# Phenytoin versus Levetiracetam for Prevention of Early Posttraumatic Seizures: A Prospective Comparative Study

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## Abstract

**Background** Antiepileptic drugs are routinely given for the prevention of early posttraumatic seizures (EPTS) occurring within the first 7 days after traumatic brain injury. The objective of this study was to compare phenytoin with levetiracetam in their effectiveness for prophylaxis for EPTS.

**Method** This single-blinded, prospective randomized study included 100 consecutive admitted patients at our center during a 3-month period from February 1, 2014, to April 30, 2014. Patients with preexisting seizure disorders and pathological brain conditions were excluded from the study. The patients were alternately assigned to a group receiving phenytoin (group P) or a group receiving levetiracetam (group L). Group P patients received phenytoin intravenously at 18 mg/kg as a loading dose followed by a maintenance dose of 5 mg/kg with phenytoin level monitoring. Group L patients received levetiracetam at a dose of 20 mg/kg loading dose and 20 mg/kg/d maintenance dose. A comparative study was done for the occurrence of EPTS and adverse effects in the two groups.

**Results** One patient in group L ($n = 50$) and four patients in group P ($n = 50$) developed EPTS after initiating treatment, but this was not statistically significant ($p = 0.362$ with odds ratio, OR = 0.24 [95% confidence interval, CI: 0.03–2.17]). There was no statistically significant difference between the two groups in the incidence of drug adverse effects ($p = 0.617$ with OR = 0.32 [95% CI: 0.03–3.18]). Adverse effects such as poor glycemic control, ataxia, nystagmus, or giddiness were seen in three patients in group P. One patient in group L had sinus bradycardia. Toxic serum drug levels (> 20 µg/mL) were observed in 6 of 50 (12%) patients of group P.

**Conclusion** There was no significant difference in the occurrence of their adverse effects, but the adverse effects because of the phenytoin were more troublesome. Levetiracetam had a better safety profile than phenytoin and it was equally efficacious for the prevention of EPTS.

**Keywords**
- phenytoin
- levetiracetam
- early posttraumatic seizures

## Introduction

Posttraumatic epilepsy is defined as a recurrent seizure disorder because of the injury to the brain following trauma.[1] The disorder is classified as immediate seizures (< 24 hours after injury), early seizures (< 1 week after injury), and late seizures (> 8 days after injury).[2] The

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incidence of early posttraumatic seizures (EPTS) has been estimated to be between 4 and 25%. Anticonvulsants are routinely used in prophylaxis for EPTS.[3] Phenytoin has been extensively used because of its easy administration intravenously and orally. However, it has drawbacks because of its adverse effects such as ataxia and poor glycemic control. Phenytoin also rarely causes other serious adverse effects such as Stevens–Johnson syndrome and anticonvulsant hypersensitivity syndrome. It also induces the hepatic cytochrome P450 system, causing significant drug–drug interactions. Phenytoin also requires laboratory monitoring of serum levels.[4,5] Levetiracetam is now often used instead of phenytoin due to its better safety profile. The aim of the study was to compare the efficacy and incidence of adverse effects between levetiracetam and phenytoin when used for the prevention of EPTS.

## Patients and Methods

This single-blinded, prospective, randomized study included 100 patients, divided equally into two groups. Patients who were admitted during the period from February 1, 2014, to April 30, 2014, were subjected to this study and alternately assigned to either of the groups. Patients with the following conditions, associated with a higher incidence of EPTS, were included in the study, such as, acute subdural hematoma, compound-depressed fractures with underlying contusions, intracerebral hematoma, diffuse axonal injury, significant cerebral contusions, and traumatic subarachnoid hemorrhage (SAH). Patients with preexisting seizure disorders and other pathological brain conditions were excluded from the study. The dose of phenytoin was 18 mg/kg loading dose followed by 5 mg/kg maintenance dose and that of levetiracetam was 20 mg/kg loading dose and 20 mg/kg/d maintenance dose.

All the patients in the study were evaluated and managed according to the Brain Trauma Foundation guidelines. Seizure prophylaxis were administered according to the prefixed protocol. Phenytoin serum levels were checked 48 hours after enrollment. The drugs were initially given intravenously and later orally once it could be started. Patients were on medications and observation for a minimum of 7 days subsequent to the injury.

The following data were collected for the patients in the study: age, sex, and mode of injury, associated comorbidities, and duration of unconsciousness, occurrence of convulsion, Glasgow Coma Scale (GCS) score, and presence of neurological deficits, computed tomographic scan findings, surgical interventions, and the presence of other systemic injuries. The antiepileptic dose, occurrence of adverse effects, occurrence of seizures, and drug levels of phenytoin were monitored.

Descriptive and inferential statistical analysis of the collected data were performed. Student *t*-test (two-tailed, independent) was used to find the significance of study parameters on continuous scale between the two groups (intergroup analysis) on metric parameters. Chi-square/ Fisher exact test was used to find the significance of study parameters on a categorical scale between the groups. Significance was assessed at 5% level of significance.

## Results

During the study period of 3 months, 100 patients with traumatic brain injury (TBI), meeting the inclusion criteria, were alternately assigned to the following two groups: group P and group L. The collected data for both the groups were analyzed and compared. The patients in the two groups were well matched in age ($39.72 \pm 17.56$ years vs. $35.36 \pm 15.95$ years, $p = 0.197$); sex (male, 88 vs. 86%, $p = 1.000$); and other clinical parameters. Causes of head injuries were statistically similar in two groups ($p = 0.100$) and motor vehicle accident was the most common cause in both the groups; 62% in group L and 80% in group P. Prevalence of comorbidities (diabetes, hypertension, and alcohol abuse) was similar ($p = 0.248$). GCS score of patients in both groups at admission and after 6, 12, and 24 hours were similar with the *p*-values of 0.929, 0.833, 0.897, and 0.848, respectively. The type and number of attacks of convulsion (before starting antiepileptics) were statistically similar in the two groups with a *p*-value of 0.553 and 0.312, respectively. Presence of neurological deficit was similar in the two groups ($p > 0.05$). Medical management alone was sufficient in 44 patients of group L (44/50) and 46 patients of group P (46/50). The remaining patients required surgical intervention.

Clinical and radiological risk factors for seizures in both groups are shown in ►**Table 2**. Occurrence of seizure rates after initiating prophylactic anticonvulsants was more in group P (4/50) than group L (1/50), but the difference was not statistically significant ($p = 0.362$; OR = 0.24; [95% CI: 0.03–2.17]). Only one patient in group L (1/50) had an adverse reaction, that is, sinus bradycardia not attributable to any cranial or cardiac condition. In group P, three patients developed adverse effects, such as hyperglycemia, giddiness, nystagmus, and ataxia necessitating discontinuation of the drug. Levetiracetam appeared to cause fewer adverse effects, but the difference was not statistically significant ($p = 0.617$, OR = 0.32 (95% CI: 0.03–3.18]). Monitoring of therapeutic levels of phenytoin showed that toxic levels ($> 20$ µg/mL) were reached in 12.6% of patients in group P (►**Tables 1–5**).

## Discussion

The use of anticonvulsants for the prevention of EPTS is a standard practice for patients with TBI at risk of developing seizures, so as to prevent secondary brain injury pharmacologic PTS prophylaxis is a part of the Brain Trauma Foundation Guidelines.[3] Phenytoin has been extensively used for seizure prophylaxis as it can be administered both intravenously and orally; besides being effective in the control of focal and generalized seizures. In the randomized trial by Temkin et al[6], patients with TBI (viz., cortical contusion, subdural hematoma, intracerebral hematoma, depressed skull fractures, penetrating brain injury, and patients with GCS score $\leq 10$) were assigned to

**Table 1** Demographic and clinical parameters

| Variable | | Group L | Group P | *p*-Value[a] |
|---|---|---|---|---|
| Age in y | Mean ± SD | 39.72 ± 17.56 | 35.36 ± 15.95 | 0.197 |
| Gender | Male | 44 (88%) | 43 (86%) | 1 |
| | Female | 6 (12%) | 7 (14%) | |
| Cause of head injury | Assault | 2 (4%) | 0 (0%) | 1 |
| | Fall at home | 0 (0%) | 2 (4%) | |
| | Fall from height | 10 (20%) | 6 (12%) | |
| | MVA | 33 (66%) | 40 (80%) | |
| | Not known | 5 (10%) | 2 (4%) | |
| H/O LOC | | 37 (74%) | 26 (52%) | |
| Comorbidities | Alcoholism | 8 (16%) | 9 (18%) | 0.023 |
| | DM | 4 (8%) | 0 (0%) | 0.248 |
| | HT | 1 (2%) | 1 (2%) | |
| | Coagulopathy | 1 (2%) | 0 (0%) | |
| | IHD | 1 (2%) | 0 (0%) | |
| | Total | 15 (30%) | 10 (20%) | |
| H/O of convulsion (before antiepileptics) | | 3 (6%) | 5 (10%) | 0.553 |
| | Type | GTCS | 4 GTCS and 1 focal | |
| GCS score | Admission | 12.38 ± 3.18 | 12.32 ± 3.57 | 0.929 |
| | After 6 h | 12.46 ± 3.06 | 12.60 ± 3.56 | 0.833 |
| | After 24 h | 13.20 ± 2.76 | 13.12 ± 3.38 | 0.897 |
| | After 7 d | 14.18 ± 1.83 | 14.10 ± 2.34 | 0.848 |
| Neurological deficit | Cranial nerve palsy | 1 (2%) | 0 | |
| | Hemiparesis | 6 (12%) | 6 (12%) | 1 |
| | Monoparesis | 1 (2%) | 0 | |

Abbreviations: DM, diabetes mellitus; GCS, Glasgow Coma Scale; GTCS, generalized tonic clonic seizure; H/O, history of; HT, history of hypertension; IHD, ischemic heart disease; LOC, loss of consciousness; MVA, motor vehicle accident; SD, standard deviation.
[a]Except history of LOC, all other parameters are statistically similar in both the groups. History of LOC is significantly more in group L with *p*-value 0.02.

treatment with either phenytoin or placebo for 1 year, with 2-year follow-up. Only 3.6% of patients who received phenytoin had EPTS as compared with 14.2% in the placebo group. However, there was no significant difference in the two groups at 1 and 2 years follow-up. Although phenytoin was effective in the prophylaxis of EPTS, it did not lead to any significant improvement in neurological outcome or mortality rate.[5,6] Hence, the current recommendation for the duration of use of prophylactic anticonvulsants is for the first 7 days.[3]

**Table 2** Risk factors for seizures

| Risk factors for seizures | Group L ($n = 50$) | | Group P ($n = 50$) | | *p*-Value |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | |
| Compound depressed fracture | 5 | 10.0 | 7 | 14.0 | 0.318 |
| Dural tear | 1 | 2.0 | 5 | 10.0 | 0.204 |
| Acute SDH | 19 | 38.0 | 20 | 40.0 | 1.000 |
| Intracerebral hematoma | 6 | 12.0 | 9 | 18.0 | 0.577 |
| Large focal cerebral contusion | 18 | 36.0 | 11 | 22.0 | 0.186 |
| CT features of diffuse axonal injury | 7 | 14.0 | 7 | 14.0 | 1.000 |
| H/O LOC > 24 h | 7 | 14.0 | 6 | 12.0 | 1.000 |

Abbreviations: CT, computed tomography; H/O, history of; LOC, loss of consciousness; SDH, subdural hematoma.

**Table 3** Management: Medical and surgical

| | Group L ($n = 50$) | | Group P ($n = 50$) | | *p*-Value |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | |
| Treatment | | | | | |
| Surgical intervention | | | | | |
| No | 44 | 88.0 | 46 | 92.0 | 0.154 |
| Craniotomy | 5 | 10.0 | 4 | 8.0 | |
| Decompressive craniotomy | 1 | 2.0 | 0 | 0.0 | |
| Antiepileptic drugs (P/L) | | | | | |
| Levetiracetam | 50 | 100.0 | 0 | 0.0 | $< 0.001$ |
| Phenytoin | 0 | 0.0 | 50 | 100.0 | |
| Time of first dose after injury (h) | | | | | |
| $\leq 2$ | 12 | 24.0 | 5 | 10.0 | 0.276 |
| 2.1–4 | 17 | 34.0 | 21 | 42.0 | |
| 4.1–10 | 18 | 36.0 | 19 | 38.0 | |
| $> 10$ | 3 | 6.0 | 5 | 10.0 | |

[a]Moderately significant (*p*-value, $0.01 < p \leq 0.05$).
[b]Strongly significant ($p \leq 0.01$).

**Table 4** Seizure episode after initiating treatment[a]

| Seizure episode after initiating treatment[a] | Group L ($n = 50$) | | Group P ($n = 50$) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Nil | 49 | 98.0 | 46 | 92.0 |
| Yes | 1 | 2.0 | 4 | 8.0 |
| Focal, $< 72$ h | 1 | 2.0 | 0 | 0.0 |
| GTCS, 1st d | 0 | 0.0 | 2 | 4.0 |
| GTCS, 5th d | 0 | 0.0 | 1 | 2.0 |
| GTCS, 7th d | 0 | 0.0 | 1 | 2.0 |

Abbreviations: CI, confidence interval; GTCS, generalized tonic clonic seizure; OR, odds ratio.
[a]Incidence of seizure episode are more in group P but not statistically significant with $p = 0.362$ with OR = 0.24 (95% CI, 0.03–2.17).

Phenytoin, although widely used, causes several dose-related adverse effects, such as diplopia, ataxia, and loss of glycemic control which can occur even when used for short periods. It is also known to cause idiosyncratic reactions, such as fever, exfoliative skin rash, Stevens–Johnson syndrome, anticonvulsant hypersensitivity syndrome, and Purple glove syndrome. It induces the hepatic cytochrome P450 system, leading to significant drug–drug interactions. Its metabolism follows first-order kinetics at very low blood levels, but when therapeutic range is reached, small

**Table 5** Adverse effects in two groups studied

| Adverse effects | Group L ($n = 50$) | | Group P ($n = 50$) | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Nil | 49 | 98.0 | 47 | 94.0 |
| Yes | 1 | 2.0 | 3 | 6.0 |
| Giddiness, nystagmus, ataxia | 0 | 0.0 | 2 | 4.0 |
| Poor glycemic control | 0 | 0.0 | 1 | 2.0 |
| Sinus bradycardia | 1 | 2.0 | 0 | 0.0 |

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adverse effects are more in group P but not statistically significant with $p = 0.617$, OR = 0.32 (95% CI, 0.03–3.18).

increments in administered phenytoin can cause toxicity. This necessitates laboratory monitoring of serum levels.[7,8] Temkin et al reported that 5.2% of patients stopped phenytoin because of adverse drug reaction. Hence, there has been a need to try other safer alternatives for prophylactic use.

Levetiracetam, a piracetam analog is effective against both partial and generalized seizures and available for intravenous and oral administration. It is a nonenzyme-inducing anticonvulsant that does not require serum-level monitoring. Recent evidence suggests that levetiracetam is both safe and efficacious in preventing seizures following severe TBI.

One recent prospective randomized, single-blinded study of 52 patients compared intravenous levetiracetam with phenytoin in patients with severe TBI.[9] 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 the groups in seizure occurrence during continuous electroencephalographic (EEG) monitoring for 72 hours or at 6 months. In the prospective, randomized, single-blinded study by Szaflarski et al,[9] only 46 patients with TBI were included with 30 on levetiracetam and 16 on phenytoin and analyzed along with 6 additional patients who were treated for SAH. This study documented both subclinical seizures on EEG for the initial 72 hours, as well as clinical seizures with and reported higher seizure incidence. They did not report any difference between the two drugs in their efficacy to prevent EPTS (levetiracetam 14.7 vs. phenytoin 16.7%, $p = 1.0$). Jones et al,[8] did not find any difference between the two drugs when 32 patients with TBI, with a GCS score of 3 to 8 receiving levetiracetam prophylaxis prospectively, were compared with a historical cohort of patients who received phenytoin. A prospective multicenter study included 813 patients with TBI and found a seizure rate of 1.5% in both the groups ($p = 0.997$). Adverse drug reactions were noted in 7.9% receiving levetiracetam as compared with 10.3% on phenytoin ($p = 0.227$) and mortality was 5.4 and 3.7%, respectively ($p = 0.236$).[10]

Our study included 100 patients with TBI at risk for developing EPTS, who were equally divided into the two groups, each receiving either phenytoin or levetiracetam. This was a prospective study of admitted patients who were observed for 7 days subsequent to trauma. Such a close observation facilitated detection of all clinical seizures and the adverse effects because of the drugs. The two groups were well matched in all demographic and clinical parameters, so that extraneous factors were less likely to affect the findings. Only one patient on levetiracetam (1/50) and four on phenytoin (4/50) developed EPTS, but there was no significant difference between the two drugs for EPTS prophylaxis ($p = 0.362$ with OR = 0.24 [95% CI: 0.03–2.17]). Levetiracetam appeared to be safer when the incidence of adverse effects was considered. In group P, three patients had adverse effects as compared with one in group L, but this difference was not statistically significant ($p = 0.617$ with OR = 0.32 [95% CI: 0.03–3.18]). Hence, levetiracetam is as effective and safe as phenytoin for EPTS prophylaxis. One drawback with phenytoin was that toxic serum drug levels were observed in 12% patients.

## Conclusion

Both phenytoin and levetiracetam are similar in their effectiveness when used in prophylaxis for EPTS. However, the adverse effects because of phenytoin were more troublesome with a need to intervene. Besides, there was also a need to monitor phenytoin drug levels. The major drawback for levetiracetam is the higher cost at present. Hence, levetiracetam can be considered a safe alternative in specific situations, such as presence of hyperglycemia, known hypersensitivity or adverse reaction to phenytoin and risk of drug interactions involving phenytoin.

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