ORIGINAL ARTICLE

Factor Associated with Seizure Control in Patients with Acute Seizure Treated by Intravenous Generic Levetiracetam

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Objective: To evaluate if any of co-morbid diseases is a predictor for seizure controlled in patients with acute seizures treated with intravenous generic levetiracetam.

Materials and Methods: The inclusion criteria were admitted patients who received intravenous generic levetiracetam treatment for seizure control. The primary outcome of the study was seizure control which was defined by no evidence of seizure within 24 hours after intravenous generic levetiracetam treatment.

Results: During the study period, there were 93 patients received intravenous generic levetiracetam. Of those, 14 patients (15.05%) had uncontrolled seizures. There were 19 patients (20.43%) with status epilepticus. Only presence of brain tumor was associated significantly with uncontrolled seizures with an adjusted odds ratio of 5.30 (95% confidence interval of 1.31, 21.40).

Conclusion: The seizure-uncontrolled rate in patients with acute seizure events by the intravenous generic levetiracetam was 15.05%. The significant predictor for seizure uncontrolled was presence of brain tumor.

Keywords: Hypertension; Diabetes; Cerebrovascular diseases; Folic acid Status epilepticus; Seizure controlled; Adverse reaction

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Epilepsy is a common neurological disorder which required a long-term care. There are several related conditions with epilepsy which may result in morbidity or mortality[1-8]. Persons with epilepsy has an increasing risk for somatic and psychiatric comorbidities by 5.44 times particularly intellectual disability 12.9 times or autism by 22.2 times[9-11]. These co-morbid diseases may be associated with epilepsy bidirectionally. In other words, co-morbid diseases are precipitating factors for seizure attack, while epilepsy may cause or associate with these diseases. A recent concept of treatment of both epilepsy and its associated comorbidities are warranted[12,13].

Several factors are associated with seizure control in persons with epilepsy including number or adherence of antiepileptic drugs[14]. Persons with epilepsy may have urgent or emergent seizure attacks including status epilepticus or acute repetitive seizures. These two conditions require prompt intravenous antiepileptic drug treatment. There are several approved intravenous antiepileptic drugs for these conditions such as phenytoin or valproic acid[15,16]. Levetiracetam is a potent antiepileptic drug with low drug interaction. It can be used for acute seizure attack including status epilepticus[16,17]. The seizure controlled rate of levetiracetam was comparable with fosphenytoin and valproate (44% vs. 46% vs. 46%) in adult patients with status epilepticus[17]. Even though levetiracetam is effective, it has an issue of cost particularly intravenous form. Previous studies found that intravenous generic levetiracetam is effective and safe[18,19]. Seizure controlled rate by intravenous generic and brand levetiracetam were comparable (65% vs. 75%; p=0.490). However, there is limited data if co-morbid diseases are related with seizure

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controlled by intravenous generic levetiracetam treatment. Therefore, this study aimed to evaluate if any of co-morbid diseases is a predictor for seizure controlled in patients with acute seizures treated with intravenous generic levetiracetam.

Materials and Methods

This was a retrospective analytical study conducted at Khon Kaen University Hospital, Khon Kaen, Thailand. The inclusion criteria were admitted patients who received intravenous generic levetiracetam treatment for seizure control. Those who received intravenous generic levetiracetam treatment for post-operative seizure or pregnant/lactating women were excluded. The study period was between June 1st, 2019 and February 15th, 2020. The study protocol was approved by the ethics committee in human research, Khon Kaen University, Thailand (HE631072).

Chart review of eligible patients was performed. Data were retrieved for baseline characteristics and co-morbid diseases. For intravenous generic levetiracetam treatment, indication, dosage, and adverse reaction were collected. Generic levetiracetam used in this study was Focale® (Great Eastern Drug Co, Bangkok, Thailand). The primary outcome of the study was seizure control which was defined by no evidence of seizure within 24 hours after intravenous generic levetiracetam treatment clinically or by electroencephalography.

Statistical analysis

Eligible patients were categorized into two groups: seizure-controlled and seizure-uncontrolled groups. Studied variables were compared between both groups; Wilcoxon rank sum test was used for numerical variables, while Fisher Exact test was used for categorical variables. A predictive model for seizure-uncontrolled was executed by logistic regression analysis. A univariate logistic regression analysis was used to execute an unadjusted odds ratio for each studied variable. Those with a p-value of less than 0.20 by univariate logistic regression analysis or clinically significant were put into multivariate logistic regression analysis. Hosmer-Lemeshow method was used to evaluate goodness of fit of the predictive model. Results were reported as unadjusted/adjusted odds ratios with 95% confidence interval. Statistical analysis was calculated by STATA software (College Station, Texas, USA).

Results

During the study period, there were 93 patients received intravenous generic levetiracetam. Of those, 14 patients (15.05%) had uncontrolled seizures. Baseline characteristics and co-morbid diseases of those with seizure-controlled and seizure-uncontrolled group were shown in Table 1. The seizure-controlled group had somewhat older age (55 vs. 48 years) than the seizure-uncontrolled group (p=0.910), while male sex accounted for 54.43% and 57.14% in both groups. There were 19 patients (20.43%) with status epilepticus. Regarding co-morbid diseases, 82 patients (88.17%) had at least one co-morbid disease. Only brain tumor was found significantly higher proportion in the seizure-uncontrolled group than the seizure-controlled group (35.71% vs. 10.13%; p=0.042).

There were five factors in the predictive model for uncontrolled-seizure after treatment with intravenous generic levetiracetam (Table 2). Only presence of brain tumor was associated significantly with uncontrolled seizures with an adjusted odds ratio of 5.30 (95% confidence interval of 1.31, 21.40). The predictive model had Hosmer-Lemeshow Chi-square value of 6.84 (p=0.55). Regarding adverse reactions of intravenous generic levetiracetam, there were eight reported adverse reactions (Table 3). The overall rate of adverse reaction was 16.13% (15 patients). The seizure-uncontrolled group had a significantly higher proportion of any adverse reaction than the seizure-controlled group (35.71% vs. 12.66%; p=0.046). Vomiting was found higher in the seizure-uncontrolled group than the seizure-controlled group (14.2% vs. 1.27%; p=0.058).

Discussion

The present study found that the prevalence of co-morbid diseases in patients who were treated with intravenous generic levetiracetam was extremely high (88.17%). Previous studies found that prevalence rate of co-morbid diseases in persons with epilepsy varied from 41% to 69.9%[1,20]. These differences with this current study may be explained by different study populations. The previous studies were conducted in the general population, while this study enrolled those patients with acute seizure events. Therefore, patients recruited in our study may be more severe.

Even though presence of any co-morbid diseases was not related to seizure outcome (Table 1), patients with brain tumor were related with seizure control outcome by both univariate and multivariate logistic regression analysis (Table 2). Those with brain tumor increased risk of uncontrolled seizure treated by intravenous generic levetiracetam by 5.30 times. These findings may be explained by more severe brain tumor-related seizures. A previous systematic review found that patients with brain tumor-related status epilepticus had higher mortality than patients with status epilepticus from other causes by 1.53 times[21]. The mortality rate was significantly higher in patients with brain tumor than patients without brain tumor (17.2% vs. 11.2%). Even though a previous systematic

Table 1. Baseline characteristics and co-morbid diseases of patients treated with intravenous generic levetiracetam categorized by seizure controlled

Factors	Controlled, n=79	Uncontrolled, n=14	p-value
Age, years*	55 (2 to 88)	48 (19 to 88)	0.910
Male sex	43 (54.43)	8 (57.14)	0.999
GFR, ml/min/1.73 m^2*	85.5 (3.6 to 139.3)	93.2 (14.4 to 121.2)	0.317
Indications			0.727
Acute repetitive seizures	62 (74.48)	12 (85.71)	
Status epilepticus	17 (21.52)	2 (14.29)	
Loading dose, mg*	1,000 (110 to 2,000)	1,000 (750 to 2,000)	0.793
Amount of AED*	1 (1 to 2)	1 (1 to 2)	0.560
Co-morbid diseases	70 (88.61)	12 (85.71)	0.669
Numbers of co-morbid diseases*	2 (0 to 4)	2 (0 to 4)	0.912
Epilepsy	42 (53.16)	10 (71.43)	0.252
Brain tumor	8 (10.13)	5 (35.71)	0.042
Alzheimer's disease	1 (1.27)	0	0.999
Cerebral hemorrhage	2 (2.53)	0	0.999
Stroke	16 (20.25)	4 (28.57)	0.491
Traumatic brain injury	3 (3.80)	0	0.999
Dementia	0	1 (7.14)	0.151
Cerebral aneurysm	4 (5.06)	0	0.999
Moya Moya disease	1 (1.27)	0	0.999
Psychosis	1 (1.27)	0	0.999
Depression	0	1 (7.14)	0.151
Hypertension	26 (32.91)	4 (28.57)	0.999
Diabetes	13 (16.46)	2 (14.29)	0.999
Atrial fibrillation	10 (12.66)	1 (7.14)	0.999
Heart failure	2 (2.53)	0	0.999
Coronary artery disease	2 (2.53)	0	0.999
Valvular heart disease	3 (3.80)	0	0.999
Dyslipidemia	8 (10.13)	2 (14.29)	0.643
Obesity	1 (1.27)	0	0.999
Cancer	3 (3.80)	0	0.999
Hepatitis	4 (5.06)	1 (7.14)	0.566
Cirrhosis	1 (1.27)	0	0.999
Alcoholism	3 (3.80)	0	0.999
Osteoporosis	2 (2.53)	0	0.999
Asthma	1 (1.27)	0	0.999
COPD	2 (2.53)	0	0.999
HIV infection	6 (7.59)	1 (7.14)	0.999

Note: Data presented as number (%) except *indicating median (range).

Table 2. Factors associated with uncontrolled seizure in patients treated with intravenous generic levetiracetam

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)
Male sex	1.11 (0.54, 3.51)	1.36 (0.39, 4.75)
Status epilepticus	0.61 (0.12, 2.98)	0.71 (0.13, 3.74)
Epilepsy	2.20 (0.64, 7.62)	2.08 (0.57, 7.60)
Brain tumor	4.93 (1.32, 18.36)	5.30 (1.31, 21.40)

review showed that using levetiracetam may have a potential role in seizure prevention in patients with brain tumor[22], this study reported that it may not be beneficial in patients with brain tumor who had acute seizures.

Table 3. Adverse reaction reported in patients treated with intravenous generic levetiracetam

Adverse reaction	Controlled n=79	Uncontrolled n=14	p-value
Any adverse reaction	10 (12.66)	5 (35.71)	0.046
Diarrhea	1 (1.27)	0	0.999
Anorexia	2 (2.53)	1 (7.14)	0.391
Vomiting	1 (1.27)	2 (14.29)	0.058
Cough	1 (1.27)	0	0.999
Asthma attack	1 (1.27)	1 (7.14)	0.280
Depression	1 (1.27)	0	0.999
Weakness	3 (3.80)	0	0.999
Suicidal idea	0	1 (7.14)	0.151

The present study found that the seizure-uncontrolled group had significantly higher adverse reaction than the seizure-controlled group: up to 35.71% (Table 3). We do not have exact reasons for these findings, but uncontrolled seizures may be related to more drug reactions as they may require higher doses. A previous study found that adjunctive cenobamate for focal seizure with dose of 400 mg had adverse events occurred 90% of patients, while 100 mg treatment had adverse events in only 65%[23]. In overall, the rates of adverse reactions in the present study were comparable with previous studies for both general side effects such as vomiting and psychiatric side effects such as depression: approximately 2 to 3%[24,25]. Suicidal thoughts were reported in 0.1% in a previous study and found slightly higher in this study (1.07%).

The present study had some limitations. First, only admitted patients with acute seizure events either acute repetitive seizures or status epilepticus were enrolled. Second, some seizure-related factors or diseases such as obstructive sleep apnea were not studied[26-31]. A meta-analysis found that prevalence of OSA in persons with epilepsy was 33.4% and treatment with a continuous positive airway pressure machine provided better seizure control than those untreated by 5.26 times[3]. Finally, the generic levetiracetam used in this study was Focale®.

The seizure-uncontrolled rate in patients with acute seizure events by the intravenous generic levetiracetam was 15.05%. The significant predictor for seizure uncontrolled was the presence of brain tumor. The seizure-uncontrolled group may have a higher rate of adverse reactions than the seizure-controlled group. However, the overall rate of adverse reaction by the intravenous generic levetiracetam was low.

What is already known on this topic?

Intravenous generic levetiracetam is effective and safe. There is limited data if co-morbid diseases are related with seizure controlled by the intravenous generic levetiracetam treatment.

What this study adds?

Persons with epilepsy who had brain tumor may be resistant to the intravenous generic levetiracetam treatment.

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Conflicts of interest

The authors declare no conflict of interest.

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