Canadian Journal of Emergency Medicine
https://doi.org/10.1007/s43678-023-00554-7

JUST THE FACTS

Just the facts: seizure prophylaxis post-traumatic brain injury (TBI)

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Received: 8 March 2023 / Accepted: 24 June 2023

Clinical scenario

A 30-year-old, 100 kg (kg), male is transported by paramedics to a tertiary care emergency department (ED) following a high-speed motorcycle crash. Bystanders report he lost control of his motorcycle and hit his head after swerving to avoid a small animal on the road. When paramedics arrived, the patient suffered a 2 min generalized tonic clonic seizure. On assessment in the ED, he is hemodynamically stable. His Glasgow Coma Scale (GCS) is calculated to be 6 (E1 V2 M3). He has obvious facial abrasions and contusions with no other major traumatic injuries. He is intubated for airway protection in the trauma bay prior to transport to radiology for imaging. CT imaging demonstrates multifocal regions of intracranial hemorrhage, traumatic subarachnoid hemorrhage and an 8 mm left subdural hemorrhage with no midline shift.

Key clinical questions

Question 1: What are post-traumatic seizures and who is at risk?

Post-traumatic seizures are a common sequala of severe traumatic brain injury (TBI, GCS of ≤ 8). Clinically apparent seizures occur in approximately 12% of TBI patients, whereas nonconvulsive seizures may be detected on electroencephalography (EEG) in up to 25% of patients with severe TBI [1]. Post-traumatic seizures are classified as early if occurring within 7 days from injury and late if occurring after more than 7 days [1]. Immediate post-traumatic seizures are a distinct category of seizures that occur at impact within seconds of injury and up to 24 h after injury [2]. There are multiple known risk factors for early post-traumatic seizures (Fig. 1) [1, 2].

Question 2: What is the benefit of seizure prophylaxis post TBI?

Seizure prophylaxis with anti-seizure medications may be administered post TBI to decrease the risk of post-traumatic seizures and minimize secondary brain injury. Seizures are known to increase metabolic demands in vulnerable brain tissue, alter cerebral blow flow, and increase intracranial pressure, which can lead to brain herniation and death. Seizure prophylaxis has been associated with a reduction in the incidence of early post-traumatic seizures [1–4]. Recent large, retrospective registry data indicates that early post-traumatic seizures may be associated with increased intensive care unit (ICU) admissions, ICU length of stay (LOS), ICU ventilation days, hospital LOS, as well as increased risk of developing a long-term seizure disorder and death (at 24 months) [5]. However, most studies demonstrate no consistent effect of seizure prophylaxis on the prevention of late post-traumatic seizures, the development of epilepsy, or mortality [1, 3].

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Published online: 13 July 2023

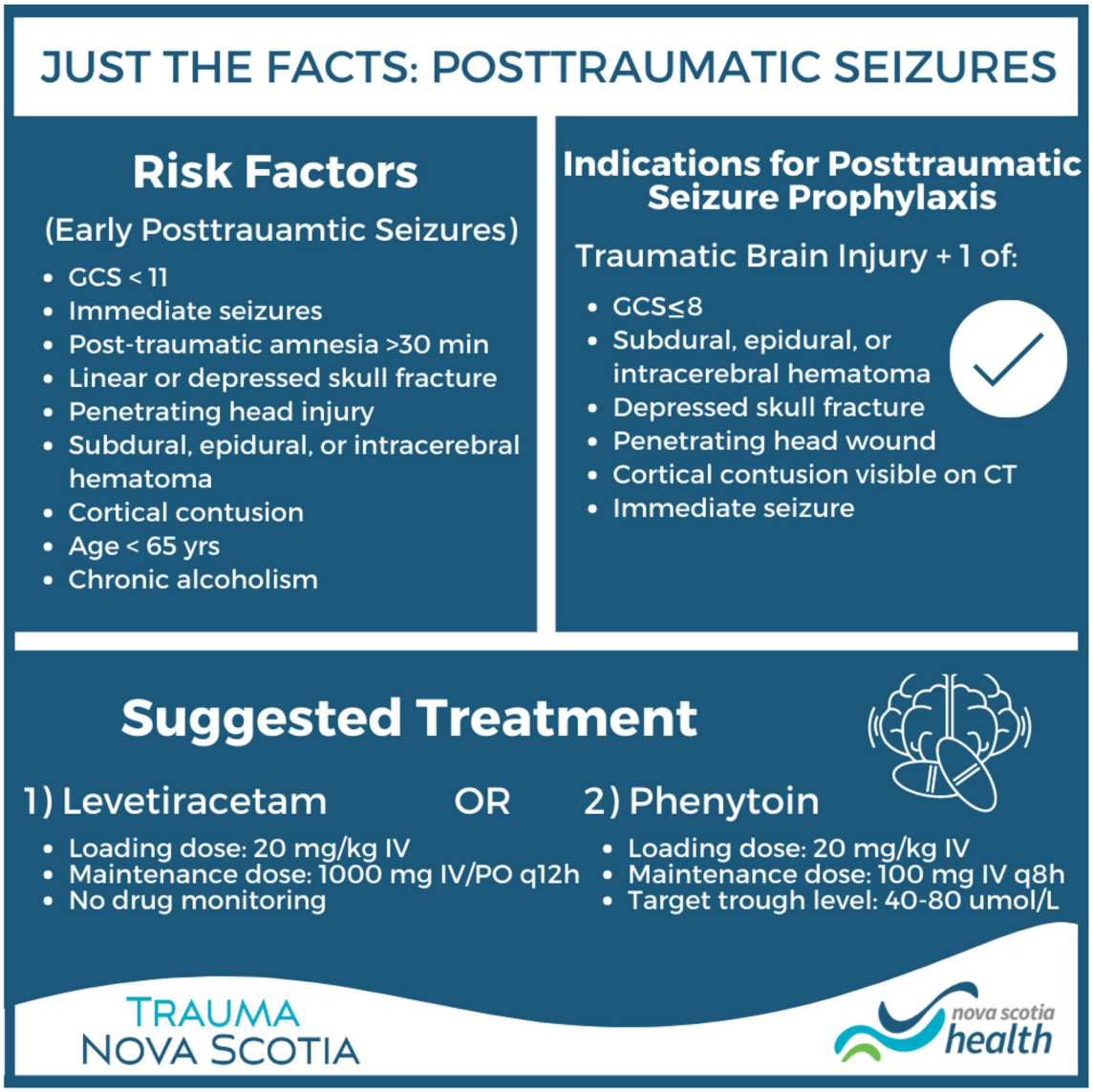

Fig. 1 Risk factors, indications for prophylaxis, and suggested treatment for posttraumatic seizures

Question 3: Who should receive seizure prophylaxis post TBI?

Both the brain trauma foundation (BTF, Level IIA) and American Academy of Neurology (AAN, Level A) recommend seizure prophylaxis be initiated for the first 7 days following injury to decrease the incidence of early post-traumatic seizures in patients with severe TBI [1, 3]. It is generally recommended for patients with severe TBI and the presence of specific clinical or radiological findings (Fig. 1). This recommendation is primarily based on evidence that phenytoin when compared to placebo resulted in an overall reduction in early post-traumatic seizures from 14.2% to 3.6% [2].

Question 4: What medication should be used and at what dose?

Historically, phenytoin has been the medication of choice and is the most rigorously studied medication for seizure prophylaxis post TBI [1]. Prescribed as a loading dose of 17–20 mg/kg intravenous (IV) followed by maintenance doses of 100 mg IV every 8 h or 5 mg/kg/day IV divided every 8 h titrated to a target trough level of 40–80 umol/L [6].

However, levetiracetam is a potential alternative to phenytoin given its more favourable side effect profile, minimal drug-drug interactions, and the lack of need for therapeutic drug monitoring [7]. A loading dose of 20 mg/

kg IV can be administered to rapidly achieve serum concentrations associated with seizure control followed by a maintenance dose of 1000 mg IV or enterally every 12 h. While robust randomized studies comparing phenytoin and levetiracetam are lacking, there is some evidence that levetiracetam offers similar efficacy to phenytoin. Inaba et al. compared levetiracetam (1000 mg IV every 12 h) to phenytoin in patients with severe TBI and found no association between anti-seizure medication choice and the incidence of seizures, complications, or mortality [8]. Szaflarski et al., conducted a prospective randomized trial comparing levetiracetam (20 mg/kg IV loading dose followed by 1000 mg IV every 12 h) to phenytoin in neurosurgical ICU patients (89% with severe TBI). They found no difference in early seizure occurrence or mortality, however survivors in the levetiracetam group were found to have less undesirable adverse effects and improved long-term functional outcomes [6].

One potential concern often raised with regards to using levetiracetam instead of phenytoin for seizure prophylaxis is the potential increased cost of levetiracetam. However, when local costs were compared for a 100 kg patient the cost of a 20 mg/kg IV loading dose of levetiracetam was $85.04 compared to $50.00 for a 20 mg/kg IV loading dose of phenytoin. Phenytoin is typically administered IV due to interactions between phenytoin and enteral nutrition that may result in decreased absorption. However, assuming a patient has enteral access and is tolerating enteral medications, there is no reason that levetiracetam maintenance doses cannot be administered enterally as levetiracetam is 100% bioavailable and quickly absorbed. Utilizing enteral levetiracetam in appropriate patients reduces the cost of the total 7 day course of medication to $88.00 for levetiracetam compared to $190.00 for phenytoin making it overall a more cost effective option.

Question 5: How long should seizure prophylaxis be continued?

The optimal duration of anti-seizure medication in patients post TBI is not well defined and depends in part on the severity of the TBI, presence of seizures, seizure recurrence, and EEG findings. However, given the lack of evidence for anti-seizure medications in preventing late post-traumatic seizures and improving long term outcomes, as well as the known side effects and drug interactions of these medications, especially phenytoin, both the BTF (Level IIA) and AAN guidelines (Level B) recommended against the routine use beyond 7 days.

Case conclusion

The patient is managed in the ED and loaded with 2000 mg of levetiracetam IV prior to admission to the neurosurgical ICU for ongoing management. In ICU he is continued on levetiracetam 1000 mg enterally every 12 h, monitored for several days, and receives an EEG which demonstrates no evidence of seizure activity. He is successfully extubated and is transferred to the neurosurgical floor for multidisciplinary rehabilitation. His levetiracetam is discontinued on day 7.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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