ORIGINAL ARTICLE

Efficacy of Levetiracetam versus Phenytoin in Neonatal Seizure in Rural Area of Thailand

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Background: Neonatal seizure is an emergency condition that affects neurodevelopment and mortality. The appropriate treatment and seizure termination is crucial. Previous studies determined the efficacy of different types of antiseizure medications (ASMs), but there is no consensus toward second-line ASMs in neonatal seizure.

Objective: To compare the efficacy of second-line ASMs in neonatal seizure, compared between levetiracetam and phenytoin.

Materials and Methods: The present study was a retrospective study. The author recruited patients with diagnosis of neonatal seizure admitted at Maharat Nakhon Ratchasima Hospital, Thailand, between January 1, 2018 and December 31, 2020. Patients who had clinical seizure refractory and were given first-line ASM (intravenous phenobarbital) and received second-line ASMs as intravenous levetiracetam or intravenous phenytoin were included. Etiologies of seizure, seizure types, and other demographic data were recorded. The efficacy of levetiracetam and phenytoin were determined by comparing the duration of seizure, the need for third-line ASMs, and morbidity as developmental outcome, diagnosis of cerebral palsy, and mortality rate.

Results: Twenty-five patients (68% male) were recruited. Sixty-four percent were diagnosed with hypoxic ischemic encephalopathy (HIE). The most common seizure type was subtle seizure at 56%. Levetiracetam was given to 56% and phenytoin was given to 44% as second-line ASMs. The duration of seizure was significantly different at 28.12 minutes in levetiracetam and 42.72 minutes in phenytoin (p=0.01). The drug adherence was higher in the levetiracetam group. Regarding third-line ASMs, 28.7% of the levetiracetam group and 45.45% of phenytoin group needed third-line ASMs, but this was not statistically significant. Mortality was 20% and 48% were diagnosed as cerebral palsy. There was no significant difference in mortality and morbidity between the two groups.

Conclusion: Levetiracetam had no superior efficacy than phenytoin in neonatal seizure.

Keywords: Neonatal seizure; Levetiracetam; Phenytoin; Efficacy

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Neonatal seizure is one of the emergencies neurological conditions in newborns. The prevalence is 1 to 5 per 1,000 live births[1,2]. Most of the etiology of neonatal seizure is hypoxic ischemic encephalopathy (HIE), especially in developing countries[1-3]. Previous studies tried to identify the best antiseizure medications (ASMs) in neonatal seizures. The first-line ASM is recommended as phenobarbital[1-5]. In respect to the second-line ASMs, there are few previous studies on phenytoin and levetiracetam. The present study aimed to study the efficacy of second-line ASMs comparing phenytoin and levetiracetam in neonatal seizure.

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Materials and Methods

The present study was a retrospective observation study. After IRB gave approval, the author recruited neonatal patients diagnosed with neonatal seizure who were admitted at Maharat Nakhon Ratchasima Hospital between January 1, 2018 and December 31, 2020. Patients who had clinical seizure refractory to first-line ASM (intravenous phenobarbital 40 mg/kg) and received second-line ASM as intravenous levetiracetam or intravenous phenytoin were included as shown in Figure 1.

Etiologies of seizure, seizure types, severity of seizure, and other demographic data were recorded. The efficacy of levetiracetam and phenytoin were determined by comparing the duration of seizure, the need for third-line ASMs, and morbidity as

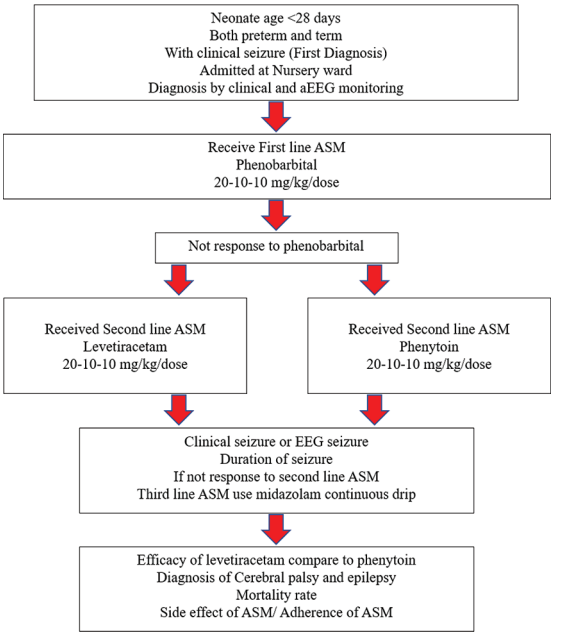

Figure 1. Algorithm of antiseizure medications (ASM) in neonatal seizure at Maharat Nakhon Ratchasima Hospital.

developmental outcome, diagnosis of cerebral palsy, and mortality rate.

The descriptive data were analyzed using mean and percentage. The difference between levetiracetam group and phenytoin group was determined by univariable analysis. The subgroup analysis was done using Fisher's exact test and Pearson deviation with multivariable analysis. For the multivariable analyses, the author used confounding factors such as etiology of seizure (HIE group), onset of seizure, and electroencephalography (EEG) monitoring. The Stata, version 10 (StataCorp LP, College Station, TX, USA) was used and the significant p-value was less than 0.05.

Results

Twenty-five patients with 68% male were recruited. Most of the patients were term and birth weight more than 2,500 g. Most common etiology of seizure was HIE in 64%. The most common seizure type was subtle seizure in 56% and most occurred in first 72 hours of life. Common mode of delivery was vaginal delivery.

Fifty six percent received levetiracetam and 44% received phenytoin as second-line ASMs. Due to limitation of the resource, the aEEG and EEG monitoring during seizure events were only 28%. The demographic data is shown in Table 1.

The mean duration of seizure was significantly different at 28.12±0.11 minutes in levetiracetam and 42.72±0.7 minutes in phenytoin (p=0.01). The drug adherence was higher in the levetiracetam group. Regarding third-line ASMs, 28.7% of the levetiracetam group and 45.45% of phenytoin group needed third-line ASMs. This was not statistically significant. Mortality was 20% and 48% were diagnosed with cerebral palsy. There was no significant difference of mortality and morbidity between the two groups as shown in Table 2.

In multivariable analysis using Pearson Deviance comparing the duration of seizure between the two groups, it was found that levetiracetam had significantly shorter duration of seizure as shown in Table 3. The incidence rate ratio (IRR) showed that the levetiracetam group had a significantly 56% shorter duration of seizure than the phenytoin group.

Table 1. Demographic data

	Levetiracetam (n=14) n (%)	Phenytoin (n=11) n (%)
Sex		
Male	10 (71.4)	7 (63.6)
Female	4 (28.6)	4 (36.4)
Gestational age		
<37 weeks	4 (28.6)	5 (45.5)
>37 weeks	10 (71.4)	6 (54.5)
Birth weight		
<2,500 g	3 (21.4)	5 (45.5)
>2,500 g	11 (78.6)	6 (54.5)
Types of delivery		
Vaginal delivery	7 (50.0)	9 (81.8)
Caesarean section	7 (50.0)	2 (18.2)
Date of life at seizure		
<72 hours	11 (78.6)	7 (63.7)
>72 hours	3 (21.4)	4 (36.3)
Etiology		
HIE	10 (71.4)	6 (54.5)
Others	4 (28.6)	5 (45.5)
EEG monitoring		
Abnormal	4 (28.6)	1 (9.1)
Normal	1 (7.1)	1 (9.1)
Not done	9 (64.3)	9 (81.8)

HIE=hypoxic ischemic encephalopathy; EEG=electroencephalography

Discussion

Neonatal seizure is one of the neurological emergencies in neonate. The first-line ASM is recommended as phenobarbital[1-6]. The second-line ASM is still debatable according to efficacy and the effect on the neurodevelopmental outcome.

Table 2. Univariable analysis

Factors	Levetiracetam (n=14); n (%)	Phenytoin (n=11); n (%)	p-value
Duration of seizure			0.120
<30 minutes	6 (42.9)	1 (9.1)	
30 to 60 minutes	8 (57.1)	9 (81.8)	
>60 minutes	0 (0.0)	1 (9.1)	
Requirement for third-line ASM			0.076
Yes	4 (28.7)	5 (45.5)	
No	10 (71.3)	6 (54.5)	
Adverse side effect of ASM			0.680
Present	2 (15.4)	1 (12.5)	
Absent	11 (84.6)	7 (87.5)	
Drug adherence			0.130
Good	12 (92.3)	5 (62.5)	
Poor	1 (7.7)	3 (37.5)	
Neurodevelopment (Denver test)			0.330
Delayed	8 (66.7)	4 (50.0)	
Normal	4 (33.3)	4 (50.0)	
Subsequent epilepsy			0.560
Yes	1 (7.1)	0 (0.0)	
No	13 (92.9)	11 (100)	
Cerebral palsy			0.690
Yes	7 (50.0)	6 (66.7)	
No	7 (50.0)	3 (33.3)	
Death			0.620
Yes	2 (14.3)	3 (27.3)	
No	12 (86.7)	8 (72.7)	

ASM=algorithm of antiseizure medication

Table 3. Multivariable analysis (Pearson Deviance)

	IRR	p-value	95% CI
Levetiracetam	0.56	0.006	0.369 to 0.849
HIE	2.18	0.015	1.16 to 4.09
Control	0.55	0.066	0.29 to 1.03

IRR=incidence rate ratio; CI=confidence interval

The present study aimed to identify the outcome of neonatal seizure by comparing second-line ASMs levetiracetam and phenytoin.

The present study reported the outcome predominant in term neonate with onset of clinical seizure at less than 72 hours of life. The common etiology of neonatal seizure was HIE. This correlated with the previous study that reported the common etiology of neonatal seizure as HIE[4].

The author noticed that seizures mostly lasted longer than 30 minutes. Furthermore, every neonate that received levetiracetam as the second-line ASM had seizure controlled within 60 minutes and 71.43% did not need third-line ASM, while only 54.45% in the phenytoin group did not need third-line ASM. This correlated with the previous studies about the efficacy of levetiracetam being at 32% to 95.3%[4-6] and phenytoin at more than 45%[7]. Even though the author identified the shorter duration of seizure in the levetiracetam group, there was no significant difference in efficacy between levetiracetam and phenytoin. This was different from the study of Mollamohammadi et al. that showed the significant efficacy of levetiracetam toward early seizure termination[5]. The author noticed the higher drug adherence and fewer side effects in levetiracetam group. This correlated with the previous study of Han et al.[6]. Because this was a retrospective study, the author could not use tools such as MMAS-4 to evaluate drug adherence. Further studies should be done to reach better conclusions.

The author identified developmental delay, subsequent epilepsy, and cerebral palsy as outcomes. However, there was no significant difference between the levetiracetam and the phenytoin group. The mortality rate was 20% in neonatal seizure but there was no significant difference in the two groups of ASMs. Previous studies have tried to identify the superior neuroprotective effects of levetiracetam, but there is still no consensus toward that theory[8-10].

The author noticed the efficacy in seizure termination in both ASMs. Even though levetiracetam had shorter duration of seizure, there was no difference in neurological outcome. Further study should be conducted as randomized controlled trial (RCT) for better conclusion.

Conclusion

The overall efficacy and neurodevelopmental outcome of levetiracetam was not superior to phenytoin.

What is already known on this topic?

Neonatal seizure is one of the emergency conditions that may affect future neurodevelopment. The common etiology of neonatal seizure is HIE. Previous studies determined the efficacy of anti-seizure medication on neonatal seizures. Levetiracetam and Phenytoin are second-line anti-seizure medications in neonatal seizures but the comparison between these two medications is limited.

What does this study add?

This study reported the comparison of efficacy of second-line anti-seizure medication on neonatal

seizure. The author identified a better response of seizure control in the Levetiracetam group. However, the overall outcome was not significantly different between Levetiracetam and Phenytoin.

Conflicts of interest

The authors declare no conflict of interest.

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