Epilepsy & Behavior 100 (2019) 106492

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Effectiveness of perampanel as a first add-on antiepileptic drug for the treatment of partial epilepsy

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ARTICLE INFO

Article history:
Received 21 May 2019
Revised 10 August 2019
Accepted 10 August 2019
Available online 21 October 2019

Keywords:
Perampanel
Partial epilepsy
First add-on
Antiepileptic drug

ABSTRACT

Background: Perampanel (PER) is a newly introduced antiepileptic drug (AED) and is used in over 50 countries. In the current study, we analyzed the efficacy of PER for patients with partial epilepsy who were recruited from two hospitals that had both an epilepsy center and a general neurosurgical unit over a 1-year period.
Methods: The present study was a retrospective observational study that evaluated the effects of PER for the treatment of partial epilepsy in 51 patients. We analyzed the effects of PER at two checkpoints, i.e., 6 and 12 months after starting adjunctive PER treatment. Following this, we analyzed the effects of PER as a first add-on (only one prior AED) and late add-on (≥2 prior AEDs) therapy, and focused on the characteristics of the patients who achieved seizure freedom.
Results: Of the initial 51 patients, 45 and 39 patients were evaluated at the 6- and 12-month checkpoints, respectively. Overall, after starting treatment with PER, 29% (13/45) and 28% (11/39) of patients were seizure-free at 6 and 12 months, respectively. The tolerance rate of PER was 67% (30/45) at 6 months and 53.8% (21/39) at 12 months following treatment. The seizure-free rate of the 30 patients who were continuously treated with PER for 6 months was significantly higher in the patients who used PER as a first add-on treatment (75.0%, 6/8) than it was in the patients who used PER as a late add-on treatment (31.8%, 7/22) ($p = 0.049$). The seizure-free rate of the 21 patients who were continuously treated with PER for 12 months was significantly higher in the patients who used PER as a first add-on treatment (100%, 5/5) than it was in the patients who used PER as a late add-on treatment (37.5%, 6/16) ($p = 0.035$). Among the patients who achieved seizure freedom, the most frequently administered dose of PER was 2 mg at 6 (62%, 8/13) and 12 months (64%, 7/11). Levetiracetam was the most frequently administered concomitant AED at both 6 (92%, 12/13) and 12 months (91%, 10/11).
Conclusion: This retrospective observational study provides evidence supporting the effectiveness of PER as a first add-on therapy in patients with partial epilepsy. Importantly, the seizure-free rate was better when PER was used as a first, rather than a second or later, add-on treatment.

1. Introduction

Epilepsy is a central nervous system disorder that affects 1–2% of the global population [1,2]. Antiepileptic drugs (AEDs) are used as the first treatment choice for epilepsy. Although two-thirds of patients with epilepsy may achieve seizure freedom following treatment with one or two AEDs, one-third of patients experience medication-resistant epilepsy [3]. Perampanel (PER) is a newly introduced, highly selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist AED [4,5] and is approved for use in over 50 countries as an adjunctive treatment for both partial and generalized seizures in patients with epilepsy over 12 years of age. Recently, several multicenter studies have reported the effectiveness of PER for treating general and partial seizures [6–8]. However, since these studies mainly analyzed patients with medication-resistant epilepsy, little is known about the general effectiveness of PER as an add-on therapy. Moreover, most seizure types treated in neurosurgical units are considered partial epilepsy, because they can be caused by various conditions, including brain tumors, stroke, trauma, or infections. Hence, the aim of the present study was to analyze the efficacy of PER in the treatment

Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBZ, carbamazepine; CZP, clonazepam; FAS, focal awareness seizures; FBTC, focal to bilateral tonic–clonic seizures; FIAS, focal impaired awareness seizures; FYDATA, follow-up of 1 year data of patients on perampanel; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; PER, perampanel; VPA, valproic acid; ZNS, zonisamide.

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https://doi.org/10.1016/j.yebeh.2019.106492
1525-5050/

of patients with partial epilepsy over a 1-year period. The usefulness of PER as a first add-on was evaluated especially based on the number of patients who achieved seizure freedom.

2. Methods

This study was approved by the institutional review board of Tokyo Medical and Dental University (approval number: M2019-026). The need for informed consent was waived owing to the retrospective nature of the study. The present study was a two-center (Tokyo Medical and Dental University and Tsuchiura Kyodo General Hospital), retrospective observational study that reviewed patients who received medical therapy with PER between January 2017 and March 2019. Patients were recruited from an epilepsy center and a general neurosurgical unit from both hospitals. Data were collected from clinical records, and patients identified as having partial epilepsy were included in the study. The diagnosis of partial epilepsy was made using electroencephalograms, magnetic resonance imaging, and clinical symptoms. All diagnoses were confirmed by two board-certified epileptologists from the Japanese Epilepsy Society before patient inclusion in the study. Baseline seizure diaries were checked at the beginning of treatment. We established the following two checkpoints: 6 months and 12 months from the first prescription of PER. The frequency of seizures at each checkpoint was defined as 0% (seizure freedom), 0–25%, 25–50%, and 50–100% as compared to that before PER administration. The patients were divided into the following two groups: patients initiating PER as a first add-on treatment (only one prior AED) and patients initiating PER as a late add-on treatment (≥2 prior AEDs). For focal seizures, seizure types were classified into focal awareness seizures (FAS), focal impaired awareness seizures (FIAS), and focal to bilateral tonic–clonic seizures (FBTC) according to 2017 ILAE classifications [9].

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [10]. The following data were listed in Table 1: age, sex, location of focus (frontal lobe, parietal lobe, temporal lobe, multiple lobes, and other), etiology (brain tumor, cortical dysplasia, stroke, trauma, infection, and other etiology), number of concomitant AEDs at baseline, and dose of PER administered. Patient characteristics are presented as means ± standard deviations or as numbers and percentages. The Fisher's exact test was used to compare the rates of seizure freedom between the two add-on groups at each endpoint. Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Patient characteristics and AED data

A flowchart describing patient inclusion and a summary of patient characteristics are shown in Fig. 1 and Table 1, respectively. Perampanel was administered as an add-on therapy in 51 patients with partial epilepsy. Six patients who did not reach the 6-month checkpoint were excluded from the analysis; among them, four patients died due to the progression of brain tumors and we were unable to obtain precise follow-up data in two patients because they were transferred to rehabilitation hospitals. The mean age of the remaining 45 patients (22 males and 23 females) was 41.8 ± 19.4 years (range, 12–97 years). At 12 months, 39 patients were available for data analysis, as 6 patients were lost to follow-up from 6 to 12 months and were excluded from the analysis. Among the 45 patients at 6 months, 15 patients discontinued PER within the 6-month period, and thus, 30 were still taking PER at 6 months. At 12 months, 21 patients were still taking PER (PER was discontinued in 3 patients).

The mean dose of PER among the 8 patients in the first add-on group was 3.0 mg and that among the 22 patients in the late add-on group was 4.0 mg at the 6-month checkpoint. The mean dose of PER was 2.0 mg in 5 patients in the first add-on group and 4.4 mg in 16 patients in the late add-on group at the 12-month checkpoint. The mean number of concomitant AEDs used by the 45 patients at 6 months was 2.3 ± 1.2 AEDs (range, 1–4 AEDs). Of the 45 patients at 6 months, 31 (68.9%)

Table 1
Characteristics of patients in the first and late add-on groups at 6 and 12 months (note: individuals who discontinued PER were excluded in this table).

	On PER at 6 months (n = 30)		On PER at 12 months (n = 21)	
	First add-on (n = 8)	Late add-on (n = 22)	First add-on (n = 5)	Late add-on (n = 16)
Mean age ± SD, (range), years	49.1 ± 14.7 (30–76)	35.0 ± 14.8 (12–58)	44.8 ± 12.0 (30–63)	37.0 ± 14.5 (12–58)
Male, n (%)	2 (25)	15 (68.2)	2 (40)	11 (68.9)
Focus, n (%)				
Frontal	3 (37.5)	4 (18.2)	3 (60)	4 (25)
Parietal	0 (0)	3 (13.6)	0 (0)	3 (18.8)
Temporal	4 (50)	6 (27.3)	2 (40)	4 (25)
Multiple	1 (12.5)	1 (4.5)	0 (0)	0 (0)
Other	0 (0)	8 (36.4)	0 (0)	5 (31.3)
Etiology, n (%)				
Brain tumor	3 (37.5)	3 (13.6)	2 (40)	2 (12.5)
Cortical dysplasia	0 (0)	3 (13.6)	0 (0)	2 (12.5)
Stroke	2 (25)	0 (0)	1 (20)	0 (0)
Trauma	1 (12.5)	0 (0)	1 (20)	0 (0)
Infection	0 (0)	0 (0)	0 (0)	0 (0)
Other	2 (25)	14 (63.6)	1 (20)	12 (75)
Number of baseline AEDs, n (%)				
One	8 (100)	0 (0)	5 (100)	0 (0)
Two	0 (0)	9 (40.9)	0 (0)	5 (31.3)
Three	0 (0)	7 (31.8)	0 (0)	5 (31.3)
Four	0 (0)	6 (27.3)	0 (0)	6 (37.5)
Five	0 (0)	0 (0)	0 (0)	0 (0)
Dose of PER, n (%)				
2 mg	6 (75)	8 (36.4)	5 (100)	5 (31.3)
4 mg	1 (12.5)	9 (40.9)	0 (0)	6 (37.5)
6 mg	0 (0)	2 (9.1)	0 (0)	2 (12.5)
8 mg	1 (12.5)	3 (13.6)	0 (0)	3 (18.8)

PER: perampanel, SD: standard deviation, AEDs: antiepileptic drugs.

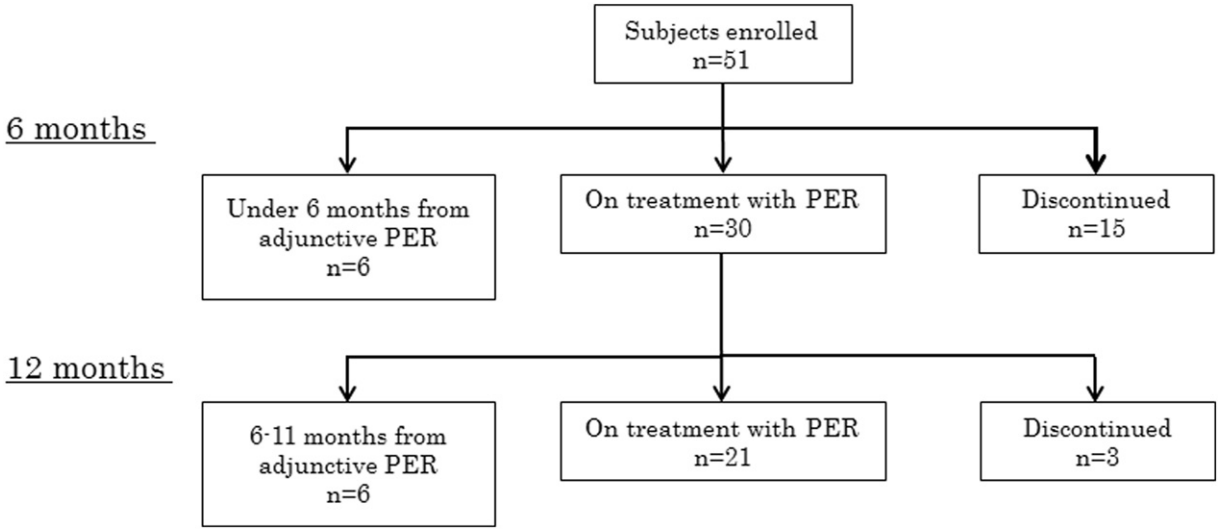

Fig. 1. Flowchart showing the patient inclusion process for this study. Fifty-one patients with partial seizure who started receiving perampanel (PER) as an add-on therapy were initially enrolled in this study. Six patients did not reach the first checkpoint (6 months), and PER was discontinued in 15 patients. An additional 6 patients did not reach the second checkpoint (12 months), and PER was discontinued in 3 patients. Thus, 21 patients were still being treated with PER at 12 months.

used levetiracetam (LEV), 17 (37.8%) used valproic acid (VPA), and 16 (35.6%) used carbamazepine (CBZ). The mean number of concomitant AEDs used by the 39 patients at 12 months was 2.6 ± 1.1 AEDs (range, 1–4 AEDs). Of these 39 patients, 28 (71.8%) used LEV, 15 (38.5%) used VPA, and 14 (35.9%) used CBZ (Table 2).

3.2. Effects of PER

Overall, the seizure-free rate at 6 months was 29% (13/45). Similarly, the seizure-free rate at 12 months was 28% (11/39). More than a 50% reduction in seizures was achieved in 53% (24/45) of the patients following 6 months of treatment and in 46% (18/39) of the patients following 12 months of treatment. The main reasons for the discontinuation of PER by 15 patients at 6 months were insufficient effects (n = 4) and adverse drug reactions (n = 11), including irritability (n = 3), drowsiness (n = 4), abdominal symptoms (n = 1), drug eruption (n = 1), and other (n = 2). The tolerance rate of PER at 6 months was 67% (30/45). As mentioned above, between 6 and 12 months, PER was discontinued in 3 patients; discontinuation of treatment in these patients was related to drowsiness (n = 1) and insufficient effects (n = 2). The tolerance rate of PER at 12 months was 53.8% (21/39). Hence, at 12 months, 18 patients had discontinued PER because of insufficient effects (n = 6) and adverse drug reactions (n = 12). As a result, PER was discontinued in 58% (7/12) of patients in the first add-on group and in 41% (11/27) of patients in the late add-on group at 12 months. Adverse effects were the main reason for PER discontinuation in 71.4% (5/7) of the patients in the first add-on group.

Outcomes according to seizure types are summarized in Table 3. The seizure-free rate and 50% seizure-reduction rate were the highest in FBTC at both 6 months and 12 months. Focal impaired awareness seizures and FAS showed similar results, with a slightly better 50% seizure-reduction rate in FIAS. In the 51 patients involved in this study,

Table 2
List of concomitant AEDs in patients in the first and late add-on groups who achieved seizure freedom at 6 and 12 months.

A. Data from all patients

Concomitant AEDs	On PER at 6 months (n = 13)		On PER at 12 months (n = 11)	
	First add-on (n = 6)	Late add-on (n = 7)	First add-on (n = 5)	Late add-on (n = 6)
CBZ	0	1	0	2
CZP	0	1	0	1
LEV	5	7	5	5
LCM	0	1	0	0
LTG	0	1	0	1
PB	0	1	0	1
VPA	1	4	0	5
ZNS	0	2	0	1

B. Data from patients who were administered 2 mg of PER

Concomitant AEDs	On PER at 6 months (n = 8)		On PER at 12 months (n = 7)	
	First add-on (n = 4)	Late add-on (n = 4)	First add-on (n = 4)	Late add-on (n = 3)
CBZ	0	1	0	2
CZP	0	1	0	1
LEV	4	4	4	2
LCM	0	1	0	0
VPA	0	2	0	3
ZNS	0	2	0	1

AEDs: antiepileptic drugs, PER: perampanel, CBZ: carbamazepine, CZP: clonazepam, LEV: levetiracetam, LCM: lacosamide, LTG: lamotrigine, PB: phenobarbital, VPA: valproate, ZNS: zonisamide.

Table 3
Results of seizure reduction according to seizure type at 6 and 12 months. Note: one patient may have two or more seizure types.

	Results at 6 months			Results at 12 months		
	FIAS	FAS	FBTC	FIAS	FAS	FBTC
Data available	17	2	17	11	2	12
Discontinued	8	6	3	11	6	3
Seizure-free	5	2	10	3	2	8
Seizure-free rate	20% (5/25)	25% (2/8)	50% (10/20)	14% (3/22)	25% (2/8)	53% (8/15)
50% reduction	11	2	17	8	2	12
50% reduction rate	44% (11/25)	25% (2/8)	85% (17/20)	36% (8/22)	25% (2/8)	80% (12/15)

Unless otherwise noted, values are the number of patients.
FIAS: focal impaired awareness seizures, FAS: focal aware seizures, FBTC: focal to bilateral tonic–clonic seizures.

the total number of all seizure types was 59, including 8 patients who had both FIAS and FBTC.

3.3. Seizure freedom in the add-on groups

Among the 45 patients who were eligible for analysis at the 6-month checkpoint, seizure freedom was observed in 43% (6/14) of the patients in the first add-on group and 23% (7/31) of the patients in the late add-on group ($p = 0.29$). Similarly, at 12 months, 83% (5/6) of the patients in the first add-on group and 33% (6/18) of the patients in the late add-on group achieved seizure freedom ($p = 0.06$). The first add-on group had a higher seizure-free rate than the late add-on group.

To fully examine the efficacy of PER as a first add-on therapy, we conducted subanalyses by excluding patients who discontinued PER administration. A 6 months, seizure freedom was observed in 75.0% (6/8) of the patients in the first add-on group and 31.8% (7/22) of the patients

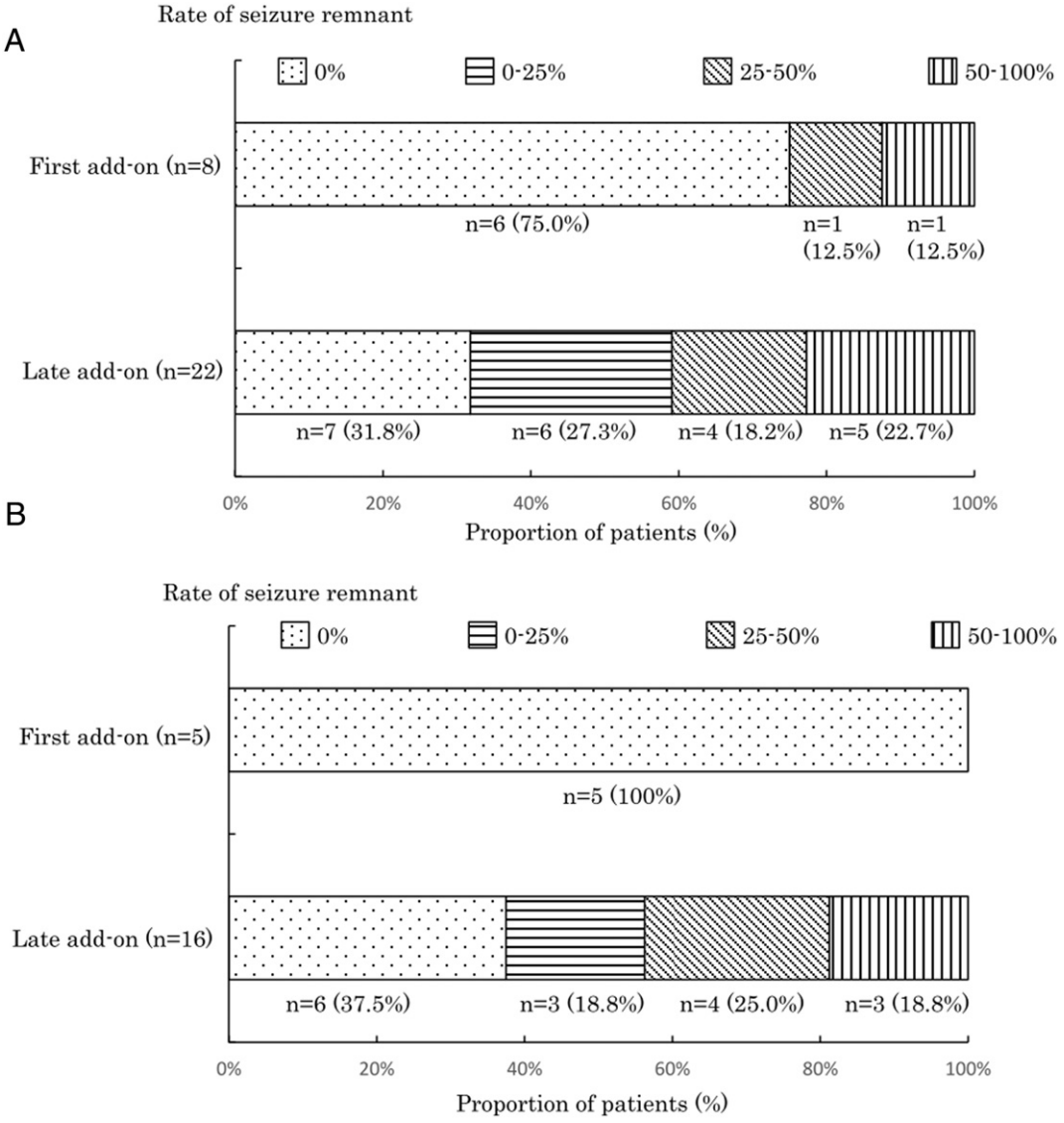

Fig. 2. Seizure outcomes at 6 months (A) and 12 months (B). Overall, 75% of the patients in the first add-on group and 31.8% of the patients in the late add-on group achieved seizure freedom at 6 months (A). At 12 months, 100% of the patients in the first add-on group and 37.5% of the patients in the late add-on group achieved seizure freedom (B). Patients who discontinued PER at each checkpoint were excluded from the analyses.

in the late add-on group. The seizure-free rate was significantly higher in the first add-on group than in the late add-on group after the administration of PER for 6 months ($p = 0.049$) (Fig. 2A). After the administration of PER for 12 months, the seizure-free rate was significantly higher in patients in the first add-on group (100%, 5/5) than in patients in the late add-on group (37.5%, 6/16) ($p = 0.035$) (Fig. 2B).

3.4. Doses of PER and concomitant AEDs

The mean dose of PER in the 13 seizure-free patients who were treated with PER for 6 months was 3.1 ± 1.8 mg (2 mg [n = 8], 4 mg [n = 4], and 8 mg [n = 1]) (Fig. 3A). The mean dose of PER in the 11 seizure-free patients who were treated with PER for 12 months was 3.1 ± 1.8 mg (2 mg [n = 7], 4 mg [n = 3], and 8 mg [n = 1]) (Fig. 3B). Among the patients who achieved seizure freedom, the most frequently administered dose of PER was 2 mg (Fig. 3A, B). Notably, LEV was used in 83.3% (5/6) of the seizure-free patients at 6 months and 100% (5/5) of the seizure-free patients at 12 months (Table 2A). Moreover, the most frequently used concomitant AEDs in the late add-on group were LEV (7/7 patients, 100%) and VPA (4/7 patients, 57.1%) at 6 months and LEV (5/6 patients, 83.3%) and VPA (1/6 patients, 16.7%) at 12 months (Table 2A). The minimum dose of PER (2 mg) was administered to 4 seizure-free patients in the first add-on group after treatment with LEV (4/4 patients, 100%) at both 6 and 12 months (Table 2B). In the late add-on group, seizure freedom was achieved in 4 patients at 6 months and 3 patients at 12 months following treatment with the minimum dose of PER (2 mg) and LEV (4/4 patients, 100%) (Table 2B).

4. Discussion

The present study analyzed the efficacy of PER for patients with partial epilepsy over a 1-year period. Importantly, although PER was previously known to be effective for the treatment of general and other types of epilepsies combined, not much has been reported on the effectiveness of PER for partial epilepsy. Here, we found that the overall seizure-free rate was 29% at 6 months and 28% at 12 months. Villanueva et al. [6] reported that seizure freedom was obtained with PER in 59% of patients with idiopathic epilepsy at 12 months, including 63% of patients with generalized tonic–clonic seizures, 65% of patients with myoclonic seizures, and 51% of patients who had an absence of seizures. In addition, the multicenter, retrospective follow-up of 1 year data of patients on perampanel

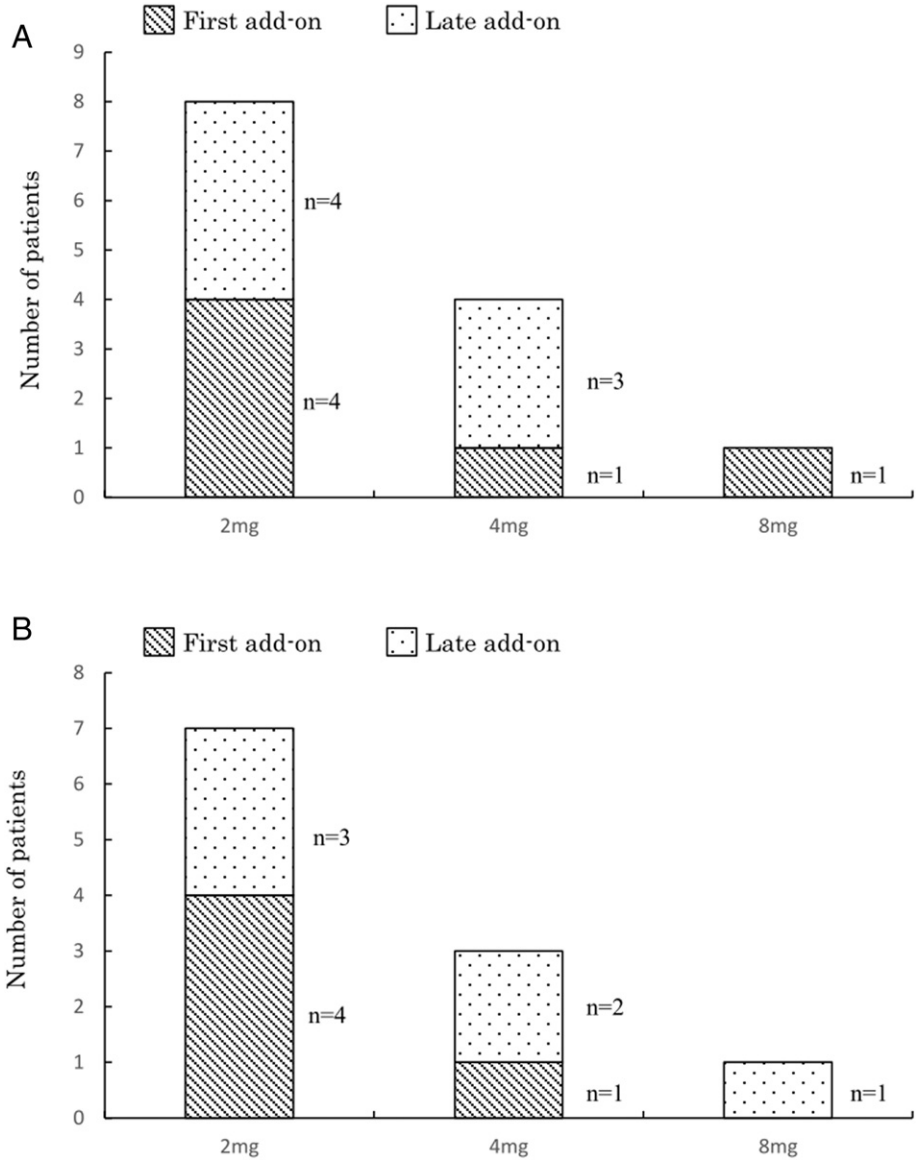

Fig. 3. Dose distributions of perampanel in patients who achieved seizure freedom at 6 months (A) and 12 months (B).

(FYDATA) study on focal epilepsy demonstrated that 7.2% of the patients became seizure-free at 12 months [7]. The seizure-free rate in the present study was lower than that observed in the patients with idiopathic epilepsy [6] but higher than that noted in patients with focal epilepsy [7]. Nishida et al. [8] analyzed the effects of PER on patients with drug-resistant focal epilepsy in the Asia-Pacific region using a randomized phase III study. In that report, the seizure-free rates in patients with partial epilepsy at 19 weeks after PER administration were 2.9% with 2 mg of PER, 4.0% with 4 mg of PER, and 4.4% with 12 mg of PER [8]. A possible explanation for the high seizure-free rate in our study is that we used PER as a first add-on therapy in as many as 31% (14/45) of the patients. In a Spanish multicenter study of PER for patients with partial epilepsy, 70% of patients received more than 5 AEDs [7]. In the Asia-Pacific phase III study, only 6.8% of patients received only one concomitant AED [8]. The high seizure-free rate that was observed after PER administration in our study may also be explained by the low number of patients with medication-resistant epilepsy compared with the numbers in the previous multicenter studies.

The present study also showed that the tolerance rate of PER was 67% (30/45) at 6 months and 53.8% (21/39) at 12 months. These results were almost the same as those from the multicenter Spanish study [7] showing that PER withdrawal was observed in 77.4% of patients at 6 months and 60.6% of patients at 12 months. In their phase III study, Nishida et al. [8] reported that the tolerance rate of PER was as high as 84% (447 out of 531 patients) at 5 months (19 weeks). Our study indicated that the first add-on group had a higher withdrawal rate than the late add-on group (58%, 7/12 and 41%, 11/27, respectively), which was driven by the occurrence of subtle adverse effects in the first add-on group (71.4%, 5/7). The relatively low tolerance rate of PER in this study may be related to the high proportion of patients in the first add-on group.

We found that the seizure-free rate was significantly higher in the first add-on group than it was in the late add-on group at both 6 and 12 months after treatment with PER, after excluding patients who discontinued treatment. Similarly, a previous study reported that 72% of patients with idiopathic generalized epilepsy achieved seizure freedom when PER was used as an early add-on treatment, while only 52% of patients achieved seizure freedom when PER was used as a late add-on treatment [6]. Villanueva et al. [7] reported that 10.4% of patients with partial seizures who were treated with PER and one or two concomitant AEDs achieved seizure freedom, while only 5.1% of patients who were treated with PER and three or more concomitant AEDs achieved seizure freedom. Further, the authors [7] reported that a higher responder rate was observed in early add-on patients, and they suggested that PER be used as an early add-on therapy. Liguori et al. [11] compared PER and LEV as first add-on therapies for patients with uncontrolled secondarily generalized seizures and concluded that PER and LEV achieved the same seizure-free rates. In the same paper [11], the seizure-free rate after PER administration was 57% at 6 months and 85% at 12 months, which was close to our seizure-free rates of 75% and 100% at 6 and 12 months, respectively. Our outcomes by detailed seizure type are summarized in Table 3. We found the highest seizure-free rate and 50% seizure-reduction rate in FBTC, followed by similar rates for FIAS and FAS. This marked reduction in seizures in FBTC (or secondarily generalized seizures) was previously reported [7,12], and is comparable to our result.

In our study, the most commonly used AED with PER in seizure-free patients was LEV. We also found that more than half of the patients achieved seizure freedom with a minimum dose of 2 mg of PER and that all of these patients were initially treated with LEV. This ability to achieve seizure freedom at the minimum dose is important because lower doses of PER are known to be associated with reduced adverse drug effects [8]. Moreover, the FYDATA study found that there were no differences in the rate of adverse effects regardless of whether patients received LEV or not [7]. The results of the present study suggest that a minimum dose of 2 mg of PER can be recommended as a first add-on therapy for seizure-remnant patients who were initially treated with LEV.

Our study has several limitations. First, the retrospective observational design may have resulted in the use of unstandardized methods for collecting information on clinical responses. Second, the number of patients included in this study was relatively small, and this may have influenced the results. Third, we could not fully conclude that PER was effective for refractory partial epilepsy as a first add-on medication due to the small number of patients; however, it is assumed that PER is an effective first add-on therapy for patients with partial epilepsy because we observed high seizure-free rates following treatment with PER. Finally, there is another limitation regarding the patient background of each group (Table 1). The difference in patient characteristics (age, etiology) might be because elder patients with histories of brain tumors or stroke who visited the general neurosurgical department tended to receive PER as a first add-on therapy. In contrast, younger patients who were referred to the epilepsy center for refractory seizures tended to receive PER as a late add-on therapy. Therefore, patient background might have affected the outcome of our study.

Further prospective, controlled studies are needed to determine the effectiveness of PER in more detail with regard to the different subtypes of partial epilepsy, including subtypes with different pathologies and seizure types in a uniform patient background. Given that PER is used as an add-on therapy, evaluations focusing on the dependence of the combination of concomitant AEDs are also warranted.

5. Conclusions

This retrospective observational study demonstrated the efficacy of PER, particularly as a first add-on therapy, in patients with partial epilepsy. Additionally, we showed that PER was able to achieve seizure freedom effectively at a low dose (2 mg) that could potentially avoid adverse drug effects.

Funding

None.

Declaration of Competing Interest

None of the authors has any conflicts of interest.

Acknowledgments

None.

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