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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Tuğçe Mengi,
Barış Yılmaz,
Uğur Koca,
Ali Necati Gökmen

Phenytoin Versus Levetiracetam for Post-traumatic Seizure Prophylaxis

Post-travmatik Nöbet Profilaksisinde Fenitoine Karşın Levetirasetam

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Tuğçe Mengi
Dokuz Eylül University Research and Application Hospital, Clinic of Neurology, İzmir, Turkey

Barış Yılmaz
Dokuz Eylül University Research and Application Hospital, Clinic of Chest Diseases, İzmir, Turkey

Uğur Koca, Ali Necati Gökmen
Dokuz Eylül University Research and Application Hospital, Clinic of Anesthesiology and Reanimation, İzmir, Turkey

Tuğçe Mengi MD (✉),
Niğde Research and Training Hospital, Clinic of Neurology, Intensive Care Unit, Niğde, Turkey

E-mail : tugceangin@gmail.com
Phone : +90 388 232 22 20
ORCID ID : orcid.org/0000-0002-0639-0957

ABSTRACT *Objective:* This study aimed to compare the efficacy of levetiracetam versus phenytoin in early post-traumatic seizure prevention and ascertain the incidence of clinical seizures in traumatic brain injury (TBI).
Materials and Methods: Adult patients with moderate to severe TBI in the neuroimaging consistent with brain injury were included in the study. Patients were categorized into two groups, the phenytoin or levetiracetam groups, based on the administration of antiepileptic drugs for seizure prophylaxis.
Results: In this study, 100 patients with TBI met the inclusion criteria between January 2012 and June 2017, wherein 60 received seizure prophylaxis with phenytoin, and 40 with levetiracetam. The incidence of early post-traumatic seizure was 8%, without significant differences between groups (p>0.05). The incidence of clinical seizures after TBI was 10%.
Conclusion: This report showed that levetiracetam and phenytoin had similar efficacy in post-traumatic seizure prophylaxis. This retrospective study design improved the reliability of comparison between phenytoin and levetiracetam for seizures in the two groups with similar features in terms of age, sex, injury mechanism, neuroimaging findings, and Glasgow coma, Marshall, and acute physiology and chronic health evaluation-II scores.
Keywords: Levetiracetam, phenytoin, seizure, trauma

ÖZ *Amaç:* Bu çalışmanın amacı, erken post-travmatik nöbeti önlenmede levetirasetamın ve fenitoinin etkinliğini karşılaştırmak ve klinik nöbet insidansını belirlemektir.
Gereç ve Yöntem: Çalışmaya orta-şiddetli travmatik beyin hasarı tanısı alan, nörogörüntülemede beyin hasarı ile uyumlu bulgusu olan erişkin hastalar dahil edildi. Hastalar nöbet profilaksisi için uygulanan antiepileptik ilaca göre fenitoin grubu ve levetirasetam grubu olmak üzere iki gruba ayrıldı.
Bulgular: Ocak 2012 ile Haziran 2017 arasında 100 travmatik beyin hasarlı hasta bu çalışmaya dahil edilme kriterlerini karşıladı. Nöbet profilaksisi, bu hastaların 60'ında fenitoin ve 40'ında levetirasetam ile sağlandı. Erken post-travmatik nöbet insidansı ise %8 idi. Gruplar arasında erken post-travmatik nöbet oranı açısından anlamlı farklılık saptanmadı (p>0,05). Travmatik beyin hasarı sonrası klinik nöbet insidansı %10 idi.
Sonuç: Bu rapor, post-travmatik nöbet profilaksisinde levetirasetamın ve fenitoinin benzer etkinliğe sahip olduğunu gösterdi. Çalışmamız retrospektif bir tasarımda olmasına rağmen iki grup yaş, cinsiyet, travma mekanizması, nörogörüntüleme bulguları, Glasgow koma skoru, Marshall skoru ve akut fizyoloji ve kronik sağlık değerlendirmesi-II skorunu açısından benzer özelliklere sahipti. Bu bulgular, nöbet açısından fenitoin ve levetirasetamı karşılaştırılmayı güvenilir kılmaktadır.
Anahtar Kelimeler: Levetirasetam, fenitoin, nöbet, travma

Introduction

Traumatic brain injury (TBI) can cause seizures and the development of epilepsy. While the incidence of post-traumatic seizure (PTS) is uncertain after mild TBI, one well-known complication of moderate to severe TBI is PTS (1). Based on the occurrence time of the seizure, PTS are divided into two subgroups: The seizure which occurs within the first seven days following TBI is classified as early PTS; whereas, those occurring after the first seven days following TBI are classified as late PTS (2). Pharmacological seizure prophylaxis is aimed to prevent early seizures. It is thought that seizure prophylaxis is not effective in late PTS (3).

Phenytoin is one of the preferred antiepileptic drugs (AEDs) for early PTS prophylaxis. It is generally well-tolerated and can be administered intravenously, and most medical practitioners have knowledge of its usage (1). However, phenytoin can cause induction of hepatic cytochrome P450 system and significant drug-drug interactions (4). In addition, it has potential side effects such as hypersensitivity reactions, irritation of the skin, phlebitis, arrhythmias, and hypotension (1). Phenytoin has a narrow therapeutic window, which requires close monitoring (5). For these reasons, alternative antiepileptic therapies have been sought.

Valproate and carbamazepine have been investigated for usage in TBI. However, valproate and carbamazepine have similar side-effect profiles and require serum monitoring like phenytoin (5). Furthermore, the intravenous formulation of carbamazepine is not yet clinically available (1). These disadvantages have led to a search for new anticonvulsants. Levetiracetam is one of the drugs that has a demonstrated efficacy in a wide variety of seizure types and status epilepticus (6). Levetiracetam comes into prominence as an alternative to phenytoin due to several advantages. Some advantages are the absence of need for drug level monitoring, ease of titration due to its linear pharmacokinetics, and lower potential of drug-drug interaction (1,3). Enzyme-inducing properties have not yet been demonstrated (1). Despite all these advantages, there have been no sufficient studies to compare the efficacy of levetiracetam vs. phenytoin for seizure prophylaxis after TBI.

The objective of this study was to compare the efficacy of levetiracetam vs. phenytoin for the prevention of early PTS and to ascertain the incidence of clinical seizures in TBI.

Materials and Methods

Ethics committee approval was obtained from the Ethics Committee of Dokuz Eylül University (decision no: 2021/02-42, date: 18.01.2021). The study population consisted of patients with TBI admitted to the anesthesiology and reanimation intensive care unit (ICU) between January 2012 and June 2017. Adult patients were included if they had moderate to severe TBI in the presence of computed tomographic or magnetic resonance imaging consistent with brain injury. Patients were excluded from the study if they were younger than 18 years, did not receive a prophylactic AED, had epilepsy prior to TBI, had a prehospital use of AEDs for any reason, had a seizure before administration of the first dose of AEDs, or underwent cardiopulmonary resuscitation in the first seven days after TBI.

The records in the hospital automation system and our database of patients with TBI were evaluated retrospectively. Age, sex, admission date to ICU, neurological comorbidities, injury mechanism, initial Glasgow coma score (GCS) following admission to ICU, Marshall score, magnetic resonance imaging and/or computed tomography (CT) findings of injury upon presentation, neurosurgical interventions, administration of mannitol, administration of AEDs, clinical seizures, timing of clinical seizures, acute physiology and chronic health evaluation-II (APACHE-II) score, mechanical ventilatory support, ventilation days, need of hemodialysis, duration of ICU and hospital stay, 28 day and 90 day mortality were recorded on the data collection forms. Clinically GCS and radiological Marshall scores were used to determine the severity of TBI. The Marshall system places patients into one of six categories (I to VI) of increasing severity based on findings on non-contrast CT scans of the brain. Higher categories have worse prognosis and survival.

Patients were categorized into two groups, phenytoin group (PG) or levetiracetam group (LG), based on the usage of AEDs for seizure prophylaxis.

Statistical Analysis

Statistical analyses were performed using SPSS 24.0 statistics package software. Categorical variables were expressed as frequency and percentage values. All variables were expressed as median (minimum-maximum). Statistical analyses were made with t-test, Mann-Whitney U test, and chi-square test. $P<0.05$ was accepted as statistically significant.

Results

In this study, 100 patients with TBI met inclusion criteria in the Anesthesiology and Reanimation ICU between January 2012 and June 2017. Of those patients, 60 received seizure prophylaxis with phenytoin, and 40 received levetiracetam.

A detailed comparison of demographics, clinical and imaging data of patients with TBI is shown in Table 1. Neurological comorbidities were present in three patients. Regarding neurological comorbidities, one patient had stroke, one patient had hydrocephalus, and one patient had Alzheimer's Disease. There was no statistically significant difference between the PG and LG groups regarding the distribution of age, sex, neurological comorbidities, injury mechanism, initial GCS following admission to ICU, Marshall score, neuroimaging findings, APACHE-II score (p>0.05), (Table 1).

Table 2 presents the interventions. There was no statistically significant difference between the PG and LG groups regarding the distribution of neurosurgical interventions, mechanical ventilatory support, ventilation days, and hemodialysis support (p>0.05). The rate of mannitol administration was significantly higher in the LG compared with PG (p=0.012).

Figure 1 graphically depicts the change in prescribing trends at our hospital over time. Between 2015 and 2016, there was a shift in prescribing away from phenytoin and

Table 1. Demographics, clinical and imaging data of patient groups

	Total (n=100)	PG[1] (n=60)	LG[2] (n=40)	p
Age, median (range), y	37 (18-89)	37 (18-86)	37.5 (18-89)	0.938
Female, % (n)	18% (18)	18.3% (11)	17.5% (7)	0.915
Neurological comorbidities, % (n)	3% (3)	1.7% (1)	5% (2)	0.338
Injury mechanism				
Motorcycle/bicycle/pedestrian, % (n)	50% (50)	51.7% (31)	47.5% (19)	0.903
Motor vehicle accident, % (n)	19% (19)	20% (12)	17.5% (7)	
Fall, % (n)	26% (26)	23.3% (14)	30% (12)	
Other, % (n)	5% (5)	5% (3)	5% (2)	0.903
GCS[3] on ICU[4] admission				
GCS-eye, median (range)	1 (1-4)	1 (1-4)	1 (1-4)	0.564
GCS-verbal, median (range)	4 (3-5)	4 (3-5)	4 (4-5)	0.581
GCS-motor, median (range)	4 (1-6)	4 (1-6)	4 (1-6)	0.416
Neuroimaging findings				
Subarachnoid hemorrhage, % (n)	62% (62)	58.3% (35)	67.5% (27)	0.355
Subdural hematoma, % (n)	49% (49)	48.3% (29)	50% (20)	0.870
Cerebral contusion, % (n)	42% (42)	45% (27)	37.5% (15)	0.457
Epidural hematoma, % (n)	27% (27)	26.7% (16)	27.5% (11)	0.927
Pneumocephalus, % (n)	25% (25)	26.7% (16)	22.5% (9)	0.637
Intracerebral hemorrhage, % (n)	18% (18)	16.7% (10)	20% (8)	0.671
Intraventricular hemorrhage, % (n)	6% (6)	6.7% (4)	5% (2)	0.731
Diffuse axonal injury, % (n)	1% (1)	1.7% (1)	0	0.412
Marshall score				
Marshall score II, % (n)	42% (42)	46.7% (28)	35% (14)	0.480
Marshall score III, % (n)	15% (15)	11.7% (7)	20% (8)	
Marshall score V, % (n)	39% (39)	36.7% (22)	42.5% (17)	
Marshall score VI, % (n)	4% (4)	5% (3)	2.5% (1)	
APACHE-II, median (range)	22 (12-41)	20.5 (12-37)	23.5 (12-41)	0.675

PG[1]: Phenytoin group, LG[2]: levetiracetam group, GCS[3]: Glasgow coma score, ICU[4]: intensive care unit, APACHE-II: acute physiology and chronic health evaluation-II

Table 2. Interventions				
	Total (n=100)	PG[1] (n=60)	LG[2] (n=40)	p
Mannitol, % (n)	33% (33)	23.3% (14)	47.5% (19)	0.012
Neurosurgical intervention, % (n)	39% (39)	56.4% (22)	43.6% (17)	0.558
Mechanical ventilation, % (n)	96% (96)	95% (57)	97.5% (39)	0.006
Ventilation days, median (range)	7 (1-72)	5.5 (1-72)	11 (2-54)	0.066
Hemodialysis, % (n)	5% (5)	5% (3)	5% (2)	1.0
PG[1]: Phenytoin group, LG[2]: levetiracetam group				

Table 3. Outcomes				
	Total (n=100)	PG[1] (n=60)	LG[2] (n=40)	p
Post-traumatic seizure, % (n)	10% (10)	11.7% (7)	7.5% (3)	0.496
Early post-traumatic seizure, % (n)	8% (8)	10% (6)	5% (2)	0.367
Late post-traumatic seizure, % (n)	2% (2)	1.7% (1)	2.5% (1)	0.771
ICU[3] stay, median (range), d	10 (1-77)	9 (1-77)	12.5 (2-59)	0.151
Hospital stay, median (range), d	21 (1-132)	17.5 (1-90)	32.5 (2-132)	0.056
28 day mortality, % (n)	20% (20)	20% (12)	20% (8)	0.983
90 day mortality, % (n)	26% (26)	25% (15)	27.5% (11)	0.863
Brain death, % (n)	13% (13)	8.3% (5)	20% (8)	0.089
PG[1]: Phenytoin group, LG[2]: levetiracetam group, ICU[3]: intensive care unit				

toward levetiracetam. Eighty-three percent of the 53 patients admitted from 2012 to 2014 received phenytoin prophylaxis, whereas 66% of the 47 patients admitted between 2015 and 2017 received levetiracetam prophylaxis (p<0.001).

The incidence of clinical seizures after TBI was 10%. There were no significant differences in clinical seizure rates between PG and LG (p>0.05). The incidence of early PTS was 8%. There were no significant differences in early PTS rates between PG and LG (p>0.05). Late PTS were observed in two patients on the 11th and 17th days. Early PTS was most common on the 7th day after trauma (4/8, 50%), (p=0.446). There were no significant differences in ICU and hospital stay, brain death rate, 28 day and 90 day mortality rates between PG and LG (p>0.05), (Table 3).

Table 4 presents the demographics, clinical data, and outcomes of the eight patients who developed early PTS. Marshall scores of 3 patients were 5 and GCS of 2 patients were 3.

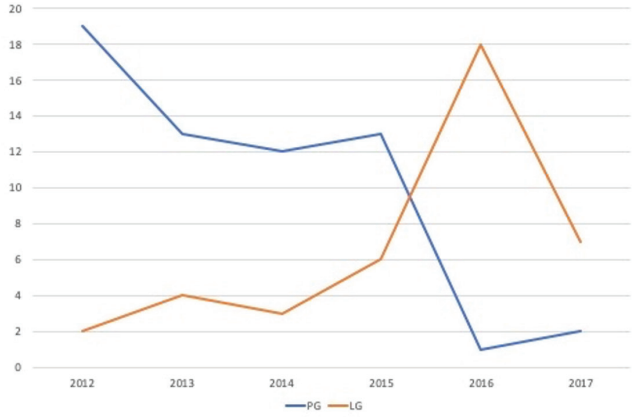

Figure 1. Prescribing trends over time
PG: Phenytoin group, LG: levetiracetam group

Discussion

Although our study was a retrospective design, two groups had similar age, sex, injury mechanism, neuroimaging findings, GCS, Marshall score, APACHE-II score (p>0.05). In our study, early PTS was higher in the PG among similar groups. However, there was no statistically significant difference in early PTS between groups. There was no statistically significant difference in seizure rate between groups in the trial of Inaba et al. (3) comparing phenytoin and levetiracetam for early PTS prophylaxis. They suggested that levetiracetam did as well but no better than phenytoin as an early PTS prophylaxis (3). Similarly, the results in the comparative trial of phenytoin vs levetiracetam for

Table 4. Demographics, clinical, imaging and outcome data of patients who developed early post-traumatic seizure

Index	Drug	Sex	Age, y	Injury mechanism	Marshall score	Neuroimaging findings	GCS[9]	APACHE-II	Time of seizure, d	28 day mortality	ICU[10] stay
1	PHE[1]	M	80	Fall	2	ICH[4], SDH[5]	$E_1V_tM_2$	26	3	1	13
2	LEV[2]	F	89	Fall	5	SDH	$E_4V_tM_5$	30	7	0	15
3	PHE	M	19	Motorcycle	3	Contusion, SAH[6]	$E_1V_tM_5$	18	5	0	10
4	PHE	M	31	Fall	5	EDH[7]	$E_2V_tM_2$	19	5	0	28
5	PHE	M	26	MVA[3]	2	IVH[8], contusion	$E_1V_tM_5$	16	7	0	8
6	LEV	M	18	Motorcycle	3	Contusion	$E_1V_tM_4$	17	7	0	4
7	PHE	M	24	Motorcycle	5	ICH, SAH	$E_1V_tM_1$	25	7	0	11
8	PHE	F	74	Fall	5	ICH, SDH	$E_1V_tM_1$	26	6	0	13

PHE[1]: Phenytoin, LEV[2]: levetiracetam, MVA[3]: motor vehicle accident, ICH[4]: intracerebral hemorrhage, SDH[5]: subdural hematoma, SAH[6]: subarachnoid hemorrhage, EDH[7]: epidural hematoma, IVH[8]: intraventricular hemorrhage, GCS[9]: initial Glasgow coma score following admission to intensive care unit, ICU[10]: intensive care unit, APACHE-II: acute physiology and chronic health evaluation-II, M: male, F: female

seizure prophylaxis study of Szaflarski et al. (7) revealed no statistically significant difference in seizure rate. In meta-analyzes evaluating efficacy in PTS prophylaxis, levetiracetam had similar efficacy with phenytoin (2,4,8). In addition to these reports which do not show superiority of the two drugs, there are also studies with a higher rate of seizures in the levetiracetam group. Conversely, there are studies suggesting that levetiracetam is more effective than phenytoin for seizure prophylaxis (4).

In the trial of Temkin et al. (9), the rate of early PTS was found to be significantly lower in the group receiving prophylactic AEDs compared to the placebo group. After this study, the usage of AEDs in the prevention of early PTS has become a standard practice for patients with TBI (3,9). However, nowadays there is an increasing number of studies questioning the benefit of routine prophylactic seizure prophylaxis in TBI. In these studies where the benefit of prophylactic AED was evaluated, the rate of seizures varied between 2-3% (10,11). In our study, despite the seizure prophylaxis, the rate of early PTS was 8%. We consider that this big difference for seizure rates is due to the different inclusion criteria in the studies. There was brain injury in neuroimaging of all patients included in our study, so that the seizure rate might be high. Additionally, patients with mild TBI were not included in our study.

Our study showed no statistically significant difference between the PG and LG in terms of mortality, length of hospital and ICU stays. In most studies comparing phenytoin and levetiracetam, no significant difference was found in mortality (2-4,7,12). Similarly, there was no significant difference in the length of hospital stay in studies comparing levetiracetam and phenytoin (3,12).

One of the remarkable points of our study is a significant shift toward the prescribing of levetiracetam over phenytoin for seizure prophylaxis after TBI. The reason for this shift may be the advantages of levetiracetam such as lack of need for drug level monitoring, ease of titration, and low drug-drug interaction.

Our study had a number of limitations, including its retrospective nature and small sample size. Another limitation is the lack of data about electroencephalography. Similar to our study, some of the studies for PTS prophylaxis evaluated clinical seizures (2,3). Long-term functional outcomes, adverse events, or economic analysis of AEDs were not evaluated in our study.

Conclusion

In conclusion, this report showed that levetiracetam and phenytoin had similar efficacy in PTS prophylaxis. Although our study was a retrospective design, the two groups had similar features in terms of age, sex, injury mechanism, neuroimaging findings, GCS, Marshall score, APACHE-II score. These similar features increase the reliability of comparison between the phenytoin and levetiracetam groups in terms of seizures. However, well-designed, prospective, randomized multicenter trials are needed to provide more precise advice on the efficacy of levetiracetam vs. phenytoin for seizure prophylaxis in TBI.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of Dokuz Eylül University (decision no: 2021/02-42, date: 18.01.2021).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: T.M., U.K., Design: T.M., U.K., Data Collection and Process: T.M., B.Y., Analysis or Interpretation: T.M., A.N.G., Literature Search: T.M., B.Y., Writing: T.M., A.N.G.

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