Heliyon 10 (2024) e26376

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Efficacy and safety of Perampanel in the treatment of post stroke epilepsy: A multicenter, real-world study

Cuihua Yan [a,b,c], Tingting Yang [c,d], Yuanping Sun [e], Junji Hu [f], Xiangming Yi [g], Chunxiao Li [e], Juan Chen [h], Kunkun Wei [i], Jing Jiang [b,c], Qi Xiang [b,c], Anru Liu [b,c], Yuxiang Han [b], Liling Yang [b], Xiaoyun Liu [b], Tao Han [b,c,j,**], Xuewu Liu [b,c,*]

[a] Department of Neurology, Shandong Provincial Hospital, Shandong University, Jinan, Shandong, PR China
[b] Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, PR China
[c] Institute of Epilepsy, Shandong University, Jinan, Shandong, PR China
[d] Department of Neurology, Qilu Hospital of Shandong University, Jinan, Shandong, PR China
[e] Qingdao University Affiliated Hospital, Qingdao, Shandong, PR China
[f] Department of Neurology, Zibo Changguo Hospital, Zibo, Shandong, PR China
[g] Binzhou Medical College Affiliated Hospital, Binzhou, Shandong, PR China
[h] The Third People's Hospital of Heze City, Heze, Shandong, PR China
[i] Qingdao Women and Children's Hospital, Qingdao, Shandong, PR China
[j] Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, PR China

ARTICLE INFO

Keywords:
Post-stroke epilepsy
Perampanel
Clinical efficacy
Safety

ABSTRACT

Background: Since 2019, Perampanel (PER) has been endorsed in China as an adjunctive treatment for focal seizures, both with and without impaired awareness, and for the transition from focal to bilateral tonic-clonic seizures. Limited research exists regarding the efficacy of PER in treating post-stroke epilepsy (PSE) in China. Empirical studies are essential to guide treatment protocols. We conducted a retrospective study to assess the efficacy and tolerability of PER in 58 PSE patients treated between October 2019 and July 2023.

Method: This study encompassed 58 patients with PSE, treated with PER either as monotherapy or as part of adjunctive therapy, and underwent follow-up for a minimum duration of 6 months. The study assessed changes in seizure frequency, adverse events (AEs), drug retention rate, maintenance dose, and adverse reactions following PER treatment.

Results: The study included 58 PSE patients, with 60.3% males and 39.7% females, ranging in age from 18 to 89, mostly within the 61–70 age group. Ischemic strokes constituted 58.6% of cases, while hemorrhagic strokes accounted for 41.4%. Focal seizures, either with or without impaired awareness, were noted in 62.1% of patients, and a transition from focal to bilateral tonic-clonic seizures was seen in 32.8%. The retention rates for PER at 3 and 6 months stood at 94.8% and 84.5% respectively, and the most commonly administered maintenance dose was 4 mg/day (41.28%). In the adjunctive therapy group, efficacy rates were 66.7% at 3 months and 78.6% at 6 months, compared to 80.0% at 3 months and 85.7% at 6 months in the monotherapy group. In the efficacy analysis, with a criterion of ≥50% reduction in seizure frequency, the overall efficacy

* Corresponding author. Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, PR China.
** Corresponding author. Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, PR China.
E-mail addresses: hantaoyhy@yeah.net (T. Han), snlxw1966@163.com (X. Liu).

https://doi.org/10.1016/j.heliyon.2024.e26376
Received 30 October 2023; Received in revised form 10 February 2024; Accepted 12 February 2024
Available online 21 February 2024

rates at 3 and 6 months were 69.1% and 79.6%, respectively. Adverse reactions occurred in 46.6% of patients, primarily involving irritability and somnolence (both 27.6%), with no marked difference in incidence between the adjunctive and monotherapy groups ($P > 0.05$).
Conclusion: PER exhibits favorable efficacy and tolerability in Chinese PSE patients, possibly at lower doses.

1. Introduction

Epilepsy, a chronic neurological disorder defined by recurrent spontaneous seizures, affects approximately 0.5%–1% of the global population [1,2]. Stroke is a major contributor to acute symptomatic seizures following hypoxic-ischemic encephalopathy. Approximately 11.5% of stroke patients develop epilepsy within 5 years [3]. Stroke represents a significant burden on society, expected to increase due to an aging population and associated co-morbidities. According to the International League Against Epilepsy (ILAE), post-stroke epilepsy (PSE) is characterized by two or more unprovoked epileptic seizures occurring at least 1 week after a stroke. The understanding of antiseizure medications (ASMs) for PSE is currently limited. Owing to the scant evidence, clear guidelines for the selection of ASMs in PSE are lacking [4].

Regrettably, a significant number of patients encounter severe complications, including post-stroke seizures and epilepsy [5]. According to the American and European guidelines [4,6], new generation ASMs like Levetiracetam (LEV) and Lacosamide are recommended as first-line treatments, attributable to their reduced adverse effects [7,8]. Perampanel (PER), a selective non-competitive antagonist of AMPA receptors—ionotropic receptors situated on postsynaptic neurons [9], has demonstrated effectiveness in epilepsy treatment in various clinical trials, both as monotherapy and as add-on therapy [10,11]. While PER is effective as monotherapy in newly diagnosed seizure patients [12], its efficacy and tolerability in post-stroke epilepsy patients remain to be fully understood.

The purpose of this retrospective study was to assess the short-term efficacy and tolerability of PER as adjunctive therapy in patients with post-stroke epilepsy.

2. Methods

2.1. Subjects

Participants in this study were post-stroke epilepsy patients treated at multiple hospitals in Shandong Province, comprising Shandong Provincial Hospital Affiliated to Shandong First Medical University, Qilu Hospital of Shandong University, Qingdao University Affiliated Hospital, Zibo Changguo Hospital, the Third People's Hospital of Heze City, and Binzhou Medical College Affiliated Hospital, between October 2019 and July 2023. Conducted in accordance with the 'Helsinki Declaration', the study received approval from the Medical Ethics Committee of Qilu Hospital of Shandong University (NO.KYLL-202209-040-1). All participants provided informed consent.

The patient inclusion criteria include:

(a) Age $\geq$18 years. (b) Epilepsy onset at least one week after a stroke, no prior history of epilepsy, and exclusion of other brain diseases and systemic illnesses that could cause seizures. (c) Diagnosed with focal seizures, either with or without impaired awareness, or focal to bilateral tonic-clonic seizures, as per the ILAE 2017 classification. (d) Adherence to oral PER treatment and regular follow-up appointments. (e) Possession of complete clinical records. (f) A minimum follow-up period of six months. (g) Willing to cooperate and actively participate in the study.

Exclusion criteria include:

(a) Patients not directly receiving medical care at a hospital. (b) Patients lacking complete clinical records. (c) Patients diagnosed with malignant tumors or degenerative disorders of the central nervous system. (d) Patients suffering from psychiatric or intellectual disorders. (e) Patients who are unable to adhere to the follow-up schedule. (f) Patients experiencing liver or kidney function impairments.

2.2. Study design

Conducted over 6 months across multiple centers, this retrospective study assessed the efficacy and safety of PER. Collected clinical data included: age, sex, epilepsy etiology, age at onset, duration of epilepsy, previous ASMs, concomitant ASMs, seizure frequency (monthly frequency over the 3 months prior to PER initiation), and seizure types (focal seizure with/without impaired awareness or evolving to bilateral tonic-clonic seizures). Enzyme-inducing ASMs (EIASMs), comprising carbamazepine, oxcarbazepine, phenobarbital, and phenytoin, were included. All other commonly used ASMs were categorized as non-EIASMs. Patients received PER once daily at bedtime, starting with a 2 mg dose and increasing by 2 mg biweekly based on clinical response and tolerability, up to the maximum tolerable dose. No changes were made to the types or doses of concomitant ASMs. Follow-up assessments occurred at 3 and 6 months post-PER initiation.

2.3. Efficacy assessment

Efficacy assessment criteria:

The baseline for evaluating efficacy was set as the average monthly seizure frequency recorded in the medical history of the 3 months prior to PER treatment. The average monthly seizure frequency during the 3rd and 6th month of treatment was compared to the baseline. The change in seizure frequency between 3 and 6 months of treatment and the baseline was compared. A reduction of seizure frequency by 100% indicated no seizures; a reduction of seizure frequency by 100% or more and above 50% was deemed effective; a reduction of seizure frequency below 50% was considered ineffective. The primary endpoint was the change in seizure frequency after 6 months of medication. Secondary endpoints included the patient's medical history, changes in seizure frequency at 3 months, PER retention rate, maintenance dose, and adverse reactions.

2.4. Safety assessment

The safety analysis included all patients who received at least one dose of PER. Adverse events (AEs) post-medication were assessed from descriptions by patients and caregivers at follow-up visits and through laboratory tests. Adverse reactions were identified from PER-related AEs recorded from treatment initiation to the last follow-up. No specific adverse reaction survey form was utilized. An intention-to-treat analysis, which included all enrolled patients, was conducted, focusing on AEs, maintenance dosages, and identifying risk factors among the ineffective group.

2.5. Statistical methods

Descriptive data for continuous variables are presented as median and quartiles. For categorical variables, absolute frequencies and percentages are calculated. A normality assessment of continuous variables is conducted prior to parametric analyses. The non-parametric Mann-Whitney *U* test compares non-normally distributed continuous variables, while Pearson's chi-square test or Fisher's exact test are used for analyzing group differences. All tests were two-sided.

Survival analysis curves, estimating retention rates for PSE patients on PER treatment, were generated using the Kaplan-Meier method. Data analysis was performed using SPSS 26.0 software. Statistical significance was set at a P-value of less than 0.05.

3. Results

3.1. Subjects

This study encompassed a total of 58 cases. Of these, 35 were males (60.3%) and 23 were females (39.7%). The most represented age group was 61–70 years. The baseline demographic and clinical characteristics of the patients are shown in Table 1.

Epileptic seizures in the patients, based on their medical conditions, were categorized into ischemic and hemorrhagic strokes. Of these, 36 cases (62.1%) were due to ischemic stroke, including 3 cases of severe cerebral infarction and 2 cases of multifocal cerebral infarction. The remaining 22 cases (37.9%) were caused by hemorrhagic stroke. Seizure types were analyzed statistically using

Table 1
Demographical and clinical characteristics of patients.

Total (n)		N = 58	Account (%)
Sex, Male/Female, n (%)	Male	35	60.3
	Female	23	39.7
Age (years)	18–30	3	5.2
	31–40	6	10.3
	41–50	8	13.8
	51–60	11	19.0
	61–70	21	36.2
	Over 71 years old	9	15.5
Etiology of epilepsy	Ischemic stroke	36	62.1
	Hemorrhagic stroke	22	37.9
Types of epileptic seizures	focal seizure with or without impaired awareness	36	62.1
	focal seizure to bilateral tonic-clonic seizures	19	32.8
Seizure frequency changes and discontinuation at 3 months	Unknown onset seizures	3	5.2
	Seizure free	24	43.6
	(100% , 50%] *	14	25.5
	(50%,0] **	17	30.9
Seizure frequency changes and discontinuation at 6 months.	Discontinuation	3	/
	Seizure free	27	55.1
	(100% , 50%] *	12	24.5
	(50%,0] **	10	20.4
	Discontinuation	9	/

Note: * Seizure frequency change controlled at <100% and ≥50%, ** Seizure frequency change controlled at <50%.

patients' electroencephalograms (EEGs) and clinical manifestations. Of the cases, 36 (62.1%) presented with focal seizures, either with or without impaired awareness, 19 (32.8%) evolved from focal to bilateral tonic-clonic seizures, and 3 had seizures of unknown onset.

Cases were categorized into four groups based on seizure frequency changes: 100% reduction (no seizures), decrease in frequency by <100% and ≥50%, decrease by <50%, and medication discontinuation.

3.2. PER dose and retention rate

Most PSE patients were on one or more ASMs before starting PER treatment. Among 10 patients who began epilepsy treatment solely with PER, 8 achieved seizure-free outcomes. The average number of simultaneous ASMs used was 2.47 ± 1.14. Of these, 16 patients (27.6%) used enzyme-inducing antiseizure medications (EIASMs) alongside other ASMs. Details of the accompanying ASMs can be found in Table 2. Valproic Acid (VPA) was the most commonly used concomitant ASM (58.6%), followed by LEV (34.5%), Oxcarbazepine (19.0%), and Lacosamide (12.0%). Concomitant ASMs were categorized as EIASMs or non-EIASMs (Table 3). No significant difference in efficacy rates was observed between patients on EIASMs (27.6%, 16/58) and those on non-EIASMs (72.4%, 42/58) as concomitant medications ($P > 0.05$).

At the 3-month follow-up, the medication retention rate was 94.8%. Three patients discontinued PER due to ineffectiveness. Of the 55 patients assessed for efficacy, 24 (43.6%, 24/55) achieved complete seizure control, 14 (25.5%, 14/55) experienced a reduction in seizure frequency of ≥50% but <100%, and 17 (30.9%, 17/55) had a decrease of <50%. By 6 months, 6 patients had discontinued the medication. Among them, 1 patient discontinued due to worsened symptoms, 1 patient voluntarily stopped treatment after achieving complete seizure control without recurrence during follow-up, 1 patient passed away due to COVID-19, 1 patient died from a recurrent acute ischemic stroke, 2 patients discontinued due to treatment ineffectiveness. Of the 49 patients evaluated at 6 months, 27 (55.1%, 27/49) experienced no seizures, 12 (24.5%, 12/49) had a reduction in seizure frequency of ≥50% but <100%, and 10 (20.4%, 10/49) saw a decrease of <50%. The medication retention rate at the 6-month follow-up was 84.5%, with the overall change in seizure frequency depicted in Fig. 1.

A subgroup analysis of patients treated with PER, either as adjunctive therapy or monotherapy, revealed that at 3 months, 45 patients in the adjunctive therapy group continued with the medication. Of these, 30 cases proved effective, resulting in an efficacy rate of 66.7% (30/45). In the monotherapy group, 10 patients continued the medication, with 8 cases demonstrating effectiveness, translating to an efficacy rate of 80.0%. This contributed to an overall efficacy rate of 69.1%. At the 6-month mark, 42 patients in the adjunctive therapy group continued medication, and 33 cases were deemed effective, yielding an efficacy rate of 78.6% (33/42). In the monotherapy group, 7 patients continued with the medication, with 6 demonstrating effectiveness, resulting in an efficacy rate of 85.7% (6/7). The overall efficacy rate reached 79.6%, closely aligning with the overall study's efficacy analysis.

The overall retention rate is shown in Fig. 2. The median follow-up time for patients was 7 months, ranging from a minimum of 2 months to a maximum of 40 months on PER medication. During the 6-month follow-up, the final maintenance doses for patients were recorded (Fig. 3). The most common maintenance dose was 4 mg per day, used by 24 patients (41.4%). 20 patients (34.5%) took 6 mg daily, 7 (12.1%) took 8 mg, 6 (10.3%) took 2 mg, and 1 (1.7%) took 10 mg daily. Patients on EIASMs had slightly higher maintenance doses than non-EIASM users (5.4 mg vs. 4.9 mg), though this difference was not statistically significant ($P > 0.05$).

3.3. Efficacy

At the 3-month follow-up, 38 out of 55 participants were deemed effective cases, resulting in an effectiveness rate of 69.1% (38/55). At the 6-month follow-up, 39 of 49 participants evaluated were effective cases, leading to an increased overall effectiveness rate of 79.6% (39/49).

Following the final follow-up, an intention-to-treat analysis was performed, encompassing all patients on PER; those who discontinued the medication during the follow-up were classified as non-responders. Patients were categorized into responders and non-

Table 2
The proportion of concomitant anti-seizure drugs.

Concomitant ASMs	N (%)
VPA	34 (58.6)
LEV	20 (34.5)
OXC	11 (19.0)
LAC	6 (10.3)
ZNS	5 (8.6)
LTG	5 (8.6)
TPM	5 (8.6)
CBZ	4 (6.9)
PHB	2 (3.4)
PHT	2 (3.4)

Note: ASMs: Antiseizure Medications; VPA: Valproic Acid; LEV: Levetiracetam; OXC: Oxcarbazepine; LAC: Lacosamide; ZNS: Zonisamide; LTG: Lamotrigine; TPM: Topiramate; CBZ: Carbamazepine; PHB: Phenobarbital; PHT: Phenytoin.

Table 3
The comparison of PER dosage between two groups of patients taking EIASMs and non-EIASMs.

EIASMs (mg)	non-EIASMs (mg)	*P*
5.4 ± 1.7	4.0 ± 2.0	0.376

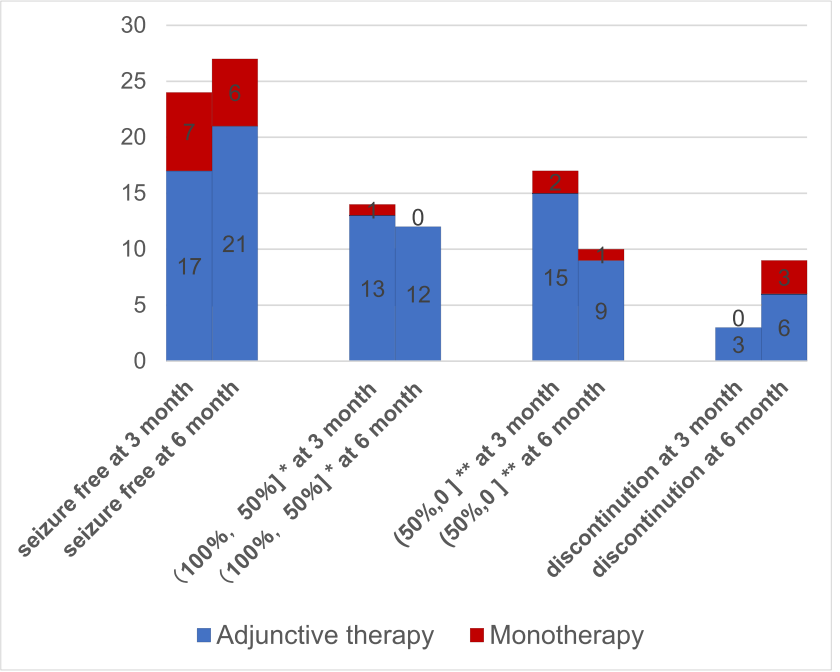

Fig. 1. Changes in seizure frequency and medication status at 3 and 6 months of PER treatment. Note: * Seizure frequency change controlled at <100% and ≥50%, ** Seizure frequency change controlled at <50%.

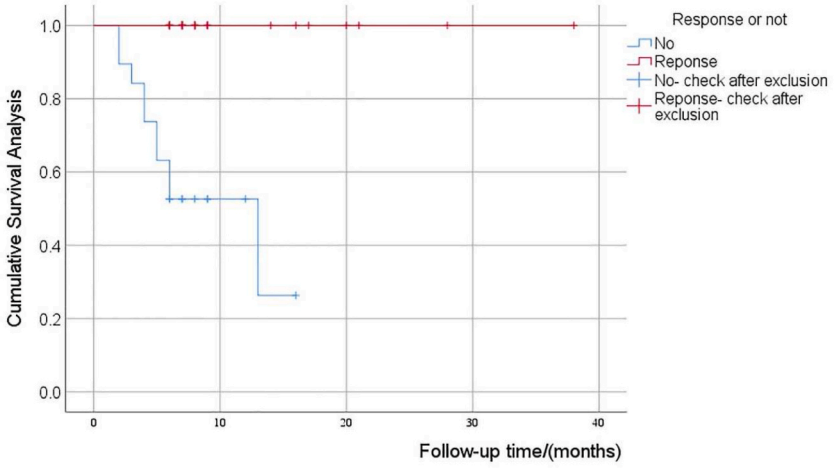

Fig. 2. The overall retention rate of PER in 58 patients.

responders, with a comparison of their demographic and relevant variables (Table 4). No significant differences were noted between responders and non-responders in terms of age, gender, duration of epilepsy, average monthly seizure frequency, and seizure type. However, a significant difference in the duration of epilepsy was observed between the groups, with responders having a longer duration compared to non-responders (P = 0.023).

Further, we analyzed the combination therapies among effective patients. The VPA and PER combination was the most prevalent in

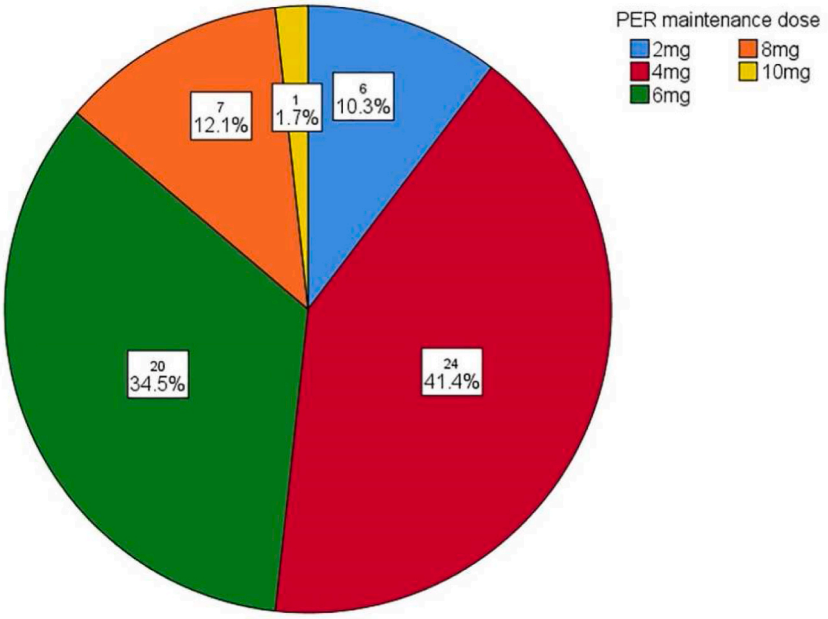

Fig. 3. The maintenance dosage of PER in patients at the 6-month follow-up.

Table 4
Factors influencing the effectiveness of treatment in the two groups of patients.

	Responders	Non-responders	*P*
Age, years	59 (46, 67)	64 (52, 69)	0.313
Sex, Male/Female, n (%)	23/16 (59.0%/41.0%)	12/7 (63.2%/36.8%)	0.760
Etiology			
Ischemic stroke/Hemorrhagic stroke，n (%)	23/16 (59.0%/41.0%)	13/6 (68.4%/31.6%)	0.486
Seizures type			0.418
focal seizure with or without impaired awareness	22 (56.4%)	14 (73.7%)	
focal seizure to bilateral tonic-clonic seizures	15 (38.5%)	4 (21.1%)	
Unknown onset seizures	2 (5.0%)	1 (5.0%)	
Epilepsy duration	45.7 ± 55.8	23.1 ± 15.5	0.023
Monthly seizure frequency			
≥4 times	9 (23.1%)	5 (26.3%)	0.378
< 4 times	30 (77.0%)	14 (73.7%)	

the effective group (17.9%, 7/39), followed by the LEV and PER combination (10.3%, 4/39), and the VPA, LEV, and PER triple therapy (7.7%, 3/39). Other ASMs including Carbamazepine, Oxcarbazepine, Lamotrigine, and additional combinations with PER were less prevalent in the effective group.

3.4. Safety

AEs were primarily identified through direct patient reporting and specific inquiries regarding PER's common adverse reactions, supplemented by patients' laboratory examinations. Overall, 27 out of 58 patients (46.6%) experienced at least one AE during PER treatment over the 6-month follow-up period (Fig. 4). Irritability and somnolence were the most common AEs, each affecting 27.6% (16/58) of patients. Laboratory test results varied during follow-up, yet stayed within normal limits, lacking clinical significance. In general, AEs were mild to moderate in severity, and were tolerable for most patients. Multiple adverse reactions were experienced by 15 patients (25.7%). Dose adjustments were made for 16 patients with AEs, involving 12 patients at 4 mg/day and 4 at 2 mg/day, with no discontinuations due to intolerable AEs. Within the monotherapy group, 4 patients (40%, 4/10) experienced adverse reactions. In the adjunctive therapy group, adverse reactions occurred in 23 patients, accounting for 48.0% (23/48) of the group. The overall incidence rate of AEs was 46.6% (27/58). Statistical analysis revealed no significant difference in AEs between the two treatment groups ($P > 0.05$).

Patients were categorized into two groups according to the occurrence of AEs, and PER dosages were compared between these groups. In the group with AEs, the mean dosage was 5.5 ± 1.8 mg, higher than the mean dosage of 4.0 ± 1.6 mg in the AE-free group, a difference that was statistically significant ($P = 0.04$).

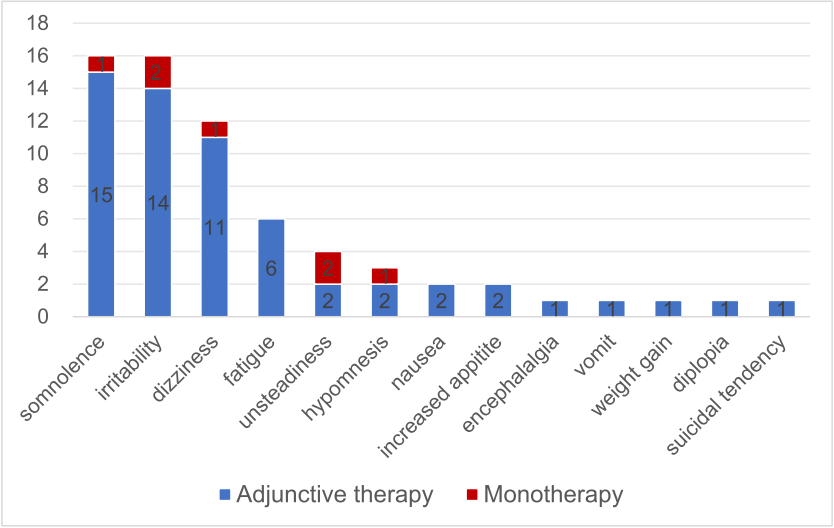

Fig. 4. AEs associated with PER treatment.

4. Discussion

This observational study evaluated the efficacy and safety of PER as either adjunctive therapy or monotherapy in treating PSE patients in China. The study included 58 post-stroke epilepsy patients, with 10 of them receiving PER as monotherapy. During the follow-up period for PER, AEs were observed in 27 cases (46.6%). However, these AEs were generally mild to moderate in severity. The study found that the efficacy rate of PER after 3 months was 69.1%, increasing to 79.6% after 6 months. At the 3-month mark, 43.6% of patients experienced no epileptic seizures, a rate that increased to 55.1% at 6 months. The seizure control rate achieved in this study is notable, particularly in comparison to first-generation ASMs (38.3%) [13]. A recent study by Tomotaka Tanaka reported a seizure-free rate of 69.6% with the use of new-generation ASMs for PSE treatment [13]. Another study, focusing on newly diagnosed elderly epilepsy patients, observed a seizure-free rate of 58.6% at 6 months [14].

This study demonstrates that PER, when used as both adjunctive therapy and monotherapy for post-stroke epilepsy, exhibits significant efficacy. At the 3- and 6-month marks, PER's efficacy in monotherapy surpassed that in adjunctive therapy. The adjunctive therapy group comprised patients with more difficult-to-control seizures, contributing to higher initial seizure control rates in monotherapy versus adjunctive therapy. Additionally, as a first-line drug in monotherapy for post-stroke epilepsy, PER's efficacy rate aligns with that of other new antiepileptic drugs, as documented in literature [15,16], reinforcing its effectiveness in PSE treatment. However, the overall seizure-free rate at 6 months was 55.1%, slightly lower than reported in other studies. This discrepancy could be attributed to the initial approval of PER solely as an adjunctive ASM in China. Consequently, our study's cohort may not consist of newly diagnosed epilepsy cases, and many may have already progressed to refractory epilepsy, diminishing the likelihood of seizure control. Further clinical trials in China are necessary to validate these findings. Furthermore, PER's effectiveness in managing focal nonconvulsive and simple partial status epilepticus indicates its potential for PSE patients with such conditions [15,16]. Regrettably, none of the enrolled cases developed status epilepticus. Future studies will further investigate PER's role in treating diverse types of post-stroke epilepsy, including status epilepticus.

PER represents the first AMPA receptor antagonist within the third-generation novel ASMs [9]. AMPA receptors, ligand-gated ion channels activated by glutamate—the primary excitatory neurotransmitter in the central nervous system—play a well-established role in promoting epileptic seizures. A study reported a significant increase in hydrogen sulfide (H2S) levels in stroke patients' brains. H2S enhances voltage-gated sodium channels, N-methyl-D-aspartate receptors (NMDAR), and AMPA receptors, thereby promoting seizure-like events (SLEs) in vitro and in vivo. Conversely, blocking these channels and receptors can prevent H2S's pro-convulsive effects on SLEs [17,18]. PER, a non-selective AMPA receptor antagonist, works by inhibiting the modulation of glutamatergic neurons via AMPA receptors, thus reducing or preventing SLEs. Given that strokes can lead to changes in the glutamatergic neural pathway, it is posited that PER, from this perspective, is particularly suited for treating post-stroke epilepsy, in comparison to other ASMs.

In comparison with previous studies [14,19], the 6-month retention rate of PER (84.5%) surpassed that of other ASMs utilized for PSE, including Lamotrigine, LEV, Oxcarbazepine, Sodium Valproate, Carbamazepine, Phenytoin, and Gabapentin. This higher retention rate may be attributed to PER's simple dosing, extended plasma half-life, and distinct mechanism of action, factors contributing to its high retention as an ASM. In this study, the predominant maintenance doses of PER were 6 mg and 4 mg daily, lower than the typical doses observed in Western countries [20]. A multicenter European study reported the most frequent PER doses as 6 mg and 8 mg [21]. Another study indicated that patients received PER at a maximum daily dose of up to 12 mg [22]. However, studies in China [23,24] found the most common PER doses to be 4 mg and 6 mg daily [23], potentially reflecting ethnic differences. A Korean study on PER reported an average daily dose of 4.39 ± 1.97 mg [25].

The increase in plasma clearance of PER due to EIASMs results in reduced blood concentration of PER, necessitating higher doses for comparable efficacy. Previous studies [20,26] remain inconclusive regarding the need for dose adjustment when PER is used concomitantly with EIASMs. In this study, patients were divided into two groups based on EIASM usage, and the correlation between ASM dosage and efficacy was analyzed. The average PER dosage in the EIASM group was 5.4 ± 1.7 mg, higher than in the non-EIASM group (4.0 ± 2.0 mg). However, when comparing efficacy between groups, no significant differences were noted based on the coadministration or non-coadministration of enzyme-inducing agents ($P > 0.05$).

In clinical practice, it is well-known that ASMs may cause adverse reactions like drowsiness, dizziness, and tremors. Several studies have indicated that both LEV and PER may induce psychiatric side effects [27]. Subgroup analyses of Phase III clinical trials, however, have revealed higher incidences of dizziness, fatigue, and falls among elderly patients, underscoring the importance of using the minimum effective dose in this demographic [28]. This study observed that the dosage levels in the group experiencing adverse reactions were higher than in the group without such reactions ($P = 0.04$). This finding suggests a significant correlation between the frequency of AEs and increased dosage levels. Differences in adverse drug reactions between the monotherapy group and the adjunctive therapy group were also analyzed. No significant difference was found between the two groups ($P > 0.05$). This implies that PER may not escalate the incidence of adverse reactions in patients on adjunctive therapy. For PSE patients, particularly the elderly who are more susceptible to drug intolerance due to polypharmacy for underlying conditions, this is a positive and encouraging outcome. Subgroup analysis additionally reported neurobehavioral disorders, alongside dizziness and drowsiness [28]. In the current study, irritability was experienced by 16 patients, and one patient exhibited suicidal tendencies. Following psychiatric consultation, the patient's suicidal tendencies significantly improved, and they continued the medication in subsequent follow-ups. Overall, nearly half of the study's participants (27 cases, 46.6%) experienced one or more adverse reactions, with irritability (27.6%, 16/58) and somnolence (27.6%, 16/58) being the most common AEs, aligning with findings from prior research [22]. Most AEs were mild, as evidenced by no patients discontinuing the medication due to adverse reactions. Discontinuation primarily occurred due to inadequate seizure control, consistent with findings from previous studies [23]. PER showed good efficacy and tolerability across the dosage range of 2–12 mg. Psychiatric side effects are possible, necessitating close monitoring during initial administration and dose escalation. During the titration period, careful clinical observation is recommended [28]. Additionally, PER might not be the best option for patients with existing psychiatric disorders or a history thereof. Close follow-up is essential for such patients receiving PER treatment.

This study has several limitations. First, being a retrospective study, the overall level of evidence provided is relatively low. Second, due to PER's initial limitation as monotherapy for epilepsy at the study's inception, most patients included were undergoing adjunctive treatment. Additionally, being a relatively new ASM in China, PER's usage was limited among epilepsy patients, with post-stroke epilepsy representing only about 10%–12.5% of this population. Consequently, the study's relatively small case number limits the evidential validity of its conclusions. Third, being retrospective, the study did not fully capture some clinical data, such as the initial NIHSS score at stroke diagnosis. Fourth, this purely clinical study encountered challenges in comparing pre- and post-treatment EEGs in some patients. The inclusion of more robust data would have strengthened the evidence. Finally, the study's relatively short follow-up period precluded a clear assessment of long-term epilepsy control rates beyond 6 months and changes in future drug retention rates.

5. Conclusion

This study's results confirm that PER, employed as both an adjunctive therapy and monotherapy, exhibits favorable efficacy and tolerability in a small-scale Chinese post-stroke epilepsy population. In the Chinese demographic, PER appears suitable for administration at slightly lower doses, typically within the 4–6 mg range, to achieve desired efficacy while ensuring good tolerability. The combination of PER with other medications has shown effective seizure control, with the incidence of adverse reactions comparable to monotherapy. Among these combinations, PER with VPA or LEV is the most prevalent and effective approach in clinical practice. While the use of PER in conjunction with EIASMs may necessitate dose adjustments, its clinical efficacy remains intact.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81873786) and Natural Science Foundation of Shandong Province (No. ZR2021QH068) and Beijing Postdoctoral Research Foundation (No. 2023-ZZ-035).

Ethics statement

This study was approved by the ethics committee of Qilu Hospital of Shandong University, with the approval number: [NO. KYLL-202209-040-1]. All patients provided informed consent to participate in the study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Cuihua Yan: Writing – review & editing, Writing – original draft, Investigation. **Tingting Yang:** Formal analysis. **Yuanping Sun:** Resources, Formal analysis. **Junji Hu:** Resources, Formal analysis. **Xiangming Yi:** Resources. **Chunxiao Li:** Resources. **Juan Chen:**

Resources. **Kunkun Wei:** Methodology. **Jing Jiang:** Formal analysis. **Qi Xiang:** Resources. **Anru Liu:** Resources. **Yuxiang Han:** Formal analysis. **Liling Yang:** Formal analysis. **Xiaoyun Liu:** Investigation. **Tao Han:** Funding acquisition, Writing – review & editing. **Xuewu Liu:** Formal analysis, Funding acquisition, Investigation, Resources, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We sincerely thank the Institute of Epilepsy, Shandong University for their technical and financial assistance.

References

[1] F.F.F. Nóbrega, M.G.S.S. Salvadori, C.J. Masson, C.F. Mello, T.S. Nascimento, J.H. Leal-Cardoso, D.P. de Sousa, R.N. Almeida, Monoterpenoid terpinen-4-ol exhibits anticonvulsant activity in behavioural and electrophysiological studies, Oxid. Med. Cell. Longev. 2014 (2014) 703848.
[2] X. Yuan, Z. Fu, P. Ji, L. Guo, A.O. Al-Ghamdy, A. Alkandiri, O.A. Habotta, A.E. Abdel Moneim, R.B. Kassab, Selenium nanoparticles pre-treatment reverse behavioral, oxidative damage, neuronal loss and neurochemical alterations in pentylenetetrazole-induced epileptic seizures in mice, Int. J. Nanomed. 15 (2020) 6339–6353.
[3] J. Burn, M. Dennis, J. Bamford, P. Sandercock, D. Wade, C. Warlow, Epileptic seizures after a first stroke: the oxfordshire community stroke project, BMJ (Clinical Research ed.) 315 (1997) 1582–1587.
[4] M. Holtkamp, E. Beghi, F. Benninger, R. Kälviäinen, R. Rocamora, H. Christensen, European stroke organisation guidelines for the management of post-stroke seizures and epilepsy, European Stroke Journal 2 (2017) 103–115.
[5] D.S. Reddy, A. Bhimani, R. Kuruba, M.J. Park, F. Sohrabji, Prospects of modeling poststroke epileptogenesis, J. Neurosci. Res. 95 (2017) 1000–1016.
[6] C.J. Winstein, J. Stein, R. Arena, B. Bates, L.R. Cherney, S.C. Cramer, F. Deruyter, J.J. Eng, B. Fisher, R.L. Harvey, C.E. Lang, M. MacKay-Lyons, K.J. Ottenbacher, S. Pugh, M.J. Reeves, L.G. Richards, W. Stiers, R.D. Zorowitz, Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the american heart association/american stroke association, Stroke 47 (2016).
[7] E. Ferlazzo, S. Gasparini, E. Beghi, C. Sueri, E. Russo, A. Leo, A. Labate, A. Gambardella, V. Belcastro, P. Striano, M. Paciaroni, L.R. Pisani, U. Aguglia, Epilepsy in cerebrovascular diseases: review of experimental and clinical data with meta-analysis of risk factors, Epilepsia 57 (2016) 1205–1214.
[8] A.M. Feyissa, T.F. Hasan, J.F. Meschia, Stroke-related epilepsy, Eur. J. Neurol. 26 (2019) 18-e13.
[9] T. Hanada, Y. Hashizume, N. Tokuhara, O. Takenaka, N. Kohmura, A. Ogasawara, S. Hatakeyama, M. Ohgoh, M. Ueno, Y. Nishizawa, Perampanel: a novel, orally active, noncompetitive ampa-receptor antagonist that reduces seizure activity in rodent models of epilepsy, Epilepsia 52 (2011) 1331–1340.
[10] N.S.N. Graham, S. Crichton, M. Koutroumanidis, C.D.A. Wolfe, A.G. Rudd, Incidence and associations of poststroke epilepsy: the prospective south london stroke register, Stroke 44 (2013) 605–611.
[11] J. Zelano, P. Redfors, S. Åsberg, E. Kumlien, Association between poststroke epilepsy and death: a nationwide cohort study, European Stroke Journal 1 (2016) 272–278.
[12] V. Punia, L. Ellison, J. Bena, P. Chandan, A. Sivaraju, P. George, C.R. Newey, S. Hantus, Acute epileptiform abnormalities are the primary predictors of post-stroke epilepsy: a matched, case-control study, Annals of Clinical and Translational Neurology 9 (2022) 558–563.
[13] T. Tanaka, K. Fukuma, S. Abe, S. Matsubara, R. Motoyama, M. Mizobuchi, H. Yoshimura, T. Matsuki, Y. Manabe, J. Suzuki, S. Ikeda, N. Kamogawa, H. Ishiyama, K. Kobayashi, A. Shimotake, K. Nishimura, D. Onozuka, M. Koga, K. Toyoda, S. Murayama, R. Matsumoto, R. Takahashi, A. Ikeda, M. Ihara, Antiseizure medications for post-stroke epilepsy: a real-world prospective cohort study, Brain and Behavior 11 (2021) e2330.
[14] A.J. Rowan, R.E. Ramsay, J.F. Collins, F. Pryor, K.D. Boardman, B.M. Uthman, M. Spitz, T. Frederick, A. Towne, G.S. Carter, W. Marks, J. Felicetta, M. L. Tomyanovich, New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine, Neurology 64 (2005) 1868–1873.
[15] J. Redecker, M. Wittstock, R. Benecke, J. Rösche, Efficacy of perampanel in refractory nonconvulsive status epilepticus and simple partial status epilepticus, Epilepsy Behav. : E&B. 45 (2015) 176–179.
[16] G.S. Cereda, R. Di Giacomo, F.M. Doniselli, C. Pastori, G. Didato, A. Stabile, M. de Curtis, F. Deleo, Perampanel efficacy on focal status epilepticus in turner's syndrome with combined generalized and focal epilepsy, Clin. Neurophysiol. : Official Journal of the International Federation of Clinical Neurophysiology 137 (2022) 59–62.
[17] Y. Luo, P.-F. Wu, J. Zhou, W. Xiao, J.-G. He, X.-L. Guan, J.-T. Zhang, Z.-L. Hu, F. Wang, J.-G. Chen, Aggravation of seizure-like events by hydrogen sulfide: involvement of multiple targets that control neuronal excitability, CNS Neurosci, Ther 20 (2014) 411–419.
[18] S. Rodkin, C. Nwosu, A. Sannikov, M. Raevskaya, A. Tushev, I. Vasilieva, M. Gasanov, The role of hydrogen sulfide in regulation of cell death following neurotrauma and related neurodegenerative and psychiatric diseases, Int. J. Mol. Sci. 24 (2023).
[19] D. Larsson, S. Åsberg, E. Kumlien, J. Zelano, Retention rate of first antiepileptic drug in poststroke epilepsy: a nationwide study, Seizure 64 (2019) 29–33.
[20] T. Nishida, S.K. Lee, T. Wu, S. Tiamkao, A. Dash, Efficacy and safety of perampanel in generalized and focal to bilateral tonic-clonic seizures: a comparative study of asian and non-asian populations, Epilepsia 60 (Suppl 1) (2019) 47–59.
[21] B.J. Steinhoff, H. Hamer, E. Trinka, A. Schulze-Bonhage, C. Bien, T. Mayer, C. Baumgartner, H. Lerche, S. Noachtar, A multicenter survey of clinical experiences with perampanel in real life in Germany and Austria, Epilepsy Res. 108 (2014) 986–988.
[22] G.L. Krauss, E. Perucca, P. Kwan, E. Ben-Menachem, X.-F. Wang, J.J. Shih, A. Patten, H. Yang, B. Williams, A. Laurenza, Final safety, tolerability, and seizure outcomes in patients with focal epilepsy treated with adjunctive perampanel for up to 4 years in an open-label extension of phase iii randomized trials: study 307, Epilepsia 59 (2018) 866–876.
[23] R. Zhang, S. Qiao, X. Fang, K. Wang, Y. Shi, Q. Du, T. Yang, X. Liu, Efficacy and tolerability of perampanel as adjunctive therapy in Chinese patients with focal-onset seizures: an observational, prospective study, Front. Neurol. 12 (2021) 731566.
[24] Y. Zhang, X. Han, P. Zhao, B. Wang, M. Li, T. Zhao, N. Wang, Y. Chen, Perampanel add-on therapy for drug-refractory epilepsy: a single-center retrospective study based on 6-month treatment outcomes in central China, Epilepsy Behav. : E&B 129 (2022) 108617.
[25] E. Trinka, B.J. Steinhoff, M. Nikanorova, M.J. Brodie, Perampanel for focal epilepsy: insights from early clinical experience, Acta Neurol. Scand. 133 (2016) 160–172.
[26] P. Sagar, O. Wawryk, S. Vogrin, E. Whitham, M. Kiley, J. Frasca, R. Carne, U. Seneviratne, M.J. Cook, N. Lawn, A. Nikpour, W.J. D'Souza, Efficacy and tolerability of adjuvant perampanel: an australian multicenter real-world observational study in refractory focal and generalized epilepsy syndromes, Epilepsy Behav. : E&B 119 (2021) 107935.
[27] R.S. Chang, W.C. Leung, M. Vassallo, L. Sykes, E. Battersby Wood, J. Kwan, Antiepileptic drugs for the primary and secondary prevention of seizures after stroke, Cochrane Database Syst. Rev. 2 (2022). CD005398.
[28] A. Schulze-Bonhage, Perampanel for epilepsy with partial-onset seizures: a pharmacokinetic and pharmacodynamic evaluation, Expert Opin. Drug Metab. Toxicol. 11 (2015) 1329–1337.