

## A COMPARISON OF SEIZURE PROPHYLAXIS IN TRAUMATIC HEAD INJURY PATIENTS: PHENYTOIN VERSUS LEVETIRACETAM

Arvin Preet Kour<sup>1</sup>, Rahul Midha<sup>2</sup>, Ajaydeep Singh<sup>3</sup>, G.S Bindra<sup>4</sup>, Ram Nandan Prasad<sup>5</sup>

Received : 06/07/2023  
Received in revised form : 03/08/2023  
Accepted : 17/08/2023

**Keywords:**

Rash, Seizure Prophylaxis, Levetiracetam, Phenytoin.

Corresponding Author:

**Dr. Ajaydeep Singh,**  
Email: drjaydeepsingh@gmail.com.

DOI: 10.47009/jamp.2023.5.5.10

Source of Support: Nil,  
Conflict of Interest: None declared

*Int J Acad Med Pharm*  
2023; 5 (5); 49-53



<sup>1</sup>Associate Professor, MD (Anaesthesia) FICCM, ACCCM, Department of Anaesthesia, Maharishi Markandeshwar Institute of Medical Science and Research, Mullana, Haryana, India.

<sup>2</sup>Assistant Professor, MD (Anaesthesia), Department of Anaesthesia, Maharaja Agrasen Medical College, Hisar, Haryana, India.

<sup>3</sup>Professor, MS Surgery DNB (Surgery) DNB (Neurosurgery) FICCM, ACCCM, Department of Neurosurgery, Maharishi Markandeshwar Institute of Medical Science and Research, Mullana, Haryana, India.

<sup>4</sup>Professor and HOD, Department of Neurosurgery, Maharishi Markandeshwar Institute of Medical Science and Research, Mullana, Haryana, India.

<sup>5</sup>Professor and HOD, Department of Anaesthesia, Maharishi Markandeshwar Institute of Medical Science and Research, Mullana, Haryana, India.

### Abstract

**Background:** Till date we have more than 15 used antiepileptic drugs, whereas the most commonly used antiepileptic drugs are Phenytoin and Levetiracetam for prevention of epilepsy by most of the physicians, neurologists and neurosurgeons. Phenytoin was approved for medical use in 1953, whereas levetiracetam became accredited for clinical use in 1999. Historically, phenytoin has been the maximum prescribed remedy for seizure prophylaxis. However, levetiracetam is a more recent AED with a whole lot fewer aspect results than phenytoin, fewer drug-drug interactions, at the same time as also having a truthful dosing regimen despite the fact that phenytoin tends to be effective in most settings, it additionally has a multiplied facet impact frequency and is basically impacted by using positive other medicinal drugs. **Aims:** To compare the efficacy of eptoin and Levetiracetam in head injury patients and to document the side effects of both the drugs. **Materials and Methods:** It was an observational study done in the department of Neurosurgery in (MMIMSR) Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, district Ambala, Haryana for a period of three years with sample size of 100 patients. **Results:** Rash was more common in Phenytoin-treated patients with 6% VS 2% in the Levetiracetam group reporting, dizziness versus 24% VS 12%. **Conclusion:** Levetiracetam for seizure prophylaxis is a better alternative than eptoin.

## INTRODUCTION

Till date we have more than 15 used antiepileptic drugs, whereas the most commonly used antiepileptic drugs are Phenytoin and Levetiracetam for prevention of epilepsy by most of the physicians, neurologists and neurosurgeons. Phenytoin was synthesized in the year 1908 as a analogue for barbiturate, but was not used due to its poor sedative properties. Its anticonvulsant activity was specifically tested in the year 1938 since then it is the drug of the choice used for prevention of the seizures, universally approved for medical use since 1953, However, levetiracetam which is a unique anticonvulsant because it suppresses kindled seizures and is ineffective against maximal electroshock. The Clinical efficacy of levetiracetam has been

demonstrated as adjuvant medication when used in combination with other anticonvulsants and when used as monotherapy in the treatment of refractory partial seizures with or without secondary generalization became accredited for clinical use universally from the year 1999. Historically, phenytoin has been the maximum prescribed drug used for seizure prophylaxis. Whereas levetiracetam is a more recent anticonvulsant drug which is with less known adverse effects, fewer drug-drug interactions than phenytoin, at the same time as also having good compliance and dosing regimen in view of the cost.<sup>[1]</sup> Despite the fact that phenytoin tends to be effective in most settings.<sup>[2]</sup> Recently, the use of levetiracetam for seizure prophylaxis has risen. Levetiracetam's easy dosing and the dearth of drug stage tracking contributes to the upward thrust in its

use. Whereas Phenytoin has also been related with a number of destructive side outcomes, inclusive of cutaneous allergy and enzyme CYP-450 induction which alters with the drugs kinetics, which aren't seen with levetiracetam. Presently, there is no clear demarcation in the physicians that which is superior for the prevention of seizures. So here, we have observed 110 patients for a period of 2 years in follow up and documented 100 patients from our institution whom had been given eptoin or levetiracetam for the comparison within the use of phenytoin and levetiracetam to determine whether or not there is a consensus of desire for antiepileptic utilization.

Phenytoin as most commonly available as eptoin it prevents repetitive detonation of normal brain cells during 'depolarization shift' that occurs in patients of seizures and consists of a synchronous and unusually large depolarization over which action potentials are superimposed. This is achieved by prolonging the inactivated state of voltage sensitive neuronal Na<sup>+</sup> channel. Phenytoin is quite protein-sure and is metabolized by means of cytochrome P450 (CYP) enzymes; it lowers the platelets and hemoglobin further to being a CYP inducer.<sup>[3]</sup>

#### **Indications**

Phenytoin has various uses, which include treatment of trigeminal neuralgia, migraine generalized tonic-clonic seizures and complex partial seizures arising from the temporal lobe epilepsy, further to the prevention and treatment of seizures taking place in the course of or following neurosurgery related to head injury or elective surgery for tumors and others related conditions like stroke and traumatic head injury.<sup>[4,5]</sup>

Levetiracetam is indicated as an accessory remedy to treat partial and tonic-clonic seizures in young adults, children and elderly population. Myoclonic seizures in adults and child less than age of 12 year<sup>3</sup>. Levetiracetam is used in the in the people who consume alcohol widespread.<sup>[6]</sup>

#### **Aim and Objectives**

1. To compare the efficacy of Phenytoin and Levetiracetam in head injury patients.
2. To document the side effects of both the drugs.

## **MATERIALS AND METHODS**

It was an observational study done in the department of Neurosurgery in (MMIMSR) Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, district Ambala, Haryana for a period of three years with sample size of 100 patients.

#### **Sample Size Calculation**

Analysis of the study was done by using the power package, (Granz Faul, university Kiel, Germany) G power version 3.1.9.2. we calculated the sample size to be 50 subjects per group at power of 0.99 and with an effect size of 2.78 with 10% chance of error, with alpha=0.05, beta=0.20 and confidence interval of 95%

#### **Inclusion Criteria**

1. All the patient of recent head injury was included in the study with single anticonvulsant.
2. GCS of 12 to 15.

#### **Exclusion Criteria**

1. Old Cases of Stroke on Anticonvulsants.
2. Patients On Multidrug Therapy of Anticonvulsants.

#### **Study Procedure**

##### **Methods**

The study was a prospective, observational randomized.

##### **Materials**

The patients inclusion criteria were randomly chosen and were allocated into 2 groups, each subset contained fifty patients. Proper history of the patients was obtained from the patient or their reliable family member whom knew the detailed history of the patient in respect to the drug intake and episodes of seizures. clinical examination with detailed neurological examination were done and noted on the progress charts. Relevant investigations, hematological and radiological were done and discussed with radiologists. Detailed Informed consent was obtained for the treatment and the study was from patient/family. The patients were admitted after the event in the neurosurgery ICU or the neurosurgery ward depending upon the GCS status of the patients.

Eptoin was given as standard 15-20 mg/Kg as loading dose and 5-8 mg/Kg/dose thrice daily as maintenance dose. A maximum of 400 mg per day.

Levetiracetam 10 milligram/kg/dose to be divided in two e daily with a maximum dose of 3 grams per day. Increase the dose every 2 weeks by 10 mg/kg/dose i.e., 22 mg-25 mg /kg/day twice daily.

##### **Following Parameters were assessed.**

1. GCS
2. Episodes of the seizures
3. Drug reactions due to anticonvulsants

##### **Statistical Analysis**

The test of Chi-square test was solicited for comparing the frequency. The p-value as standardized as, less than 0.05. was considered to be significant and crucial. We used the software SPSS version 25.0 for statistical analysis. T-test was used for comparing the 2 groups.

## **RESULTS**

For one year from period 2019 to 2020, Observational study was carried out in which 170 patients were treated with either Phenytoin or Levetiracetam, single therapy was given in 110 patients which were included in the study. Glasgow Coma Score (GCS) of 12 or more. The patients were followed up for 2 years; we have lost contact with 10 patients, so they were not included in the study group. The mean age of patients in eptoin group was 32.27±11.31 years and mean age of patients in Levetiracetam group was 33.98±11.18 years. Our

study enrolled 20% females and 80% male patients in eptoin group and 18% of females and 82% males in Levetiracetam group. (Insignificant P value)

The 100 patients which were included in the study, 21 patients underwent craniotomy, all the patients were of acute SDH, 10 in eptoin group and 11 in the Levetiracetam group. The baseline characteristics for Phenytoin versus Levetiracetam were comparable (all  $p > 0.05$ ) for demographics, GCS on admission, neuro ward and neuro ICU stay, duration of AED, surgery, or seizure (Table 1)

The complications observed in the groups are depicted in table no 2. Rash was more common in Phenytoin-treated patients with 6% VS 2% in the Levetiracetam group.

Figure 1 shows the rash of the patient which was controlled with antiallergic and skin emollients and stoppage of the drugs. The most serious problem with the eptoin is the rash with the most severe form as Stevens-Johnson syndrome, 2 patients developed Stevens-Johnson syndrome, and these were treated as recovered.

Figure 2 shows the maculopapular rash arising by the use of Levetiracetam. This was the single case of the rash and was treated with changing the drug with sodium valproate and skin emollients.

Dizziness versus 24% Vs 12% (P significant). Phenytoin levels were routinely measured, and dizziness did not appear to be concentration dependent. The blood concentration of the patients who had the adverse symptoms were done and they

ranged between 8.5 and 22.34  $\mu\text{g/ml}$  (the effective blood concentration is 10–20  $\mu\text{g/ml}$ ). 2 patients had 21.21  $\mu\text{g/ml}$  22.34  $\mu\text{g/ml}$  those presented with ataxia (Altered walking) The dose of eptoin was reduced to 200 mg per days and both of them recovered. A few patients had neurological symptoms at levels below 20  $\mu\text{g/ml}$ , which may be related to their earlier history of Hepatitis B and Hepatitis C, one patient had deranged renal function tests which was attributed to the stroke.

Nervousness was significantly higher seen in the Levetiracetam group. All the eight who suffered from nervousness were in the age group of 37 to 45 years. The use of Levetiracetam has been attributed with psychosis and most of the patients who are admitted in the ICU have shown the psychotic behaviour, which was either improved by some degree by shifting the patients out to the ward or sending them home, but it still persisted, decreasing the dose produced another marked effect of feeling of discomfort and headaches. The exact cause of this phenomenon is not known. The mechanism of action is not known. None of the major anticonvulsant mechanisms which are known appear to be applicable to levetiracetam. However, it may modify release of glutamate/GABA in the synapse, which is either don't contribute to its antiepileptic property. Ten patients experienced nausea initially which decreased with the time and only 2 patients had severe nausea which required antiemetic.

**Table 1: Characteristics of patients treated with Phenytoin and Levetiracetam**

	Phenytoin n = 50	Levetiracetam n = 50	p value
Demographics			
Age (years)	32.27±11.31	33.98±11.18	0.52
Male	40 (80%)	41 (82%)	0.72
Female	10(20%)	9(18%)	0.54
GCS on admission			
GCS 12	24 (48%)	25 (50%)	0.68
GCS 13	14 (28%)	10(20%)	
GCS 14	10(20%)	12(24%)	
GCS 15	12(24%)	13(26%)	
Surgery	10(20%)	11(22%)	0.45
Seizure	11(22%)	12(24%)	0.55
Duration of drug therapy.	2 years	2 years	0.44

**Table 2: Complications noted in the patients.**

COMPLICATIONS	Phenytoin group	Levetiracetam group
Rash	3	1
Dizziness	12	6
Nausea	10	2
Nervousness	4	8
Altered walking	2	none



**Figure 1: Initial phase of the macular rash due to phenytoin use.**



**Figure 2: Late phase of the maculopapular rash due to Levetiracetam use.**

## DISCUSSION

Our data suggest that Eptoin and Levetiracetam both have similar results in control of seizures for long term, whereas eptoin use is having more of the complications as compared to the Levetiracetam group.

Fuller KL et al in their study in 2013 had noticed predominant decrease in the incidence of early attacks of seizures in patients with postoperative and traumatic head injury treated with Phenytoin, of 3.6% vs 14.2%.<sup>[7]</sup> Whereas long term use of both the drugs over a period of one year and more has shown equally efficacious of Phenytoin and Levetiracetam in preventing early seizures in post-traumatic and post operative Head injury. This is supported.<sup>[8-11]</sup> by Krueger RM et al 2013, Chakravarthi S et al 2015, Khan SA et al and Singh K et al 2018.

Further meta-analyses from 2016 and 2020 identified no difference in efficacy between Phenytoin and Levetiracetam for seizure prophylaxis. Stevens-Johnson syndrome was observed in one patient and eptoin was stopped and sodium valproate was started in the patient.

In one patient Levetiracetam caused severe maculopapular rash.<sup>[12]</sup> so it was also stopped and sodium Valproate was started.

The current trend in most of the hospitals is changing from use of eptoin to Levetiracetam consistent with the literature.<sup>[13]</sup>, and that is justifiable looking

towards the adverse effects where as to the contrary, one important thing is note that, eptoin and phosphonetoin are the preferred drugs for loading to prevent the episode of seizure and eptoin if far more cheaper which is an important aspect for the compliance of the patient in our country. Whereas The use of levetiracetam is preferred as it does not interact with hepatic microsomal enzymes, the drug is completely and rapidly absorbed after oral intake, its excreted in urine unchanged to 70 percent, so it can be safely given in renal and hepatic failure patients. The best advantage of the drug is that it can be safely given in the females of childbearing age, till now its considered safe for breast feeding and pregnant females and no known teratogenic side effects are proven till date.

Limitation: Although our common sample size is big i.e 100 patients, it's exceedingly small for sub-organization evaluation, particularly Phenytoin which is a very commonly used drug. We assume the power of the significance to be little to a generalized large population. We is unable to evaluate the use of 2 drugs relevance at a same time in the same patient.

## CONCLUSION

Levetiracetam for seizure prophylaxis is a better alternative than eptoin in younger population.

## REFERENCES

1. Radic JA, Chou SH, Du R, Lee JW. Levetiracetam versus phenytoin: a comparison of efficacy of seizure prophylaxis and adverse event risk following acute or subacute subdural hematoma diagnosis. *Neurocrit Care.* 2014;21:228–237.
2. Inaba K, Menaker J, Branco BC, Gooch J, Okoye OT, Herrold J, Scalea TM, Dubose J, Demetriades D. A prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. *J Trauma Acute Care Surg.* 2013 Mar;74(3):766-71.
3. Rai S, Drislane FW. Treatment of Refractory and Super-refractory Status Epilepticus. *Neurotherapeutics.* 2018 Jul;15(3):697-712.
4. Debenham S, Sabit B, Saluja RS, Lamoureux J, Bajsarowicz P, Maleki M, Marcoux J. Can J A critical look at phenytoin use for early post-traumatic seizure prophylaxis. *Neurol Sci.* 2011;38:896–901.
5. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, Bare M, Bleck T, Dodson WE, Garrity L, Jagoda A, Lowenstein D, Pellock J, Riviello J, Sloan E, Treiman DM. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr.* 2016 Jan-Feb;16(1):48-61.
6. Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care.* 2010;12:165–172.
7. Fuller KL, Wang YY, Cook MJ, Murphy MA, D'Souza WJ: Tolerability, safety, and side effects of levetiracetam versus phenytoin in intravenous and total prophylactic regimen among craniotomy patients: a prospective randomized study. *Epilepsia.* 2013, 54:45-57.
8. Krueger RM, Harris LH, Goodwin H, Kornbluth J, Thomas KP, Slater LA, Haut ER: Changing trends in the use of seizure prophylaxis after traumatic brain injury: a shift from phenytoin to levetiracetam. *J Crit Care.* 2013;28:883

9. Chakravarthi S, Goyal MK, Modi M, Bhalla A, Singh P: Levetiracetam versus phenytoin in management of status epilepticus. *J Clin Neurosci*. 2015, 22:959-63.
10. Khan SA, Bhatti SN, Khan AA, et al.: Comparison of efficacy of phenytoin and levetiracetam for prevention of early post traumatic seizures. *J Ayub Med Coll Abbottabad*. 2016, 28:455-60.
11. Singh K, Aggarwal A, Faridi MMA, Sharma S: IV levetiracetam versus IV phenytoin in childhood seizures: a randomized controlled trial. *J Pediatr Neurosci*. 2018, 13:158-64.
12. Kour, Arvinpreet; Singh, Ajaydeep. Levetiracetam-Induced Drug Reaction: Violaceous Discrete Maculopapular Rash. *Apollo Medicine* 20(1);p 83-84, Jan–Mar 2023.
13. Debenham S, Sabit B, Saluja RS, Lamoureux J, Bajsarowicz P, Maleki M, Marcoux J: A critical look at phenytoin use for early post-traumatic seizure prophylaxis. *Can J Neurol Sci*. 2011, 38:896-901.