




## Comparison of Efficacy and Safety of Levetiracetam Versus Phenytoin for Post-craniotomy Seizure Prophylaxis

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### Abstract

**Background:** Superiority of levetiracetam over phenytoin for postcraniotomy seizure prophylaxis in patients with a supratentorial brain tumor is controversial. We aimed to evaluate the efficacy of levetiracetam versus phenytoin for postcraniotomy seizure prophylaxis in supratentorial brain tumor.

**Methods:** In a randomized controlled trial study, 80 patients with a supratentorial brain tumor who underwent craniotomy were allocated to levetiracetam or phenytoin group, 40 patients each. Seizure prophylaxis was started 5 days before the surgery and continued until 90 days after surgery. Phenytoin group received 100 mg oral phenytoin 3 times a day. The levetiracetam group received 500 mg oral levetiracetam 2 times a day. The primary outcome was the incidence of postcraniotomy seizures. The secondary outcome measure was the safety profile of the drugs.

**Results:** All patients of the phenytoin group and 39 patients of levetiracetam completed the study. Two seizures developed in the study population, 1 in the phenytoin group (2.5%) and 1 in the levetiracetam group (2.6%) ( $P = 0.710$ ). Renal or hepatic dysfunction was not observed in any patients. Wound hematoma was seen in 5 patients (12.5%) of the phenytoin and 6 patients (15.4%) of the levetiracetam group ( $P = 0.481$ ). Skin rash developed in 3 patients (7.5%) of the phenytoin group and no patient of the levetiracetam group ( $P = 0.132$ ). Thrombocytopenia was detected in 1 patient of the phenytoin group (2.5%) and no patient of the levetiracetam group ( $P = 0.511$ ). None of the adverse events led to drug withdrawal.

**Conclusion:** These results reveal no superiority of levetiracetam over phenytoin for postcraniotomy seizure prophylaxis in supratentorial brain tumor.

**Keywords:** Levetiracetam, Phenytoin, Craniotomy, Seizure, Prophylaxis, Supratentorial Brain Tumor

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### Introduction

For patients with resectable supratentorial brain tumors, surgical resection is the standard treatment of choice (1). Intraoperative irritation of the cortex, haemorrhages at the micro and macro level, focal cerebral hypoxia, and acidosis

are among factors that predispose incidence of the immediate postoperative seizure (2).

The estimated risk of immediate postoperative seizures in patients undergoing craniotomy for supratentorial brain tumors is about 15% to 20% when antiepileptic drugs

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#### ↑What is “already known” in this topic:

The efficacy and safety of levetiracetam versus phenytoin with different mechanisms and side effects for seizure prophylaxis in patients undergoing craniotomy for a supratentorial brain is not entirely clear.

#### →What this article adds:

The rate of postcraniotomy seizure was not significantly different between the levetiracetam and phenytoin groups for this duration of prophylaxis. These results reveal no superiority of levetiracetam over phenytoin for postcraniotomy seizure prophylaxis in patients with a supratentorial brain tumor.

(AEDs) are not used for prophylaxis (2). This risk is even higher in patients with meningiomas, low-grade gliomas, and those with a history of preoperative seizures (1). Postoperative seizures are considered an important cause of morbidity and reduced quality of life in these patients (3). Therefore, effective prevention of postoperative seizure after the craniotomy for a supratentorial brain tumor is of significant value.

Conventionally, phenytoin is the most commonly used AED to prevent postcraniotomy seizures (4). Despite its acceptable effectiveness, it is associated with a variety of side effects, including neurotoxicity and cardiotoxicity. Phenytoin metabolism is highly affected by the polymorphisms in genes coding for phenytoin-metabolizing enzymes such as cytochrome P450 (CYP) 2C9 and CYP2C19. Of note, CYP2C9\*3 variant is strongly associated with increased plasma concentrations of phenytoin and consequently a higher likelihood of cardiac adverse drug reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Specific HLA variants, namely HLA-B\*15:02, HLA-B\*13:01, and HLA-B\*51:01, are also significant risk factors for phenytoin-associated adverse events, particularly in Asian populations (5). To avoid serious complications of phenytoin, new AEDs are increasingly investigated to find a better postoperative prophylactic agent (6).

Levetiracetam is a novel AED that does not require monitoring serum levels and has better tolerability compared with phenytoin (7, 8). It binds to the synaptic vesicle protein SV2A and disrupts SV2A-regulated synaptotagmin function, thereby decreasing neurotransmitter release in hippocampal slices (9). Besides, levetiracetam has revealed neuroprotective effects in both epileptic and nonepileptic disorders such as closed head injury and subarachnoid hemorrhage (10). These properties have made levetiracetam an ideal alternative for phenytoin as a prophylactic agent for postoperative craniotomy-dependent seizures. The major mechanism of action by which levetiracetam prevents postoperative seizures is its action as a nonspecific sodium channel blocker. This property decreases the influx of sodium into neurons, and thereby reduces neuronal hyperexcitability and prolongs depolarization (9).

Despite the popularity of levetiracetam for the management of postcraniotomy seizures, studies comparing levetiracetam and phenytoin for seizure prophylaxis in supratentorial brain tumor surgery contain a high risk of bias and moderate methodological quality (11). For this reason, we have designed the present trial study to compare the safety and efficacy of levetiracetam versus phenytoin as postoperative seizure prophylaxis in patients undergoing supratentorial brain surgery.

## Methods

This randomized controlled study has been approved by the institutional research ethics committee of Tehran University of Medical Sciences before the experiment was started and has been conducted in accordance with the principles outlined in the Helsinki Declaration. The protocol of the study was registered on the Iranian Registry of Clinical Trials under the code IRCT20150419021837N1. Patients

provided written consent before enrolment in the study. Between 2017 and 2019, patients who underwent craniotomy for supratentorial brain tumors were evaluated for eligibility to be included in the study. Patients who were receiving anticonvulsant therapy before the surgery because of the seizure caused by the tumor itself, were not included in the study. The inclusion criteria were the age  $\geq 18$  years and normal laboratory indices of renal and hepatic function. Patients with a history of seizure, history of colostomy due to impaired gastrointestinal absorption of the drug or electrolyte disturbance, and patients with cranial tumor and concurrent brain lesions such as cerebrovascular accidents, were excluded from the study. Pregnant patients and patients allergic to any of the antiepileptic drugs (AEDs) were also excluded from the study. The eligible patients were randomly assigned into the 2 study groups in a 1 to 1 ratio, 40 patients each. The block randomization method with stratification, with the random block size of 4, was used for randomization to have the same number of patients in each group. The flow diagram of the study population is demonstrated in Figure 1.

## Intervention

For all patients, seizure prophylaxis was started 5 days before the surgery and continued until day 90 after surgery. Both patients and the researcher who collected data were not aware of the type of the AED. In patients in the levetiracetam group, the drug was administered orally 500 mg twice daily and the same dose was given by injection on the day of surgery. Phenytoin 100 mg was given 3 times daily, either orally or intravenously. If the patient had not received dose of medication, the initial preoperative dose of 10 to 15 mg per kg body weight was given intravenously (loading dose).

Throughout the study, the patient and the physician were aware of the type of treatment. The researcher who observed the patients and the statistician were not aware of the type of treatment.

They started the treatment 5 days before to reach the plasma level of the drug to the appropriate level and evaluate the drug reaction in this patient. They continued treatment for up to 3 months to prevent seizures related to structural and electrolyte disorders.

## Outcome Measures

The patients were visited on days 7, 30, and 90 by a neurosurgeon who was blinded to the type of AED. A phone number was given to the patients to immediately inform the research group if they had a seizure or side effect. The primary outcome measure was the prophylaxis efficacy assessed by the incidence of postcraniotomy seizures regardless of their duration and severity. The secondary outcome measure was the safety of the drugs assessed by the incidence of renal, hepatic, hematologic, and skin side-effects of the drugs. In each follow-up visit, a blood analysis was performed to monitor renal function using serum BUN and creatinine level, hepatic function using alkaline phosphatase and aminotransferases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels, and hematologic side effects using complete blood count.

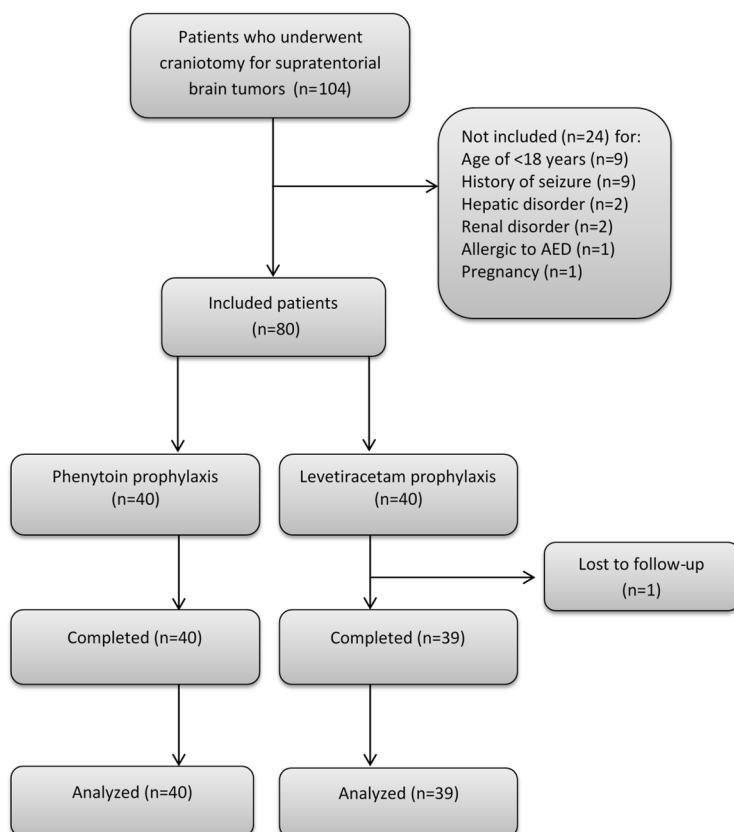


Figure 1. Flowchart of the study inclusion and exclusion

The presence of hematoma and skin rash was also evaluated clinically (12).

### Statistical Analyses

According to the study of Iuchi et al (12), the incidence of postcraniotomy seizure was 1.4% in the levetiracetam group and 15.4% in the phenytoin group. With a type I error of 5% and a power of 80%, the number of 30 patients in each group was enough for this trial. To cover the dropout and improve the power of the study, we included 40 patients in each group.

Statistical assessments were performed using SPSS for Windows Version 16. The descriptive data was presented with a mean  $\pm$  standard deviation or number and percentage. The data normality was checked with a Kolmogorov–Smirnov test. An independent t test or its nonparametric counterpart (Mann–Whitney U test) was used to compare the mean values of the 2 quantitative variables. A Fisher exact test was used to compare the categorical variables between the 2 study groups. A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

### Baseline Characteristics

All patients of the phenytoin group and 39 patients of the levetiracetam group completed the study. The study population included 31 (39.2%) men and 48 (60.8%) women, with a mean age of  $53.6 \pm 1.9$  years. Gross and subtotal resection was performed in 48 (60.8%) and 31 (39.2%) patients, respectively. The characteristics of the 2 study

groups are summarized in Table 1. We found no statistically significant difference in any of the variables between the 2 groups.

### Primary Outcome Measure

In total, 2 seizures developed in the study population during the 90 day follow-up period, 1 in the phenytoin group (2.5%) and 1 in the levetiracetam group (2.6%). This difference was not statistically significant ( $P = 0.710$ ). In the phenytoin group, the seizure occurred 6 days after the surgery. In the levetiracetam group, the seizure occurred during the surgery.

### Secondary Outcome Measures

Renal and hepatic dysfunction was not observed in any patients of the study population. Hematoma was seen in 5 patients (12.5%) of the phenytoin group and 6 patients (15.4%) of the levetiracetam group. This difference was not statistically significant ( $P = 0.481$ ). Skin rash developed in 3 patients (7.5%) of the phenytoin group and no patient of the levetiracetam group. This difference was not statistically significant ( $P = 0.132$ ). Thrombocytopenia was detected in 1 patient of the phenytoin group (2.5%) and no patient of the levetiracetam group (0%). This difference was not statistically significant ( $P = 0.511$ ). None of the adverse events led to drug withdrawal. Primary and secondary outcome measures in the 2 study groups are demonstrated in Table 2.

**Table 1.** Comparison of Characteristic Features Between the 2 Study Groups

Variable	Phenytoin Group (n=40)	Levetiracetam Group (n=39)	P value
Age (year)	53.5±1.9	53.8±2.1	0.912
Gender			0.891
Male	16 (40)	15 (38.5)	
Female	24 (60)	24 (61.5)	
Tumor size at largest dimension (cm)	4.4±0.2	4±0.2	0.135
Surgical duration (h)	4.1±0.3	3.8±0.2	0.278
Tumor type			0.732
Glioblastoma	13 (32.5)	16 (41)	
Meningioma	19 (47.5)	17 (43.6)	
Others	8 (20)	6 (15.4)	
Resection type			0.894
Subtotal	16 (40)	15 (38.5)	
Gross total	24 (60)	24 (61.5)	
Mass number			0.835
One	36 (90)	37 (95)	
More than one	4 (10)	2 (5)	

Data are presented as mean ± SD or number (%). A P value < 0.05 is considered significant.

**Table 2.** Comparison of the outcome measures between the two study groups

Variable	Phenytoin group (n=40)	Levetiracetam group (n=39)	P value
Seizure	1 (2.5)	1 (2.6)	0.710
Renal dysfunction	0	0	-
Hepatic dysfunction	0	0	-
Thrombocytopenia	1 (2.5)	0	0.511
Skin rash	3 (7.5)	0	0.132
Wound hematoma	5 (12.5)	6 (15.4)	0.481

Data are presented as number (%). A P value < 0.05 is considered significant.

## Discussion

In this trial, we compared the efficacy and safety of levetiracetam versus phenytoin for seizure prophylaxis in patients undergoing craniotomy for a supratentorial brain tumor. According to our results, the seizure preventing capability of levetiracetam and phenytoin was comparable. Moreover, the rate of adverse events, including renal, hepatic, hematologic, and skin complications, was not significantly different between the 2 evaluated AEDs (13).

Fuller et al (13) in a randomized control trial compared the tolerability, safety, and side effects of levetiracetam versus phenytoin for seizure prophylaxis after craniotomy. According to their results, the rate of discontinuation because of side effect was not significantly different between the patients receiving levetiracetam and phenytoin. Also, the number of patients with side effect was not significantly different between the 2 groups. However, postoperative seizure was significantly more in the phenytoin group (6 versus 0). In the present study, the rate of side effects and postoperative seizure was not significantly different between the levetiracetam and phenytoin groups. However, they included any patients with neurosurgical indications requiring craniotomy, while we only included patients with supratentorial tumors who underwent craniotomy.

Kern et al (14) in a retrospective study compared the efficacy of levetiracetam (n = 81) versus phenytoin (n = 154) for the postoperative prevention of seizures after craniotomy for intracranial tumors. Levetiracetam was only used when phenytoin was contraindicated. During the first 7 days after craniotomy, 2 patients of the levetiracetam group (2.5%) and 7 patients of the phenytoin group (4.5%) had a seizure. This difference was not statistically significant. No

side effect was recorded in any of the study groups. Similar to the study of Kern et al, the rate of postoperative seizure was not significantly different between the levetiracetam and phenytoin groups of our study.

Luchi et al (12) in a prospective randomized study, compared the efficacy of levetiracetam with phenytoin in patients with supratentorial tumors within 7 days after the surgery. A total of 146 patients were randomly assigned to the 2 study groups, 73 patients each. According to this study, the rate of postcraniotomy seizure was 1.4% in the levetiracetam group and 15.1% in the phenytoin group. This difference was statistically significant. While levetiracetam was completed in all cases, phenytoin was withdrawn in 5 patients due to liver dysfunction (n = 1), skin eruption (n = 2), and atrial fibrillation (n = 2). They recommended levetiracetam for postoperative prophylactic use owing to its higher safety and efficacy. By contrast to the study of Luchi et al, we observed no significant difference between the efficacy of levetiracetam and phenytoin. In addition, none of the adverse events in the present study led to drug withdrawal.

The efficacy and safety of levetiracetam versus phenytoin for postcraniotomy seizure prophylaxis have been evaluated in many other studies (11, 15). Pourzitaki et al performed a systematic review and meta-analysis to evaluate the efficacy and safety of levetiracetam for seizure prophylaxis after supratentorial brain tumor surgery. The combined results of 3 studies, including 243 patients, revealed that levetiracetam administration is associated with a significantly lower rate of postcraniotomy seizure than phenytoin. The rate of side effects was also significantly

lower in the levetiracetam group compared with the phenytoin group (11). The efficacy and safety of levetiracetam administration were not superior to phenytoin in the present study.

Reviewing the literature reveals that there is still no consensus regarding the superior efficacy of levetiracetam over phenytoin for postcraniotomy seizure prophylaxis in patients with a supratentorial brain tumor. However, in the majority of the studies, the rate of side effects was lower with levetiracetam administration. The rate of side effects was lower in the levetiracetam group of the present study, although not significantly.

The present study examined 2 medications for the prevention of postcraniotomy seizures; neither medication was found to be superior to the other. However, more and shorter prophylaxis periods should be the subject of comparative studies to our study in order to compare the duration of prophylaxis. The present study has some limitations. The main limitation is that the number of events in the 2 study groups is limited and may adversely affect the power of statistical analysis. Moreover, we did not evaluate the plasma levels of drugs, which is a determining factor in controlling post craniotomy seizures. Besides, more side effects such as psychological ones can be evaluated. Therefore, future complementary studies are required with more attention to these deficiencies.

### Conclusion

The rate of postcraniotomy seizure was not significantly different between the levetiracetam and phenytoin groups. These results reveal no superiority of levetiracetam over phenytoin for postcraniotomy seizure prophylaxis in patients with a supratentorial brain tumor. Yet, future large-scale studies are required to shed more light on this subject.

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None.

### Ethical Approval

This study was approved by the review board of Tehran University of Medical Sciences under the code IR.TUMS.MEDICINE.REC.1395.428.

### Authors Contributions

Morteza Faghihjoubari: Study design and supervision  
 Masoud Khadivi: Data collection and methodology  
 Reza Rouhani: Data collection and methodology  
 Hamidreza Pazoki Toroudi: Study design and supervision  
 Masoud Nazari: Reviewing manuscript critically  
 Mahgol Sadeghian: Statistical analysis  
 Mehdi Abolfazli: Drafting the manuscript and data collection

### Conflict of Interests

The authors declare that they have no competing interests.

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