Seizure Prophylaxis in Traumatic Brain Injury

Introduction

1. Traumatic brain injury (TBI) is a leading cause of death and disability in the United States.
2. The Brain Trauma Foundation updated its guidelines for the management of severe TBI in 2016; however, there remains a lack of randomized clinical trials addressing many aspects of care in TBI patient.
3. The incidence of early post-traumatic seizures may be as high as 30 percent in patients with severe TBI
4. Antiseizure medications in acute management of TBI has been shown to reduce incidence of early seizures but has not been shown to prevent later development of epilepsy
5. Prevention of early seizures is beneficial in order to prevent status epilepticus, further aggravating systemic injury.
6. The Brain Trauma Foundation guidelines recommend phenytoin for early post-traumatic seizures for 7 days following injury, however levetiracetam is commonly used in this setting.

Pharmacology				
	Phenytoin	Valproic Acid	Levetiracetam	Lacosamide
Dose	Loading dose: 17 to 20 mg/kg IV (max dose 2 g) Maintenance dose: 100 mg every 8 hours or 5 mg/kg/day divided q8h (individual doses not to exceed 400 mg) Duration not to exceed 7 days	10 - 15 mg/kg/day	Loading dose: 20 mg/kg IV infused over 5-20 min Maintenance dose: 1 g IV over 15 min every 12 hours for 7 days (may be increased to 1.5 g q12)	50 - 100 mg IV twice daily May give loading dose of 200 mg
Administration	IV piggyback rate of ≤50 mg/minute	IV piggyback over 60 minutes at a rate ≤20 mg/minute	IV push or piggyback over 5-20 min	Bolus: May be administered undiluted at ≤80 mg/minute Infusion: over 30 to 60 minutes
PK/PD	Onset: 30 min - 1 hour Half-life:10 to 12 hours.	Peak: <1 hour Half-life:9 to 19 hours	Peak: 5-30 minutes Half-life: 6-8 hours	Peak: < 1 hour Half-life: ~13 hours
Adverse Effects	Hematologic effects, cardiovascular effects, CNS effects, gingival hyperplasia, hepatotoxicity	CNS effects, hematologic effects, hepatotoxicity, encephalopathy, pancreatitis	CNS depression, hypersensitivity reactions, psychiatric and behavioral abnormalities, increased blood pressure, asthenia	Cardiac arrhythmias including bradycardia, AV block, CNS effects
Warnings	Vesicant, acute toxicity	Not recommended for post-traumatic seizure prophylaxis in patients with acute head trauma	Caution in renal impairment.	Administer loading doses under medical supervision due to increased incidence of CNS adverse reactions

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Guideline Recommendation	
Journal	Recommendations
Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition - 2017	• Phenytoin is recommended to decrease the incidence of early PTS (within 7 d of injury), when the overall benefit is thought to outweigh the complications associated with treatment. • There is insufficient evidence to recommend levetiracetam compared with phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity.

Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Temkin, 1990	A randomized, double-blind study N = 404	Phenytoin vs Placebo	Within the first week 3.6% of phenytoin patients experienced seizure compared to 14.2% ($p<0.001$) Between day 8-1 year 21.5% of patients in phenytoin group experienced seizure compared to 15.7% in placebo group **Phenytoin is effective in reducing seizures within the first 7 days after severe head injury**
Young, 2004	Randomized, Double-Blinded, Placebo-Controlled Trial in pediatric patients (age < 16 yo) N = 102	Phenytoin vs Placebo for prevention of early posttraumatic seizures	During the 48-hour observation period, 3 of 46 (7%) patients in the phenytoin group and 3 of 56 (5%) patients in the placebo group experienced a posttraumatic seizure. No significant difference in survival or neurologic outcome between the two groups. **Phenytoin did not significantly reduce the rate of posttraumatic seizures at 48 hours, neurologic outcomes, or overall survival at 30 days.**
Jones, 2008	Prospective, single-center trial N = 32	Phenytoin vs Levetiracetam in patients with severe TBI (GCS 3-8)	Patients treated with levetiracetam and phenytoin had equivalent incidence of seizure activity ($p = 0.556$) Patients receiving levetiracetam had a higher incidence of abnormal EEG findings ($p = 0.003$). **Levetiracetam is as effective as phenytoin in preventing early posttraumatic seizures but is associated with an increased seizure tendency on EEG**

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Szaflarski, 2009	Prospective, single-center, randomized, single-blinded comparative trial N = 52	Levetiracetam vs Phenytoin in patients with severe traumatic brain injury (sTBI) or subarachnoid hemorrhage	**Levetiracetam patients experienced better long-term outcomes than those on phenytoin.** No differences between groups in seizure occurrence during cEEG (levetiracetam 5/34 vs. phenytoin 3/18; P = 1.0) or at 6 months (levetiracetam 1/20 vs. phenytoin 0/14; P = 1.0), or mortality (levetiracetam 14/34 vs. phenytoin 4/18; P = 0.227). **Lower frequency of worsened neurological status (P = 0.024), and gastrointestinal problems (P = 0.043) in levetiracetam group** **Levetiracetam improved long-term outcomes of compared to phenytoin with less ADRs and may be an alternative.**
Chi-yuan, 2010	Retrospective, cohort study N = 171	Sodium Valproate vs Placebo in early posttraumatic seizures in traumatic brain injury (TBI) patients.	No patients who received sodium valproate treatment experienced seizures; however, this was not statistically significant. **Sodium valproate is effective in decreasing the risk of early posttraumatic seizures in severe TBI patients**
Inaba, 2012	Prospective, comparative study N = 1,191	Levetiracetam vs Phenytoin for prevention of early post-traumatic seizures	**No difference in seizure rate (1.5% vs.1.5%, p = 0.997)** **No difference between levetiracetam and phenytoin in the prevention of early post traumatic seizures, mortality or ADRs in patients following TBI.**
Caballero, 2013	Multicenter retrospective analysis N = 90	Phenytoin vs Levetiracetam in TBI with at least one day of EEG monitoring	Prevalence of EEG-confirmed seizure activity **was similar between the levetiracetam and phenytoin groups (28% vs 29%; p = .99).** The median daily cost of levetiracetam therapy was $43 compared to $55 for phenytoin therapy and monitoring (p = .08). **Levetiracetam may be an alternative treatment option for seizure prevention inTBI patients in the ICU while also providing lower costs for drug therapy and monitoring.**

Kruer, 2013	Retrospective observational study N = 109	Phenytoin vs Levetiracetam in patients with a TBI and GCS < 8.	79 out of 81 (98%) patients admitted between 2000 and 2007 received PHT, whereas 18 of 28 (64%) patients admitted between 2008 and 2010 received LEV. 1 patient out of 89 receiving phenytoin had a posttraumatic seizure and 1 patient out of 20 recieving levetiracetam experiences a posttraumatic seizure **Only 2 patients experienced posttraumatic seizure after receiving AED, indicating low incidence of posttraumatic seizures.**
Gabriel, 2014	Single-center, prospective cohort analysis N = 19	Phenytoin vs Levetiracetam after severe TBI	No difference in Glasgow Outcome Scale–Extended score assessed ≥6 months after injury No difference in early seizures (p = 0.53) or late seizures (p = 0.53) Higher days with fever experienced in the hospital in the phenytoin group. **Long-term functional outcome in patients who experienced a TBI was not affected by treatment with PHT or LEV.**
Khan, 2016	Randomized controlled trial N = 154	Phenytoin vs Levetiracetam in patients with moderate to severe head trauma	Phenytoin was effective in preventing early post traumatic seizures in 73 of 77 patients (94.8%) Levetiracetam effectively controlled seizures in 70 of 77 patients (90.95%) cases **No statistically significant difference in the efficacy of Phenytoin and Levetiracetam in prophylaxis of early post-traumatic seizures in moderate to severe traumatic brain injury.**

Conclusions

- The Brain Trauma Foundation guidelines recommend phenytoin for early post-traumatic seizures for 7 days following injury, however levetiracetam is commonly used in this setting.
- In recent studies, lacosamide and levetiracetam showed no difference compared to phenytoin in prevention of early post-traumatic seizures following TBI
- Less side effects were associated with levetiracetam and lacosamide compared to phenytoin when used in seizure prophylaxis in TBI.

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