# A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis

**BACKGROUND**

- Traumatic brain injury (TBI) remains a major problem in the United States, with more than a million injuries occurring each year. TBI is responsible not only for deaths but also for a tremendous burden of long-term disability.
- For patients who have sustained a TBI, anticonvulsants are used to decrease the incidence of posttraumatic seizures; these seizures are classified as early (occurring within 7 days of injury) or late (occurring after 7 days).
- Untreated the incidence of early posttraumatic seizures has been estimated to be between 4% and 25%.
- Recently the use of levetiracetam (LEV) for seizure prophylaxis has increased, owing in part to the ease of dosing and lack of need for drug level monitoring.
- Phenytoin (PHE) has been associated with several rare serious adverse effects including cutaneous hypersensitivity and CYP450 induction, leading to drug interactions not seen with LEV.
- Although convenient, very little evidence exists to support the efficacy of LEV for early PTS. In addition, the cost of LEV is several fold that of PHE.

**OBJECTIVE**

- To compare the efficacy of phenytoin to levetiracetam for the prevention of early posttraumatic seizures

**METHODS**

- **Design:** Dual site, non-blind, controlled experimental, nonrandomized parallel trial; Duration: 3 years
- **Inclusion criteria:** Patients 18 years or older who experienced severe blunt TBI (Glasow Coma Scale [GCS] score $\leq$8 or GCS >8 in the presence of computed tomographic [CT] imaging findings consistent with brain injury: subarachnoid hemorrhage [SAH], subdural hematoma [SDH], epidural hematoma [EDH], intracerebral hemorrhage [ICH], or diffuse axonal injury [DAI])
- **Exclusion criteria:** Individuals who were pregnant, suffered devastating brain injury with expected or confirmed brain death within 48 hours of hospital admission, used anticonvulsants preadmission, or developed seizures before enrollment could be achieved
- **Primary outcome measure:** The incidence of clinical seizures
- **Secondary outcome measure:** Clinical adverse events, mortality, complications, and hospital length of stay
- 813 patients were non-randomly assigned to receive one of the study drug regimens upon presentation to either the Los Angeles County + University of Southern California Medical Center (LAC-USC) or the R. Adams Cowley Shock Trauma Center
- **Drug regimens:**
    - 406 patients received levetiracetam 1,000mg IV every 12 hours, given over 15 minutes
    - 407 received a phenytoin 20mg/kg IV loading dose (maximum of 2,000mg) given at 50mg/minute. These patients were then started on a maintenance dose of 5mg/kg/day (rounded to the nearest 100mg) IV administered every 8 hours, given over 15 minutes. Phenytoin serum levels were checked daily after enrollment and dosing was adjusted by an institutional pharmacist as needed to maintain therapeutic levels.
        - 340 were admitted to LAC-USC (329—levetiracetam and 11—phenytoin)
        - 473 were admitted to R. Adams Cowley Shock Trauma Center (77—levetiracetam and 396—phenytoin)
- Once tolerating a diet, patients were switched to oral administration
- All drugs given were documented, including date and time of administration and reason for use.
- All patients were maintained on study medications for 7 days; if no clinical seizures were detected at this time, the study medication was discontinued
- In the event of a seizure, the clinical neurology team was consulted and antiseizure medication was individualized
- Power 80% with an alpha level of 0.05 to detect a 0.22 difference between 8% and 14% (the early seizure rate with PHE and LEV, respectively, in previous trials). This was calculated to be sufficient for at least 392 patients in each group.
- Data handling method was intent-to-treat

**RESULTS**

- **Primary outcome measure:**
  - There were no significant differences in seizure rates (LEV 1.5% vs. PHE 1.5%, p=0.997) between patients receiving levetiracetam or phenytoin.
- **Secondary outcome measure:**
  - There were no statistically significant differences in adverse drug reactions (LEV 7.9% vs. PHE 10.3%, p=0.227), complications (LEV 28.3% vs. PHE 27%, p=0.679), or mortality (LEV 5.4% vs. PHE 3.7%, p=0.236).
  - Patients who received levetiracetam had increased hospital lengths of stay (LOS) (LEV 11.8 vs. PHE 7.5, p<0.001)
    - When adverse drug reactions were analyzed individually, patients who received LEV had a significantly lower incidence of leukocytosis (LEV 1.2% vs. PHE 9.6%, p<0.001).
    - More patients who were started on PHE had their treatment discontinued owing to an adverse effect (LEV 0% vs. PHE 2.9%, p<0.001); however, in each of these cases prophylaxis was transitioned to LEV with no adverse outcomes or seizures noted after the medication change.

**STRENGTHS**

- Parallel study design
- Medications were dosed appropriately and in a comparable manner for a sufficient duration.
- Due to the nature of the study adherence and dropout were not issues.
- None of the authors declared any conflicts of interest.

**LIMITATIONS**

- EEG monitoring to detect subclinical seizures was not performed at either of the two study centers.
- Only blunt trauma patients were enrolled.
- Patients and investigators were not blinded to the treatment regimens.
- Patients were not randomized to an anticonvulsant treatment regimen.
- Differences between institutions in discharge planning and ability to place these patients into rehab settings affected hospital length of stay time.
- Alcohol use was not examined.

**CONCLUSIONS**

- There is no apparent efficacy advantage for use of levetiracetam over phenytoin in early posttraumatic seizure prophylaxis.
- There are no statistically significant differences in the overall complication, adverse reaction, or mortality rate between the two agents.
- In practice, the cost and need for serum monitoring should be considered in guiding the choice of prophylactic agent.
- Currently, levetiracetam is several fold more expensive than phenytoin, but these agents will become increasingly comparable as the price per course of levetiracetam declines over time.
- Future Research:
  - Additional multicenter, double-blind, randomized trials are needed to confirm the findings of this investigation.

**REFERENCE:** Inaba K, Menaker J, Branco BC, Gooch J, Okoye OT, Herrold J, et al. A prospective comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. *Trauma Acute Care Surg* 2012;74(3):766-773.

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