Epilepsy & Behavior 137 (2022) 108961

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Effectiveness and tolerability of adjunctive perampanel in the treatment of pediatric patients with uncontrolled epilepsy: A retrospective, single-center, real-world study

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ARTICLE INFO

Article history:
Received 5 July 2022
Revised 6 October 2022
Accepted 15 October 2022
Available online 31 October 2022

Keywords:
Epilepsy
Efficacy
Pediatric patients
Perampanel
Real-world data

ABSTRACT

Objective: The main aim of this study was to assess the efficacy, safety, and tolerability of adjunctive perampanel (PER) in the treatment of children and adolescents with epilepsy.
Methods: Pediatric patients who visited the pediatric epilepsy clinic of Henan Provincial People's Hospital between May 2020 and December 2021 were recruited. All participants were treated with PER as adjunctive therapy and were seen routinely (minimum: a baseline and 12-week visit). The efficacy and tolerability of adjunctive PER for the treatment of epilepsy were investigated.
Results: One hundred and fourteen patients were enrolled, among whom 7 (6.1%) were lost to follow-up. At 12 weeks, the responder rate and the seizure-free rate were 56.1% (60/107) and 32.7% (35/107), respectively. The responder rate increased with the duration of PER administration and was significantly higher when PER was used as an early add-on (after ≤2 prior antiseizure medications (ASMs)) than a late add-on (after >2 prior ASMs). However, there was no significant difference in the treatment efficacy of adjunctive PER in patients with different epilepsy etiologies or types. Adverse events, including irritability, dizziness, somnolence, ataxic gait, weight gain, and tinnitus, were reported in thirty-two patients (29.9%).
Conclusions: In a routine clinical setting of pediatric patients with epilepsy, good effectiveness and tolerability of adjunctive PER were demonstrated. Notably, patients initiating PER as an early add-on showed a better seizure outcome than those initiating PER as a late add-on.

1. Introduction

Epilepsy is one of the most common neurological disorders. Approximately 75% of all epilepsy begins in childhood [1]. The estimated prevalence of epilepsy among the pediatric population is 0.5–1% [2]. Antiseizure medications (ASMs) are the mainstay of treatment. However, the epilepsy of 25–30% of pediatric patients remains refractory to medical therapy (refractory epilepsy, defined as the failure of two tolerated and appropriately chosen ASM schedules to achieve sustained seizure freedom) [3,4]. Additionally, seizures that are still uncontrolled after one ASM is used have the potential to be refractory. Patients with uncontrolled epilepsy have an increased risk of disability, comorbidity, psychological and social dysfunction, and premature death [5,6]. Hence, it is essential to choose the appropriate ASMs to treat uncontrolled epilepsy. A comprehensive therapeutic strategy may be more effective than a second or third chance in ASM for patients with uncontrolled epilepsy [7,8].

Perampanel (PER) is a highly selective, noncompetitive antagonist of the postsynaptic ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor [9]. It depresses the excitability of neurons and controls seizures by inhibiting AMPA-induced Na^+ and Ca^{2+} influx [9–11]. In China, PER was first approved in 2019 as an adjunctive therapy for focal onset seizures (FOSs) with/without focal to bilateral tonic-clonic seizures (FBTCSs) in patients aged 12 years and older. Since July 2021, PER has been approved as monotherapy and adjunctive therapy for FOSs with/without FBTCSs in patients 4 years and older. It has also been approved as an adjunctive therapy for primary generalized tonic–clonic seizures (PGTCSs) in pediatric patients with epilepsy in the United States and the European Union. Perampanel is a potentially broad-spectrum ASM with a novel mechanism of action for patients with epilepsy with various seizure types [12]. In previous studies, the efficacy of PER in the treatment of multiple generalized seizure types including myoclonic, absence, and tonic

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https://doi.org/10.1016/j.yebeh.2022.108961
1525-5050/

seizures has been demonstrated [13]. Moreover, adjunctive PER was highly recommended for the treatment of refractory epilepsy by the American Academy of Neurology & American Epilepsy Society (AAN&AES) [14]. However, adjunctive PER therapy in pediatric patients has been understudied, and there is a lack of large-sample studies in China. In the present study, we investigated the efficacy, safety, and tolerability of adjunctive PER in pediatric patients with epilepsy in real-world clinical settings.

2. Materials and methods

2.1. Patients

For this retrospective, observational, single-center, real-world study, pediatric patients with epilepsy who visited the pediatric epilepsy clinic of Henan Provincial People's Hospital between May 2020 and December 2021 were recruited. The study was approved by the Ethics Committee of Henan Provincial People's Hospital. Written informed consent was received from a parent/legal guardian for each participant.

Inclusion criteria: a diagnosis of epilepsy on the basis of symptoms, signs, or diagnostic examinations; a diagnosis of uncontrolled epilepsy (defined as the failure of at least one tolerated and appropriate ASM to achieve sustained seizure freedom); age 2–18 years; at least one seizure in the 4 weeks prior to enrollment; and follow-up after ≥12 weeks of PER as adjunctive therapy.

Exclusion criteria: duration of PER as adjunctive therapy <12 weeks (except for patients for whom PER was discontinued due to poor seizure control or adverse events (AEs), a history of emotional or psychiatric disorders, poor compliance, and incomplete follow-up data.

2.2. Treatment

All patients were treated with PER once daily at bedtime. The initial dose was 1 mg/day or 0.03–0.05 mg/kg/day. The dose of PER was up-titrated every 2 weeks until the target dose or seizure-free status was reached. The target dose was 4–8 mg/day or 0.1–0.15 mg/kg/day.

2.3. Data collection

Data at baseline: Sex, age, the duration of epilepsy, the age of onset, the type of epilepsy, etiology, prior ASMs, concomitant ASMs, seizure frequency, and associated data were collected from patient's clinical records. Seizure frequency at baseline was defined as the mean monthly seizure frequency over the last 12 weeks.

Efficacy: Seizure frequency after adjunctive PER therapy was evaluated and recorded. Efficacy was evaluated according to the change in seizure frequency at the follow-up period relative to baseline. Responders were patients with a ≥50% seizure reduction from baseline. Responders other than seizure-free patients were called 50–99% responders.

Tolerability: Adverse events were evaluated and recorded.

2.4. Statistical analysis

Normally distributed continuous variables are presented as the mean ± standard deviation (SD) and were analyzed by using a *T*-test or an analysis of variance. Skewed distributed continuous variables are presented as the median value and interquartile range (IQR). Categorical variables are presented as frequencies and percentages. Skewed distributed continuous variables and categorical variables were analyzed by using the chi-square test or Fisher's exact test. The Kaplan–Meier method was performed to analyze the relationship between the responder rate and the duration of PER treatment.

All statistical analyses were performed using SPSS version 23.0 (IBM corporation, Armonk, New York). The significance threshold was set to 0.05.

3. Results

3.1. Demographic and baseline characteristics of patients

One hundred and fourteen patients were enrolled, among whom seven patients (6.1%) were lost to follow-up. The demographic and baseline characteristics of the one hundred and seven patients are shown in Table 1. Five patients in our study had undergone epilepsy surgery before initiating PER. They included surgery for moyamoya disease, surgery of the right lateral frontal lobe, surgery of the left frontal lobe, obstructive cerebral spinal ventriculoperitoneal shunt, and vagus nerve stimulation + deep brain stimulation (VNS + DBS). The previous ASMs before the enrollment and the concomitant ASMs at baseline are shown in Table 2.

Etiological characteristics: One hundred and seven patients underwent MRI. Structural brain abnormalities were observed in fifty-eight patients (54.2%). The most common structural abnormalities of these patients were brain atrophy (*n* = 22, 37.9%), encephalomalacia (*n* = 16, 27.6%), signal of brain metabolic abnormalities (*n* = 14, 24.1%), abnormalities of hippocampus (*n* = 12, 20.7%), and white matter demyelination (*n* = 9, 15.5%). Some patients (*n* = 25, 43.1%) suffered from ≥2 abnormalities. There was no significant difference in the incidence of structural brain abnormalities between patients with focal onset epilepsy and those with generalized onset epilepsy (54.6% versus 62.5%, *P* = 0.518). When patients with focal onset epilepsy and those with generalized onset epilepsy were compared with those with epileptic syndromes, a statistically significant difference was observed

Table 1
Demographic and baseline characteristics of patients.

Characteristics	Data for patients receiving PER (*n* = 107)
Male, *n* (%)	70 (65.4%)
Age, years (IQR)	8.6 (5.8,10.7)
Duration of epilepsy, years (IQR)	3.8 (2.1, 6.5)
Age of onset, years (IQR)	4.0 (1.1, 6.5)
≤1 year	25 (23.4%)
>1 and ≤3 years	18 (16.8%)
>3 and ≤6 years	32 (29.9%)
>6 and ≤12 years	30 (28.0%)
>12 years	2 (1.9%)
Type of patients, *n* (%)	
Patients with refractory epilepsy	91 (85.0%)
Patients whose PER was the first concomitant ASM	16 (15.0%)
Type of epilepsy, *n* (%)	
Focal onset epilepsy*	22 (20.6%)
Generalized onset epilepsy	56 (52.3%)
Epileptic syndrome	29 (27.1%)
Dravet syndrome	12 (11.2%)
Infantile Epileptic Spasm Syndrome	8 (7.5%)
SeLECTS/variants of SeLECTS	6 (5.6%)
Doose syndrome	2 (1.9%)
Generalized epilepsy with febrile seizure	1 (0.9%)
Seizure frequency at baseline, 4 weeks (IQR)	4.0 (1.0, 16.5)

* Six patients with FBTCSs were included; SeLECTS, self-limited epilepsy with centrotemporal spikes.

Table 2
The prior ASMs and concomitant ASMs used in patients.

Prior ASMs or concomitant ASMs	Patients
Number of prior (including current) ASMs, *n* (%)	
1	16 (15.0%)
2	19 (17.8%)
3	24 (22.4%)
4	11 (10.3%)
5	14 (13.1%)
More than 5	23 (21.5%)
Most common prior ASMs (≥10% of patients), *n* (%)	
Valproic acid	89 (83.2%)
Levetiracetam	70 (65.4%)
Oxcarbazepine	49 (45.8%)
Clonazepam	45 (42.1%)
Topiramate	27 (25.2%)
Lamotrigine	26 (24.3%)
Lacosamide	21 (19.6%)
Phenobarbital	14 (13.1%)
Number of concomitant ASMs associated with PER, *n* (%)	
1	27 (25.2%)
2	40 (37.3%)
3	29 (27.1%)
4	9 (8.4%)
Most common concomitant ASMs (≥10% of patients), *n* (%)	
Valproic acid	73 (68.2%)
Levetiracetam	50 (46.7%)
Clonazepam	31 (29.0%)
Oxcarbazepine	27 (25.2%)
Topiramate	16 (15.0%)
Lamotrigine	15 (14.0%)
Lacosamide	11 (10.3%)

(37.9%, P = 0.039). In patients with structural abnormalities who had poor response to PER, 3 cases had indications for surgery based on the PET/MR results and MDT conclusion. The structural abnormalities of these patients were focal cortical dysplasia (FCD) in the left central region, FCD in the right parietal lobe, and FCD in the left frontal lobe. They continued PER after surgery and remained seizure-free up to the last visit. Genetic testing was performed for forty-three patients, and among them, positive results occurred in thirty-one patients (72.1%). The most common genetic abnormalities were associated with ion channels, accounting for 64.5% of positive cases (20/31). Eleven de novo mutations (55%) and 5 complex mutations (a combination of 3 or 4 mutations, 25%) were identified among the 20 mutations described above. The incidence of genetic abnormalities in epileptic syndrome was 79.0% (15/19), and all mutations were associated with ion channels. *SCN1A* mutations accounted for 80% of positive cases (12/15), including 10 de novo mutations and 3 heterozygous mutations (Tables 3 and 4).

3.2. Efficacy assessments

The responder rate and the seizure-free rates were 56.1% (60/107) and 32.7% (35/107), respectively (Table 5), at 12 weeks. The responder rate increased with the duration of PER administration. At 48 weeks, the responder rate reached 77.1% (27/35). Kaplan–Meier analysis revealed similar results (Fig. 1). In twelve patients diagnosed with drug-resistant Dravet syndrome, the responder rate and the seizure-free rate were 50.0% (6/12) and 25.0% (3/12), respectively. Among sixteen patients for whom PER was the first concomitant ASM, thirteen patients were responders (82.8%), and ten patients became seizure-free (64.1%).

Etiology and type of epilepsy: At 24 weeks, the responder rate was 52.6% in patients with structural abnormalities (20/38) and 75.8% in patients without structural abnormalities (25/33); the difference was not statistically significant (P = 0.052). In patients in whom genetic abnormalities, ion channel-associated mutations, and *SCN1A* mutations were identified, the responder rates were 54.6% (12/22), 56.2% (9/16), and 66.7% (6/9), respectively. There was also no significant difference in the responder rates among the focal onset epilepsy, generalized onset epilepsy, and epileptic syndrome groups (P = *0.657*) (Table 6).

Early add-on versus late add-on: Perampanel was used as an early add-on (after ≤2 prior ASMs) in thirty-five patients and as a late add-on (after >2 prior ASMs) in seventy-two patients at 12 weeks. The responder rates were significantly higher in the early add-on group than in the late add-on group at 12 weeks and 24 weeks (P = 0.01 at 12 weeks, P = 0.004 at 24 weeks). At 48 weeks, the responder rate of the former was also higher, although the difference was not statistically significant (P = 0.073). The results are shown in Table 7.

3.3. Safety and tolerability assessments

Thirty-two patients (29.9%) suffered from AEs, including irritability (14/32, 43.8%), dizziness (6/32, 18.8%), somnolence (5/32, 15.6%), ataxic gait (4/32, 12.5%), weight gain (2/32, 6.3%), and tinnitus (1/32, 3.1%) (Fig. 2). Most AEs were observed during the initial follow-up period. The severity of AEs gradually decreased with prolonged administration time. Patients taking topiramate (TPM) or levetiracetam (LEV) showed more obvious symptoms. After discontinuing TPM/LEV and controlling seizures, the AEs of these patients were alleviated.

4. Discussion

In this study, we explored the efficacy and safety of PER as adjunctive therapy in children and adolescents with epilepsy from real-world data. Our retrospective data analysis demonstrated that the responder rate and the seizure-free rates were 56.1% (60/107) and 32.7% (35/107), respectively, at 12 weeks. In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, 133 adolescents (12–17 years) on a regimen of 1–3 ASMs for FOSs were randomized [15]. The 50% responder rate during the 13-week maintenance period was 37.0% in the placebo group versus 59.0% in the PER group (P = 0.0144) [15]. In another study, twenty-two patients (3.1–11.4 years) with refractory epilepsy were included [16]. After an average of 9.2 months of follow-up, 68.2% of the patients showed a ≥50% reduction in seizure frequency, including 22.7% of patients who achieved seizure freedom [16]. Chang et al. reported that the responder rate and the seizure-

Table 3
Etiological characteristics of the patients.

Etiology (*n*/*n*) [a]	Focal onset epilepsy, *n* (%)	Generalized onset epilepsy, *n* (%)	Epileptic syndrome, *n* (%)
Structural (58/107)	12 (20.7%)	35 (60.3%)	11 (19.0%)
Genetic (31/43)	3 (9.7%)	13 (41.9%)	15 (48.39%)
Immune 4	1 (25.0%)	3 (75.0%)	0 (0.0%)
Unknown 31	8 (25.8%)	14 (45.2%)	9 (29.0%)

[a] Positive patients/tested patients.

Table 4
Mutation analysis of genetic epilepsy.

Mutation (n/n) [a]	Focal onset epilepsy	Generalized onset epilepsy	Epileptic syndrome
Genetic (31/43)	3/2/17[b]	13/6/37[b]	15/4/10[b]
	1 (*CACNA1H*) [c] 1 (*DEPDC5*[n], *NPRL3*[e]) 1 (*SPTBN5*[f], *SETD1B*[k])	1 (*SLC9A6*) [c] 1 (*SCN2A* de novo) [c] 1 (*GRIN2A*) [d] 2 (*SCN8A*) [c] 1 (*PLEKHG2*) [f] 1 (*GPR98* de novo) [d] 1 (*GABRD*[g], *SLC2A1*[h], *CACNA1A*[c], *CHD2*[i]) 1 (*DLAPH3*[f], *POLG2*[j], *GRIN3B*[b]) 1 (*NFIX*) [l] 1 (*TBC1D24*[e], *PRRT2*[g]) 1 (*GABRB2*) [d] 1 (*PTPN23*) [m]	9 (*SCN1A* de novo) [c] 3 (*SCN1A* heterozygous mutations) [c] 1 (*SCN2A* de novo) [c] 1 (*KCNQ2*) [c] 1 (*KCNQ4*) [c]
Total (n)	3	13	15

[a] Positive patients/tested patients.
[b] Positive patients/negative patients/untested patients.
[c] Ion channel.
[d] Receptor.
[e] Enzyme modulator.
[f] Regulator of cytoskeleton formation.
[g] Neurotransmitter.
[h] Glucose transporter.
[i] Chromatin remodeler.
[j] Mitochondrial polymerase.
[k] Epigenetic regulator of gene transcription.
[l] CCAAT-binding transcription factor.
[m] Transporter.
[n] Unknown in OMIM.

Table 5
Efficacy outcomes for different follow-up durations.

Duration of follow-up, weeks	Patients, *n*	Seizure-free, *n* (%)	50–99% responders, *n* (%)	Non-responders, *n* (%)
12	107	35 (32.7%)	25 (23.4%)	47 (43.9%)
24	71	20 (28.2%)	25 (35.2%)	26 (36.6%)
48	35	7 (20.0%)	20 (57.1%)	8 (22.9%)

free rates were 43.4% and 12.5%, respectively, after 6 months of PER treatment in young children with refractory epilepsy [17]. The results of the present study were concordant with those of previous studies with regard to the clinical efficacy of PER. This study provides strong evidence to support the application of PER in the adjunctive treatment of epilepsy in the pediatric population.

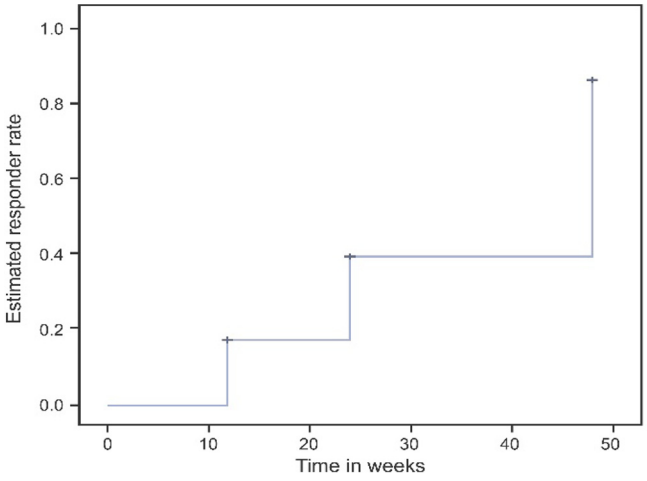

Fig. 1. Kaplan–Meier survival analysis of follow-up data.

Our series included twelve patients with Dravet syndrome; after PER treatment, the responder rate was 50.0% (6/12), and the seizure-free rate was 25.0% (3/12). In two previous studies, the responder rate was 67.0% and 80.0% in patients with Dravet syndrome [17,18]. These results indicated that PER may be efficacious for the treatment of seizures in patients with Dravet syndrome. *SCN1A* mutations were detected in nine patients. The responder rate in these patients reached 66.7% (6/9). *SCN1A* mutation represents the archetypal channelopathy associated with a wide phenotypic spectrum of epilepsies ranging from genetic epilepsy with febrile seizures plus to developmental and epileptic encephalopathies [19]. Ishikawa et al. described a female patient with early myoclonic encephalopathy due to an *SCN1A* mutation [20]. Her apneic seizures, which were refractory to many ASMs, were successfully treated with adjunctive PER [20]. Perampanel also showed good efficacy in patients with Lennox–Gastaut syndrome (LGS). Auvin et al. and Crespel et al. stated that the responder rate was 69.2% and 64.8% [21,22]. Based on the evidence, we considered that PER could be used for a variety of types of pediatric epilepsy, especially for Dravet syndrome and other epileptic encephalopathies.

The effectiveness of several emerging new treatment options in the treatment of Dravet syndrome or other encephalopathies has

Table 6
Efficacy analysis of different etiologies and types of epilepsy.

Etiology or type of epilepsy	Patients, *n*	Seizure-free, *n* (%)	50–99% responders, *n* (%)	Non-responders, *n* (%)	*P* value
Structural abnormalities	38	9 (23.7%)	11 (28.9%)	18 (47.4%)	0.052
Without structural abnormalities	33	11 (33.3%)	14 (42.4%)	8 (24.2%)	
Genetic abnormalities	22	4 (18.2%)	8 (36.4%)	10 (45.5%)	/
Mutations associated with ion channels	16	2 (12.5%)	7 (43.8%)	7 (43.8%)	/
SCN1A mutations	9	0 (0.0%)	6 (66.7%)	3 (33.3%)	/
Focal onset epilepsy	12	5 (41.7%)	4 (33.3%)	3 (25.0%)	0.657
Generalized onset epilepsy	36	10 (27.8%)	12 (33.3%)	14 (38.9%)	
Epileptic syndrome	23	5 (21.7%)	9 (39.1%)	9 (39.1%)	

Table 7
Comparison of efficacy between the early add-on group and the late add-on group.

Duration of follow-up, weeks	Patients, *n*	Patients in different groups, *n*	Responders, *n* (%)	Non-responders, *n* (%)	*P* value
12	107	Early add-on *n* = 35	28 (80.0%)	7 (20.0%)	**0.01**
		Late add-on *n* = 72	32 (44.4%)	40 (55.6%)	
24	71	Early add-on *n* = 23	20 (87.0%)	3 (13.0%)	**0.004**
		Late add-on *n* = 48	25 (52.1%)	23 (47.9%)	
48	35	Early add-on *n* = 10	10 (100.0%)	0 (0.0%)	0.073
		Late add-on *n* = 25	17 (68.0%)	8 (32.0%)	

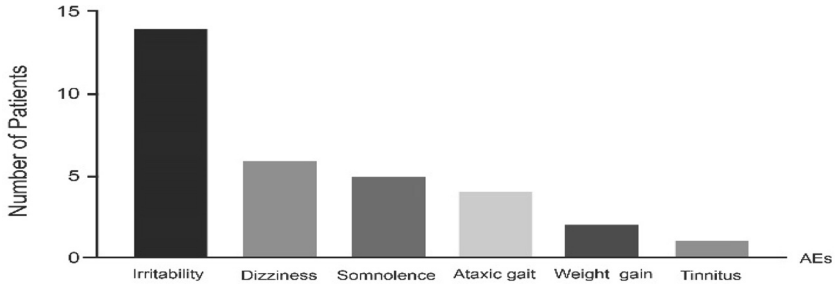

Fig. 2. Adverse events during the follow-up period.

been demonstrated in previous studies. Lagae et al. and Knupp et al showed that the responder rates of fenfluramine (FF) (0.7 mg/kg) for the convulsive seizures in Dravet syndrome and the drop seizures in LGS were 68.0% and 25.3%, respectively [23,24]. However, there is an association between FF and valvular heart disease and pulmonary arterial hypertension, which limits the use of FF [25,26]. In two Meta-Analysis associated with adjunctive cannabidiol (CBD), the responder rate for the convulsive seizures in Dravet syndrome and the drop seizures in LGS were 45.4% and 40.0%, respectively [27,28]. Significantly, response to treatment with FF and CBD could be observed in patients with other epileptic conditions (e.g., CDKL5 deficiency disorder, *SCN8A* developmental and epileptic encephalopathy, and Aicardi, Dup15q, and Doose syndromes) as well [29,30]. In view of the comparative effectiveness, we considered that PER can be used as an option for the treatment of epileptic syndromes in clinical practice. Whereas, the efficacy of PER for epileptic syndromes needs to be verified by further research because of the small sample size of patients with epileptic syndromes in the previously performed studies. Besides, the comparison of the efficacy of PER, FF, and CBD should be investigated in future clinical trials.

We also analyzed the primary factors affecting the efficacy of PER. No significant difference in efficacy was observed among patients with different etiologies and epilepsy types. This finding was consistent with those of other studies, indicating that PER was efficacious for the treatment of various types of epilepsy [16]. Additionally, PER was more effective in the early add-on setting than after 3 or more ASMs. Villanueva V et al. also showed that the seizure-free rate and the retention rate in idiopathic generalized epilepsy patients starting PER as an early add-on were markedly higher than those in patients starting PER as a late add-on (seizure-free rate, 71.7% vs 52.1%, $P = 0.02$; retention rate, 92.5% vs 78.1%, $P = 0.038$) [31]. Another multicenter, retrospective, observational study included One hundred and forty-nine patients who experienced inadequate seizure control on ASM monotherapy and tried $\leq$3 ASM monotherapies before initiating PER as a first add-on therapy [32]. The responder rate was 84.6% at 12 months [32]. Therefore, the use of PER as an early add-on was more appropriate than its use as a late add-on. To the best of our knowledge, the current study is the first to compare the efficacy of PER as an early add-on or late add-on in a pediatric population, and the result that higher efficacy was observed in the early add-on group is consistent with the results of previous studies in adults.

The incidence of AEs in our study was 29.9% (32/107). No serious AEs were observed. In the study reported by Qu et al., the common AEs in Chinese patients (2–14 years) with refractory epilepsy included irritability (12.5%), somnolence (9.4%), dizziness (7.3%), and headache (5.2%) [33]. Perampanel was generally safe and well tolerated in the pediatric population based on these results. Several studies also investigated the safety and tolerability of PER in the adults or elderly [34,35]. According to the results from our study and previous studies, the tolerability profile of PER in children, adults, and the elderly was similar while the proportion of these AEs was different. In general, the most common AEs of PER treatment were irritability, somnolence, and dizziness.

The main limitations of this study are its retrospective design, lack of randomization, and lack of a control group. Furthermore, there may be some bias in the analysis of efficacy as a result of

the heterogeneity of the recruited patients. Further follow-up studies are needed to evaluate the long-term efficacy and safety of adjunctive PER. However, there are several strengths of the study as well: the sample of patients included was relatively large, the real-world setting represents clinical practice, and the superior efficacy of PER as early add-on therapy in pediatric patients was demonstrated for the first time.

5. Conclusion

Data from real-world clinical settings were analyzed. Efficacy assessments revealed that adjunctive PER was efficacious for uncontrolled epilepsy in pediatric patients. The etiology and type of epilepsy did not influence the efficacy of adjunctive PER. In particular, PER was more effective in the early add-on setting than in the late add-on setting, which has not been reported in pediatric patients in previous studies. Safety assessments revealed that PER was well tolerated.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

We would like to thank all the patients for participating in the study.

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