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SEIZURE PROPHYLAXIS IN PATIENTS WITH TRAUMATIC BRAIN INJURY (TBI)
Evidence Based Medicine Guideline

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SUMMARY
Post-traumatic seizures (PTS) are common complications of TBI. Early PTS are linked to a high incidence of late PTS and chronic epilepsy. EEG is a promising, but currently underdeveloped technique for the prognostic evaluation of PTS. Pharmacoprophylaxis for early PTS includes phenytoin and levetiracetam. Pharmacoprophylaxis of late PTS is not routinely recommended. Valproate is not recommended for prophylaxis of PTS.

NOTE: *Patients with a history of epilepsy and on antiepileptics prior to their TBI should have their home therapy resumed and no additional agents added without expert consultation.*

RECOMMENDATIONS

- **Level 1**
  - None
- **Level 2**
  - PTS prophylaxis in patients with mild TBI (GCS ≥13) is not routinely recommended – see Table 1 (page 2) for risk factors for PTS.
  - Phenytoin is NOT recommended for early PTS prophylaxis due to long-term neurologic sequelae**.**
  - Levetiracetam may be considered first line for early PTS prophylaxis over phenytoin in patients with moderate to severe TBI due to easy dosing, no lab needs, and lack of long-term neurologic sequelae.
  - Routine prophylaxis of late PTS is not recommended.
- **Level 3**
  - Levetiracetam 1000 mg IV/PO/Per Tube Q12H for 7 days is the recommended dosing at our institution (see Table 2, page 3, for age / renal dose adjustment recommendations).
  - Prolonged antiepileptic therapy (> 7 days) should be determined by expert consultation.
  - Patients with a history of seizures on antiepileptic therapy should be continued on their home antiepileptics with no additional prophylaxis and expert consultation obtained if they experience breakthrough seizures.
  - If PTS prophylaxis is initiated, reassess need at 24 hours post-initiation
  - Consider obtaining a spot EEG to rule out PTS in patients with GCS ≤ 10 for > 24 hours.
  - Patients presenting with a seizure – initiate antiepileptic therapy, consider obtaining expert consultation and refer to the Status Epilepticus Guideline.

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, 4-25% develop post-traumatic seizures (PTS). For patients sustaining a severe TBI (GCS ≤ 8), up to 12% will develop clinical PTS and the rate increases

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.

to 25% with the detection of subclinical seizures by electroencephalography (EEG) (1-3). Exposure to penetrating missile injuries is associated with a PTS rate as high as 50% (4-6).

PTS may cause secondary brain injury as a 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 (1,7,8):

Table 1. Risk Factors for PTS.

• Alcoholism	• Loss of consciousness
• Cerebral contusions	• Moderate to severe TBI (GCS < 13)
• Depressed skull fracture	• Penetrating injuries
• Focal neurologic deficits	• Retained bone and metal fragments
• Intracranial hemorrhage	• Requires neurosurgical intervention
• Length of posttraumatic amnesia	• Younger age
• Lesion location	

Patients presenting with mild TBI (GCS 13-15) do not need routine PTS prophylaxis (9). A study by Zaher M et al., evaluated 839 with mild TBI showed no difference in seizure rates for those who received prophylactic AEDs and those without (0.7% vs 2.9%, p = 0.25) (10).

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 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 (14,15). Similar variability was seen in the care of head injured patients referred to a rehabilitation center (16).

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

LITERATURE REVIEW

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 (17-20). 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 (21). 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 (22). 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 (23). Based on this information, routine use of EEG monitoring to discern abnormal EEG patterns and identify electrographic seizures is encouraged. It is recommended to obtain at least a spot EEG within 24 hours of admission for all patients with a GCS ≤ 10 (24).

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). The majority of the data is with phenytoin and levetiracetam. Valproic acid has also been studied and is not recommended for PTS prophylaxis due to a higher mortality rate (1,25-31).

Pharmacotherapy for PTS Prophylaxis

Phenytoin

Although several antiepileptic drugs are available for early PTS prophylaxis in the setting of severe TBI, phenytoin was the first to show benefit in prevention of early PTS (32,33). 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 (33). Young et al. evaluated a similar phenytoin regimen in a smaller but similar cohort and found no significant difference (34). 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. In the decades since the Tempkin trial, there has been increasing evidence of long-term neurocognitive harm in patients treated with phenytoin. So although it first established the pharmacoprophylaxis is effective in preventing early PTS, it is no longer recommended as the preferred agent (1,35,36).

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 (37). 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 ($p = 0.003$) (38). Khan NR, et al., conducted a metanalysis of levetiracetam vs phenytoin for PTS prophylaxis in TBI. This study included 1186 patients and found no significant difference in PTS between the two groups (levetiracetam 5.4% vs phenytoin 3.4%, $p = 0.96$). (39).

One area of controversy remains the optimal dose of levetiracetam for seizure prophylaxis. The majority of TBI patients will have augmented renal clearance (ARC). Spencer DD, et al. conducted a pharmacokinetic study of levetiracetam in neurocritical care patients – including patients with TBI and aneurysmal subarachnoid hemorrhage, the two populations known to exhibit ARC. They studied a dose of levetiracetam 500mg IV Q12H and targeted a trough levetiracetam level of 6-20 mcg/mL. It was identified that the majority of patients had trough levels below the target range (mean 3.1 ± 1.8 mcg/mL). Based on the information obtained, for at least 50% of patients with ARC to achieve a target trough to 6-20 mcg/mL, the levetiracetam dose needs to be either 1000mg Q12H or 500mg Q8H (40). Elderly patients and patients with poor renal function still require dose and/or frequency reduction (41). The following table outlines the recommended levetiracetam dosing for PTS in TBI patients:

Table 2: Levetiracetam Dosing for PTS Prophylaxis.

Age and/or Renal Function	Levetiracetam Dose for PTS Prophylaxis
Age < 75 years AND CrCl > 50 mL/min	1000 mg IV / PO / Per Tube Q12H x 7 days
Age ≥ 75 years AND/OR CrCl ≤ 50 mL/min	500 mg IV / PO / Per Tube Q12H x 7 days
End-Stage Renal Disease (ESRD)	500 mg IV / PO / Per Tube QHS x 7 days

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