (36). Young et al. reported one patient to experience the side effect of a rash during the first week of phenytoin therapy (33). Debenham et al. reported a total of five patients (0.8%) who had adverse reactions to phenytoin including bradycardia, face and trunk redness, skin itchiness without a rash, and elevated liver enzymes (15).

Levetiracetam
Recent evidence suggests that levetiracetam (Keppra) is both safe and efficacious in preventing PTS following severe TBI. There is an increasing trend in the use of levetiracetam versus phenytoin for seizure prophylaxis (35). In 2010, one prospective randomized, single-blinded study of 52 patients (Class II) compared IV levetiracetam with IV phenytoin in patients with severe TBI (39). Patients treated with levetiracetam experienced better long-term outcomes than those on phenytoin, based on the Disability Rating Scale score and the Glasgow Outcomes Scale score. There were no differences between groups in seizure occurrence during continuous (performed in the first 72 hrs) EEG or at 6 months. There were no differences in mortality or side effects between groups except for a lower frequency of worsened neurological status and gastrointestinal problems in levetiracetam-treated patients. Another Class II study supported these findings with an equivalent incidence of seizure activity in patients treated with levetiracetam and phenytoin. However, patients receiving levetiracetam had a higher incidence of abnormal EEG findings (p = 0.003) (40). A recent prospective, observational study of 813 patients (class 2) showed no benefit of levetiracetam over phenytoin, with no significant difference in seizure rate, adverse drug reactions, or mortality in between the two groups (p= 0.997, 0.227, and 0.236, respectively) (43).

- Dosing
A loading dose of 20 mg/kg IV (rounded to the nearest 250 mg and administered over 60 min) followed by a maintenance dose of 1000 mg IV every 12 hrs (given over 15 min) (37). The dose may be adjusted as needed for therapeutic effect up to 1500 mg every 12 hrs (3000 mg/day).

- Serum levels
Levetiracetam is a non–enzyme-inducing anticonvulsant that does not require serum level monitoring. This provides a clinical advantage over phenytoin dosing.

- Adverse effects
Levetiracetam is not known to have significant pharmacokinetic interactions or cutaneous hypersensitivity reactions (41). Szaflarski et al. recorded the following adverse effects in order of decreasing frequency: fever, increased intracranial pressure, stroke, worsening neurologic status, hypotension, cardiac arrhythmia, anemia, low platelets, coagulation deficits, abnormal liver function tests, renal, gastrointestinal, etc. (37). There were no differences between phenytoin and levetiracetam treated patients in the occurrence of fever, increased intracranial pressure, stroke, hypotension, arrhythmia, thrombocytopenia/coagulation abnormalities, liver abnormalities, renal abnormalities, or early death (all p>0.15). Levetiracetam-treated patients experienced worsening neurological status less

frequently (p=0.024) and had fewer gastrointestinal problems (p=0.043); there was tendency toward a lower incidence of anemia in patients treated with phenytoin (p=0.076).

- Cost-benefit analysis
  Although levetiracetam represents a safe and effective alternative to phenytoin and obviates the need for serum level monitoring, the literature disagrees on its cost-effectiveness. (42). One experimental study showed that levetiracetam has the potential to be a more financially conservative option. Kazerooni et al. calculated the incremental cost-effectiveness ratio of levetiracetam versus phenytoin for each successful seizure prophylaxis regimen to be 360.80 USD (44), Controversially, another cost-minimization analysis revealed the superiority of phenytoin over levetiracetam from both the institutional (mean cost per patient $151.24 vs. $411.85, respectively) and patient (mean charge per patient $2,302.58 vs. $3,498.40, respectively) perspectives. Varying both baseline adverse event probabilities and frequency of laboratory testing did not alter the superiority of the phenytoin treatment. Levetiracetam replaced phenytoin as the dominant strategy only when the cost/charge of treating mental status deterioration was increased markedly above baseline (42). Therefore, although both treatments may have similar therapeutic efficacy, the issue of increased cost with levetiracetam use should be noted.

Carbamazepine
One class II study found a significantly lower rate of early seizures among 139 patients with severe TBI receiving carbamazepine prophylaxis (RR 0.37) (43). Carbamazepine was started immediately after the injury and was continued for 1.5-2 years. The dosage was adjusted to provide serum levels within therapeutic range. Recommended duration of treatment was one year.

Valproate
Two class I studies recommended against the use of valproate for early PTS prophylaxis in patients with severe TBI. Temkin et al. showed no benefit of valproate therapy over short-term phenytoin therapy for prevention of early seizures and stated that neither treatment prevents late seizures (46). Dikmen et al. concluded that valproate does not prevent PTS (47). Both studies established a trend toward a higher mortality rate among valproate-treated patients (46,47).

Several other drugs and drug combinations have been tested for the prophylaxis of early PTS including phenobarbital, combination phenytoin-phenobarbital, and magnesium. None are recommended for prophylaxis measures based on study outcomes (48-52).

Late PTS Prophylaxis in Patients with TBI
The 10 year incidence of post traumatic epilepsy (PTE) after TBI is about 2 percent. In contrast to early seizures after TBI, older age (greater than 65 years) is a risk factor for PTE (3). However, the 2016 Trauma Brain Foundation guidelines do not recommend prophylactic use of phenytoin or valproate for prevention of late PTS (29). The limitation of these guidelines is their focus on adults with severe traumatic brain injury (Glasgow Coma Scale score 3-8).

Several studies assessed the effect of antiepileptic drugs on late PTS prevention in TBI patients. Two randomized placebo controlled double blinded Class I studies evaluated the efficacy of phenytoin in seizure prophylaxis (53, 54). McQueen et al. enrolled patients who met at least one criterion for severe TBI, while Young et al. enrolled only those patients estimated to have a 15% or higher chance of developing late posttraumatic epilepsy. Neither of these studies was able to demonstrate a significant difference in late seizure rates between the treated group and control group. Three class II studies evaluated the efficacy of phenytoin, carbamazepine and valproate respectively on PTS prophylaxis in TBI patients (33,45,55). None of these studies demonstrated a significant difference in the rate of late seizures between the treated and control groups. High rates of late seizures were demonstrated in both treated and control groups in the carbamazepine study while each of two other class II studies had RR greater than 1.0. Three class III studies assessed the efficacy of phenytoin, phenobarbital and combination phenytoin-phenobarbital respectively (48,56,57). Pechadre et al. and Servit et al. demonstrated a decrease in late seizure rate (RR 0.14 and 0.08 respectively) in patients with TBI. However, the reliability of these two studies is uncertain

due lack of random assignment, masked assessment or use of placebos in the control group. Another class III study by Manaka et al. showed no difference between treatment and control groups. Additional analysis involving pooled data from five class I and II studies resulted in a pooled RR of 1.05 (95% CI 0.82 – 1.35) demonstrating no effect of antiepileptic drugs on late PTS prevention in patients with TBI.

Adverse effects observed in the studies assessing the efficacy of anticonvulsants in late PTS prophylaxis in patients with TBI were similar to the ones encountered with early PTS prophylaxis. Rash was the most common adverse effect in patients treated with phenytoin (33,46,53). Lethargy and fatigue were the most common side effects in patients treated with valproate (47,58). In addition, treatment with valproate was associated with increased mortality.

PTS Prophylaxis in Patients with Mild to Moderate TBI
The majority of studies on PTS prophylaxis focus on patients with severe TBI and tend to exclude those with mild to moderate head trauma. In general, patients with mild TBI have lower rates of PTS when compared with severe TBI (59). At the same time, an excess PTS risk of 1.5 (95% CI 1.0 - 2.2) was found in patients with mild TBI in one study, and the risk in this group continued to be elevated for five years (4). Another study reported a moderate, but not significant excess of seizures after mild TBI (59). The mechanisms of mild TBI are often different from those encountered in severe TBI patients (33).

Currently, a limited number of studies report data on PTS prophylaxis in patients with mild TBI. Debenham et al. conducted a retrospective study (class III) with 73% of patients assigned to a mild TBI group based on GSC scale (15). 1008 patients treated with IV phenytoin for seizure prophylaxis were included of whom 5.4% developed early PTS, which is comparable to the rates observed in patients with severe TBI. Phenytoin levels were drawn in 42.2% of those enrolled: 52% therapeutic, 41% low, 7% high. More studies in this group of patients are needed in order to definitively establish the guidelines.

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