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# Impact of Perampanel for First-Episode Seizures versus Usual Care on Clinical Outcome and Safety Profile Aspects of the Thai Experience

Panu Boontoterm, MD, FRCNST, Siraruj Sakoolnamarka, MD, FRCNST, Karanarak Urasyanandana, MD, FRCNST, Pusit Fuengfoo, MD, FRCST

*Neurological Surgery Unit, Department of Surgery, Phramongkutklao Hospital, Bangkok, Thailand*

**Background and Purpose:** Epilepsy increases poor outcomes in patients with post-traumatic brain injury and brain tumor-related epilepsy, for whom early seizure control is essential. Perampanel (PER) was a known third-generation antiepileptic drug for treatment all types of seizures. The objective of the study is to compare clinical outcomes and safety of PER administration as monotherapy.

**Methods:** A prospective study of all 84 patients assigned to PER monotherapy (PER group, n=36) and other first-line antiepileptic drugs (n=48). Clinical outcomes parameters were measured by the prevalence of patients with a diminish in seizure frequency at 50% in 28 days. From November 1, 2020 to April 30, 2024, comparing the PER group with usual care. Clinical outcomes included adherence rate and seizure-free proportion at 28 days and 6 months. Adverse drug reactions were recorded in both groups.

**Results:** There was no difference in demographic data and incidence of adverse drug reactions between two groups. Median PER dosage was 4 mg (range, 2-12 mg). Compared to other antiepileptic drugs, the PER group had a prevalence of 50% responder rate at 28 days and 6 months significantly were 75%, 81%, 65%, and 51% respectively. Common adverse drug reactions were somnolence and dizziness.

**Conclusions:** PER administration as monotherapy demonstrated good efficacy and less adverse drug reactions. Low dosages helped to decrease adverse drug reactions andimproved retention rate. **(2024;14:81-93)**

**Key words:** Traumatic brain injury, Antiepileptic drugs, Seizures, Epilepsy, Adverse drug reaction

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Corresponding author:
Panu Boontoterm, MD, FRCNST
Neurological Surgery Unit, Department of Surgery, Phramongkutklao Hospital, Bangkok 10400, Thailand
Tel. +6687-912-8696
Fax. +662-763-3450
E-mail; sapiens_panu@hotmail.com

## Introduction

Perampanel (PER) is an antiepileptic drug approved for the treatment of epilepsy and has broad-spectrum efficacy.[1-3] PER is approved by the food and drug administration for administration in patients with the onset of focal seizures, with or without awareness, and focal seizures with or without evolving to bilateral tonic-clonic seizures in patients more than 4 years old. It is also used as monotherapy or as adjunctive therapy to first-line antiepileptic drug therapy, as well as add-on therapy for the treatment of the first episode of all seizure types in patients over 4 years old. Moreover, PER is a once-per-day dosage that promotes improvement in patient retention rate.[4-8] There are few studies regarding clinical outcomes and safety of PER when applied as monotherapy and switched from other antiepileptic drugs to monotherapy, especially in humans. This study provides supportive evidence support that may be a beneficial information for exploring the administration of anti-seizure medications (ASM) with PER monotherapy in the Southeast Asia regions.[9]

PER monotherapy may be useful in clinical neurological practice in epilepsy management due to it decrease the likelihood of adverse drug reactions, reduce the risk of drug interactions, especially when applied together with chemotherapy or anticoagulant agents, high retention rate, easy to evaluate when used in combination with other antiepileptic drugs, and low cost of treatment compared with other anti-seizure drugs.[10] The incidence of seizure patients who cured with ASM monotherapy, patients had seizure freedom at 47% with the first-line ASM, and the other achieved remission from seizures by use of the second-line monotherapy therapy at 13% with each guideline for ASM regimen management,[11] the chance of successful seizure free decreases substantially; most seizure patients who had seizure freedom with the first-line or second-line antiepileptic drug.[12] Therefore, early clinical application of an initial monotherapy ASM, or

as an early adjunctive ASM therapy, is important and essential for the best possible favorable neurological outcomes. To become a curative monotherapy, ASM for new episodes of seizure treatment should follow these recommendations. 1) Promptly choosing an effective antiepileptic drug appropriate for the specific seizure type; 2) selecting an ASM with less adverse drug reactions; 3) using antiepileptic drugs that are easy to administer, such as those with a once-daily dosage, to improve patient compliance; and 4) ensuring the antiepileptic drug can be titrated slowly to the desired dose.

PER is an antiepileptic drug with a mechanism of action as a selective of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist.[13] Based on the studies that demonstrated the efficacious antiepileptic drug and the safety drug profile.[14] As a real-world treatment for epilepsy, many ASMs that demonstrate efficacy as add-on regimens have also been shown to possess an effective and safe drug profile when administered as ASM monotherapy. Due to the fact that many epileptologists question whether a separate, once-daily antiepileptic drug indication is necessary in routine clinical practice, once the drug has been demonstrated to be safe and efficacious in adjunctive therapy trials. Additionally, data from several studies[15,16] focused on patients who were administered PER by switching to ASM monotherapy, as some seizure patients were initially treated with PER monotherapy. Moreover, clinical practice guidelines for PER monotherapy in all types of seizures, particularly in patients with severe comorbidities-especially those with heart, liver, and kidney diseases, as well as elderly patients-have not been specifically demonstrated.[17] The objective of the study was to provide data on the retention, effectiveness, and safety profile of PER monotherapy, specifically related to adverse drug reactions in a clinical setting, based on the Thai experience and this includes switching from first-line ASM to PER monotherapy and evaluating initial PER monotherapy during the first 6 months of treatment.

## Methods

This study was a prospective cohort study. Eighty-four patients were assigned to PER administration as monotherapy (n=36) and other first-line antiepileptic drug therapy (phenytoin administration) (n= 48). Clinical outcomes parameters were measured by prevalence of patients with a diminish in seizure frequency at 50% in 28 days. From November 1, 2020 to April 30, 2024, comparing the PER group with usual care. Clinical outcomes included adherence rate and seizure-free proportion at 28 days and 6 months. Adverse drug reactions were recorded in both groups. Data collection was composed of patients' baseline characteristics regarding seizure types and PER dosage, as well as patients' retention rate and seizure freedom rate at the 28-day and 6-month follow-up periods. The safety profile, adverse drug reactions, and treatment outcomes implemented in Phramongkutklao Hospital to investigate the dosage and clinical outcomes of the responder rate, and adverse drug reactions of PER administered as ASM monotherapy to patients with their first new episode seizure. The data were recorded prospectively for patients who presented with their first new episode of any type of seizure and received PER as the first antiepileptic drug in monotherapy at the time of their initial seizure onset. By using prospective as the first antiseizure medication in patients presenting with the first seizure investigated and monitored by electroencephalography for 24 hours. Patients who had the first episode of seizures were identified from electronic or paper medical records of individuals and were prescribed PER as the first antiseizure medication monotherapy. After obtaining approval from the Ethics Committee and the Thai Clinical Trials Registry Committee, as well as written informed consent, patients were enrolled based on the inclusion criteria of being over 4 years old and presenting with their first episode of seizures.

Patients were recruited from the outpatient clinic in case of neurosurgery or neurology, with the agreement and participation of all site-based. Informed consent was obtained from the participants. The dosage of oral PER was 2 mg per day before bedtime at least 2 weeks. If there were no adverse drug reactions issues to demonstrate, then the PER dosage would be increased to 4 mg per day as the maintenance dosage. On the other hand, if the patients had adverse drug reactions, the PER dosage was titrated down to the previous PER dosage at another 2 weeks. If they experienced seizure symptoms, then the PER dosage would be gradually increased to 6, 8, 10 mg, and a maximum of 12 mg per day, with weekly monitoring. In cases where patients do not tolerate the adverse effects, but seizures continue to occur and clinical deterioration is observed, then this study will be stopped and switched to use other antiepileptic drugs. The patients who had not completed response to the PER, if patients do not achieve seizure-free status after trying PER monotherapy, the patients will be switched to administer polytherapy or an alternative antiepileptic drug monotherapy.

The primary outcome of this study was to assess changes in seizure frequency over a 28-day period when PER was administered as monotherapy. The patients who were administered PER monotherapy for at least 6 months have to be included in data analysis. The definition of patient retention rate was the number of seizure patients who continued using PER monotherapy at each observation

point. Seizure-free status is defined as complete seizure control after PER monotherapy has been administered since the previous visit to the emergency department or the medical/neurological surgery department; which for the 6-month follow up period defined as no seizures during at least the prior 6 months, and for 28 days, visits meant no seizures since baseline, or 28 days and 6 months follow up period, respectively. The definition of changing in frequency of seizure was demonstrated by the median frequency change in seizure symptom collected per day at 28 days.

The PER dosage in this study was recorded. Treatment-emergent adverse events (TEAEs) were the relation to safety aspects after PER monotherapy, were divided into the adverse events and frequency of TEAEs and not tolerated PER monotherapy that had been recorded when initiated PER monotherapy until the last observation period. The sample size was based on a study of the effectiveness and safety of PER monotherapy for all types of seizures. Experience from a national multicenter registry published in epilepsia 2020 about the efficacious and retention of PER monotherapy in treatment of seizures. As a priority assumption, we hypothesized that proportions of reduction in seizure frequency would be associated with PER monotherapy. Accepting a *p*-value

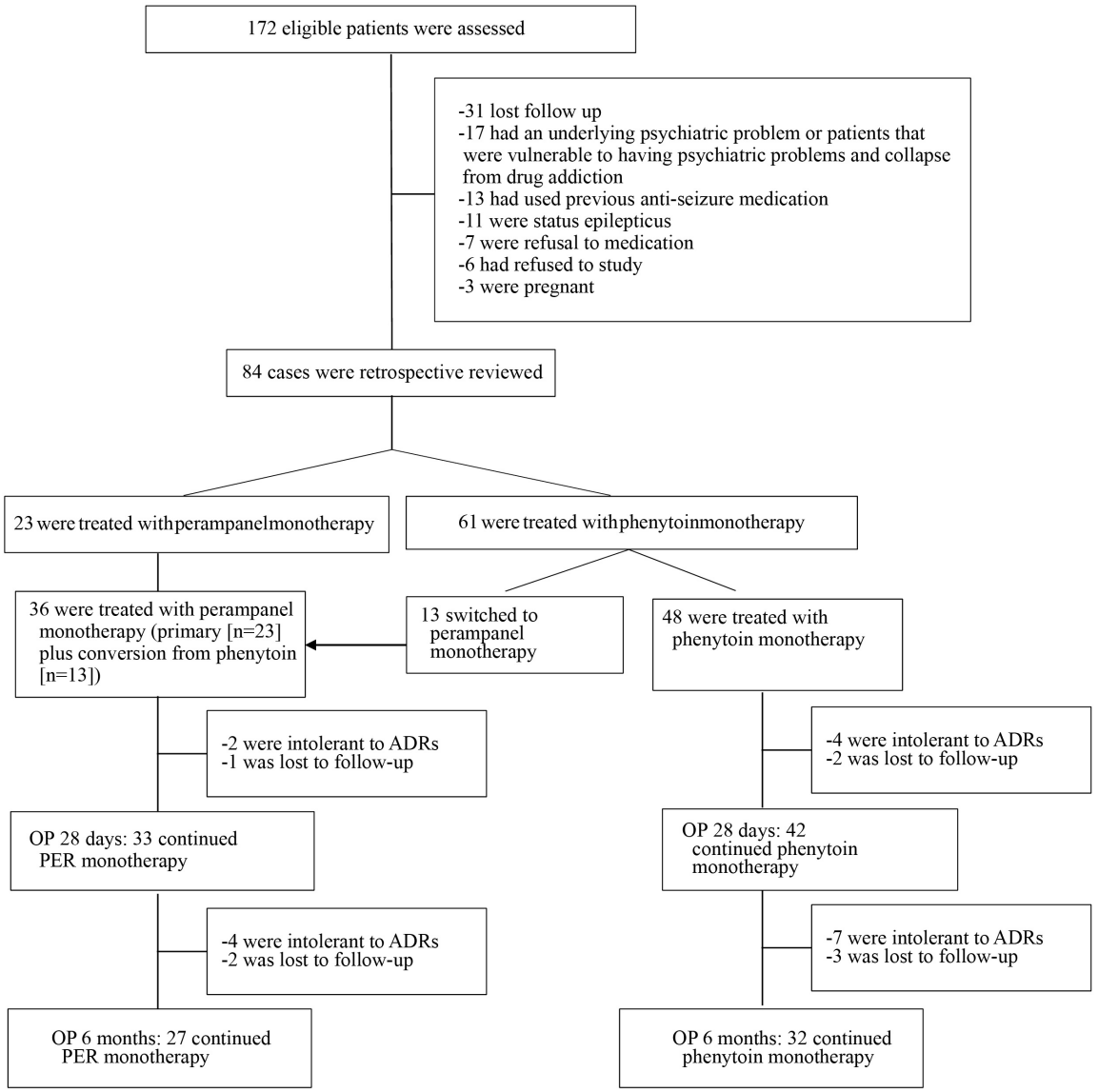


**Figure 1.** Illustration of the number of patients evaluated at each visit who have been treated with perampanel (PER) monotherapy and phenytoin monotherapy at some point during the first 6 month. ADRs, adverse drug reactions; OP, observation point.

<0.05 for statistical significance and a β error of 0.2, we determined that at least 25 patients were required for this study. Categorical data are demonstrated as numbers (percentages) and were analyzed using contingency table analysis, Fisher's exact test, and chi-square tests. Continuous variables are presented as mean±standard deviation using an unpaired *t*-test or analysis of variance for analysis. The exclusion criteria were patients who have pregnancy, refusal to medication, known case status epilepticus, use of previous anti-seizure medication, patients who had an underlying psychiatric problem or patients that were vulnerable to having psychiatric problems and collapse from drug addiction and known metabolic causes. The exclusion criteria included patients who were pregnant, refused medication, had known status epilepticus, had used previous anti-seizure medications, had underlying psychiatric problems, were vulnerable to psychiatric issues, collapsed from drug addiction, or had known metabolic causes. The number of patients evaluated at each visit who have been treated with PER monotherapy and phenytoin monotherapy at some point during the first 6 month was demonstrated in Fig. 1.

## Ethics approval and consent to participate

The Thai Clinical Trials Registry Committee approved the study under opinion number TCTR20240429003 on April 29, 2024, and the Ethics Committee of the Institutional Review Board of Medical Department Ethics approved the study under opinion number: IRBRTA 1731/2559. The study was done owing to the Declaration of Helsinki and the Foundation for Human Research Promotion in

**Table 1.** Baseline characteristic of each group classify in perampanel group and usual care group

| | Perampanel (n=36) | Usual care (n=48) | *p*-value |
|---|---|---|---|
| Male | 22 (61.1) | 34 (70.8) | 0.239 |
| Age (years) | 65.8±14.62 | 59.5±14.18 | 0.086* |
| Body weight (kg) | 63.1±8.47 | 59.3±9.16 | 0.921 |
| BMI (kg/m$^2$) | 19.23±2.84 | 18.18±2.91 | 0.949 |
| Seizure frequency per month | 2.5 (1, 4) | 1.5 (1, 4) | 0.25 |
| Focal seizures | | | |
| Focal onset with awareness | 21 (58.0) | 29 (60.0) | 0.470 |
| Focal onset with impaired awareness | 13 (36.0) | 15 (31.0) | 0.721 |
| Evolving to bilateral tonic-clonic seizure | 2 (5.6) | 4 (8.0) | 0.83 |
| Etiology not known | 3 (10.0) | 2 (5.0) | 0.231 |
| Etiology known | | | |
| Cranial trauma | 18 (50.0) | 17 (35.4) | 0.065 |
| Cerebrovascular | 9 (25.0) | 15 (31.3) | 0.999 |
| Neurodegenerative | 2 (5.5) | 4(8.3) | 0.605 |
| Cerebral neoplasm | 2 (5.5) | 4 (8.3) | 0.231 |
| Malformations of cortical development | 1 (2.8) | 2 (4.2) | 0.906 |
| Mesial temporal sclerosis | 1 (2.8) | 1 (2.1) | 0.762 |
| Hippocampal atrophy | 1 (2.8) | 2 (4.2) | 0.843 |
| AVM | 1 (2.8) | 1 (2.1) | 0.864 |
| Other | 1 (2.8) | 2 (2.1) | 0.968 |
| Perampanel dosage | | NA | NA |
| 2 mg | 2 (5.5) | NA | NA |
| 4 mg | 26 (72.2) | NA | NA |
| 6 mg | 4 (11.1) | NA | NA |
| 8 mg | 3 (8.3) | NA | NA |
| 12 mg | 1 (2.8) | NA | NA |

Values are presented as mean±standard deviation, median (min, max), or number (%).
BMI, body mass index; AVM, srteriovenous malformation; NA, not assessed.
**p*-value analyzed using Chi-square test.

Thailand. Since this is a prospective study with no specific intervention, but only using inpatient department medical record data and other review of clinical information that created results in an aggregate manner, without demonstrating the identification of participants, the written consent was obtained in accordance with the Council for International Organization of Medical Sciences guidelines 2012 and the Good Clinical Practice guidelines of the International Conference on Harmonization.

## Results

A total of 84 patients from Phramongkutklao Hospital were included

**Table 2.** Demographic data comparison seizure status, treatment-emergent adverse event and secondary outcomes between two patient groups

| | Perampanel (n=36) | | Usual care (n=48) | | *p*-value | |
|---|---|---|---|---|---|---|
| | 28 days | 6 months | 28 days | 6 months | 28 days | 6 months |
| Retention rates | 33 (91.0) | 27 (75.0) | 42 (87.0) | 32 (67.0) | 0.48 | 0.51 |
| 50% responder rate | 27 (75.0) | 29 (81.0) | 31 (65.0) | 25 (51.0) | 0.026* | 0.010* |
| Seizure-free status | 27 (75.0) | 26 (72.0) | 25 (52.0) | 23 (47.0) | 0.017* | 0.048* |
| Type of seizure in seizure-free status | | | | | | |
| Focal seizures | 15 (41.0) | 15 (41.0) | 8 (16.0) | 9 (18.0) | 0.851 | 0.71 |
| Focal onset with awareness | 6 (16.0) | 6 (16.0) | 8 (16.0) | 7 (14.0) | 0.874 | 0.025* |
| Focal onset with impaired awareness | 3 (8.0) | 3 (8.0) | 5 (10.0) | 5 (10.0) | 0.52 | 0.062 |
| Evolving to bilateral tonic-clonic seizure | 3 (8.0) | 2 (5.0) | 2 (4.0) | 2 (4.0) | 0.27 | 0.16 |
| Treatment-emergent adverse event | | | | | | |
| Any AEs | 8 (22.0) | 7 (19.0) | 12 (25.0) | 11 (23.0) | 0.273 | 0.228 |
| Serious AEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA | NA |
| Severe AEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA | NA |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA | NA |
| Discontinuation due to AEs | 1 (3.0) | 1 (3.0) | 4 (8.0) | 3 (6.0) | 0.999 | 0.75 |
| Incidence of individual AEs | | | | | | |
| Dizziness | 6 (16.0) | 5 (13.0) | 9 (18.0) | 8 (16.0) | 0.78 | 0.61 |
| Somnolence | 3 (8.0) | 4 (11.0) | 4 (8.0) | 3 (6.0) | 0.66 | 0.73 |
| Ataxia | 2 (5.0) | 1 (3.0) | 3 (6.0) | 4 (8.0) | 0.34 | 0.49 |
| Dry mouth | 1 (3.0) | 1 (3.0) | 3 (6.0) | 2 (4.0) | 0.89 | 0.52 |
| Depression | 1 (3.0) | 1 (3.0) | 3 (6.0) | 4 (8.0) | 0.92 | 0.67 |
| Confusion | 0 (0.0) | 1 (3.0) | 2 (4.0) | 1 (3.0) | 0.46 | 0.37 |

Values are presented as number (%).
AEs, adverse effects; NA, not assessed.
*$p$-value analyzed using Mann-Whitney test and Chi-square test.

**Table 3.** Baseline characteristics of treatment-emergent adverse event classified in dosage of PER

| TEAEs | Perampanel dosage | | | | |
|---|---|---|---|---|---|
| | 2 mg | 4 mg | 6 mg | 8 mg | 12 mg |
| Dizziness | 1 (16.0) | 1 (16.0) | 1 (16.0) | 2 (33.0) | 1 (16.0) |
| Somnolence | 0 (0.0) | 1 (33.0) | 1 (33.0) | 1 (33.0) | 1 (33.0) |
| Ataxia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) |
| Dry mouth | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) |
| Depression | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) |
| Confusion | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) |

Values are presented as number (%).
PER, perampanel; TEAEs, treatment-emergent adverse events.

**Table 4.** Treatment-emergent adverse event comparison between perampanel monotherapy and phenytoin monotherapy

| | Perampanelmonotherapy (n=36) | | Phenytoinmonotherapy (n=48) | | *p*-value | |
|---|---|---|---|---|---|---|
| | 28 days | 6 months | 28 days | 6 months | 28 days | 6 months |
| Treatment-emergent adverse event | | | | | | |
| Any AEs | 8 (22.0) | 7 (19.0) | 12 (25.0) | 11 (23.0) | 0.273* | 0.228* |
| Serious AEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA | NA |
| Severe AEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA | NA |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA | NA |
| Discontinuation due to AEs | 1 (3.0) | 1 (3.0) | 4 (8.0) | 3 (6.0) | 1 | 0.75 |
| Incidence of individual AEs | | | | | | |
| Dizziness | 6 (16.0) | 5 (13.0) | 9 (18.0) | 8 (16.0) | 0.78 | 0.61 |
| Somnolence | 3 (8.0) | 4 (11.0) | 4 (8.0) | 3 (6.0) | 0.66 | 0.73 |
| Ataxia | 2 (5.0) | 1 (3.0) | 3 (6.0) | 4 (8.0) | 0.34 | 0.49 |
| Dry mouth | 1 (3.0) | 1 (3.0) | 3 (6.0) | 2 (4.0) | 0.89 | 0.52 |
| Depression | 1 (3.0) | 1 (3.0) | 3 (6.0) | 4 (8.0) | 0.92 | 0.67 |
| Confusion | 0 (0.0) | 1 (3.0) | 2 (4.0) | 1 (3.0) | 0.46 | 0.37 |

Values are presented as number (%).
AEs, adverse effects; NA, not assessed.
**p*-value analyzed using Mann-Whitney test and Chi-square test.

**Table 5.** Treatment-emergent adverse events occurred in phenytoin monotherapy group

| | Phenytoin monotherapy (n=48) | |
|---|---|---|
| | 28 days | 6 months |
| Treatment-emergent adverse event | | |
| Any AEs | 12 (25.0) | 11 (23.0) |
| Arrhythmia | 3 (6.0) | 2 (4.0) |
| Hypotension (mean arterial pressure ≤65 mmHg) | 2 (4.0) | 1 (3.0) |
| Withdrawal of drugs | | |
| Discontinuation due to AEs | 4 (8.0) | 3 (6.0) |
| Lack of efficiency | 2 (4.0) | 1 (3.0) |
| Adverse effects and lack of efficiency | 4 (8.0) | 3 (6.0) |
| Increased frequency of seizures | 2 (4.0) | 1 (3.0) |
| Incidence of individual AEs | | |
| Gum hypertrophy | 4 (8.0) | 3 (6.0) |
| Rash | 2 (4.0) | 1 (3.0) |
| Ataxia | 2 (4.0) | 1 (3.0) |
| Headache | 3 (6.0) | 2 (4.0) |
| Excessive sleepiness | 3 (6.0) | 4 (8.0) |
| Difficulty with coordination | 2 (4.0) | 1 (3.0) |
| Itchiness | 2 (4.0) | 1 (3.0) |
| Nausea | 2 (4.0) | 1 (3.0) |
| Vomiting | 2 (4.0) | 1 (3.0) |
| Tingling, ''pins and needles'' sensation | 2 (4.0) | 1 (3.0) |
| Nervousness | 2 (4.0) | 1 (3.0) |
| Lack of energy or strength | 2 (4.0) | 1 (3.0) |
| Liver function impairment | 3 (6.0) | 2 (4.0) |

Values are presented as number (%).
AEs, Adverse effects.

in this study. The mean age was 65 years, with a range 51 to 79 years (Table 1). Thirty-three patients continued administration of PER monotherapy for the first month, while 27 patients continued using PER for 6 months (Table 2). The median PER administration was 4 mg, ranging

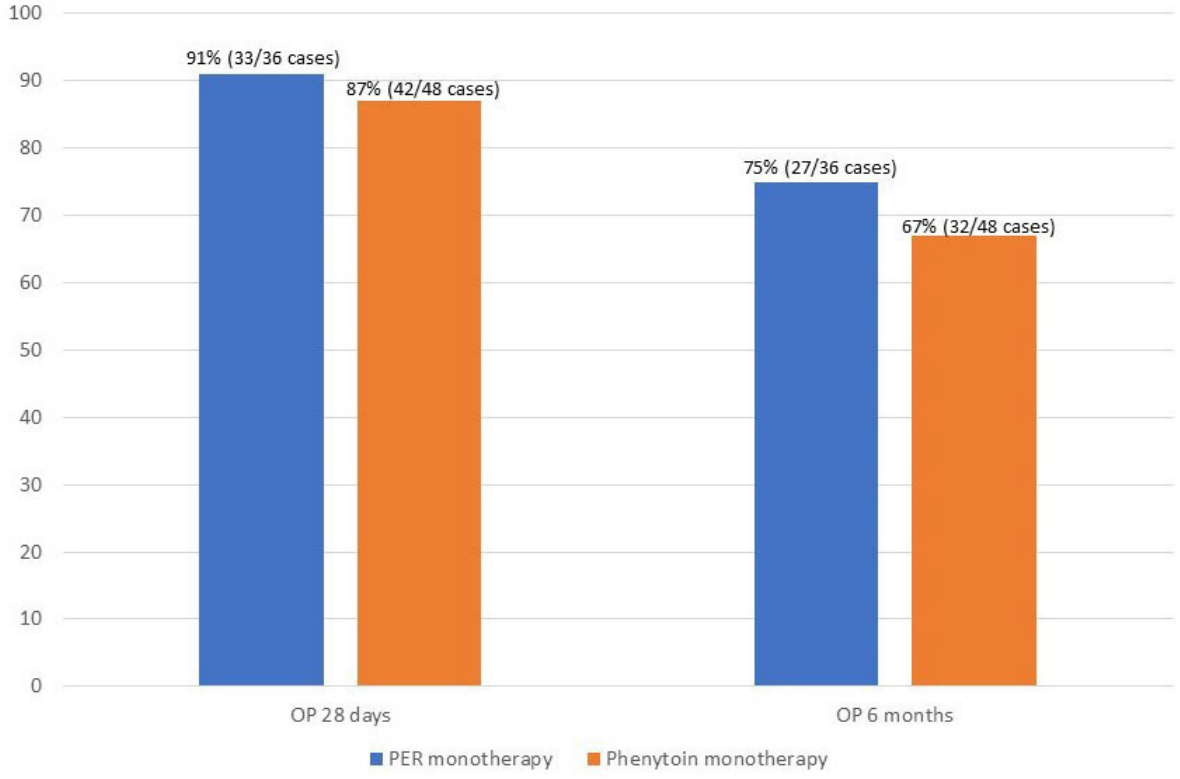


**Figure 2.** Comparison between retention rates on perampanel monotherapy and phenytoin monotherapy evaluated at each visit at some point during the first 28 days and 6 months. OP, observation point; PER, perampanel.

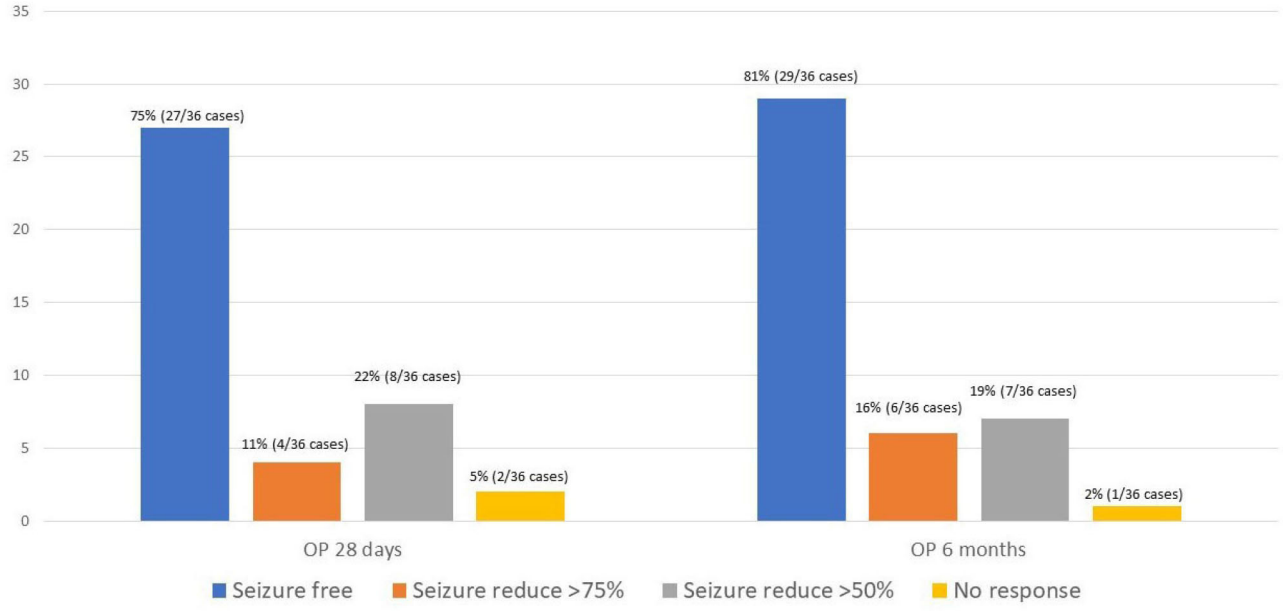


**Figure 3.** Seizure-response status and seizure-free status at OP 28 days and 6 months on perampanel monotherapy. OP, observation point.

from 2 to12 mg. The most common dosage was 4 mg (72%), 6 mg (11%), 8 mg (3%), 2 mg (5.5%), and 12 mg (2.8%), respectively. At the 28-day observation point, the patients' retention rates were 91% (two cases lost in the observation period, intolerant PER monotherapy, n=3; one case withdrawn PER due to adverse drug reactions in both dizziness and somnolence). At the 6-month observation point, the retention rates were 75% (six cases lost in the observation period, intolerant PER monotherapy, n=6; all had stopped PER due to adverse drug reactions, and three cases switched to polytherapy to achieve seizure control) (Table 2). Changes in seizure frequency at

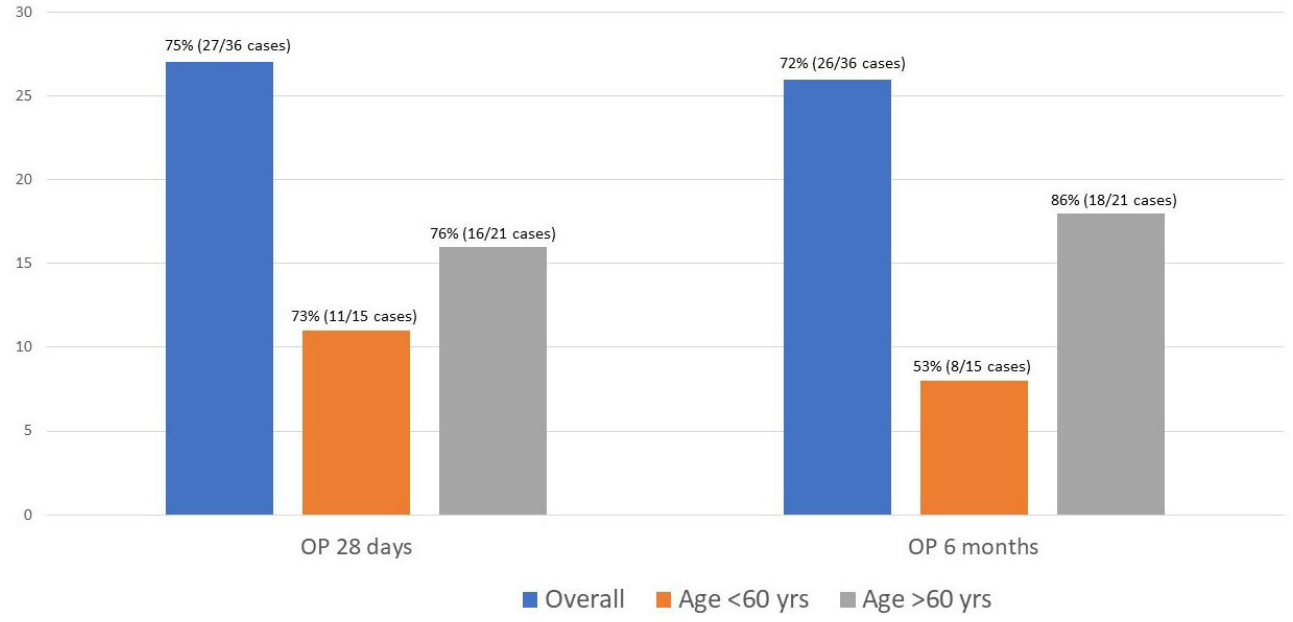


**Figure 4.** Seizure-response status and seizure-free status at different age at OP 28 days and 6 months on perampanel monotherapy. OP, observation point.

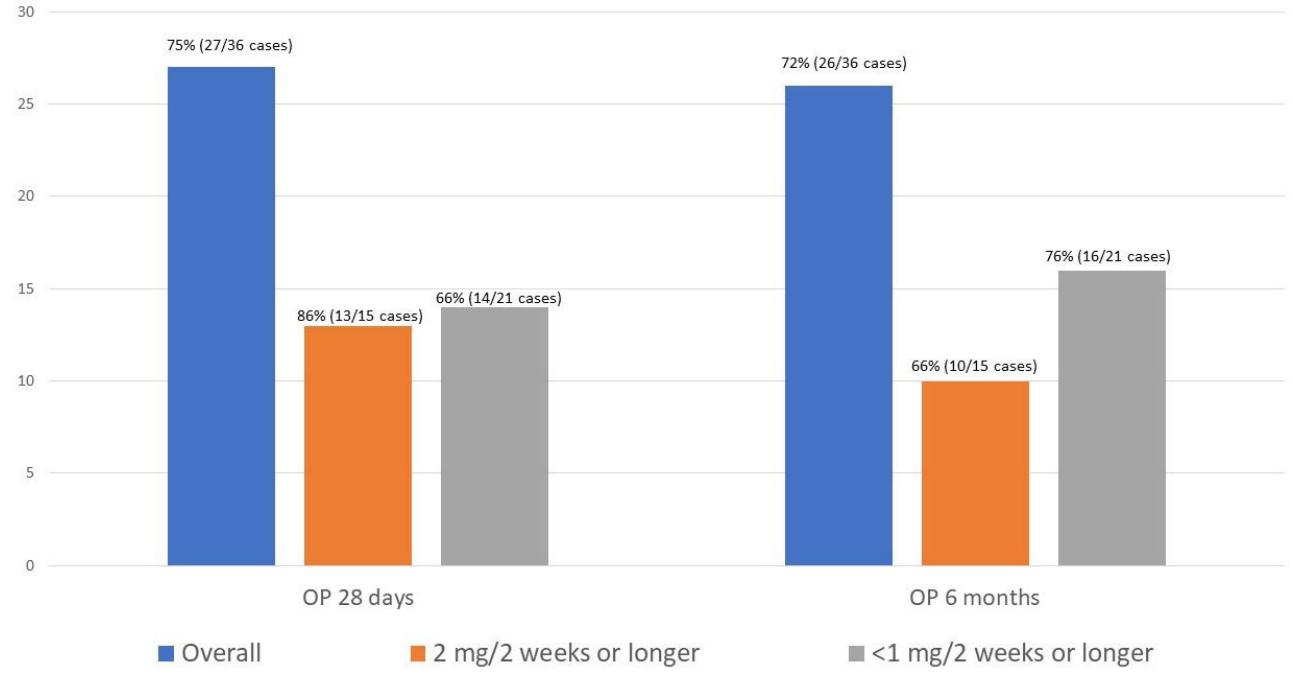


**Figure 5.** Seizure-response status and seizure-free status at titration speed at OP 28 days and 6 months on perampanel monotherapy. OP, observation point.

the 28-day and 6-month period of follow-up for the 36 patients who had seizure frequency data affordable and were included in this analysis: 75% (n=27/36 cases) and 72% (n=26/36 cases), respectively, were seizure-free while receiving PER monotherapy. Regarding the 27 patients who were seizure-free, 41% had focal seizures, 16% had focal seizures with awareness, 8% had focal seizures with impaired awareness, and 8% had focal seizures evolving to bilateral tonic-clonic seizures. PER monotherapy was significantly associated with a greater

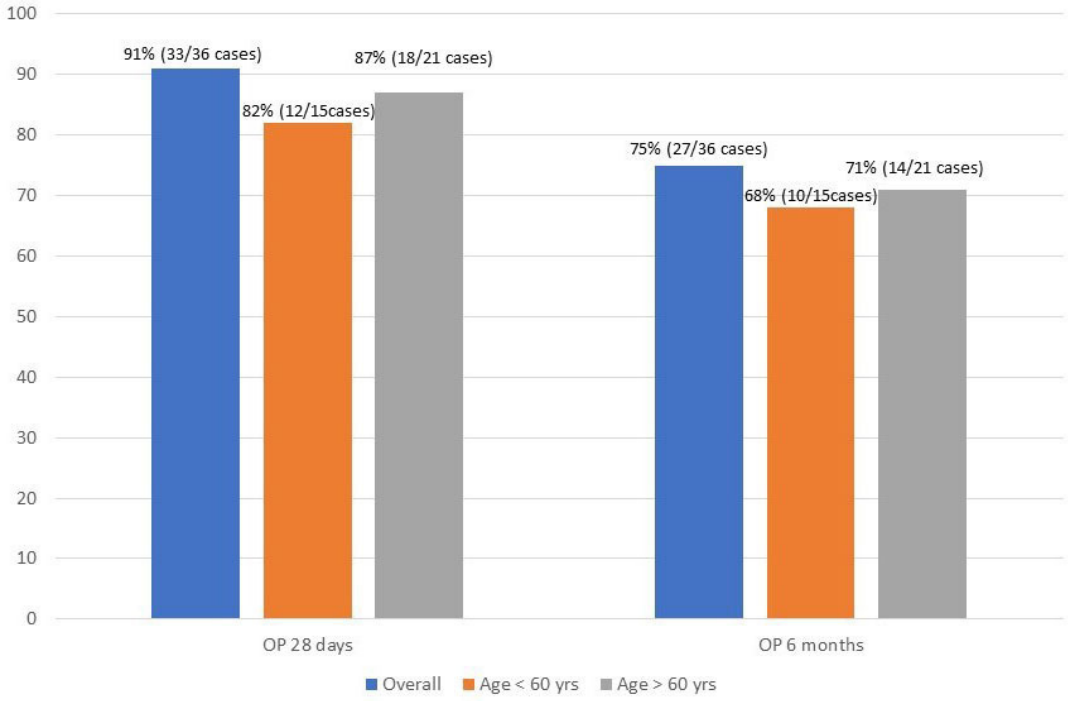


**Figure 6.** Retention rate at different age at OP 28 days and 6 months on perampanel monotherapy. OP, observation point.

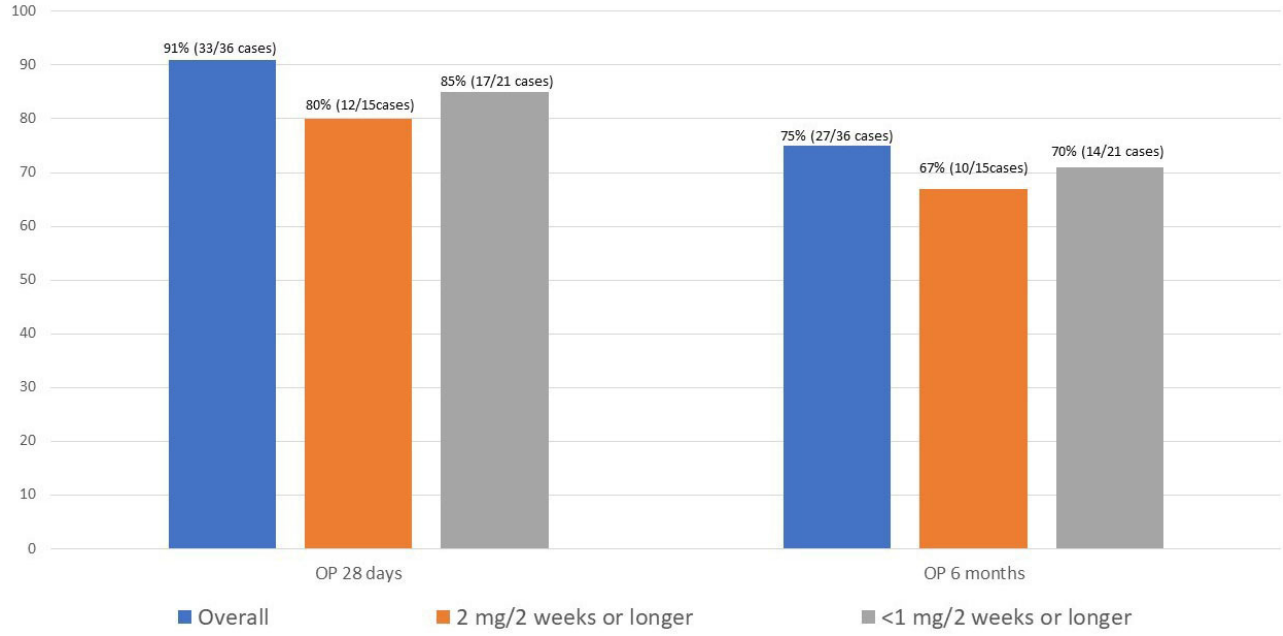


**Figure 7.** Retention rate status at titration speed at OP 28 days and 6 months on perampanel monotherapy. OP, observation point.

rate of seizure-free outcomes than usual care in patients with focal seizures with awareness. The baseline characteristics of adverse drug reactions classified in dosage of PER are demonstrated in Table 3. The most common adverse drug reactions were dizziness, somnolence, ataxia, and depression. There were no serious TEAEs occurred in both groups during PER monotherapy. Adverse drug reactions associated with PER monotherapy included dizziness, somnolence, ataxia, and depression, as detailed in Table 3.

No serious TEAEs were reported in either group. Comparative demographic data on TEAEs for PER and phenytoin monotherapy are presented in Tables 4, 5, respectively. Figs. 2-9 illustrate differences in efficacy and retention rates based on age groups and PER dosage

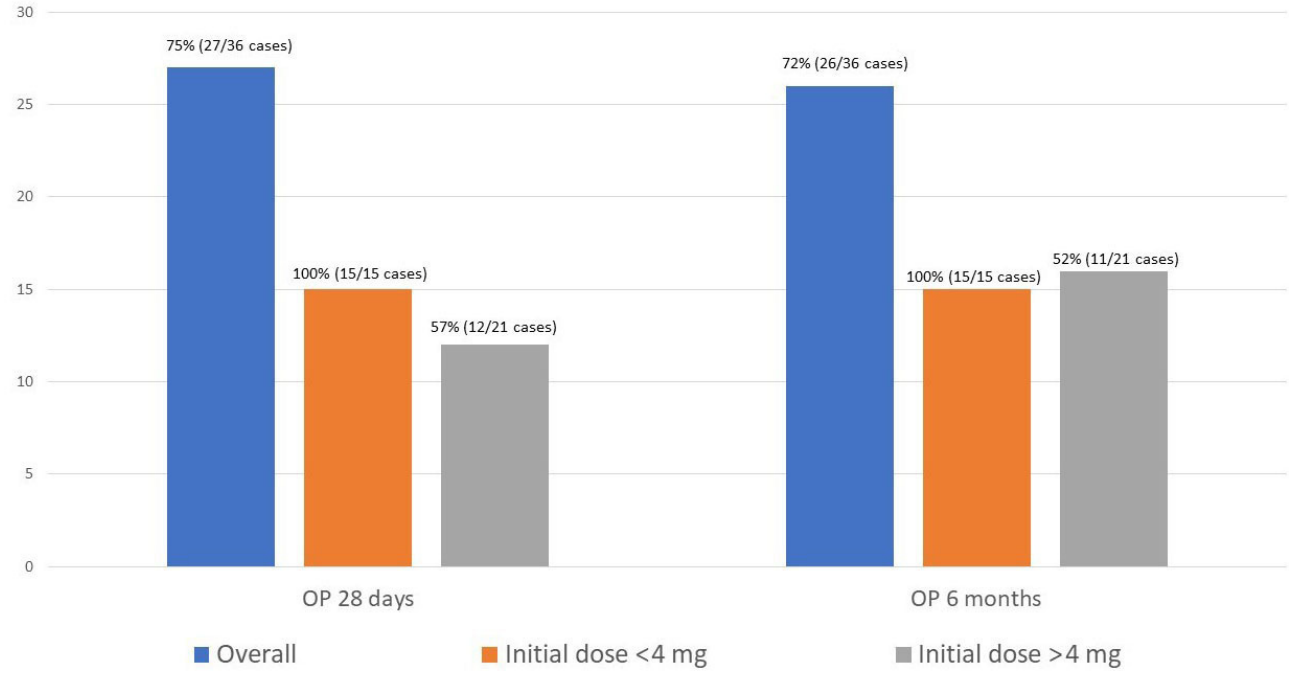


**Figure 8.** Seizure-response status and seizure-free status at initial dosage at OP 28 days and 6 months on perampanel monotherapy. OP, observation point.

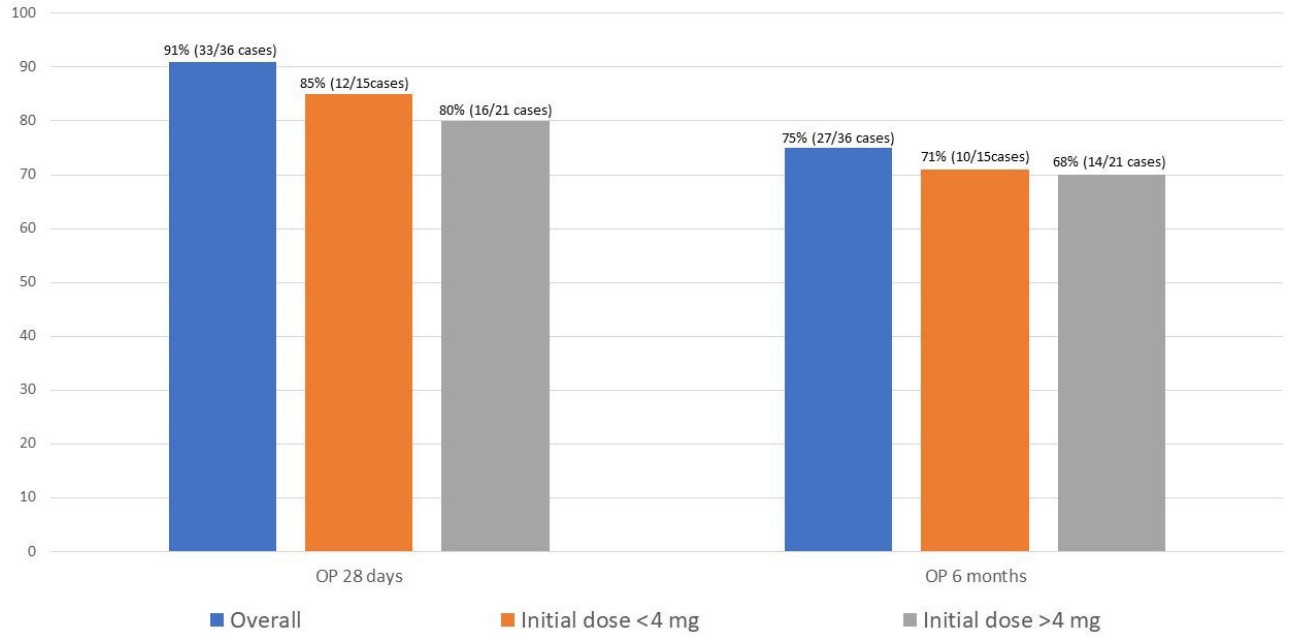


**Figure 9.** Retention rate status at initial dosage at OP 28 days and 6 months on perampanel monotherapy. OP, observation point.

titration. Figs. 10, 11 compare PER with phenytoin. The median percentage changes in seizure frequency were -33.3% ($p$=0.041), -38.5% ($p$=0.025), and -26.0% for PER ≤4 mg, PER ≥4 mg, and phenytoin groups at 28 days, respectively, and -35.0% ($p$=0.048),

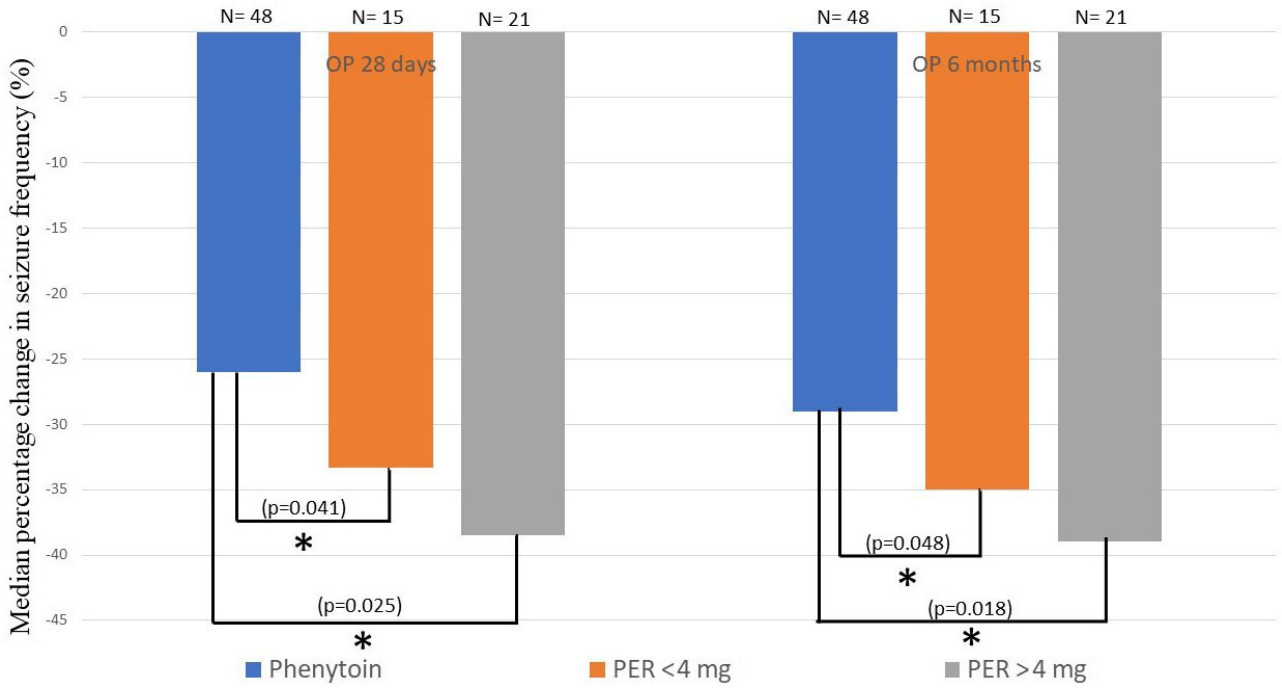


**Figure 10.** Comparison statistics between PER and phenytoin in median percentage change in seizure frequency per 28 days and 6 months. OP, observation point; PER, perampanel. *$p$-value analyzed using Chi-square test.

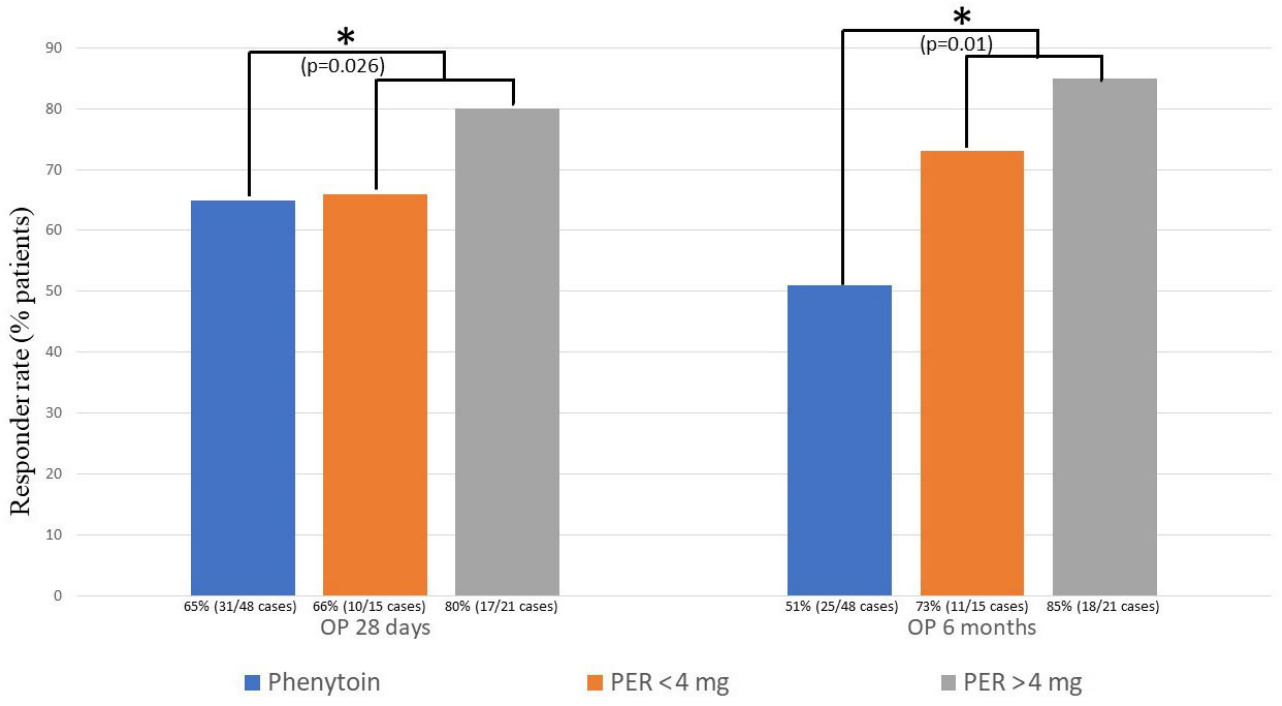


**Figure 11.** Comparison statistics between PER and phenytoin in responder rates (percentage of patients achieving a 50% reduction in seizure frequency per 28 days and 6 months). OP, observation point; PER, perampanel. *$p$-value analyzed using Chi-square test.

-39.0% ($p$=0.018), and -29.0% at 6 months (Fig. 10). Responder rates were 75.0% for PER monotherapy at 28 days ($p$=0.026) and 81.0% at 6 months ($p$=0.01), compared to 65.0% and 51.0% for phenytoin monotherapy at these respective time points (Fig. 11).

## Discussion

This was a prospective cohort study that enrolled 36 individuals with new episodes of seizures who were administered PER monotherapy as the first antiepileptic drug. Because antiseizure medications usually lead to increased toxicity, low retention rates in long-term follow-up, adverse drug reactions, and increased treatment expenditures, PER monotherapy may be useful in some clinical practices for epilepsy patients. It may also encourage patient drug compliance, as PER is administered as a daily bedtime dosage. There are few studies of clinical trials in Thailand and Southeast Asia regarding PER administration as monotherapy. Current studies support and demonstrate that PER monotherapy can be applied to all types of epilepsy patients. Previous clinical trials,[18-20] an open-label, phase III study of the efficacious and safety profile of PER administration as monotherapy in patients with first episode seizures and had epilepsy or difficulty controlling seizures after a period of seizure freedom for 2 years after withdrawal of the last antiepileptic drug. Patients were prescribed at least 4 mg per day of PER monotherapy, which was increased to 8 mg per day. PER monotherapy was effective, as 63.0% of patients receiving a daily dosage of 4 mg achieved seizure freedom, which was similar to the results of this study. The rate of seizure freedom in our study was stabilized within a 6-month period of follow-up. Most PER treatment dosage applied in our study was 4 mg (72%), 6 mg (11%), 8 mg (3%), 2 mg (5.5%), and 12 mg (2.8%), respectively. In this study, elderly patients with any types of seizures (age more than 60 years old), PER dosage per day was not different from adults in the general population.[15] This dosage provides effective seizure control and decrease seizure frequency while minimizing treatment-emergent adverse drug reactions in most seizure patients.

This study found that an incremental titration of PER dosage might be effective and useful in the elderly group by increasing the dosage by 2 mg daily every 4 weeks. The strategy of initiating a minimized PER dose of 2 mg per day for elderly seizure patients, with a gradual increase in dosage every 2 weeks, would be reasonable in clinical practice. Moreover, PER administration as suspension form is available, a consideration for future clinical practice guideline to titrate PER dosage by 1 mg per day in every 2 weeks would likely improve patients' tolerability to treatment-emergent adverse events. The strategy of administering PER monotherapy with a low initiating dosage and a gradual titration dosage would encourage a decrease in adverse events, improve patients' compliance, and increase their adherence rates. PER monotherapy is prescribed once daily at bedtime due to its long half-life, which demonstrates its usefulness in increasing patient retention rates and is important for seizure patients who miss a daily dose. The antiepileptic drug options are recommended for elderly patients due to results showing a safety profile that is not different from other antiepileptic drugs. However, this study demonstrated that applying PER in the first episode of focal seizure with awareness shows significantly good efficacy. The most common adverse drug reactions that led to the withdrawal of PER monotherapy in this study were somnolence, ataxia, dizziness, dry mouth, depression, and confusion. This is similar to the most common treatment-emergent adverse events leading to the withdrawal of PER monotherapy in previous clinical trials, which included dizziness and vomiting. In our study, PER monotherapy demonstrated a good retention rate with a small frequency of mild adverse drug reactions (22% in this study) compared to overall population in previous studies.[21-23] The PER dosage of 4 mg/day was effective as a treatment, and elderly patients can tolerate this strategy, and no significant differences in TEAEs were identified in our study. The discontinuation of PER due to an adverse event a very low incidence, with only 3% of patients withdrawing because of insensitivity to TEAEs. Our study found that the occurrence of nonserious reactions was associated with increasing dosages of PER monotherapy. Reiterating the necessity of administering PER before bedtime was recommended when dizziness or somnolence occur. If TEAEs develop during the early phase of PER monotherapy, it is required to titrate down the PER monotherapy dosage for 1 week and maintain this dosage until the adverse events improve and resolved. Once the adverse events have resolved, the PER monotherapy dosage can be gradually titrated up every week, as long as the seizure patients can tolerate the maintenance dosage.

The study demonstrated the impact of AMPA receptor antagonists (PER monotherapy) in Thai patients experiencing their first seizure episode. PER is good efficacious antiepileptic drug when administered as monotherapy at minimal dosage, with a dosage of 4 mg per day in elderly patients. The great compliance rate was demonstrated in our study, which showed improvement in patients' tolerability, a small treatment-emergent adverse events and benefits for seizure patients, especially those with focal-onset epilepsy with awareness. A small ini-

tial dosage and a gradual use of titration strategy are suggested to decrease adverse effects, increase compliance, and achieve a greater adherence rate of PER monotherapy.

PER administration as monotherapy demonstrated good efficacy and less adverse drug reactions. Low dosages helped to decrease adverse drug reactions andimproved retention rate.

### Conflict of Interests

There is no conflict of interest between the authors.

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