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ORIGINAL RESEARCH

The Efficacy and Cognitive Impact of Perampanel Monotherapy in Patients with Self-Limited Epilepsy with Centrotemporal Spikes: A Retrospective Analysis

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Objective: The third generation of antiepileptic medication (ASM) perampanel (PER), is mostly used as an add-on treatment for refractory epilepsy patients, and rarely used as a monotherapy. This study aims to observe the efficacy and assess the cognitive effects of PER monotherapy in patients with self-limited epilepsy with centrotemporal spikes (SeLECTS).

Patients and Methods: Through screening, 86 patients who were first diagnosed with SeLECTS and treated with PER monotherapy were included in this study. All patients were followed up at least 12 months, and Evaluated the efficacy and safety of PER by observing the seizures of patients. At the same time, we used the P300 event-related potential (ERP) component and Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) to evaluate the cognitive changes in children before and after treatment with PER.

Results: Ten percent of the children experienced adverse effects, such as dizziness, gait instability, and irritability. The drug retention rate at the last follow-up was 98.83%. Further more, the P300 ERP component and WISC-IV tests were performed no significant difference before and 12 months after PER monotherapy in SeLECTS children.

Conclusion: The third-generation of ASM PER monotherapy had a clear effect in children with SeLECTS. A small dose of PER can control seizures well and has no obvious effect on cognitive development.

Keywords: self-limited epilepsy with centrotemporal spikes, P300 ERP component, Wechsler Intelligence Scale for Children-Fourth Edition, perampanel, monotherapy

Introduction

SeLECTS is the most common focal epilepsy in childhood, accounting for 10–20% of patients with childhood epilepsy.[1] PER is a third-generation and novel ASM that suppresses the neurotransmission of the excitatory transmitter glutamate by binding to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and limits the production and diffusion of the epileptic electrical activity, thus exerting an anti-seizure effect.[2,3] In 2017, PER received FDA approval as monotherapy for the treatment of focal-onset seizures (FOS), with or without focal to bilateral tonic-clonic seizures (FBTCS), in patients aged ≥12 years, and is currently approved in approximately 48 countries for use as monotherapy for FOS (with or without FBTCS).[4] China has already approved PER as monotherapy and add-on therapy in patients aged ≥4 years for FOS (with or without FBTCS) in 2021.

Children with FOS may have difficulties with sociocognitive skills,[5–7] it's especially important for pediatric patients to choose a drug that is well tolerated for cognitive profiles.[8] Studies have shown that,[9] among single ASMs, levetiracetam

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could slightly improve cognitive function, whereas carbamazepine led to deteriorations in cognitive functioning. PER did not negatively affect cognitive function in add-on therapy and was well tolerated.[10]

Husni and Chinvarun showed that,[11,12] PER monotherapy in newly diagnosed FOS (with or without FBTCS) had a seizure-free rate of approximately 63–80%, with well tolerated and no new safety concerns. Masses of foreign clinical evidence also supports the use of PER monotherapy in both newly diagnosed patients and those who have been unable to control their seizures with other oral ASMs.[4] Patients receiving PER monotherapy had good retention and robust efficacy, and are similar to those reported for other ASMs when administered as monotherapy.[13–16] PER may be a particularly valuable monotherapy option for the treatment of FOS (with or without FBTCS).

However, currently in China, PER is limited to being an add-on treatment for FOS in children; showing good efficacy and safety, and there are almost no reports about PER monotherapy in children with epilepsy. In this study, after obtaining informed consent from the patient's family, the first choice of PER monotherapy was used for children with a first diagnosis of SeLECTS; then, we would observe all children for 3, 6 and 12 months to determine the efficacy and safety of SeLECTS, and to research its effect on cognition.

Materials and Methods

This research was conducted from July, 2021, to January, 2022, in XuZhou Children's Hospital. The protocol of this study was approved by the Ethics Committee of the Ethics Committee of Xuzhou Children's Hospital, and it was conducted according to the Declaration of Helsinki.

Participants

All patients were recruited from the Department of Neurology of Xuzhou Children's Hospital, who were first diagnosed of SeLECTS and preferred PER monotherapy, and followed-up more than 12 months. We collected data on sex, age, age of onset, duration of disease, seizure type, seizure frequency, seizures before and after PER monotherapy, adverse reactions, intelligence tests, etc. By the way, we used a Diary of seizure to monitor seizure frequency in outdoor patients. The inclusion criteria are as follows: (1) Patients met the diagnostic criteria of SeLECTS established by the International League Against Epilepsy,[17] that is, onset as sleep-related FOS with unilateral or bilateral central and parietal regions with or without spike and slow spike emission in the middle and posterior temporal regions as seen on the electroencephalogram (EEG); (2) Patients were 6–14 years old when diagnosed; (3) Patients did not take any ASMs before hospital visit; (4) Cranial magnetic resonance imaging showed no obvious abnormalities; (5) total WISC-IV score $\geq$ 80. Exclusion criteria: (1) Patients who combined psychomotor retardation, total WISC-IV score < 80; (2) Patients who received other ASMs before enrollment; (3) Patients with a history of birth trauma or asphyxia; (4) Patients with poor compliance or noncooperation.

Treatment Methods

Treatment was administered referring to the starting dosing regimen in the European Medicines Agency PER instructions. For children aged 4–12 years, the starting dose was 2 mg/d for children weighing >30 kg, 1 mg/d for children weighing 20–30 kg, and 0.5 mg/d for children weighing <20 kg. The dose was increased once a week, with each increase by 1 starting dose, to a target dose of 2–8 mg/d. The specific starting dose, increment and maintenance treatment amount were determined by individual conditions, if there was seizure-free, the lowest dose was maintained, otherwise the dose was gradually increased. And the PER must be used continuously for more than 12 months. In cases of serious adverse reactions during PER dosage treatment, the drug was stopped immediately.

Cognitive Function Assessment Methods

The P300 ERP Component Inspection

In this study, we used a BrainMR 64 channel EEG analyzer produced by the German Brain Products Company to inspect P300 ERP component.[18] The electrodes were placed according to the international 10~20 system, with bilateral earlobes (A1, A2) used as reference electrodes. The impedance between electrodes was less than 5 kΩ, the sensitivity was 5 V/D, and the bandpass range was 0.1~3.5 Hz. Patients who undergoes this examination were required to sit in a chair 80

centimeters away from the computer screen, with their eyes fixed on the center of the screen and focused as much as possible. Then, the "oddball" sequence would be presented on the screen. The ERP EEG analyzer recorded EEG signal shapes, and E-Prime software compiled stimulus graphics. The stimulus graphics included the target stimulus and nontarget stimulus. The target stimulus was a blue square with a frequency of 20%, and the nontarget stimulus was a red square with a frequency of 80%. The red or blue square appeared randomly 300 times, with a duration of 400 millisecond (ms) for each stimulus. The interval between the two stimuli was 1000 ms. The stimulus pattern was displayed in the center of the screen. When patients observed the target stimulus, they pressed the space bar, otherwise, when they saw nontarget stimulus, they did not press the key. If the patient's discrimination error rate exceeded 20%, doctor believed that this test was invalid, and needed to be trained again. The brain waves were led by scalp electrodes, and the latency and wave amplitude of the P300 component in the central (C3, C4), parietal (P3, P4), frontal midline (Fz), central midline (Cz), and parietal midline (Pz) leads were measured. The ERP components of the Cz leads were analyzed by Analyzer 2.0 software, and the signals were superimposed by the brain evoked potentiometer to automatically identify and exclude EEG artifacts, display the averaged potentials, and measure the latency and wave amplitude of the P300 component elicited by the target stimulus.

WISC-IV Test

We used WISC-IV[19] to test four aspects: verbal comprehension (Similarities, vocabulary, and Comprehension), perceptual reasoning (block design, picture concept, and matrix reasoning), working memory (digit span and letter-number sequencing), and processing speed (coding and symbol search). The scores of each test item were counted, and the results were input into the Chinese version of the WISC-IV software designated for score processing. First, we composed four composite scores, namely, the verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI); then, we synthesized a second-order factor index, and finally obtained the full-scale IQ (FSIQ). FSIQ scores range from 40 points to 160 points, with an average of 100 points and a standard deviation of 15 points. The grades are divided according to the FSIQ scores: 130 points and above are extremely abnormal; 120–129 points are abnormal; 110–119 points are higher than usual; 90–109 is normal; 80–89 is below normal; 70–79 is borderline; and below 69 is mentally retarded. The test before starting monotherapy was the baseline data, all patients were followed by the same test sequence, and the test process is monitored by the same child psychologist who is familiar with standardized test procedures to ensure homogeneity.

Observation Indicators

Seizure Conditions

In this study, we collected the outpatient or inpatient data of the children in Xuzhou Children's Hospital during PER monotherapy, evaluated the seizures of children before PER monotherapy, and recorded the baseline seizure level as well as the seizures of the children before and 3, 6 and 12 months after PER use.

Primary Outcome Indicator

Effectiverate = seizure − free period + effective period. The seizure-free period was defined as the seizure-free duration at the last follow-up that was at least 3 times the longest seizure interval before drug administration, and the patient continued to be seizure-free for ≥ 3 months. The effective period was defined as a ≥50% reduction in seizure frequency at the last follow-up (within the last 1 month) compared with that of the baseline period.

Occurrence of Adverse Reactions

In the assessment of the safety of PER as a monotherapy for SeLECTS, We evaluated the safety of PER monotherapy for SeLECTS through recording the adverse reactions and tolerance of children during PER monotherapy by telephone and outpatient follow-up.

Impact on Cognition

The ERP P300 examination and WISC-IV test results of children before and 12 months after using PER were collected, and the cognitive impact of single-drug treatment with PER was evaluated for SeLECTS children.

Statistical Methods

SPSS 25.0 statistical software was used for data analysis. Normally distributed measurement data were expressed as mean±standard deviation ($\overline{X}$±SD), while non-normally distributed measurement data were expressed as median (95% confidence interval), and the comparisons were examined by Student-*t*-test and Mann–Whitney test (non-parametric distribution). The categorical data were expressed as n (%), and the differences between the two groups were examined by chi-square analysis or Fisher's Exact Test. $P < 0.05$ means the difference is statistically significant.

Results

General Information of Patients

A total of 86 children aged 6–13 years diagnosed with SeLECTS were evaluated, including 38 males and 48 females. The age at the time of hospital admission was 5.8–13 years, And the age of onset was 5.4–11.5 years old. The duration of epilepsy before treatment was 1–18 months, accompanied by 2–7 seizures, lasting from 20 seconds to 10 minutes. All 86 children were focal epilepsies, seizure types included FOS in 54 cases, and FBTCS in 32 cases, followed up for more than 1 year and had complete seizure data recordings (Table 1). Parents consented to the use of anti-seizure medication, and all patients received PER as their first anti-seizure medication.

Table 1 General Information of the Patients ($\overline{X}$± SD)

	SeLECTS (N=86)
Gander	
Male	44% (38/86)
Female	56% (48/86)
Weight (Kg)	
<20	34% (29/86)
20–30	40% (34/86)
>30	26% (23/86)
Age (years)	
6–11	98% (84/86)
≥12	2% (2/86)
Onset age	5.4–11.5
Average age	8.62 ± 2.03
Number of seizures	2–7
Average number of seizures	2.94 ± 4.17
Seizure Type	
FOS	63% (54/86)
FBTCS	37% (32/86)
Seizure duration	20 s - 10 min
Seizure time	
Status epilepticus	1% (1/86)
Waking phase	5% (4/86)
Sleep phase	82% (71/86)
Waking phase and sleep phase	12% (10/86)
Formerly medical history	
History of birth asphyxia	1% (1/86)
History of febrile seizures	16% (14/86)
Family history of febrile seizures	36% (5/14)
Family history of epilepsy	2% (3/86)
Localization of EEG characteristic spikes	
Central and temporal areas	53% (46/86)
Frontal area	33% (28/86)
Parietal area	14% (12/86)

Note: "$\overline{X}$± SD" means "mean ± standard deviation".

The Efficacy of PER Monotherapy for SeLECTS

Of the 86 children, at the third month of treatment with PER monotherapy, 98.83% (85/86) had a ≥ 50% reduction in seizure frequency from the baseline level, of which 97.6% (84/86) were seizure-free. A total of 98.83% (85/86) of the 86 children were followed up for 6 months or more. Among them, 86.04% (74/86) had a ≥ 50% reduction in seizure frequency from baseline, and 81.39% (70/86) were seizure-free. At 1 year of follow-up, 84.89% (73/86) had a ≥ 50% reduction in seizure frequency from the baseline level, of which 79.07% (68/86) were seizure-free. By the time of the final follow-up, 98.83% (85/86) remained adherent to oral PER, demonstrating a high retention rate (Table 2).

Safety and Tolerability of PER Monotherapy

Among all patients, adverse reactions were detected in 8 patients, including 4 who experienced gait instability, 3 who experienced dizziness, and 1 who had a rash. The main adverse event was gait instability, which was mainly related to the rapid dose increase at the beginning of the disease; then, the dose was decreased to 2 mg after 2 weeks, and the symptoms gradually decreased and finally disappeared. Three children complained of dizziness, but it was tolerable, and the symptoms gradually disappeared after 10 days of adherence. One child developed a rash after taking PER 1 week, and adhered to the drug regimen without considering the side effects of PER, then the rash disappeared. Although the rash disappeared, we still classified it as a side effect. Adverse reactions in all patients (9.3%, 8/86) occurred at the beginning of treatment (most patients had remission or substantial resolution of adverse reactions after more than 2 weeks of dosing) at PER doses ≤ 4 mg/d, indicating that the incidence of adverse reactions was not significantly correlated with the dose (Table 3). All observed adverse reactions disappeared after discontinuation of the drug or after a period of dosing.

Effect of PER Monotherapy on Cognition

The differences in P300 latency and wave amplitude between children before treatment and after 12 months of preferred PER monotherapy were not statistically significant ($P > 0.05$) (Table 3). Analysis of the WISC-IV scale scores revealed no statistically significant differences ($P > 0.05$) in either the child's total intelligence quotient or in the VCI, PRI, WMI, and PSI scores before and after treatment (Table 4). Concurrently, we also found that there was no correlation between the WISC-IV score and the frequency of seizures before and after treatment (Table 5). The above tests showed that there had no effect of PER monotherapy on cognition in children with SeLECTS, and there might be no correlation between cognition and seizure frequency.

Table 2 The Efficacy and Drug Retention Rate of PER Monotherapy

Therapy Time	Seizure Frequency	Effective (%)	Seizure-Free (%)	Drug Retention Rate (%)
3 months	Once / a month	98.83% (85/86)	97.6% (84/86)	98.83%
6 months	Once / 3 months	86.04% (74/86)	81.39% (70/86)	98.83%
12 months	Once / 6 months	84.89% (73/86)	79.07% (68/86)	98.83%

Table 3 Drug Use and Adverse Reactions at 12 Months of Treatment

Groups	Number of Initial Drug Users (n)	Initial Dose (mg/Day)	Maintenance Dose (mg/Day, n)	Incidence Rate of Adverse Reactions (%)	Drug Retention Rate (%)
<20 (Kg)	29	0.5	2 (26) 4 (3)	0	100
20–30 (Kg)	34	1	2 (24) 4 (10)	2 (5.88%)	98.83%
>30 (Kg)	23	2	2 (20) 4 (3)	6 (26.08%)	100%

Table 4 Analysis of ERP P300 and WISC-IV Results After 12 Months of PER Treatment

Test	Total Number (n)	Before Treatment M (95%)	After Treatment M (95%)	*P*
ERP P300				
P300 latency (ms)	86	362.00 (361.98, 368.02)	365.00 (362.75, 369.37)	0.690
P300 amplitude (uv)	86	11.45 (11.16, 11.54)	11.34 (11.13, 11.54)	0.710
WISC-IV				
VCI (score)	86	84.00 (84.60, 84.91)	85.00 (84.87, 86.89)	0.95
PRI (score)	86	85.00 (84.50, 86.16)	85.00 (84.48, 86.24)	0.837
WMI (score)	86	85.00 (84.51, 86.27)	84.00 (84.34, 86.01)	0.580
PSI (score)	86	84.00 (83.82, 85.73)	85.00 (84.05, 85.85)	0.550
FSIQ (score)	86	85.00 (84.77, 86.03)	85.00 (84.83, 86.01)	0.960

Notes: "M (95%)" means "median (95% confidence interval)"; before and after treatment, p>0.05.
Abbreviations: VCI, speech comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index; FSIQ, total IQ.

Table 5 Correlation Analysis Between WISC-IV Scores and Seizure Frequency Before and After 12 Months of per Treatment

Group	Seizure Frequency M (95%)	FSIQ (Score) M (95%)	Correlation Coefficient	P
Before treatment	4.00 (3.50, 4.03)	85 (84.77, 86.03)	0.009	0.935
After treatment	0.00 (0.16, 0.43	85 (84.83, 86.01)	−0.19	0.865
Difference before and after treatment	−3 (−3.69, −3.00)	0.00 (−0.23, 0.24)	0.004	0.968

Notes: "M (95%)" means "median (95% confidence interval)"; Difference before and after treatment=After treatment-Before treatment.

Discussion

The indications for PER have gradually increased since its launch in China and were approved in July 2021 for monotherapy and add-on treatment of FOS (with or without FBTCS) in patients aged 4 years and older with epilepsy. Prior to this, PER has been approved as monotherapy for FOS (with or without FBTCS) in several countries.[20–22] In a multi-center retrospective study in Europe and Russia,[23] the 3-month and 6-month retention rates of PER monotherapy were 95% and 74%, respectively, and 55% of patients were seizure-free for at least 3 months during primary or secondary monotherapy for PER. Another single-arm, open-label, Phase III study of PER monotherapy in Japan and South Korea found[11] that 63% (46/73) of patients were seizure-free on 4 mg/d PER monotherapy, and 74% (54/73) of patients were seizure-free at the final assessed dose of 4 or 8 mg/d. This suggests that PER is of great significance as a monotherapy for FOS (with or without FBTCS) and can achieve seizure-free control with effective doses. There were very few studies of PER had been reported in China. Fang et al[24] found that the 6-month treatment efficiency of 38 cases of FOS (with or without FBTCS) children was 61% by treated with PER, but it was only used as an add-on treatment and was not reported as the preferred monotherapy. In this study, we observed the effectiveness and tolerability of PER monotherapy in children with SeLECTS over 6 years old for 6 months, starting from July 2021, when PER was approved for use as a monotherapy. We found that PER monotherapy was effective in children with SeLECTS, with a seizure-free rate of 81.39% and a seizure efficiency of 86.04%. We generally preferred 2 mg/d as the maintenance dose; if there was a seizure, the dose was increased, and if there was seizure-free, the original dose was maintained. The powerful therapeutic effect demonstrated by using a smaller dose certainly adds to the clinical rationale for PER as the medicine of choice for the treatment of SeLECTS children.

In addition, PER has a low probability of adverse events during the treatment of epilepsy. In this study, 8 children had adverse reactions, mainly gait instability, dizziness, and rash. One child had a rash, which later disappeared after maintaining the dose and treatment regimen, suggesting that the rash was not a side effect of PER, but we still classified the rash as a side effect. The remaining 7 children had adverse reaction symptoms that gradually decreased and disappeared approximately 10 days after the dosing rate was decreased. No other serious adverse reactions were observed. Some studies[25–28] have shown that an increase in PER dose is associated with an increase in the incidence of adverse events, but others have concluded that there is no relationship between the incidence of adverse events and PER dose. In fact, our clinical data showed that rapid dosing

was associated with adverse reactions in some children, while slowing down the dosing rate led to a gradual disappearance of adverse reactions in children with good tolerance and adaptation. In other studies,[29–31] 48% to 67% of patients experienced adverse events, and the main adverse event reported for PER was irritability, followed by rash, dizziness, drowsiness, ataxia, and anxiety. No other adverse events, such as anxiety or irritability, were observed in our patients, which may be related to the low dose of PER, mostly less than 4 mg, and the slow dosing rate.

PER is an effective monotherapy in patients with SeLECTS for several reasons. (1) Age: the children enrolled in our current study were 6 years old and above. A previous study by Biró[32] found that the overall efficiency of PER added the treatment regimen for children aged 2 to 17 years (10.5) with drug-refractory epilepsy was 31.0% (18/58), while the effectiveness rate was 36.2% (17/47) for children aged 6 to 12 years and 40.0% (10/25) for children aged 12 years and older. Operto et al[33] found that in the study of 8–10-year-old children with absence epilepsy, 75% (15/20) of the children were seizure-free after additional PER treatment, and 60% (9/15) of the children were still seizure-free after switching to PER monotherapy. All above indicated that age is an important factor affecting the efficacy of PER and PER is more effective in older children. Eighty-six children aged 6 years and older with SeLECTS were included in this study, including 84 children aged 6 to 12 years and 2 children aged 12 years and older. The overall efficiency of PER treatment was 86.04% (74/86), 88.09% (74/84) for children aged 6–12 years, and 100% (2/2 cases) for children aged 12 years and older, using 6 months of seizure-free status as the criterion for effectiveness. This study also showed a trend toward better PER outcomes in older children compared to that in foreign studies. (2) Seizure type: Steinhoff et al[34] assessed the effects of PER administration in patients and found an efficiency of 48.0% in patients with complex partial seizures and an efficiency of 57.0% in those with generalized tonic–clonic seizures. The efficacy of PER may vary widely among seizure types. The children with SeLECTS included in this study were FOS, a single seizure type, relatively low seizure frequency, and a mostly benign disease course. The overall efficiency after PER monotherapy was 98.83% at 3 months, and the seizure-free rate at 6 and 12 months were as high as 81.39% and 79.07%.

This study also combined ERP P300 and WISC-IV data to assess the cognitive function of the children more comprehensively. The results showed that P300 latency, wave amplitude and WISC-IV test scores of children with SeLECTS were did not change significantly after 12 months of PER monotherapy compared to that before treatment. And there was no significant correlation between the seizure frequency and the cognitive function before and after PER monotherapy for SeLECTS children. All those demonstrated that PER had no significant effect on cognition in children. Previous systematic studies on the objective cognitive effects of PER also found that the cognitive profile of PER was neutral, with no systematic cognitive deterioration or improvement.[6,8,35,36]

There were still some limitations in our study. First, as an newly ASM applied to pediatric patients, the sample size was small, and the patients heterogeneity were large, which may lead to bias in the efficacy statistics. Second, the follow-up period was short, and the effectiveness of long-term PER administration for some patients with low seizure frequency remains to be confirmed. Additionally, this study failed to monitor the serum drug concentration of patients or the changes in EEG during the treatment. Although PER has demonstrated encouraging effects in preliminary observations, clinical data from larger sample sizes and longer clinical observations are needed in the future to further evaluate the effectiveness, tolerability and safety of PER administration and to provide more adequate data to support standardized clinical applications of PER.

Conclusion

In conclusion, the present clinical study for the application of PER monotherapy in patients with SeLECTS showed an overall seizure-free rate of 79.07%, a higher overall efficiency, and relatively good safety and tolerability. Moreover, there was no significant effect on cognition in children before and after oral administration of PER; thus, PER can be used as the preferred monotherapy for SeLECTS.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Statement of Ethics

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Xuzhou Children's Hospital (protocol code 2021-05-13H11). The procedures complied with institutional guidelines. Given the retrospective enrollment, patient consent for participation was waived by Xuzhou Children's Hospital. We promise that patient privacy data will not be available and published.

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Disclosure

The authors report no conflicts of interest in this work.

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